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European Commission

Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe

Final Report

Written by Copenhagen Economics
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Copenhagen Economics

EUROPEAN COMMISSION

Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs
Directorate F — Innovation and Advanced Manufacturing
Unit GROW-F.5 — Intellectual property and Fight against Counterfeiting

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EUROPEAN COMMISSION

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Abstract

In this study, we utilise a unique, new dataset to assess the economic impact of supplementary protection certificates (SPC's) and the pharmaceutical incentives and rewards in the EU. We develop a measure called the 'Effective protection period'. It reflects the time that elapses from a medicinal product obtains a marketing authorisation until the last measure of protection on it expires; this could be the original patent, an SPC or one of the other incentives and rewards in the pharmaceutical legislation. We find that 45% of the medicinal products in our dataset have obtained an SPC in at least one of the European countries. We find that the SPC has added years to the effective protection period for those innovator products where the SPC is the last measure of protection to expire. While the protection for medicinal products in the EU is amongst the strongest in the world, we find that for the medicinal products in our dataset the average effective protection period has decreased by approximately two years from 15 to 13 years since 1996 (with variations in individual cases). We find that a longer effective protection period stimulates research and development into new medicinal products. We also find that it delays an average price drop of approximately 50 pct. following the entry of generics. We find that companies choose to launch more medicinal products faster in larger and wealthier countries. Hence, not all new products are made available in all European countries and not at the same time.

Reading guide

OUR TASK AND MANDATE

The information and views set out in this study are those of Copenhagen Economics and do not necessarily reflect the official opinion of the European Commission. The Commission cannot guarantee the accuracy of the data included in this study. The Commission or any person acting on its behalf cannot be held responsible for the use which may be made of the information contained therein."

Reflecting the statement above, we take full responsibility for our work and the contents of this report.

It is, however, important for the reader to know the limits to the scope of the study, which are defined in combination by the technical specifications (publicly available)[1], the winning proposal written by Copenhagen Economics and specific requests from the European Commission. Based on this, there are a number of issues that we have not analysed. We cannot rule out that including one or more of these issues could affect one or more of our conclusions.

In the following, we briefly list relevant issues that we have not analysed due to them being beyond the scope of our study, given the technical specifications and/or requests from the European Commission:

Taxation is regarded as a member state issue and is as such beyond the scope of this study even though it is recognised as a driver of (localisation of) innovation (R&D).

Parallel trade is regarded as an issue related to the internal market in general and not to IP rights or pharmaceutical incentives and rewards in the EU specifically and thus beyond the scope of our study. This is despite the fact that the feasibility of parallel trade is likely to have a significant impact on the price setting and launching behaviour of pharmaceutical companies.

IP rights other than patents and SPCs are (or could become) important to the pharmaceutical industry. For example, companies use copyrights, database protection, trademarks and trade secrets to protect their intellectual property. While analysing the prevalence and impact of these rights is beyond the scope of this study, the shift from product to process-oriented R&D is likely to influence the importance and application of both patents and SPCs. Process-oriented R&D is for example a feature of biological medicinal products where the production process itself is pivotal for the effect of the product. For clarity, it should be emphasised here that in addition to patents and SPC's we do, of course, analyse the incentives and rewards in European pharmaceutical legislation.

Competition law is an important factor in the pharmaceutical sector. One application area is collusion (e.g. pay-for-delay schemes). However, a review of the impact of competition law falls outside the scope of this study.

INPUT BY STAKEHOLDERS

During the course of the study, all input, including comments and relevant studies provided by Member States and other stakeholders have been considered by Copenhagen Economics.

Together with interviews, literature review and the analyses conducted, this forms the base of knowledge utilised in the present study.

1 https://etendering.ted.europa.eu/cft/cft-display.html?cftId=2025

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Executive summary

Motivation

In April 2017 the European Commission awarded Copenhagen Economics the task of carrying out the study entitled 'Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe' (call for tender 590/PP/GRO/SME/16/F/121). This report represents the results of the study.

Two recent events prompted the need for the study as spelled out in the tender specifications.

First, the European Commission Single Market Strategy of October 2015 had identified a need to *"...consolidate and modernise the intellectual property (IP) rights as a way to stimulate innovation and growth within the European Union and to engage in a reflection on ways to improve the patent system in Europe...for pharmaceuticals..."*.

Second, Council Conclusions of 17 June 2016, invited the Commission to prepare an analysis of the impact of the pharmaceutical incentives and rewards on innovation, availability and accessibility of medicinal products.

Incentive and rewards

So what are supplementary protection certificates and pharmaceutical incentives and rewards? In total there are five. We now go through each of them.

1: The supplementary protection certificate (SPC) adds years of patent protection to an innovative medicinal product. In 1992, the then 12 Member States of the European Union decided to introduce SPCs. The motivation was that the patent protection period of 20 years a new molecule enjoyed universally, in practice provided less than 20 years of protection for the resulting medicinal product. The reason was, and still is, that it takes several years for a company to develop an actual product based on a patented molecule. During that period, the medicinal product undergoes important testing regarding quality, safety and efficacy, but at the same time it implies a 'loss of patent time'. The SPC adds up to a maximum of 5 years of additional patent time in the cases where the medicinal product has lost more than 5 years of patent time. This means that if it takes longer than 5 years from the patented molecule is discovered until it ends up in a product for patients, companies can get up to 5 years of extra protection of the product. In essence it works like an extension of the patent. Since 1992, with the growth of the EU, all current 28 Member States (plus Iceland and Norway) have introduced the SPC.

2+3: Data Protection (DP) and Market Protection (MP) basically guarantee the innovator pharmaceutical company a minimum of protection of its new medicinal product of 10 years even in the cases where the original patent and the SPC would sum up to fewer than ten years. Each of the two measures play specific roles. As the name indicates, DP makes sure that another pharmaceutical company cannot re-use the clinical trials data for 8 years and MP makes sure that the medicinal product cannot be copied and marketed until after 10 years. More precision is added in the body of the report, but here it suffices to say that together they guarantee a pharmaceutical company protection from generic (copy) products for 10 years.

4: Market exclusivity for orphan medicinal products is an incentive relevant only for orphan medicinal products, i.e. products that are intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union. The incentive protects such medicinal products from competition from similar medicinal products targeting the same rare disease for 10 years.

5: Paediatric investigations of medicinal products is rewarded 6 months of extension of the SPC if an SPC exists. Paediatric means that it can be used for treating children aged 0 to 18. If the paediatric investigation concerns an orphan medicinal product, the market exclusivity (incentive 4 above) may be extended from 10 to 12 years.

Executive summary

Parallel use

The original patent and the 5 incentives and rewards work in combination with each other for each innovative medicinal product.

For example, one medicinal product may experience a short time from discovery of a new patented molecule until a medicinal product is ready to be marketed to patients. In this case, even with an SPC and in light of the DP and MP, it is still the patent protection that expires last and thus provides the longest period of protection. If it took two years from the patented molecule discovery to a marketed product, this product would be protected from generic competition for 18 years. That is a result of the 20 years of patent protection minus the 2 years it took to go from molecule to an actual product.

Another medicinal product may experience many years from discovery of a new patented molecule until a medicinal product is ready to be marketed and reach patients. In this case, the MP's protection period of 10 years may be the longest one and thus the one that applies to the medicinal product. In that case, the product will enjoy 10 years of protection.

In between 'very short' and 'very long' from molecule to product, a pharmaceutical company will find use for the SPC. For example, if it took 12 years from the patented molecule discovery to a marketed product, this product would be protected from generic competition for a total of 13 years exploiting the SPC as the longest lasting measure. That is a result of the 20 years of patent protection minus the 12 years it took to go from molecule to an actual medicinal product resulting in an initial 8 years of protection. On top of that the SPC adds 5 additional years in this case. The final result is 13 years of protection from generic competition (8+5 years). The MP would provide 10 years of protection, but since the company in this example had applied for and received an SPC resulting in 13 years in total, the SPC dominates the other incentives and rewards.

A unique dataset

In order to comply with the study objective of evaluating the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards we measure the combined effect on protection offered by the patent and the 5 incentives and rewards.

For that purpose we have gathered and combined data from more than six databases in order to finally arrive at the study dataset. At its core, the dataset covers 558 unique medicinal product names including all relevant information to allow us to identify for each of them, which of the patents, incentives and rewards expires last and how many years of protection that implies. The dataset covers the period from 1996 to 2016 and 28 European countries.

The dataset is supplemented with additional data in order to carry out certain of the more complicated statistical analyses in the study.

Hence, the dataset(s) represent the core analytical basis for the study. However, the analyses carried out based on the dataset(s) have been supplemented with more than 20 interviews with stakeholders, a EU Member State workshop, 21 case studies on specific medicinal products and a wealth of literature.

We will now delve into our findings. First we will present the novel measure of 'effective protection period' and the insights it has provided. Second, we will present the results of the statistical analyses where we aimed for identifying the effect of the 'effective protection period' on innovation, availability and accessibility – the three main objectives of the study.

Effective protection period

For all 558 unique medicinal products in our dataset, we have developed a novel measure, which we throughout the report refer to as the *effective protection period*. It measures the time that elapses from a product obtains a marketing authorisation until the last measure of protection expires; i.e. the period where the medicinal product enjoys protection from primarily generic competition in any of the EU countries.

The *effective protection period* also allows us to identify which of the 5 incentives and rewards and patent(s) is last to expire. This is interesting when assessing the practical implication for the protection period of patent and the 5 incentives and rewards.

Consequently, the effective protection period is a very helpful way of looking at the commercial implications for pharmaceutical companies of the patent and the 5 incentives and reward regime.

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So what are the results when looking at the effective protection period?

We find that the effective protection period for the medicinal products in our dataset has declined from an average of 15 years to 13 years during the period 1996 to 2016.

We speculate that part of the reason for this decrease may be attributed to the increase in regulatory requirements both at the EU and national level. The decrease in the average effective protection period could also reflect that companies have been taking on more complex and risky research and development projects with longer expected development times. Both fit with our finding that the average development time of a medicinal product – defined as the time that elapses from the first patent filing protecting the molecule to the first marketing authorisation of the final product in the EU – has increased from 10 years to 15 years in the analysed period based on our dataset. Increased risk taking would be further supported by a general growing global demand for health care services.

A higher risk profile of investments requires a higher expected revenue and profit. Since some (many) of the investments will fail to secure a marketed product in the end, it is not uncommon to witness very profitable single medicinal products, as witnessed in the blockbuster section of the case studies in chapter 5.

When looking at the entire period in our dataset and across all 28 countries where the 558 unique medicinal products have been made available, we find that the bulk of the medicinal products enjoy an effective protection period of between 10 and 15 years. This is the case for 62% of them. Very few (4%) enjoy less. It makes sense that 10 years is a minimum since the MP always provides 10 years of protection (the reason that 4% in our dataset enjoy fewer than 10 years of protection reflects the regime prior to the introduction of the MP incentive in 2005).

An additional 24% enjoy an effective protection period between 15 and 20 years, the 20 years being the original patent protection period.

Then comes the last 10%, which enjoy more than 20 years of protection. At first this is surprising as the maximum period of protection is 20 years offered by the original patent. However, the explanation is the existence of the so-called secondary patents. A secondary patent is a patent taken out after the initial patent. The secondary patent is just like any other patent and provides 20 years of protection. But since it is taken perhaps years after the initial patent it effectively pushes the effective protection period beyond 20 years. Some of the case studies in chapter 5 demonstrate this implication of secondary patents.

We now turn to the marginal properties of each of the patent and the 5 incentives and rewards.

Patents

We find that for 51 % of the 558 medicinal products across all 28 countries a patent is the last measure of protection to expire (omitting any secondary patents this share drops to 38%). For the remaining 49% either the SPC or one of the other incentives and rewards are the last measure of protection to expire.

The SPC

Looking at the timing of the SPC, we focus on the 558 medicinal products alone. We want to know for how many of these products an SPC has been granted in at least one country.

We find that an SPC has been granted in at least one country to 45% of the 558 unique medicinal products in our dataset equal to 251 products. The average duration of protection for all granted SPC's is 3.5 years. Analysing cumulative incentives, where the SPC expires last it adds on average 2.6 years beyond the patent, market or data protection, whichever would have been the final one to expire in the absence of an SPC.

Data protection (DP) and market protection (MP)

Looking again at the 558 medicinal products but now across all 28 European countries, we find that for 39% of the medicinal products in our dataset either DP or MP is the last measure of protection to expire. They have provided an average of 4.8 years of additional protection.

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Market exclusivity for orphan medicinal products
Since the introduction of the Orphan Regulation, the yearly number of applications for orphan medicinal product designation submitted by pharmaceutical com-panies has risen from 72 in the year 2000 to 329 in 2016. This has resulted in a total of 128 products with a marketing authorisation as an orphan medicinal product during that period. Our dataset covers 24 of these. For those where the market exclusivity is the last measure of protection to expire, it has added 1.6 years of additional protection to the medicinal products.

Paediatric rewards
Seen across all pharmaceutical products in our dataset, the extra effective protection obtained through the rewards for paediatric investigation is very limited. Focusing only on the products with a positive paediatric investigation plan compliance check does not change this picture. However, for individual medicinal products in the market for adult use the added (marginal) effective protection can be up to 6 months.

Summing up
We have now presented main insights from analysing the measure called 'Effective protection period'. We have presented results reflecting the entire protection period of the medicinal products in our dataset. We have also presented results for each of the incentives and rewards showing how often they are the last measure of protection to expire and the corresponding additional number of years of protection they provide.

The incentives and rewards are quite often the last measure to expire, not the original patent. Hence, a first conclusion is that the incentives and rewards provide the additional protection that they were designed to do. However, what have been the implications of that additional protection? That is a question to be answered empirically.

We therefore now turn to the results of the empirical analysis. We estimate, using statistical models, the effect of the effective protection period on the three objectives of the study namely innovation, avail-ability and accessibility (although we design the analysis slightly different for the accessibility analysis due to data constraints).

Impact on innovation

Before diving into the results of the statistical model-ling, we first highlight the outcome of our literature review. We find that existing empirical evidence is ambiguous with respect to the effect of patents, incentives and rewards on innovation in the pharmaceutical sector. The literature covers different samples of medicinal products in different countries over different time periods, using different methods.

We now turn to our statistical modelling, which together with insight from 21 case studies embodies our empirical research. We test empirically the relationship between the length of the effective protection period for all the medicinal products in our dataset across 28 European countries and the companies' level of pharmaceutical research and development in the individual countries.

Since the effective protection period consists of the patent and the 5 incentives and rewards, it represents a consistent way of concluding on the impact of the 5 incentives and rewards, which was the main objective of this study.

The results from our statistical modelling point to a positive relationship between the effective protection period and the level of pharmaceutical research and development. Specifically, we find that when medicinal products experience a longer effective protection period in the markets where they are sold, pharmaceutical companies increase their innovation efforts. The implication is that a reduction of the effective protection period will negatively affect the investments in research and development inside the EU. It will also reduce the pharmaceutical invest-ments in research and development *outside* of the EU, e.g. for the pharmaceutical companies located in the USA and Japan as they also sell their medicinal products in the EU. The global reach of medicinal products means that changes in incentives and rewards in one jurisdiction have implications for pharmaceutical investments in other jurisdictions.

We also find that as wealth, measured by income per capita, increases in the countries that constitute the most important markets for medicinal products, pharmaceutical companies increase their innovation efforts. We interpret this to mean that when countries become wealthier their demand for healthcare services including medicinal products increase. As companies anticipate this, they will invest more in innovation.

Executive summary

Zooming in on the 28 individual European countries in our sample, our empirical analysis does not find any relationship between the effective protection period in one country and investments in pharmaceutical research and development in that same country. This means that incentives and rewards in a specific European country have no direct effect on pharmaceutical location and spending in that same country. We interpret this to mean that pharmaceutical research and development location decisions are primarily driven by other factors than the protection period provided in a given country. Such other factors could be the quality of the labour force, the tax level and research and development subsidies. Only in the case where the protection regime in a country mirrors its general view on the industry might there be an indirect effect. For example, a company might consider a country that tightens its protection regime more likely to also tighten other regulations more important for the company's decision on where to locate its innovation activities, such as tax level and research and development subsidies.

Impact on availability

We find that companies do not launch medicinal products in all countries in the EU and not at the same time. We find that companies choose to launch more medicinal products faster in wealthier countries, a trend, which is reinforced in countries with larger (patient) populations.

This launch sequence fits with how some wealthier countries include poorer countries in their 'external reference pricing' basket. This practice incentivises pharmaceutical companies to launch first and foremost in (large) wealthy countries as these countries have then no poorer country benchmark to refer to when bargaining for lower prices.

Analysing the launches based on level 1 ATC codes (Anatomical Therapeutic Chemical Classification System - classification of active ingredients of medicinal products according to the organ or system on which they act) shows that availability varies greatly across this categorisation. The pharmaceutical products with the highest availability belong to the ATC1 category of "Antineoplastic and immunomodulating agents", which contains many cancer medicines. These products launch in more than half of the EU Member States within 2 to 3 years. The pharmaceutical products with the lowest availability belong to the ATC1 category of "Dermatologicals" (skin care products). These products launch in less than a quarter of the Member States even after 15 years of first market introduction.

Impact on accessibility

Once a medicinal product is available in a country, actual accessibility often becomes a matter of price. We find that as protection from generic competition runs out, generic medicinal products enter the market at a significantly lower price than the original medicinal product pushing down the price of the original product as well.

Based on a small sample of products, we find that the prices of innovator medicinal products drop by approximately 40% on average in the period from 6 quarters before to 5 quarters following generic entry. However, innovator companies may find it optimal to increase prices even in light of generic entry. This is for example the case if healthcare professionals are reluctant to switch existing patients to new medicinal products. Furthermore, we find that when generic medicinal products enter the market their price is on average 50% lower than the initial price of the corresponding innovator product in the first five quarters after the launch of the generic product. This means that the innovator product remains more expensive.

We find some evidence to suggest that the regulation spurs innovator-on-innovator competition. By this we mean competition between two or more medicinal products that are protected from generic competition by patents or the 5 incentives and rewards. We base this insight on the previous finding that the regulation stimulates innovation, and that more innovation, all else equal, leads to more medicinal products, which eventually result in more innovator-on-innovator competition. Our data on competition between innovator and generic medicinal products does not allow us to analyse competition between innovator medicinal products.

Unintended consequences

This study also identifies examples of consequences of the regulation that might not have been the intention of lawmakers when they passed the legislation.

<u>Secondary patents</u>

Secondary patents may for example cover improved variants of the basic product, new therapeutic indications, or new combinations.

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Still, the fact that some medicinal products are eventually protected by multiple and in some cases a large number of patents can be argued to be against the intention of the original 20-year patent protection period. It is of course important to note that these patents are being granted by the national patent offices (NPOs). Initiatives have been taken to ensure that NPOs and the European Patent Office (EPO) only grant patents when this is warranted by actual novel innovation (see e.g. the EPO 'Raising the Bar' initiative).

Market exclusivity

There have been concerns from some Member States that the market exclusivity granted to orphan medicinal products provides too much protection, driving up prices. We have not been able to test this empirically. However, from a theoretical perspective the small market size for orphan medicinal products might in some cases yield a natural monopoly, while the protection from competition from similar medicinal products through the market exclusivity also discourages the development of similar alternatives to the medicinal product, which comes to market first for a given indication. This may allow the companies a very strong bargaining position in price negotiations with payers.

Paediatric investigation plans

The reward introduced by the paediatric regulation aims to compensate the obligation introduced by the paediatric regulation for pharmaceutical companies to conduct paediatric studies for every medicinal product developed. However, when agreeing on a paediatric investigation plan the paediatric committee under the European Medicines Agency may grant a waiver instead (e.g. based on lack of significant therapeutic benefit).

The reward for non-orphan medicinal products equates to an extension of 6 months of the SPC. Thus, there are examples where the reward for conducting paediatric studies is zero (e.g. because there is no SPC to extend) and other examples where it is very high (e.g. for medicinal products that are blockbusters for use in adults). This value proposition may not always be optimal for the development of medicinal products for children.

A trade off

The empirical analysis in this study finds a trade off between innovation of new medicinal products and lower prices of medicinal products through faster availability of generics.

On the one hand, the protection offered by the IP rights and incentives and rewards stimulate innovation in the EU (and abroad). We find that the 5 pharmaceutical incentives and rewards in the EU are the most attractive when compared to Canada, China, India, Japan and the United States.

On the other hand, the protection delays entry of generic medicinal products and a subsequent downward push on prices. Hence, later entry of generic medicinal products pushes up total expenditure on medicinal products, which, all else equal, drives up overall healthcare expenditure.

In an attempt to shed light on possible savings generated by faster entry of cheaper generic medicinal products, we have applied scenario analysis. Today, around 76% of the EU expenditure on medicinal products goes to originator products and the remaining 24% to generic products. In a hypothetical scenario, we calculate the immediate, short term effect on health care expenditure of changing this split to 66% and 34%, respectively, i.e. reducing spending on originator products by 10%-points and instead using that money to buy the same volume of cheaper generic products. The result is a saving of less than 1% of the total EU health care expenditure. The scenario includes no long term effects. However, implications of reducing protection in order to pave the way for faster generic product availability are many and complex. One obvious one is that on development of future originator products. We have described possible implications in detail in the report.

In the end, it is not within the scope of this study to advise on the 'right' balance between innovation and lower prices of medicinal products through faster availability of generics; it is ultimately a political decision.

Summing up, it would seem that one cannot exploit the regulation around protection to get the best of both worlds; more innovative medicinal products *and* faster generic entry to push down prices. A first best policy path seems to be one where the trade off is circumvented. It would be ideal to secure a sufficient period of protection and reduce uncertainties associated with developing medicinal products in order to incentivise innovation, while finding other ways of curbing high prices.

Glossary

MARKETING AUTHORISATION

Before a medicinal product can be placed on the market, a marketing authorisation for the given product must be obtained. This is done to ensure that medicinal products are safe, of sufficient quality and efficacious. The decision on whether to grant marketing authorisation is made by the appropriate authorities based on an application supported by data such as pre-clinical data and data from clinical trials, submitted by the a pharmaceutical company.

DATA PROTECTION

Period during which pre-clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.

MARKET PROTECTION

Period during which generic companies cannot place a generic version of the medicinal product on the market. However, an application for marketing authorisation of the generic medicinal product may be submitted (providing data protection has expired), and the authorities are allowed to process the application, but the product cannot be placed on the market until the end of the market protection period.

MARKET EXCLUSIVITY

Specific regulatory exclusivity period relevant only for orphan medicines. Period during which the authorities cannot grant a marketing authorisation to a similar medicinal product treating the same orphan indication, unless a derogation applies[1].

EFFECTIVE PROTECTION PERIOD

Period from marketing authorisation is granted until expiry of the last protection scheme protecting the medicinal product. Protection schemes are both IP rights, such as patents and SPCs as well as all regulatory protection such as data and market protection, market exclusivity and any extensions thereof.

PRIMARY PATENT

The first patent applied for (and granted), protecting a given medicinal product against imitation by other companies. For medicinal products, the primary patent primarily protects the active ingredient.

SECONDARY PATENT

All patents granted at a later point in time than the primary patent, protecting any part of the same medicinal product. Secondary patents could e.g. be granted for chemicals related to the active ingredient, methods of use, formulations or dosages.

PERSONALISED MEDICINE

In Council conclusions on personalised medicine for patients (2015/C 421/03) point 8, personalised medicine is described as
"…a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. Personalised medicine relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs".

DEVELOPMENT TIME OF MEDICINAL PRODUCT

Time elapsed from the first date on which the first patent grants protection until the product is introduced on the market.

1 There are three derogations which are given in Regulation (EC) 141/2000, Article 8(3).

Copenhagen Economics CE

CHAPTER 1

Overview of economic incentives and rewards supporting pharmaceutical innovation and analysis of their actual use by pharmaceutical innovators

Outline of chapter 1

1.1 Current EU legislative instruments

1.2 Interaction between incentives

1.3 IP framework and pharmaceutical incentives in other countries

1.4 Actual use of the above incentives and rewards by pharmaceutical innovators

Chapter 1 – Main conclusions

REVIEW OF INCENTIVES

In the European Union additional protection mechanisms and legislative incentives concerning medicinal products exist. The various schemes protect medicinal products to a varying degree and have different duration.

Patents protect a given invention for 20 years. An SPC is an IP right, that extends the duration of the protection provided by a patent by a maximum of 5 years. An SPC is attached to a patent and a product[1].

Besides these IP rights, regulatory incentives running from the date of marketing authorisation exists. These are data and market protection. Market protection runs for 10 years, while data protection runs in parallel for 8 years. For orphan medicinal products a market exclusivity, which runs for 10 years, can be obtained given that certain conditions are met.

If paediatric studies are completed, a 6 month extension of an existing SPC or a 2-year extension of market exclusivity can be obtained. Furthermore, there are other extensions and further protection periods available, to incentivise pharmaceutical innovation.

IP FRAMEWORK IN OTHER COUNTRIES

In the US, incentives granting exclusivity to the first generic to enter the market exist. This works to motivate generic manufacturers to enter the market as soon as possible and in many cases challenge patents held by originator companies.

In the US, Canada and Japan the possibility of patent term restoration exists. This is comparable to the EU regulation on SPC. India and China generally have less regulatory incentives for medicinal products than the other countries.

ACTUAL USE OF INCENTIVES

From 2013 to 2016 the number of new medicines introduced using the centralised procedure per year has been fairly stable.

The number of granted SPCs has been slightly increasing over time, which is in part a consequence of the fact that the SPC framework has been implemented in more countries over time.

The number of paediatric investigation plans has likewise been increasing over time. The same goes for orphan designations. The number of orphan marketing authorisations have been increasing in the period from 2000 to 2016; the EU orphan legislation was adopted in 2000.

Our analysis shows that especially two regulatory incentives find limited use. These are the one-year extension for a well-established substance and the one-year data protection for a classification change.

A UNIQUE DATASET

For the analysis in the present report a unique dataset as been compiled using several sources. The dataset exploits the connection between products and patents available in the Orange Book[2] in the US, to link patents and products within the EU. To our knowledge this report is the first of its kind to utilise such as dataset. The final unique dataset links products with patents, SPCs and regulatory incentives within the European Union.

DEVELOPMENT TIME

Development time of a medicinal product is defined as the time from the first patent to the first marketing authorisation anywhere in the EU. To a certain degree, this measure shows the time elapsed from discovery of a new invention until commercialisation.

Our dataset indicates that from the 1990s to the 2010s the average development time across EU countries has increased from around 10 years to around 15 years. 50% of the products introduced during this period had a development time between 5 and 15 years.

EFFECTIVE PROTECTION PERIOD

The effective protection period is defined as the time from marketing authorisation until the last form of protection in the form of patents, SPCs, or regulatory incentives and rewards expire. I.e. the effective protection period measures the time a product is on the market and enjoys protection from generic competition via either IP rights or regulatory incentives and rewards.

Our dataset indicates that since the 1990s the average effective protection period in the EU has decreased from around 15 years to around 13 years.

The conclusion that the average effective protection period has decreased over time is robust to the exclusion of secondary patents. This means that even if we exclude all secondary patents in the data the conclusion that the average effective protection period has declined, stands.

1 The SPC framework has been gradually implemented in more countries over time..

2 The Orange Book is the common name for the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations". It is a publication and an online database which identifies medicinal products and their related patents and exclusivity information in the US.

1.1 CURRENT EU LEGISLATIVE INSTRUMENTS

Patents (1/5)

INTELLECTUAL PROPERTY

A fundamental characteristic of innovation is that discovery in the first place might take an ample investment, whereas using the knowledge obtained after discovery might involve minimum effort.

Coming up with the idea of e.g. penicillin was rather coincidental, and the development process took more than 15 years and included intense research and development. However, copying the compound when the right formula was finally found was easier than developing it in the first place[1].

If an entity copies a novel invention, it has not endured the often high R&D cost of developing the invention and hence might be able to sell any would-be resulting product at a price significantly below the originator.

The prospect of this happening might discourage innovation, as without any protection from copying, the inventor cannot be sure to recoup the initial investment that has gone into the R&D process, i.e. the risk associated with the investment is considerable.

It is important to realise that IP protection does not necessarily protect against competition. There might e.g. be several ways of curing a given disease, and obtaining IP protection for one such way does not prevent others from entering the same market, as long as their product does not use the same molecule as the one already patented.

PATENT

The basic way of protecting a new invention is through patenting it.

In the EU, as is the case in most of the rest of the world, a patent is valid for 20 years[2].

A patent confers the negative right for the owner to prevent third parties from using, making, selling or importing the invention without the consent of the patent holder.

When an innovator takes out a patent on a new innovation, the invention becomes the intellectual property (IP) of this individual or legal entity. For a new innovation to be patented, it must first and foremost fulfil the requirements of being eligible for a patent.

This means that the patent application must cover subject matter which is deemed patentable. Subject matter which is excluded from patentability comprises e.g. *discoveries, scientific theories and mathematical methods; aesthetic creations; schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers; presentations of information*[3].

If the eligibility requirement is met, the invention must fulfil the three additional requirements of being *new*, *involve an inventive step* and *being susceptible of industrial application*[4].

This means that if e.g. a new use of an existing medicinal product, a new formulation, a new form or a new dosage fulfils these criteria it is possible to take out a patent protecting this. The implication of this is that in some cases a medicinal product, or its subcomponents and processes might be protected by several patents, granting a patent protection period of more than 20 years.

Patentability requirements

- **New** means that there cannot exist any prior public documents describing the invention. This is known as prior art.
- **Involve an inventive step** means that the invention must be non-obvious to a person skilled in the art. Thus, it cannot cover common knowledge within a given trade.
- **Susceptible of industrial application** means that it can be made or used in any kind of industry including agriculture.

Built in to the patent scheme is a 'social contract', where in turn for the IP protection provided, the patentee must provide full disclosure of the invention, making it possible for others to make and use it at the end of the patent protection period.

This *quid pro quo* is meant to provide profit incentives for innovating firms, while promoting more disclosure than would be the case if only trade secrets could protect innovations.

A patent is granted by a sovereign state or an international entity such as the European Patent Office and is geographically bound. A consequence of this is that for the IP behind an innovation to be completely covered by legal protection, the inventor has to seek patent coverage in all relevant markets. Realising that this is quite a task, several international agreements simplifying this process have been enacted[5].

1 Tan, S. Y. and Tatsumura, Y. (2015), Alaxander Fleming (1881-1955): Discoverer of penicillin.
2 Article 33 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and Article 63 of the European Patent Convention.
3 Article 52(1) of The European Patent Convention.
4 Article 52(2), (a), (b), (c) and (d) of The European Patent Convention.
5 E.g. the Paris Convention for the Protection of Industrial Property and World Intellectual Property Organisation and the Patent Cooperation Treaty described on the next page.

Patents (2/5)

THE PARIS CONVENTION FOR THE PROTECTION OF INDUSTRIAL PROPERTY

This agreement was the first major step taken to ensure that intellectual property is protected in other countries besides the country of the originator.

The Paris Convention applies to industrial property in a wide sense. This includes *patents, trademarks, industrial designs, utility models, service marks, trade names and geographical indications*[1].

There are three main elements in the agreement.

1. **National treatment**
   Countries partaking in the agreement must grant the same protection to nationals from other contracting states as it would to its own nationals.

2. **Right of priority**
   After applying for a patent in one contracting country, the applicant may, within 12 months file for a patent in other contracting states. If the patents are granted, the applicant has the option of using as the date of commencement of the patent the date the application for a patent was filed in the first country of the agreement, the so-called priority date.

3. **Common rules**
   Mainly these rules state that the process of granting patents in each contracting state is independent of each other.

Being a contracting state to the Paris Convention gives access to participation in the Patent Cooperation Treaty managed by the World Intellectual Property Organisation (WIPO).

WORLD INTELLECTUAL PROPERTY ORGANISATION AND THE PATENT COOPERATION TREATY

The World Intellectual Property Organisation (WIPO) manages the Patent Cooperation Treaty (PCT), which first entered into force in 1978. From the original 18 contracting states, the PCT has grown to include 152 countries.

Participation in the PCT is open to all states party to the Paris Convention for the Protection of Industrial Property from 1883.

Through the PCT it is possible for an applicant to file an international patent application, which is then processed by the WIPO.

An important point is that the PCT system is a patent filing system, not a patent granting system. No PCT or international patent is granted at the end of the process, nor does something like that exist.

During the process, an international search for prior art is carried out by an International Searching Authority (ISA). Prior art is the existence of any evidence that the invention is already known. This need not be in the form of an actual product. Any description in any form of the invention previously made can be prior art.

After the search, the ISA files a written opinion on the patentability of the invention, along with the search report. After the international process is concluded, the inventor must decide where to file for national patents. Hereafter the national procedure begins.

The advantage of the international procedure is that the international search carried out can be used by the national patent offices. Another advantage is that as the national procedures are delayed, this provides the applicant more time to assess the value of the patent and how best to commercialise it and in which countries to seek national patents.

If national patents are granted in the end, the date from which the patents are in force can be that of the earliest filed patent application (the so-called priority date).

1 WIPO website on the Paris Convention http://www.wipo.int/treaties/en/ip/paris/ (accessed 1 December 2017).

Patents (3/5)

THE TRIPS AGREEMENT

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) came into effect in 1995 and is a multilateral legal agreement managed by the World Trade Organisation (WTO), setting out common rules for the patent framework.

The agreement sets out a range of minimum requirements for the protection of intellectual property in the participating countries. Furthermore, it sets out domestic procedures for the enforcement of intellectual property rights as well as dispute settlement.

Among the requirements is e.g. a minimum patent period of 20 years, for all fields of technology without discrimination.

All WTO member countries must adhere to the TRIPS agreement. However, certain Least Developed Countries (LDC) have been given some leeway regarding the latest date by which the TRIPS provisions must be implemented. This is especially important in the case of pharmaceuticals as this has been one of the main areas of concern[1].

Before the TRIPS agreement came into force, some countries did not provide any IP protection for pharmaceuticals on the grounds that providing affordable medicine to the general public was a more pressing concern than providing a legal framework for the protection of IP[2].

1 Kyle, M. and Qian, Y. (2014), Intellectual property rights and access to innovation: Evidence from TRIPS.
2 Kyle, M. and McGahan, M. (2012), Investment in pharmaceuticals before and after TRIPS.

Patents (4/5)

THE EUROPEAN PATENT OFFICE AND THE UNIFIED PATENT

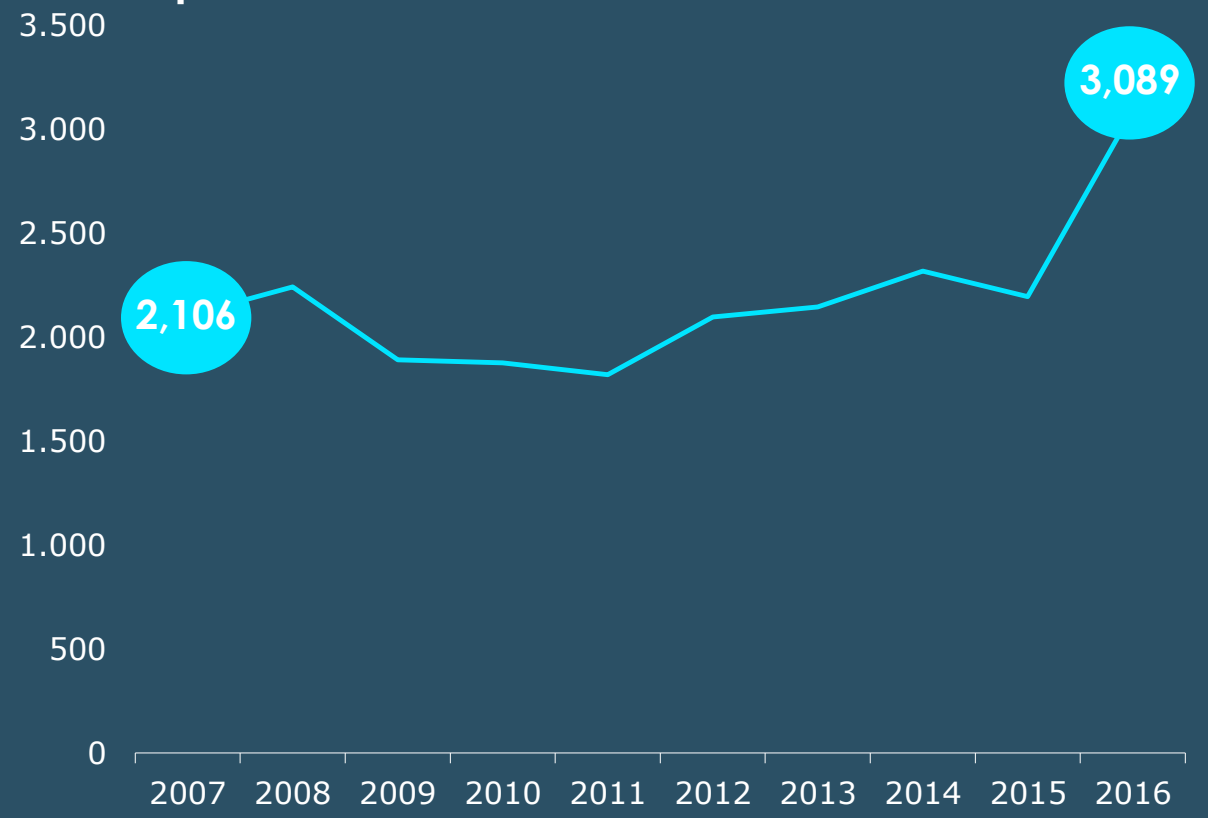
In Europe, the supranational European Patent Office (EPO) has the authority to grant European patents. A European patent is examined and granted centrally by the EPO. However, after being granted, European patents must be validated and maintained in each member state separately. Fees and requirements differ between countries.

Work has been undertaken to establish a Unitary Patent within the EU. This would give the EPO the possibility of granting a Unitary Patent which uniformly conveys IP protection in up to 26 member states through a single request filed with the EPO[1]. The Unitary Patent will build on the current European patent. After being granted a European patent, the patentee will be able to request unitary effect by filing an application with the EPO. If granted, the patent will apply uniformly in all EU member states having signed the agreement. The EPO will as such act as a one-stop-shop to obtaining and maintaining patent protection in all of Europe.

The Unitary Patent agreement is, however, still awaiting ratification in some countries, and the process has been postponed several times.

In the same vein, a Unified Patent Court is to be established to address questions of infringement etc. The date of its enactment is, however, still uncertain.

Number of European patents granted by the European Patent Office in the field of pharmaceuticals



Note: Graph showing the yearly number of individual European patents granted by the European Patent Office, classified as being within the technology area of pharmaceuticals. The classification builds on the International Patent Classification (IPC) codes. The codes for each patent are based on the product or process which is to be patented and/or on the possible use of it. Being done on a case by case basis, secondary patents receive their own IPC code. This might be the same as the IPC code of the primary patent or not, depending on what they actually protect.
Source: European Patent Office

1 Croatia and Spain have not yet signed the agreement. Croatia entered the EU after the agreement was signed, but can sign it at a later time. Spain has chosen not to sign the agreement but may in principle do so at any time. The unitary patent may enter into force before all countries have ratified the agreement as long as 13 countries, including France, Germany and United Kingdom have done so. Initially, the unitary patent may therefore cover less than 26 countries.

Patents (5/5)

MULTIPLE PATENTS

Quite often a medicinal product is protected by more than one patent[1]. This may be the case if the characteristics of the product can be shown to fulfil the previously discussed patentability requirements of being eligible, new, involve an inventive step and be susceptible of industrial application.

One example of when it is possible for the same product to be protected by multiple patents is if both the molecule itself is patented and also the process with which the medicinal product is produced. The latter is then called a process patent.

NOMENCLATURE

The literature on patents protecting pharmaceuticals often talk of *primary* and *secondary* patents. In the example above, the patent on the molecule would be the primary patent, while the patent on the manufacturing process would be a secondary patent.

It is, however, important to mention that in the eyes of patent law, there are no such things as primary and secondary patents. The statutory patentability criteria are the light in which patents are viewed, not the order in which they are applied for.

Referring to a patent as a secondary patent should not be understood to mean that it is of lesser 'quality' or protecting the product to a lesser degree than the primary patent. It merely means that chronologically it was applied for a at later stage and protects different inventions.

In this report, we will use the terms primary patent and secondary patent, as the terms are well-established in the literature on pharmaceutical patents. We use them merely to indicate the order in which patents are applied for and as an assessment of the legal 'strength' of patents[2].

SECONDARY PATENTS

In the Sector Inquiry[3] from 2009, it was found that the ratio of primary to secondary patents within pharmaceuticals was 1:7[4]. This means that for every primary patent protecting a product, there were found to be 7 patents applied for at a later point in time.

Secondary patents can e.g. cover production processes, dosage forms, alternative formulations of the medicinal product, routes of administration, uses in new therapeutic classes, new combinations etc.

Having secondary patents protecting more inventions in a medicinal product might extend the 'total' IP protection period beyond the 20 years conferred by the primary patent. If e.g. the primary patent protects the molecule, while the secondary patent protects the process used to produce the product and the product cannot possibly be produced using any other production processes, the secondary patent effectively protects the product against imitation. If the date of commencement of the secondary patent is e.g. three years later than that of the primary patent, the total IP patent protection period for the product would be 23 years instead of 20 years.

A **primary patent** is chronologically the first patent applied for to protect a certain medicinal product.

Secondary patents are all patents applied for after the primary patent, protecting different inventions to the primary patent.

1 European Commission (2009), Sector Inquiry – Final Report.

2 The legal 'strength' of a patent is to be understood as indicating the probability that the patent would hold up in court. However, only a court of law can actually decide this based on patent litigation, and as such any conjecture as to whether a patent is 'strong' or 'weak' will always be a subjective assessment, until a court decision exists.

3 European Commission (2009), Sector Inquiry – Final Report.

4 This ratio includes both patents granted and patents applied for. The unique dataset used in this study does not include patent applications and hence it has not been possible to calculate a corresponding ratio.

Supplementary Protection Certificates (1/3)

The Supplementary Protection Certificate (SPC) scheme is an intellectual property right protection scheme applicable to pharmaceutical and plant protection products in the EU. An SPC is always linked to a patent and a product.

R&D PERIOD

Developing pharmaceuticals is a process involving extensive research and development (R&D) both in a laboratory setting (pre-clinical) and later in a real-world clinical setting (clinical trials) to assess the efficacy and safety of a medicinal product[1]. As the process is often lengthy and the potential gains high if the resulting medicinal product shows considerable clinical potential, pharmaceutical companies tend to patent their discoveries rather early in this development process.

However, due to the often lengthy R&D processes and the legally mandatory testing to protect consumers, the period in which a product is both on the market and protected by IP schemes is shorter than the 20-year patent protection period[2].

A medicinal product can be sold in the market once it obtains a marketing authorisation (MA) from the relevant authorities. The shorter the period between the granting of the marketing authorisation and the expiry of the patent, the shorter the period during which the pharmaceutical companies can recoup their R&D investments before generics enter the market.

When generics enter, competition increases. This might result in prices being driven down or decreasing market share for the originators[3]. Having a limited period before generics can enter the market does not necessarily mean that the R&D investment cannot be recouped. This also depends on e.g. the price obtained and the size of the market. Furthermore, the originator company might still earn considerable revenue after generic entry.

However, seen in isolation the protection period provided by a basic patent might discourage future innovation by pharmaceutical companies, compared to a situation where a longer protection period was obtainable.

To address this, the EU has enacted Regulation (EC) No 1768/92, followed by Regulation (EC) No 469/2009 regarding Supplementary Protection Certificates.

SPC

An SPC extends the IP protection period by up to 5 years, depending on the duration of the R&D and testing processes[4].

The SPC period is calculated as:

$$\begin{aligned}&\textit{Duration of SPC}\\&= \textit{date of first MA in the EEA}\\&- \textit{date of filing of corresponding patent}\\&- 5\ \textit{years}\end{aligned}$$

With the restriction that an SPC can maximally last for 5 years.

This means that no SPC is granted if the period between patent filing and marketing authorisation is less than 5 years (there are exceptions to this and SPCs with zero or negative duration have been granted[5]). If the time from patent filing to first MA is between 5 and 10 years, the inventor is compensated fully for the 'loss' of protection period after MA. If the time between patent commencement and MA is more than 10 years, the maximum SPC period of 5 years is granted, regardless of the exact development period beyond 10 years. As such, when both a patent and an SPC are granted, the maximum combined protection period is 15 years (plus possibly 6 months, see next page).

The conditions for granting an SPC are:

1. **The product must be protected by a basic patent**
2. **A valid marketing authorisation must already exist**
3. **An SPC for the product cannot already exist**
4. **The valid marketing authorisation is the first to place the product on the market**

NATIONAL GRANT

SPCs are granted nationally by the competent domestic authorities in each member state. Even though there is work being undertaken to establish a Unitary European Patent, a unification of the granting of SPCs is not part of this process[6].

1 In the case of e.g. an abridged marketing authorisation application, the company relies on data already in the hands of the authorities and hence the development process is limited.

2 See e.g. Prasad, V. and Mailankody, S. (2017), who find development times ranging from 5.8-15.2 years, or Keyhani, S., Diener-West, M. and Powe, N. (2006), who find development times ranging from 2-17.3 years.

3 There are many nuances to the effect of generic entry. See literature description in section 2.3.

4 Regulation (EC) No 469/2009.

5 See next page and e.g. Merck - Case C 125/10.

6 However, the possibility of a European SPC title is a topic of the current "Public consultation on supplementary protection certificates (SPCs) and patent research exemptions".

Supplementary Protection Certificates (2/3)

SPC AND PATENT

SPCs are distinct from patents in multiple regards. As has been documented in the previous sections, the requirements for obtaining a patent and an SPC are very different.

Moreover, a patent does not necessarily protect a certain product, but more often the chemical moiety (the active molecule or part of it) in it. Legally, an SPC confers the same protection as the patent on which it is based, but extends this only to a product with a valid marketing authorisation[1].

Unlike patents in the EU, no centralised procedure exists for the granting of SPCs. As such, an SPC must be applied for individually in each EU member state[2].

The start date of an SPC is always the expiry date of the patent on which it is based. It is, however, not an extension of the patent, but an IP protection scheme in itself.

As is the case with the protection granted by a patent, the SPC is independent of and runs parallel to any regulatory protection periods (e.g. market exclusivity, data protection and market protection. See next pages for further explanation).

EXTENSION OF AN SPC

Should the inventor undertake studies agreed upon with the authorities in a Paediatric Investigation Plan (PIP), a 6-month extension of the SPC can be granted, regardless of the outcome of the study.

The possibility of obtaining a paediatric extension provides a reason for seeking an SPC even if the calculated duration should be negative.

The Court of Justice of the European Union (CJEU) has established that SPCs with a negative duration may be granted[3]. If a paediatric extension is subsequently granted to an SPC with a negative duration, the negative duration of the SPC must be subtracted from the 6-month duration of the paediatric extension. As such, if an SPC has a negative duration of 2 months, a paediatric extension will extend the protection period by 4 months.

If the product for which a PIP is undertaken is an orphan medicinal product, a 2-year extension of the regulatory market exclusivity period enters into force instead of the 6-month extension of the SPC even if an SPC has been granted[4].

If the product is an orphan medicinal product, the company cannot choose to have the paediatric reward in the form of a 6-month extension of the SPC, rather than the 2-year extension of the market exclusivity if an SPC has been granted. This applies for as long as the product is registered in the orphan register. However, the company can 'choose' to request that the product be removed from the orphan register.

If an SPC plus a 6-month extension expires later than the market exclusivity plus 2 years, the company would be able to obtain a longer total protection period, if allowed to choose between the two forms of paediatric rewards. However, the protection conferred by the two instruments discussed here is not the same. Market exclusivity is a protection against similar products granted by the regulatory authorities, while the protection provided by the an SPC confers the same IP rights as the patent to which it is connected.

PRICING CONSIDERATION

If a company's only concern is to recoup its initial investment, the longer the IP protection period, the lower the price the company ought charge for its products.

However, if a company aims to maximise its profits, as standard economic theory would suggest, a longer IP protection period will have no effect on pricing, and the company will charge the highest price possible given the competitive status of the market for a longer period[5]. This would mean increased profits for the pharmaceutical companies at the expense of payers.

This is a key concern when interfering with the competition situation by granting protection periods, either in the form of patents and SPCs or data and market protection (or exclusivity).

The problem is the asymmetric information possessed by the parties. Generally, the authorities will not be able to check whether the pharmaceutical companies have recouped their R&D investment and obtained a return on investment sufficient to reinvest in developing new innovative medicinal products in the future.

1 Regulation (EC) 469/2009, Article 4.
2 Regulation (EC) No 469/2009, Article 9(1).
3 See CJEU ruling on case C-125/10, Merck Sharp & Dohme v DPMA.
4 Regulation (EC) No 1901/2006, Article 37.
5 The competitive status of the market reflects whether there are other medicinal products available for treating the same indication.

Supplementary Protection Certificates (3/3)

Facts on the SPC

The legislation covering the SPC was enacted in 1993 and adopted immediately in nine countries. Since then, several countries have joined, and the agreement is now in force in all EU member states and the EEA countries Norway and Iceland[1].

Since the enactment in 1993 an up until 2015, applications had been made for 20,900 SPCs for medicinal products in the participating countries[2].

SPCs are applied for in the individual member states, independently of each other. In many cases, this practice leads to contradictory decisions on the granting of rights. In Finland, Italy and the Czech Republic, less than 5% of applications are refused, while in Germany, Sweden and Spain, more than 15%[3] of applications are refused[2].

Twenty separate entities filed 57% of all SPC applications in 2015[2]. The three companies having filed the most SPC applications in the past 10 years are Novartis, MSD and GSK[2].

Market size seems to influence decisions to seek an SPC. In smaller markets, fewer SPCs are applied for than in larger markets. As such, less than 40 SPCs where applied for in Croatia, Malta and Norway in 2015, while more than 80 were applied for in Spain, Italy, Germany, the UK and France[2].

1 SPCs are governed by Regulation (EC) No 469/2009.
2 Alice de Pastors (2016), Latest news on medicinal product SPCs in Europe.
3 Germany, Sweden and Spain all have a rather high number of filed SPCs. However, so does Italy.

Data protection and market protection (1/3)

Patents are granted by the appropriate patent offices in each country and confer intellectual property rights to patent holders. In the case of pharmaceuticals, patents are often taken out early in the development process, when the invention is still far from being an actual product.

In parallel with patents and SPCs, regulatory protection is enshrined in EU pharmaceutical legislation. For medicinal products in the EU, the schemes include e.g. *data protection* and *market protection*[1]. These two legal protection schemes relate directly to the final medicinal product, and the protection periods provided by them are independent of any patents and SPCs, and hence run parallel to any such IP protection.

The periods of both data and market protection run from the date of granting of the marketing authorisation.

DATA PROTECTION

The data produced by a pharmaceutical company during testing and clinical trials of a new innovative medicinal product is private knowledge. However, for the medicinal product to obtain a marketing authorisation, this data has to be handed over to the relevant authorities.

If a generic manufacturer wishes to market a generic version of an existing medicinal product, the generic company can refer to the data already produced by the originator company, in its application for marketing authorisation. This is called the abridged procedure[2].

In recognition of the substantial investments made by originator companies to produce the pre-clinical and clinical trial data needed to obtain marketing authorisation, a period of 8 years of data protection is granted. During these 8 years, generic manufacturers are prohibited from referring to the data produced by the originator company and enclosed in its application for marketing authorisation. After 8 years, generics can obtain a marketing authorisation based on the data produced by the originator company.

MARKET PROTECTION

Parallel to the 8 years of data protection run 10 years of market protection[3]. During these 10 years, a generic medicinal product cannot be placed on the market even though a marketing authorisation has been obtained.

This, however, does not completely protect against competition[4].

Firstly, originators with another distinct product for treating the same indication may enter the market. This is known as competition by innovation or originator-originator competition.

Secondly, a second company willing to undertake studies to create their own full dossier with which to apply for marketing authorisation may do so, provided that no patents or SPCs are infringed upon.

An example of this would be the following. Company A has placed product M on the market, containing molecule Z. Molecule Z is not protected by either a patent or an SPC. However, product M has data and market protection. Company B now creates their own product, called N containing molecule Z. Company B undertakes clinical trials and creates their own proprietary data on the efficacy and safety of product N. Company B now applies for marketing authorisation for product N using its own data material. Marketing authorisation is granted. Now there are two products on the market, both containing molecule Z, even though product M by company A is covered by data and market protection.

Through our interviews with key stakeholders and experts within the area of pharmaceuticals, we have, however, not found any readily available examples of this happening. As such, this seems to be a rather theoretical possibility and not something that often takes place in practice.

If the above were to take place, it means that the second company entering the market must expect the market to be large enough for them to recoup the extra costs of running clinical trials to produce the data required for marketing authorisation.

1 Generally there is no consensus as to which nomenclature to use. In Regulation (EC) No 726/2004, Article 14(11), the wordings *data protection* and *marketing protection* are used. However, in the literature and the field in general, several other terms are used to describe the same incentives. To avoid any confusion as to the terms, we consistently use the terms *data protection* to describe the 8 years where generics cannot refer to the data created by the originator and *market protection* to refer to the 10 (+1) years where a generic product cannot obtain marketing authorisation. For orphan medicinal products we use the term market exclusivity as this is in many ways distinct from the market protection granted to non-orphan medicinal products.

2 See Regulation (EC) No 726/2004, Article 3(3), Directive 2001/83/EC, Article 10 and Directive 2001/82/EC, Article 13.

3 The 8 years of data protection and 10 years of market protection running in parallel combined with the possibility of an extra year of market protection for authorisation for a new indication are often referred to as the 8+2+1 scheme.

4 Directive 2001/83/EC, Article 10.

Data protection and market protection (2/3)

Furthermore, if only the first originator company is in the market, the second company is entering into price competition with an incumbent company. The incumbent has the advantage of currently having full market share, and also it might already have recouped the R&D investment. This means that the incumbent company might be able to dump the price to drive competitors out of the market.

On the other hand, if a second company undertakes clinical trials to create its own data on the efficacy and safety of a product which is already on the market, but protected by market protection and perhaps data protection, but no patent and SPC, the outcome of the trials is already known. This significantly reduces the second company's risk in undertaking the development.

These considerations taken together imply that the possibility of placing the same product on the market, even though the first originator company has data and market protection, is probably most interesting for blockbusters or at least products profitable enough to give an expected positive profit despite competition.

EXTENSIONS

If a product is approved for one or more new therapeutic indications during the 8 years of data protection, and if it brings significant benefits compared to existing therapies, the market protection period can be extended by an additional year[1].

According to Directive 2001/83/EC, a granted marketing authorisation is to be considered as being global, in the sense that *"When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1)"*[2].

This means that any change which belongs in the above legal provision is to be considered as being included in the 'original' marketing authorisation. As such, if a company already has a medicinal product on the market and subsequently obtains a marketing authorisation for the same product, but with a new strength, this does not trigger a new period of regulatory market protection or data protection. A combination of two existing active molecules in the same pharmaceutical form is not included in the above, and hence such a product would obtain its own new period of market protection and data protection[3].

INTERACTION BETWEEN DATA PROTECTION AND MARKET PROTECTION[4]

The collective effect of the data protection and market protection period is that 8 years after the originator's medicinal product has obtained marketing authorisation, generic companies can submit an application for marketing authorisation using the abridged procedure, whereby they refer to the data produced by the originator company. Should they obtain marketing authorisation, they are, however, not allowed to put the product on the market before the remaining two years of market protection have elapsed.

The process of being able to obtain marketing authorisation before the expiry of the market protection period, however, does effectively mean that it should be possible to put a generic medicinal product on the market as soon as the market protection period has expired, without further delay.

INTERACTION BETWEEN PATENTS AND SPCS

The above considerations regarding entry of generics at the end of the data protection and market protection period are, of course, only relevant in cases where a patent or the combination of a patent and SPC has expired at an earlier date than data protection and market protection (or market exclusivity in the case of orphan designation).

BOLAR EXEMPTION

The strategy of entering the market as soon as the market protection period has expired would in many cases not be possible without the Bolar exemption[5]. Before the Bolar exemption was introduced in 2004, producers of generics could not commence research before the patent and SPC had expired, because of the risk of infringing IP rights[6].

1 Regulation (EC) No 726/2004, Article 14(11).
2 Directive 2001/83/EC, Article 6(1).
3 See Notice to Applicants, Volume 2A, Chapter 1, Revision 7, December 2017, section 2.3.
4 Or Market exclusivity in the case of orphan medicinal products.
5 Directive No 2004/24/EC, 8(6).
6 See e.g. the current "Public consultation on supplementary protection certificates (SPCs) and patent research exemptions".

Data protection and market protection (3/3)

This put European generic manufacturers at a disadvantage as it meant that they had to delay their research longer than companies in countries without patent protection or e.g. the United States where a Bolar exemption already existed. As such, it could force some manufacturers to place their facilities in locations where no patents had been taken out or in other non-EU locations. This potentially moved employment out of the EU.

The Bolar exemption at least partly remedied this. Following its enactment in 2004, generic companies are allowed to research generic products before the original patent (and potential SPC) has expired, without infringing the patent[1].

The Bolar exemption, however, only allows production of a patent-protected active ingredient for experimental use. This means that stockpiling, i.e. mass producing the medicinal product during the protection period, for immediate sale after end of said period is not allowed[2].

The effect of this is that generic producers can develop their generic version of a medicinal product even though it is patent-protected, but they cannot commence large-scale manufacturing in the EU until after the expiry of the patent.

Stockpiling while the product is protected by a patent (and SPC) in the EU might be possible in a non-EU country where less extensive patent protection rules are in place. However, production facilities outside the EU wishing to export products to the EU must comply with Good Manufacturing Practice (GMP), which ensures that imported products live up to EU quality standards.

This means that if a generic manufacturer wants to be able to market its product in the EU as soon as the patent protection period expires, there is an incentive to undertake the manufacturing outside the EU, in countries with less patent protection, unless adherence to the GMP rules prevent this.

ADDITIONAL DATA PROTECTION INCENTIVES

If a marketing authorisation is granted for a new indication for a well-established substance, a non-cumulative one-year period of data protection is granted[3]. A well-established substance is a substance where at least 10 years have elapsed since the granting of the first marketing authorisation for it.

If a classification change in the legal status of a medicinal product has been granted, a period of one year of data protection is granted[4].

1 Directive 2001/83/EC, Article 10(6) and Directive 2001/82/EC, Article 13(6).
2 Directive No 2004/24/EC, Article 8(6).
3 Directive 2001/83/EC, Article 10(5).
4 Directive 2001/83/EC, Article 74a.

Rules and incentives for orphan medicinal products (1/3)

ORPHAN DESIGNATION CRITERIA

For a medicinal product to be able to obtain an orphan designation, the product must fulfil the following criteria in the EU:

"*that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons* [0.05%] *in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.*" [1]

This means that firstly the medicinal product must be intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition which affects no more than 5 in 10,000 (0.05%) persons within the EU, or that without the orphan incentives the pharmaceutical company will be unable to earn a sufficient return on the product to justify the initial investment.

Furthermore, no satisfactory and authorised method of diagnosis, prevention or treatment of the condition concerned may already exist. An exception to this criteria is if the new medicinal product brings significant benefit to those affected by the condition.

To summarise, a medicinal product must meet the following criteria to be able to obtain an orphan designation in the EU:

1. The disease must be life-threatening or chronically debilitating
2. The prevalence of the disease must be less than 5 in 10,000 persons, or there is no hope of recovering the initial investment without the orphan medicinal product incentives
3. There must currently be no way of treating, diagnosing or preventing the disease, or the new medicinal product must be of significant benefit compared to existing methods

Proving that a given medicinal product complies with the prevalence criteria can sometimes be challenging. The prevalence of no more than 5 in 10,000 citizens is for the union as a whole, and it is conceivable that prevalence levels in the individual Member States differ. Another challenge can be finding reliable prevalence measures, as some of these diseases are very rare, and hence reliable data records might be scarce[2].

MARKET EXCLUSIVITY

If a medicine obtains an orphan designation and maintains it through the authorisation stage, it enjoys 10 years of market exclusivity[3] with the possibility of a 2-year extension if research is undertaken according to an agreed paediatric investigation plan (PIP)[4].

However, the market exclusivity period can be reduced to 6 years, if after 5 years it is established that the medicinal product no longer lives up to the criteria on which an orphan designation was granted.

For the prevalence criteria, this could e.g. be if the number of individuals affected by the condition has increased beyond 5 in 10,000 citizens.

For the criteria based on the non-return on investment argument, it could e.g. be if the generated revenue can be shown to have been much higher than expected and thus sufficient to generate enough of a return within the first 5 years to justify the initial investment[5].

The review process can be initiated by a member state and is handled by the EMA.

It is possible for a medicinal product to be authorised both for treating an orphan indication and a non-orphan indication. In such cases the product must have two different marketing authorisations with different names.

1 Regulation (EC) No 141/2000, Article 3.
2 COMP (2002), Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation.
3 Regulation (EC) No 141/2000, Article 8(1).
4 Regulation (EC) No 1901/2006, Article 37.
5 Regulation (EC) No 141/2000, Article 8(2).

Rules and incentives for orphan medicinal products (2/3)

If a medicinal product is authorised for treating both an orphan and a non-orphan indication, the different regulatory protection periods run in parallel. This means that when the product is authorised for an orphan indication, it obtains market exclusivity. When it is authorised for a non-orphan indication, it obtains data and market protection. The market exclusivity period of 10 years for the orphan medicinal product runs in parallel with and independently from the 10 years of data and market protection for the product authorised for the non-orphan indication.

The purpose of the EU Orphan Regulation[1] is to encourage the development and innovation of medicines targeting diseases which only affect a small part of the population. Logically, the lower the number of people affected by a disease, the fewer people to share the cost of the R&D investment undertaken to develop the medicine. The likelihood of recouping an R&D investment depends on the obtainable price and the patient base. As such, if the patients' willingness to pay is high enough, a small market is not necessarily an unattractive market.

However, without special incentives, it is sometimes argued that far fewer treatments for diseases affecting smaller patient groups would have sufficient commercial incentive to be developed[2].

The market exclusivity period for orphan medicinal products is different from the market protection period for non-orphan medicinal products as during the market exclusivity period for orphan medicinal products

"…the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product."[3]

This means that during the period of market exclusivity for an orphan medicinal product, another similar medicinal product used for the same indication cannot obtain marketing authorisation within the EU.

This is a crucial point as it means that an orphan medicinal product is essentially protected from competition from similar medicinal products.

However, during the period of market exclusivity, marketing authorisation may be granted to a similar medicinal product for the same therapeutic indication if

"(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior."[4]

This means that during the market exclusivity period it is possible for a new applicant to obtain market authorisation if one of the following three criteria are met.

1. The current holder of a marketing authorisation granting market exclusivity allows the second applicant to apply.
2. The current holder of a marketing authorisation granting market exclusivity cannot supply sufficient quantities of the orphan medicinal product to the Community.
3. The new applicant can show that the new medicinal product brings benefits to patients beyond what the product which currently is authorised and enjoys market exclusivity does.

From a theoretical point of view, this might give rise to an increased ex ante risk in the R&D decisions made by pharmaceutical companies. This is so if two companies are working on two similar medicinal products simultaneously[5]. The company that obtains marketing authorisation first will gain the whole market, while the second company will not be able to enter the market because of the regulatory market exclusivity. This will potentially reduce the value of the second companies' R&D to zero if it cannot be repurposed.

However, this will also increase the potential revenue as the company which is first to reach the market, in the example above, obtains the full market share.

1 Regulation (EC) No 141/2000.
2 EMA website on orphan designation.
3 Regulation (EC) No 141/2000, Article 8(1).
4 Regulation (EC) No 141/2000, Article 8(3).
5 In Regulation 847/2000, Article 3(3) it is defined that "*(a) 'active substance' means a substance with physiological or pharmacological activity; (b) 'similar medicinal product' means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication; (c) 'similar active substance' means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism*".

Rules and incentives for orphan medicinal products (3/3)

As such, from a theoretical viewpoint, when making the ex ante R&D decision the company faces a higher risk because of the regulatory market exclusivity period but does likewise face a higher potential revenue.

Besides the market exclusivity granted to medicinal products with orphan designation, once they obtain marketing authorisation there are protocol assistance (scientific advise) and the possibility of fee reductions. For micro, small and medium-sized enterprises there are further incentives, such as administrative and procedural assistance and further fee reductions. Medicinal products receiving an orphan designation are also eligible for certain earmarked research grants administered by e.g. the EU[1].

DESIGNATION AND MARKETING AUTHORISATION

An important point is that obtaining an orphan designation and a marketing authorisation for an orphan medicinal product are two distinct processes. The request for orphan designation can be filed anytime during the medicinal product development process before the application for marketing authorisation is made, while the application for marketing authorisation typically demands more clinical data. This means that multiple medicinal products can receive an orphan designation for the same indication, while only the first to obtain marketing authorisation can enjoy the 10 years of market exclusivity, unless one of the derogations described on the previous page exist[2].

MULTIPLE DESIGNATIONS

A single medicinal product may obtain multiple orphan designations and can obtain marketing authorisation for one or more orphan as well as non-orphan indications. Obtaining multiple designations for the same medicinal product is very positive for patients, as this means that more people can receive treatment. However, it does raise questions about the incentives enjoyed by orphan designation.

As an objective of the orphan regulation is to promote R&D into medicines with supposedly low revenue, obtaining multiple marketing authorisations and perhaps even reaching blockbuster status, can seem to be detrimental to this objective.

However, when a medicinal product is undergoing development it might often not be possible to predict whether it in the future can be proven to treat more than one indication. As such, it is crucial to distinguish between an ex ante and an ex post view[3]. This means that before undertaking the R&D process there might be much uncertainty as to the final effect of the substance in question. After developing the substance and testing it, much of this uncertainty disappears. As such, there is a large difference between evaluating whether development of a certain substance makes up a good business case *before* development and *after*.

1 Giannuzzi, V., Conte, R., Landi, A., Ottomano, S. A., Bonifazi, D., Baiardi, P., Bonifazi, F. and Ceci, A. (2017), Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: and increased common effort is to be foreseen.
2 Regulation (EC) No 141/2000, Article 8(3).
3 See section 4.1.2 for a further discussion of this.

Marketing authorisation (1/2)

MARKETING AUTHORISATION

In the EU, there are four different routes to obtaining a marketing authorisation.

Through the **centralised procedure** it is possible to obtain marketing authorisation in all EU member states at the same time[1]. For products containing a new active substance that are orphan medicinal products, products derived from biotechnology and products intended for the treatment of AIDS, cancer, neurodegenerative disorders and diabetes, the centralised procedure is mandatory[2].

Using the **mutual recognition procedure**, a company can seek to have an existing national marketing authorisation recognised in one or more other member states.

The **decentralised procedure** is identical to the mutual recognition procedure, with the exception that it can only be used when no member state has yet granted a marketing authorisation for the product.

The **national procedure** is a country-specific approval procedure.

When marketing authorisation is granted, the period of data protection and market protection begins.

A medicinal product might be authorised for new therapeutic indications if it is shown to have an effect in this area after the original authorisation was granted[3]. Most often this is based on new clinical trials conducted by the sponsor, but this can sometimes be based on literature which may capture off label use.

CONDITIONAL MARKETING AUTHORISATION[4]

If a medicine falls into one of the following categories, it is eligible for a conditional marketing authorisation:

1) It is aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases,
2) it is intended for use in emergency situations or
3) it is designated as orphan medicines.

If a conditional marketing authorisation is applied for, certain rules regarding e.g. documentation requirements apply. This could be for life-threatening orphan diseases, where so few people are affected that clinical trials with the same data requirements as for other medicinal products simply are not feasible within a satisfactory time frame.

The medicinal products obtaining a conditional marketing authorisation are authorised based on the assessment that the expected benefits outweigh the possible risks. Furthermore, it must be likely for the applicant to be able to provide comprehensive data at a later point, unmet medical needs must be fulfilled, and the benefit to public health of the medicinal products' immediate availability on the market must outweigh the risks due to need for further data[5].

Without this possibility some products would take a longer time to reach the market and hence have a shorter period of patent protection when they did. It would also mean that some patients would have to wait longer before they could receive the medicinal product.

Conditional marketing authorisations are valid for one year. Holders of conditional marketing authorisations are obliged to continually provide data and evidence that support the conclusion that the benefits continually outweigh the risks. As such, it is expected that a comprehensive set of data will be generated by a certain deadline.

1 Regulation (EC) No 726/2004, Article 3.
2 Regulation (EC) No 726/2004, Annex point 3.
3 If this happens during the 8 years of data protection for a new active substance, this prolongs the market protection period to 11 years. See Regulation (EC) 726/2004, Article 14(11).
4 See Regulation (EC) No 726/2004, Article 14(7), Regulation (EC) No 507/2006 and EMA website http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/g_and_a/g_and_a_detail_000167.jsp&mid=WC0b01ac0580b18196 section 1.9.
5 Regulation (EC) No 507/2006, Article 4.

Marketing authorisation (2/2)

In the period from July 2006 to June 2016, 30 medicines were granted a conditional marketing authorisation[1]. None of these have been revoked or suspended.

The typical basis for granting a conditional marketing authorisation has been results from two main phase II or III studies, with further studies ongoing[1]. As clinical testing before marketing authorisation goes through phases I, II and III, the medicinal products receiving conditional marketing authorisation have all been relatively far in that process.

The conditional marketing authorisation is granted in cases where it is believed that comprehensive data can be collected within an agreed time frame after the authorisation is granted. As such, a conditional authorisation is granted in the belief that it should not remain conditional indefinitely.

AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES[2]

If it is not believed that comprehensive data regarding the efficacy and safety of a medicine can be obtained even after the product is marketed, a marketing authorisation might be granted under exceptional circumstances.

It might e.g. be that collection of data is either impossible or unethical.

An authorisation granted under exceptional circumstances is initially valid for five years, but must be reassessed annually.

With1out this possibility some products might never have reached the market, whereby some patients might never have been treated.

PAEDIATRIC-USE MARKETING AUTHORISATION

Through the paediatric regulation in the EU, a paediatric-use marketing authorisation (PUMA) is available. The PUMA is available for medicines fulfilling the following three criteria.

1. Is already authorised
2. Is no longer covered by an SPC or a patent qualifying as an SPC
3. Is to be developed exclusively for use in children

The PUMA confers an 8-year period of data protection and a parallel period of 10 years of market protection[3]. This protection period is for a medicinal product which has already enjoyed the same protection schemes once when it was first approved for use in adults. Through the further development exclusively for children it can now obtain another period of market protection and data protection. Furthermore, certain fees are reduced.

This scheme was introduced to strengthen the incentives for developing pharmaceuticals for use in the paediatric population.

The first product to be granted a PUMA was in 2011 and by 2017 three products had been approved by this route[4].

1 EMA (2016), Conditional Marketing Authorisation – Report on ten years of experience of the European Medicines Agency.
2 See Regulation (EC) No 726/2004, Article 14(8) and EMA website http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000167.jsp&mid=WC0b01ac0580b18196 section 1.10.
3 Regulation (EC) No 1901/2006, Article 38.
4 Numbers provided by the European Medicines Agency.

1.2 INTERACTION BETWEEN INCENTIVES

Combining and stacking incentives

On the following pages, the interactions between patent, SPC, market protection and data protection are presented. The examination also looks as the incentives for paediatric and orphan designations.

For convenience, a short recap of the various protection mechanisms is presented here.

Patent and SPC

A patent runs for 20 years in the EU. At the end of this period, it is possible to obtain an SPC for up to 5 additional years of protection. The SPC can then be extended by a further 6 months, following studies in the paediatric population. This effectively means that the maximum protection period provided by IP law is 25.5 years.

The protection period described above runs from filing of the patent. Until marketing authorisation is obtained, the company cannot directly capitalise on its IP rights[1].

If more than one patent protecting different inventions concerning a given medicinal product is taken out, the period during which a product enjoys IP protection for some associated invention can be longer than the 25.5 years described above.

A patent gives the owner intellectual property rights to an invention.

SPCs are attached to a patent and a product.

Data and market protection

Independently of and parallel to patents and SPCs, 8 years of data protection and 10 years of market protection can be obtained for medicinal products. These periods start when the product obtains a marketing authorisation, and market protection can be extended by an immediate extra year if the medicinal product is authorised for a new indication during the 8-year data protection period.

If a change in classification is made on the basis of new clinical evidence, another year of data protection can be obtained.

If a medicinal product has been in use for at least 10 years, and new clinical evidence shows that the medicinal product can be used to treat a new clinical indication, another year of data protection can be obtained.

Market protection and data protection are granted for the product when marketing authorisation is obtained. These protection periods are often referred to as the 8+2(+1) rule.

Orphan medicinal products

If a medicinal product receives a marketing authorisation for an orphan medicinal product, a market exclusivity period of 10 years is granted, with the possibility of a further 2 years if studies following a PIP are carried out and approved.

An orphan designation can be obtained at any time during the development process. Having an orphan designation confers certain incentives and allows the holder to seek marketing authorisation for an orphan indication.

The orphan market exclusivity period runs from the marketing authorisation for an orphan medicinal product is granted and in parallel to any protection period in effect if the medicinal product is also authorised to treat non-orphan diseases[2].

The market exclusivity granted for medicinal products treating an orphan indication prevents other companies from marketing similar medicinal products for treating the same disease unless clinical superiority can be proven.

1 The company can, however, license or sell the research to capitalise on it before marketing authorisation. Furthermore, successfully progressing through the different phases of clinical trials might increase the market value of the company and attract investors or potential buyers.
2 An exemption to this is if studies following a PIP are completed. In that case, a 6-month extension of the SPC cannot be combined with a 2-yearextension of orphan market exclusivity. For a medicinal product to obtain both a marketing authorisation for treating an orphan indication and a non-orphan indication, the product must have two different marketing authorisations and hence different names.

Incentives for medicinal products

Protects the **invention**

Patent
20 years

Runs from **filing date** of patent

Marketing authorisation can be granted at any point during the life of the patent (and even before or after)

SPC
max 5 years

Runs from expiry of patent

Paediatric extension
6 months

Runs from expiry of SPC

These two incentives cannot be combined (see p. 44).

Medicinal products obtaining marketing authorisation

8 +2 +1

Protects the **product**

Market protection
10 years

Market protection extension
1 year

Protects the **data**

Data protection
8 years

Runs from grant of **marketing authorisation**

If authorised for new therapeutic indication and significant benefit compared to existing therapies during the 8-year data protection period can be proven

Periods separate from the periods running from marketing authorisation

Data protection
1 year

Classification change (prescription to over the counter)

Data protection
1 year

New therapeutic indication for well-established substance (used for 10 years or more)

Orphan medicinal products obtaining marketing authorisation

Protects the **product per condition**

Market exclusivity
10 years

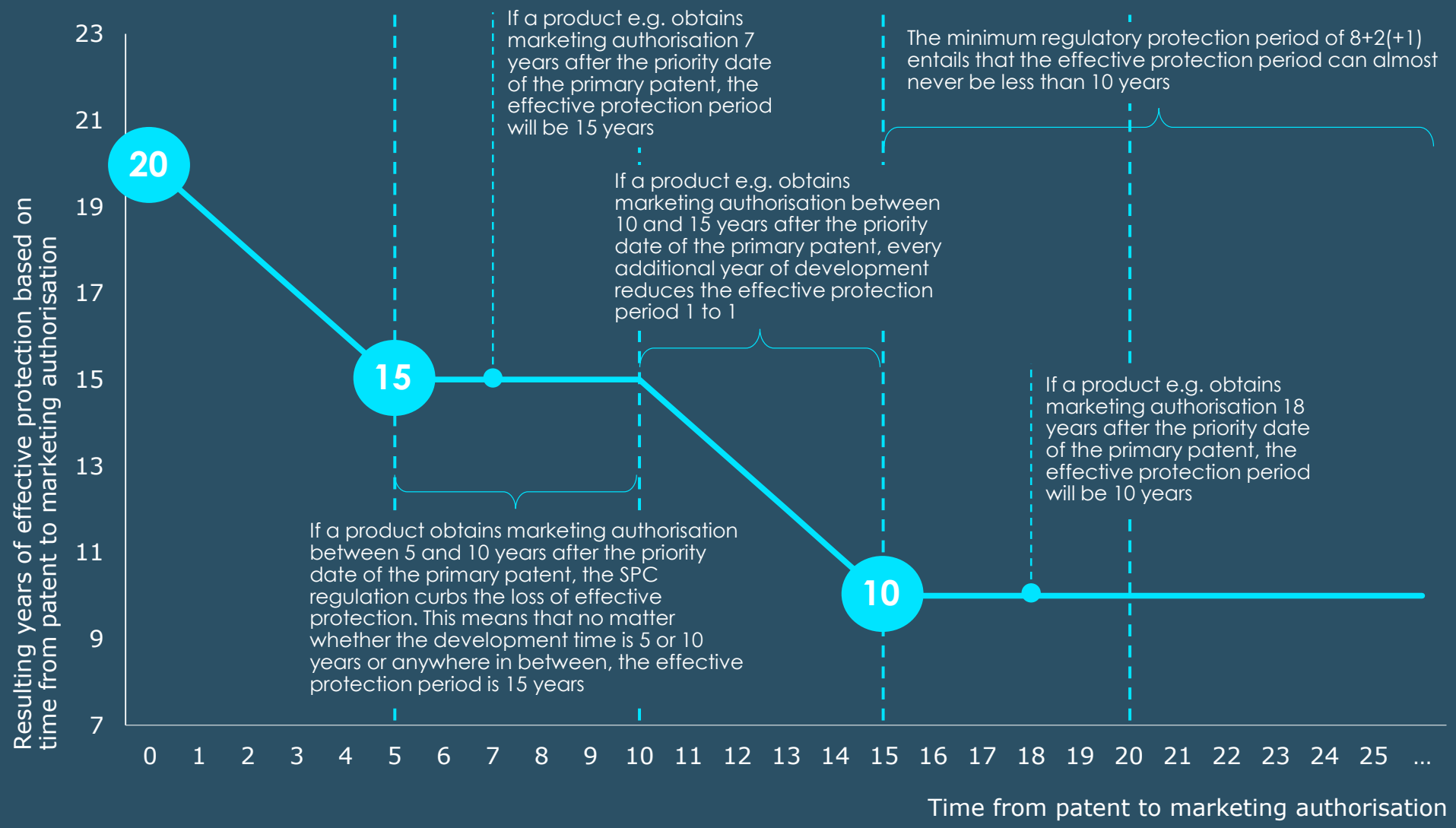
Runs from grant of **marketing authorisation**

Market exclusivity extension
2 years

If studies following a Paediatric investigation plan (PIP) are completed

Regulation (EC) No 726/2004, Article 14(11).
Regulation (EC) No 469/2009, Article 13.
Regulation (EC) No 141/2000, Article 8.
Regulation (EC) No 1901/2006, Article 36.
Directive 2001/82/EC and Directive 2001/83/EC.

The effective protection period is an interaction between the various protection schemes



Notes: Graph showing the total effective protection period depending on the time that has elapsed from a patent protecting the product or part hereof was granted, until marketing authorisation has been obtained. The effective protection period is the time from marketing authorisation is granted, until the last scheme protecting the product or the market expires. Extension of SPC due to paediatric studies, extension of market protection due to new therapeutic indication, extension of data protection due to classification change or new use of well-established substance and orphan incentives are not depicted in the graph.

Source: Copenhagen Economics based on Regulation (EC) No 726/2004, Article 14(11), Regulation (EC) No 469/2009, Article 13 and Regulation (EC) No 141/2000, Article 8.

Mutually exclusive and non-cumulative incentives (1/2)

In some cases, incentives can be mutually exclusive meaning that they cannot be combined. If a company is entitled to the benefits from two mutually exclusive incentives for the same medicinal product, the company will have to choose whether to go for one or the other. In the European pharmaceutical legislation we have identified two examples of mutually exclusive incentives, which are analysed here.

DATA PROTECTION FOR NEW INDICATIONS FOR WELL-ESTABLISHED SUBSTANCES

The European pharmaceutical legislation on incentives and rewards for pharmaceutical companies stipulates that:

"Where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data protection will be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication".[1]

This incentive, however, differs from most other incentives in that it does not extend the existing protection for other indications:

"The data protection period is non-cumulative to other periods of protection: it refers exclusively to the data concerning the new indications. Therefore, the concerned medicinal product could be used as reference medicinal product with the exclusion of the indication(s) which is covered by this data protection if the medicinal product fulfils the general requirements of reference medicinal product. Such data protection period is an incentive for development of new indications whilst data protection would not otherwise apply".[2]

This is contrary, for example, to the way in which the incentives to conduct a paediatric investigation plan (PIP) extends the SPC and thus the protection for all pharmaceuticals affected by the part of the patent on which the SPC is based (typically a specific molecule).

While this is a clear example of a non-cumulative incentive, there is not much of a choice between the two incentives involved, since the choice is really between whether to apply for the data protection for the new indication or not. If the market for the new indication is already covered by another type of protection during the period which would be covered by the extension of data protection, there is no incentive to apply for the extra protection.

The extra protection is thus only relevant for well-stablished pharmaceuticals that can apply for a new indication. In this case, the extra protection creates an economic incentive to incur the costs of obtaining the new indication, since the costs may be recouped. This might otherwise have been difficult, since generic competitors could enter the market (almost) immediately.

No such extensions have been granted[3].

1 Directive 2001/83, Article 10(5).
2 Notice to Applicants, Vol. 2A, chapter 1, p. 44.
3 Data provided by the European Medicines Agency.

Mutually exclusive and non-cumulative incentives (2/2)

SIX-MONTH SPC EXTENSION AND ONE-YEAR EXTENSION OF MARKET PROTECTION FOR PAEDIATRIC INDICATIONS[1]

The incentives related to the development of pharmaceuticals for use in children will in some cases lead to the pharmaceutical company having to choose between the use of two incentives:

"In the case of an application under Article 8 [in Regulation (EC) No 1901/2006]*, which leads to the authorization of a new paediatric indication, paragraphs 1, 2 and 3 [i.e. 6 month extension of SPC] shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or the fourth subparagraph of Article 10(1) of Directive 2001/83/EC".*[2]

This means that for this to be relevant for a company several criteria must be met:

- The medicinal product must be authorised in the adult population
- The company must hold a valid, non-expired SPC for the product
- The company must have undertaken studies in the paediatric population and on the basis of this have obtained marketing authorisation for paediatric use
- The medicinal product must provide significant clinical benefit for paediatric use, compared to previous treatments
- The paediatric authorisation must be obtained during the 8 years of data protection

If these five criteria are all met, the company must choose between either extending its SPC by 6 months or extending its market protection by one year.

This case is an interesting choice between two types of protection. Besides the obvious difference in the duration of the extra protection, the protection yielded is also different. The SPC extension is a wider protection as it extends the protection of the part of the patent that the SPC is based on (e.g. a specific molecule), which means that it also protects the use of the patented innovation in other medicinal products for use in other therapeutic areas.

Contrary to the above, the extra year of market protection covers more narrowly the medicinal product for which the market authorisation was granted. This means that the choice is between the shorter, but wider protection from the SPC and the longer but narrower market protection.

The optimum choice for the pharmaceutical company depends on several market factors:

- If, for example, the market is expected to be taken over by a new innovative pharmaceutical from the pipeline of a competitor in six months, then the last six months of market protection beyond that has little value.

- If the patent on which the SPC is based has no relevance beyond the medicinal products to which the PIP and the new indication relate, then the wide scope of the SPC protection has little value and is to be seen as similar to the market protection.

- In the case above, the SPC extension is only relevant if it expires after the market protection including the possible one-year extension would have expired.

To analyse the choice between the two incentives, data would be needed for medicinal products which were eligible for both. There are two situations where this is the case, but only one of them is (partly) observable in the data available:

1. If a medicinal product obtains the 6-month extension of the SPC based on a new paediatric indication, we cannot know whether it provides sufficient clinical benefit such that it would have been awarded an extra year of market protection, since the company cannot apply for this.

2. If a medicinal product obtains the one-year extension of the market protection based on significant clinical benefits and the company has conducted a PIP beforehand, we know that the company chose to go for this incentive instead of the 6-month SPC extension. However, as elaborated upon above, in the available data it is not possible to identify the firms which had the choice, but chose the 6-month extension of the SPC instead. As such, identifying those that had the choice and chose market protection does not allow us to calculate the frequency with which this choice is made.

1 The two incentives discussed in this section are the 6-month extension of SPC based on completion of paediatric studies (Regulation (EC) No 1901/2006, Article 36(1)) and the one-year extension of market protection if a medicinal product is approved for a second indication within the first 8 years after marketing authorisation where it brings significant clinical benefit (Regulation (EC) No 726/2004, Article 14(11)).
2 Regulation (EC) No 1901/2006, Article 36(5).

Safeguards ensuring proper use

In some cases, European pharmaceutical legislation provides so-called 'safeguards' that allow regulators to intervene if an incentive yields results which are different from what was expected when the incentive was granted. We have identified two such safeguards, which are analysed in the following.

REVIEW OF CLAUSE FOR ORPHAN MEDICINAL PRODUCTS

Pharmaceutical companies receiving an orphan designation for a medicinal product must prove that the requirements for the orphan designation are met at several instances[1]:

1. At the time of application for orphan designation
2. At the stage of application for marketing authorisation
3. If a member state informs the EMA that the requirements may no longer be fulfilled

Item 1 comes before the granting of marketing authorisation for the orphan medicinal product, item 2 coincides with the time of processing of an application for marketing authorisation, while item 3 comes after the market authorisation is granted.

While item 2 is part of the procedure leading up to the marketing authorisation for medicinal products based on an orphan designation, item 3 is a 'safeguard' that ensures that action can be taken if the criteria on which orphan designation is granted are no longer met after authorisation. Item 3 is thus the only ex post measure of the three.

If by the end of the fifth year of market exclusivity for an authorised orphan medicinal product based on a request from a member state it is established that the criteria on which the orphan designation is granted are no longer met, the market exclusivity period can be reduced to 6 years. The decision is made by the Committee for Orphan Medicinal Products under EMA[2].

Example of request from a Member State <u>not</u> yielding a reduction of the period of market exclusivity:

"During its meeting of 21 to 23 March 2016, the Committee for Orphan Medicinal Products (COMP) assessed whether Plenadren (hydrocortisone) still met the criteria for orphan designation as there appeared to be an increase in the prevalence of the condition. Plenadren has been authorized in the European Union for the treatment of adrenal insufficiency since November 2011. At the time, because Plenadren met the criteria for orphan designation, it was granted 10 years of market exclusivity in the EU.

A Member State can ask that this period of market exclusivity be reduced to 6 years if at the end of 5 years the criteria for orphan designation no longer apply and the medicine is sufficiently profitable. At the request of the United Kingdom, the COMP therefore reviewed the criteria for orphan designation for Plenadren. The Committee looked at the seriousness and prevalence of the condition and the existence of other methods of treatment. As other methods of treatment are authorized in the European Union (EU), the COMP also considered whether the medicine is of significant benefit to patients with adrenal insufficiency. As these criteria continue to be met, the COMP recommended that the 10-year period of market exclusivity granted to Plenadren in 2011 for the treatment of adrenal insufficiency should not be reduced."[3]

Based on present research, the above example seems to be the only example of a review initiated at the request of a member state. Thus, there do not seem to be any examples of a review initiated by a member state leading to the period of market exclusivity for an orphan medicinal product being reduced.

OBLIGATION TO SUPPLY SUFFICIENT QUANTITIES

A marketing authorisation can legally be granted to another similar medicinal product, during the 10-year market protection period, if:

"... the holder of the marketing authorization for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product"[4].

This obligation could effectively deter the holder of the marketing authorisation from choosing not to supply specific markets.

Through research input by stakeholders, we have not identified any cases where the inability to supply members states actually led to a loss of market exclusivity. This could be either due to the strong incentive to supply, due to barriers to or lack of enforcement or difficulty in demonstrating lack of supply.

1 Regulation (EC) No 141/2000.
2 Regulation (EC) No 141/2000, Article 8(2).
3 http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_review/2016/05/WC500205975.pdf
4 Regulation (EC) No 141/2000, Article 8(3, b).

1.3 IP FRAMEWORK AND PHARMACEUTICAL INCENTIVES IN OTHER COUNTRIES

United States (1/2)

Patents granted in the United States convey 20 years of protection. As is the case with the European SPC, there is a possibility of obtaining *Patent Term Restoration* for marketing time lost during development and government approval. The patent restoration period and the other schemes available for pharmaceuticals in the US, which are reviewed in the following section, are governed by the Hatch-Waxman act[1].

The maximum period of patent restoration is 5 years, but depends on the total effective patent life after marketing authorisation. The effective patent protection period, i.e. the time between granting of marketing authorisation and expiry of the patent, cannot exceed 14 years (15 years in the EU).

The calculation of patent restoration is done as follows. The regulatory period is divided into a testing phase and an agency phase. The testing phase is the time the company spends developing the medicinal product. The agency phase is the time the authorities spend reviewing the marketing application and attached data and documents.

All the time spent in the agency phase (unless the company has not acted with due diligence) plus half the time spent in the testing phase is eligible for restoration. Limitations are that the total effective protection period cannot exceed 14 years and that the restoration period cannot exceed 5 years.

EXCLUSIVITY PERIOD

In the US, there are multiple types of exclusivity, whereas in the EU there are mainly data and market protection as well as market exclusivity.

New chemical exclusivity runs for 5 years. It is granted to medicinal products containing no active moiety (molecule or part thereof) that has previously been approved by the FDA. Prevents submission of an abridged new drug application (ANDA) by generic firms. As the protection prevents an ANDA (see next page), it corresponds to the 8 years of data protection in the EU.

New clinical investigation exclusivity runs for 3 years. It is granted to medicinal products where the active moiety has already previously been approved by the FDA, but new clinical studies have now been undertaken and the application is based on results from these. This could e.g. be for new strength, new dosage form, route of administration or new indication[2].The exclusivity precludes the FDA from approving an ANDA, but does not prohibit companies from submitting it.

Orphan medicinal product exclusivity runs for 7 years. It is granted to medicinal products treating diseases affecting fewer than 200,000 individuals in the US population (around 0.06%, compared to 0.05% in the EU). As is the case in the EU, the designation can also be granted if there is no hope of recovering the initial investment, even though the disease affects more than 200,000 patients. Treatments for e.g. bioterrorism might fall in this category. If a competitor can prove clinical superiority to the medicinal product, the competitor can bypass the exclusivity of the lesser effective medicinal product and obtain a marketing authorisation.

Paediatric exclusivity adds 6 months to either existing patent or exclusivity, whichever expires at the latest date. It is granted when studies in the paediatric population are carried out, as requested by the FDA, regardless of the outcome of the trial. As such, the duration of the extension is equivalent to that granted in the EU, but its addition to either patent or exclusivity is distinct[3].

Biologic License Application (BLA) exclusivity runs for 12 years. The special period of protection for biologics[4] seeks to accommodate the fact that the development of biologic medicine is often a very lengthy process. Biologic pharmaceuticals can also receive orphan medicinal product designation as well as paediatric extension. In the EU, there are currently no special protection incentives for biologic medicinal products specifically, but they can in some cases be classified as orphan medicinal products or advanced therapy medicinal products and hence enjoy the incentives of these classifications.

First biosimilar exclusivity. In the US, there is a market exclusivity provision for the first approved interchangeable biologic product (biosimilar[3]). It varies between 12 and 42 months, depending on ongoing litigation. This blocks future subsequent biosimilar products from entering the market in the designated period. The rationale behind this is that it provides an incentive for manufacturers to get their subsequent product approved as fast as possible, both to take advantage of the exclusivity period and to make sure that others do not come first.

Generating Antibiotic Incentives Now (GAIN) exclusivity, adds 5 years to certain exclusivities for products having received a Qualified Infectious Disease Product designation.

1 The Hatch-Waxman act is the informal name of the "Drug Price Competition and Patent Term Restoration Act" from 1984.

2 FDA: https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069962.htm (accessed on 1 December 2017).

3 This essentially builds upon the same line of thinking used in this study, namely that what matters to pharmaceutical companies is the total effective protection period, not whether protection necessarily stems from patent or regulatory protection periods.

4 A biologic product is a medicinal product manufactured using biotechnology methods and other cutting-edge technologies. Biologic products are often highly complex mixtures. Biologic products include vaccines, blood and blood components, gene therapy, tissues etc. As biologic products are highly complex entities, direct copies of a given drug are often impossible to make. As such, in the area of biologics, a "generic" version is called a biosimilar, as it can never be exactly the same, but provides the same effect.

United States (2/2)

ABRIDGED NEW DRUG APPLICATION

An ANDA uses the data produced in studies of an innovative medicinal product to show safety and efficacy of a generic version of the originator medicinal product. An ANDA may be submitted after 4 years, if it contains a paragraph 4 challenge to a medicinal product holding a new chemical exclusivity.

ANDA

To obtain approval of a generic medicinal product, an "abridged new drug application" (ANDA) can be filed. In this application, the generic manufacturer has to state, for each patent protecting the innovative medicinal product, that either

1. the required patent information has not been filed
2. the patent has expired
3. the patent will expire on a given date
4. the patent is invalid or the new medicinal product will not infringe the patent.

If 1) or 2) is applicable, the medicinal product can be approved immediately. If 3) is applicable, the medicinal product can be approved at the given date. If 4) applies, it constitutes a so-called paragraph 4 challenge, and a legal process begins.

PARAGRAPH 4 CHALLENGE

When filing a paragraph 4 challenge, the generic manufacturer must inform the patent holder of the application. The patent holder can then file a patent infringement lawsuit. If this is done, a 30-month stay on the approval of the generic medicine is in force. This can change if the court reaches a verdict before 30 months or decides to prolong the period.

If the generic manufacturer wins the court case against the originator firm, or if no court case is started, a 180-day exclusivity period before other generics can enter the market is granted to the generic company filing the paragraph 4 challenge. During this period, only the originator company and the generic company having won the paragraph 4 challenge can supply the given medicinal product to the market.

This potential exclusivity period awarded to a generic company which challenges an existing patent creates an incentive for generic companies to keep close check of whether the patents taken out by originator firms are strong enough to keep generics out of the market. Furthermore, it creates the incentive to be the first generic company to enter the market.

It is a combination of the metaphorical 'stick and the carrot'. Additional risk is created for generic manufacturers as others might reach the market before them. In the most extreme case, possible market entry by the second generic may be delayed by 30 months due to a court case (maybe even longer) plus an additional 180 days of exclusivity for the first generic, giving a total delay of 3 years. However, being the first generic to reach the market is rewarded with 180 days of exclusivity before the next generic can enter. An incentive granting protection from further competition for being the first generic to enter the market does not exist in the EU.

DIFFERENCES BETWEEN THE EU AND THE UNITED STATES

As a large share of the global R&D within pharmaceuticals is undertaken in the US, it is worth noting the differences in various elements between US and EU legislation[1].

The US is often highlighted as a very large market, but the sheer size of the population is actually smaller than the total number of people living in the European Union[2]. However, as a share of GDP, no country in the world spends as much on healthcare as the US[3].

Through the FDA, it is possible to get access to the whole US market through one marketing authorisation, but this is likewise the case with the centralised procedure going through the EMA in the EU. The patent protection period is likewise the same, the only difference being that the patent "restoration" period is capped at a total maximum of 14 years of protection in the US, while it is 15 years in the EU.

There are certain differences in the protection periods conferred by the authorities after authorisation. Here, it seems that the data protection period is much more favourable to firms entering the EU market, than in the US. However, the US has a provision for biologics that enjoy a rather long data protection period compared to the other protection periods. The EU has not implemented special rules in this area.

Another major difference is the possibility of a generic company issuing a paragraph 4 challenge in the US. The EU has no similar scheme. The US scheme was introduced to enhance generic competition by providing a further incentive to be first on the market.

Research into what these differences in schemes have meant for the location of R&D would be quite useful in guiding any future changes to the incentives provided in the EU.

1 In OECD (2015), "Research and development in the pharmaceutical sector", in *Health at a Glance 2015: OECD Indicators*, OECD Publishing, Paris, p. 188 it is reported that world industry spending on pharmaceutical R&D was USD 92 billion and that in the US alone spending on pharmaceutical R&D was close to USD 50 billion.

2 There are around 323 million people living in the US, while the EU is home to around 508 million people.

3 World Health Organization Global Health Expenditure database, 2014 available at the World Bank website https://data.worldbank.org/indicator/SH.XPD.TOTL.ZS?year_high_desc=true

Japan

A Japanese patent is valid for 20 years. Furthermore, Japan offers the possibility of patent term restoration of up to 5 years (same as the EU). The possible restoration period is calculated from the start date of clinical trials or patent, whichever is the latest, and ends on the day before the authorities send the final authorisation to the company[1].

POST-MARKETING SURVEILLANCE PERIOD

After a medicinal product is granted marketing authorisation in Japan, it enters a period of Post Marketing Surveillance (PMS), also called the re-examination period. It is a period for carrying out post-marketing examination of the efficacy and safety of a medicinal product. During this period, no generic company can apply for marketing authorisation. Hence, it effectively conveys much the same protection as the data protection period in the EU.

However, the Japanese system has a different way of viewing the exclusivity period. The re-examination period is constructed so that companies can gather additional information on the efficacy and safety of a medicinal product in a larger population. After expiry of this period, the additional data is re-examined by the authorities to determine continued use. The fact that generics cannot enter the market during this period is thus, at face value, a consequence of the fact that the medicinal product is still being tested and not a specific policy to grant protection to the innovative pharmaceutical company. However, the effect in terms of possible entry by generics is the same as for the system used in the EU.
It should be noted, that as no generic company can apply for a marketing authorisation during the re-examination period, the effective protection period conveyed is the re-examination period plus the time it takes for the authorities to approve a generic application once the re-examination period has expired. As such, it is equivalent to the data protection period in the EU.

RE-EXAMINATION PERIOD

The duration of the re-examination period varies for different designations. For a medicinal product containing a new active entity, i.e. an innovative medicine, the re-examination period is 8 years (same as the data protection period in the EU). New combination medicinal products have a 6-year re-examination period[1].

Medicinal products approved for a new indication are subject to a 4-year re-examination period from subsequent approval if less than 4 years remain of the original re-examination period (1 additional year granted in EU, if significant clinical benefit)[2].

If a medicinal product is approved as having a new route of administration, and if less than 6 years remain of the original re-examination period, a new 6-year period takes effect from the new approval[2].

The re-examination period is 10 years for orphan medicinal products (less than 50,000 patients in Japan, which is around 0.04%, compared to 0.05% limit in the EU). Orphan medicinal products obtaining a new orphan indication are subject to a 10-year re-examination period for the subsequent approval. As such, this is the same coverage as in the EU[3].

Japan offers an additional 2-year re-examination period for the production of paediatric data.

Biologics do not enjoy a longer re-examination period than regular small-molecule medicinal products.

PRICE LISTING

Japan has a so-called Price Listing System, controlling the prices of medicinal products. Under this regime, patients can only receive National Health Insurance reimbursement for medicinal products that are listed. Generic medicinal products can only be listed twice a year. This, plus the fact that generic marketing applications cannot be filed until after the expiry of the re-examination period, effectively grants the patent holder an extra period of market exclusivity beyond that conveyed by the re-examination period.

DIFFERENCES

As such, even though the Japanese system is based on a principle of post-marketing surveillance, the effective working of the system is similar to the system in the European Union. Generally, there is not much difference between the protection periods provided; however Japan has a more granulated system for granting further protection for new indications.

1 See e.g. https://uk.practicallaw.thomsonreuters.com/6-560-2578?transitionType=Default&contextData=(sc.Default)&firstPage=true&bhcp=1
2 See e.g. http://tokyo-acti.com/2015/09/26/how-long-is-pms-post-marketing-surveillance-period-in-japan/
3 EMA presentation by Daisuke Tanaka of the Ministry of Health, Labour and Welfare, Japanese Orphan Drug Designation, available at http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/10/WC500152531.pdf

Canada

THE CANADIAN FRAMEWORK

A patent is valid for 20 years in Canada. Three components make up the legal framework surrounding IP protection for pharmaceuticals. The *Patent Act*, the *Patented Medicines (Notice of Compliance) Regulation* and *Data Protection*.

Until 1992, Canada had readily been using the possibility of compulsory licensing. The changes made in 1992 eliminated compulsory licensing in Canada to prepare the legal framework for the TRIPS agreement in 1994.

MARKET PROTECTION AND DATA PROTECTION

Pharmaceuticals receiving marketing authorisation in Canada are subject to 6 years of data protection and 8 years of market protection which run in parallel[1]. Both periods are 2 years shorter than in the EU. The market protection period is extendable by 6 months if paediatric studies are undertaken. No distinct period exists for biologic pharmaceuticals.

Canadian law offers no distinct protection for orphan medicinal products.

In conjunction with the EU-Canada Comprehensive Economic and Trade Agreement (CETA), Canada has recently passed a bill enacting a patent term restoration period of up to 2 years[2]. Patent term restoration corresponds to the SPC in the EU.

Generic manufacturers can seek market authorisation before the patent protecting the originator medicinal product expires if they claim the patent is invalid or not infringed. If this path is chosen, the originator company can trigger a judicial process which stalls the approval of the generic medicinal product for 24 months or until the court has settled the matter, whichever comes first. This procedure is somewhat similar to the paragraph 4 challenge generic companies can file in the United States[3].

Triggering the judicial procedure of the Patented Medicines (Notice of Compliance) Regulation described above does not confer a complete infringement case, but merely a summary judicial review aimed at determining whether the allegation is justified. This is in contrast to the similar laws in the US, where proceedings continue as a regular infringement court case.

DIFFERENCES

The key differences between Canada and EU is that market and data protection are both 2 years shorter in Canada than in the EU. Furthermore, Canada provides no distinct protection for orphan medicinal products. Besides this, patent restoration is available for a maximum of 2 years compared to up to 5 years in the EU through the SPC.

1 Food and drug regulations, section C.08.004.1. See Guidance Document on Data Protection under C.08.004.1 of the Food and Drug Regulations, available at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html

2 https://openparliament.ca/bills/42-1/C-30/

3 See p. 48.

India

In India, 22% of the population lives below the poverty line[1]. As such, there is some increased focus in India on helping the poor. The policies on IP protection are no different. One of the focal points for changing Indian governments has been to provide the general public with easy and affordable access to essential medicine. This goal seems to have been pursued at the expense of protection of intellectual property.

PATENTS

The international Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), agreed upon by all WTO members sets out minimum standards for intellectual property protection to be enforced by the participating countries.

One of the main provisions in the TRIPS agreement is that patents must have a minimum term of 20 years without discrimination towards any technological field. To comply with these requirements, the Indian government introduced product patents on pharmaceuticals in 2005. Before this, no such patents existed in India, contributing to growing the domestic generic pharmaceutical industry.

DATA PROTECTION

India does not provide a period of data protection for newly authorised medicine. Under TRIPS, member countries must provide safeguards against "unfair commercial use" of data produced by an innovator. However, nowhere in the agreement is it mentioned that this is equivalent to a period of data protection, and hence India has not been obliged to enact any such protection.

As such, the only protection enjoyed by medicinal products in India is the 20-year patent period.

PATENT ENFORCEMENT

Despite India's 20-year patent period on pharmaceuticals, the US 2017 Special 301 Report on IP in various countries described it as "*... one of the world's most challenging major economies with respect to protection and enforcement of IP*"[2].

One recurring matter of concern for global pharmaceutical companies is their claim that the patent courts of India are applying narrow patentability criteria.

Facts on India's pharmaceutical industry

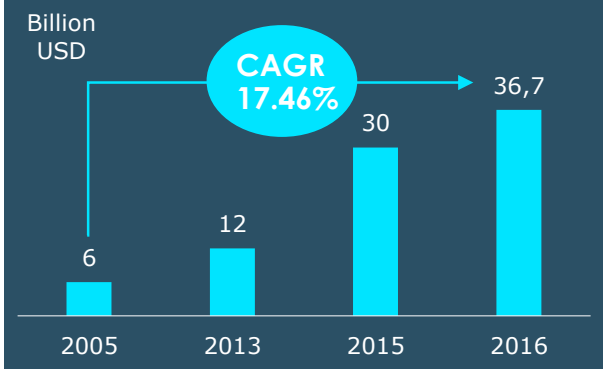
The pharmaceutical industry in India is the third-largest in the world in terms of volume and ranks number thirteen in terms of value.

70% of revenue in the Indian pharmaceutical sector comes from generics.

The Indian pharmaceutical industry attracted USD 14.53bn between 2000 and 2016 in foreign direct investments.

Supplying 20% of global generic pharmaceutical export volume, the Indian generic industry is the largest in the world.

Revenue of the Indian pharmaceutical sector



Note: CAGR is the Compound Annual Growth Rate.
Source: India Brand Equity Foundation.

1 http://www.iiprd.com/2017/01/11/india-need-patent-term-extension-non-patent-exclusivities-pharmaceuticals/
2 Office of the United States Trade Representative (2017), 2017 Special 301 Report, p. 42.

China

CHINESE IPR UNTIL NOW

The Chinese Patent Law was first enacted in 1984 and has since been amended three times, in 1992, in 2000 and in 2008[1].

The amendment in 1992 added pharmaceuticals to the list of patentable subject matter. The second amendment in 2000 made sure that the Chinese Patent Law was in compliance with the TRIPS agreement. The third amendment in 2008 included, among other things, changes to the novelty requirement for patentability and the patentability possibilities of inventions relying on genetic resources or traditional knowledge. Furthermore, the third amendment made it more feasible for the Chinese authorities to issue compulsory licenses[1].

Currently a patent provides intellectual property protection for 20 years in China. Besides patent protection, the Chinese authorities provide a period of 6 years of regulatory data protection[2].

An interesting provision granted by the Chinese Patent Law is that for medicinal products patented in China generic manufacturers may submit their application for marketing authorisation two years prior to the expiry of the patent.

CHINESE IPR IN THE FUTURE

A draft order published on 12 May 2017[3] proposed additional data protection beyond the current 6-year period for orphan medicinal products, paediatric medicinal products, biologic products and first generic product. The draft order proposed to provide 10 years of data protection to orphan and paediatric medicinal products, with three years for an improvement medicinal product within these two classes. Furthermore, it proposed 10 years of data protection for biologic products. It likewise proposed 18 months of data protection for generics, if a generic is either the first domestic generic or has proved a linked patent to be invalid (bears certain similarities to the on paragraph 4 challenge in the US)[3]. regulation

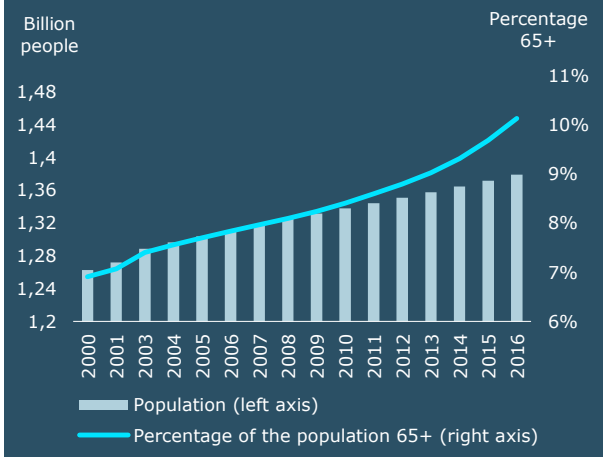
As such, the draft order seems to suggest that the Chinese authorities might be moving towards more IP protection in the future.

Pharmaceuticals in China

China is the second-largest pharmaceutical market in the world. The Chinese population is growing, and at the same time the percentage of citizens older than 65 is increasing rapidly.

The value of the Chinese market is forecast to grow from USD 108bn in 2015 to USD 167bn by 2020. This would equate to annual growth of 9.1%. During the same period, the global market for pharmaceuticals is predicted to grow by 4.3% annually.

Source: Department of Commerce, USA, International Trade Administration and *Evaluate Pharma, World Preview 2017, Outlook to 2020.*



Source: World Bank.

1 https://www.hg.org/article.asp?id=33387
2 https://www.ip-watch.org/2016/03/15/chinas-pharmaceutical-sector-and-the-ip-puzzle/ and http://www.managingip.com/Article/3322867/Following-pharmaceutical-data-protection-in-China.html
3 Relevant Policies to Encourage Innovation and Protect Innovators' Rights (Order 55). See e.g. https://www.bakermckenzie.com/en/insight/publications/2017/09/cfda-drug-registration-china/ for description.

IPR scheme	European Union	United States	Canada	Japan	India	China
Patent term	20 years.	20 years.	20 years.	20 years.	20 years.	20 years. Application for generic authorisation can be submitted 2 years prior to expiry for products patented in China.
Patent term restoration	Up to 5-year SPC. Combined with patent conveys a maximum of 15 years of effective protection.	Up to 5 years. Combined with patent conveys a maximum of 14 years of effective protection.	Up to 2 years.	Up to 5 years.	n/a.	n/a.
Data protection	8 years. +1 year for change of classification. +1 year for new indication for well-established substance.	5 years for new chemical substance (only 4 years if a paragraph 4 challenge is lost). 12 years for biologics. +5 years for products having received a Qualified Infectious Disease Product designation.	6 years.	8-year re-examination period for new chemical substance. 6 years for new combination. 4 years for new indication. 6 years if approved for new route of administration.	n/a.	6 years for new chemical entity.
Market protection	10 years. +1 year for new indication with significant clinical benefit.	3 years for new clinical studies. 180 days for first generic to file a paragraph 4 challenge and win. 12-42 months for first biosimilar.	8 years.	n/a.	n/a.	n/a.
Orphan medicinal product incentives	10 years of market exclusivity.	7 years.	n/a.	10 years re-examination period.	n/a.	n/a.
Paediatric incentives	+ 6-month extension of SPC. + 2-year extension of orphan medicinal product market protection.	+ 6-month extension of either patent or exclusivity, whichever lasts longest.	+ 6-month extension of market protection.	+ 2-year re-examination period.	n/a.	n/a.

Source: See previous pages for references.

Comparing incentive frameworks

In the following, we compare and describe differences and similarities between the incentive framework in the different countries/regions, described in the table on the previous page.

PATENT TERM

A period of 20 years duration of a patent is present in all the countries/regions, compared in the table on the previous page.

PATENT TERM RESTORATION

The EU, US and Japan all have up to 5 years of patent term restoration. In the EU this is conveyed by the SPC. A main difference between the EU and the US is that, in the US the maximum period of protection from marketing authorisation until expiry of the patent term restoration is 14 years. In the EU it is 15 years. Canada only provides up to 2 years of patent term restoration. India and China provides no possibility of patent term restoration.

As such, the patent term restoration provided in the EU is the most generous in this comparison.

DATA PROTECTION

The EU and Japan both provide 8 years of data protection for a new substance. However, Japan provides fewer years of data protection if the authorised product is a new combination, for a new indication or if it is approved for a new route of administration.

In the US, the period of data protection is 5 years, possibly only 4 if a paragraph 4 challenge is lost[1]. However, for biologic products, the period of data protection is 12 years.

China and Canada provides 6 years of protection, while India provides none.

The data protection scheme in the EU seems to be the most generous, except for biologics, where the US provides a longer period of protection.

MARKET PROTECTION

In the EU the market protection period is 10 years. The US only provides 3 years. However, if a paragraph 4 challenge is won by a generic company, they receive 180 days of market protection, before other generics can enter the market[1]. This creates an incentive for generic companies to be the first to market, and challenge the patents of originator companies.

Canada provides 8 years of market protection, while Japan, India and China provides none.

The market protection period provided in the EU is the most generous among the compared countries/regions. However, the US in some cases provide market protection to the first generic to enter the market.

ORPHAN MEDICINAL PRODUCTS INCENTIVES

The EU and Japan both provide a 10 year protection period for orphan medicinal products. The US provides 7 years, while Canada, India and China have no special protection period for orphan medicinal products.

In this case, the EU and Japan provide the same coverage of protection of orphan medicinal products.

PAEDIATRIC INCENTIVES

Japan provides an extension of the protection period of 2 years, following paediatric studies. The EU provides the same period, but only for orphan medicinal products. For non-orphan medicinal products the EU provides a 6 month extension of the SPC. The US and Canada likewise provide 6 month extensions.

The extra period of protection, provided for carrying out paediatric studies is the most generous in Japan. For non-orphan medicinal products the extra period of protection provided, is the same in the EU and the US. However, the US 'attaches' the period of protection to the protection scheme that last longest. In the EU the extension is always provided in extension of the SPC. As such, the US rules are likewise more generous than the EU.

COMPARISON

On many of the parameters reviewed here, the incentive framework in the EU is the most attractive one. However, regarding e.g. biologic medicinal products and the paediatric incentives for non-orphan medicinal products, other countries have more attractive frameworks.

1 See p. 48 for a further description of this.

1.4 ACTUAL USE OF THE ABOVE INCENTIVES AND REWARDS BY THE PHARMACEUTICAL INNOVATORS

1.4.1 USE OF THE INDIVIDUAL INCENTIVES

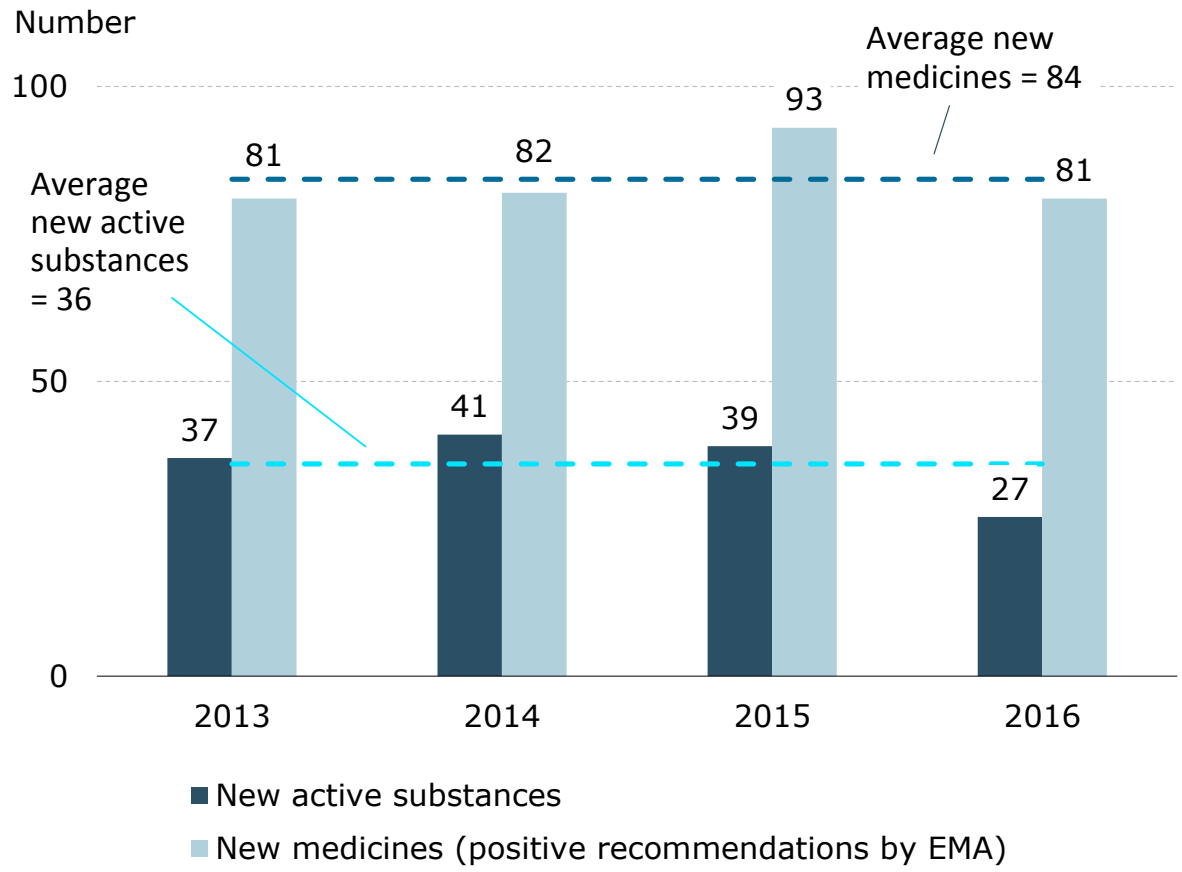
Stable numbers of new medicines in the past four years

During the years 2013-2016, the European Medicines Agency issued an average of 84 positive opinions recommending marketing authorisation per year[1], including an average of 36 new active substances each year[1]. Both these figures pertain to centrally authorised medicinal products.

Some of the new active substances might be used to treat more than one indication. Additionally, some of the positive opinions might comprise already known active substances for use in the treatment of more indications. These are the reasons for the number of positive opinions being more than twice as high as the number of new active substances.

There seems to be a fall in the number of new active substances approved in 2016 compared to the other years. However, as there are only four years of available data, it is not possible to derive any robust conclusions based on this. At the same time, the number of new medicines does not seem to deviate from the other years in 2016.

Number of new medicines and new active substances centrally approved by the European Commission, 2013-2016



Note: Graph showing the number of new active substances centrally approved per year by the European Commission for the years 2013-2016. New active substances are substances that have never previously been authorised in a medicinal product in the EU. The number of new medicinal products signifies the number of positive recommendations provided by the EMA.
Source: European Medicines Agency annual reports 2013-2016.

1 European Medicines Agency annual reports 2013-2016.

The number of SPCs granted has been increasing slightly over time

The number of SPCs granted shows some variation across the years, with noticeable spikes in e.g. 1992, 2007 and 2013. Each time a country implemented the SPC regulation, medicinal products approved in the country in the years leading up to this year became eligible for applying for an SPC. This e.g. explains the spike in 1992 as this is when the regulation entered into force in the first EU member states. Notably, the spike in 2007 is not driven by any one country in particular, but rather a general increase in applications across most countries. The same is true for 2013.

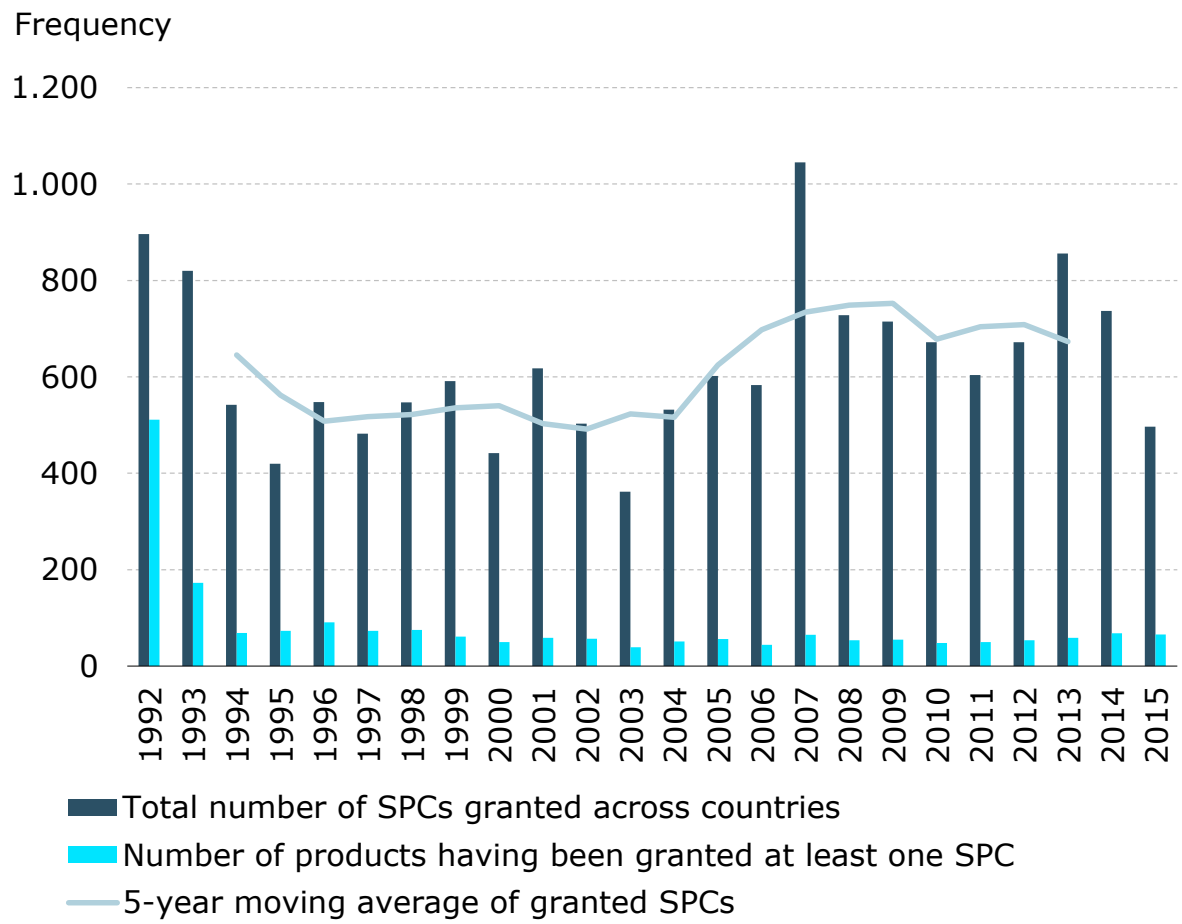
The overall trend shows a slight increase over time. One should keep in mind that the number of countries offering the possibility of obtaining an SPC is likewise increasing over time, which might explain much of the general increase.

The total number of SPCs granted in all countries within the European union is depicted in the graph to the right as the columns with the navy colour. If a product is granted SPCs in multiple countries, each of these SPCs counts.

The columns with the light turquoise colour depict the number of individual products having obtained one or more SPCs. If a product is granted SPCs in multiple countries, it only counts once. The product is counted in the year it is granted the first SPC.

From the graph it can be seen that the number of unique products receiving an SPC has been fairly stable over time, and hence the fluctuation in the total number of SPCs is mostly driven by the number of countries in which a given product obtains SPCs.

Number of SPCs granted in Europe, 1992-2015



Notes: Includes human and veterinary use. Excludes plant protection products. Covers 1991 to April 2016. The "Number of products having been granted a least one SPC" depicts the unique number of medicinal products having been granted an SPC. As such a SPC given to the same product in multiple countries is only counted once in this series.
Source: Alice de Pastors dataset.

Signs of increasing use of paediatric investigation plans

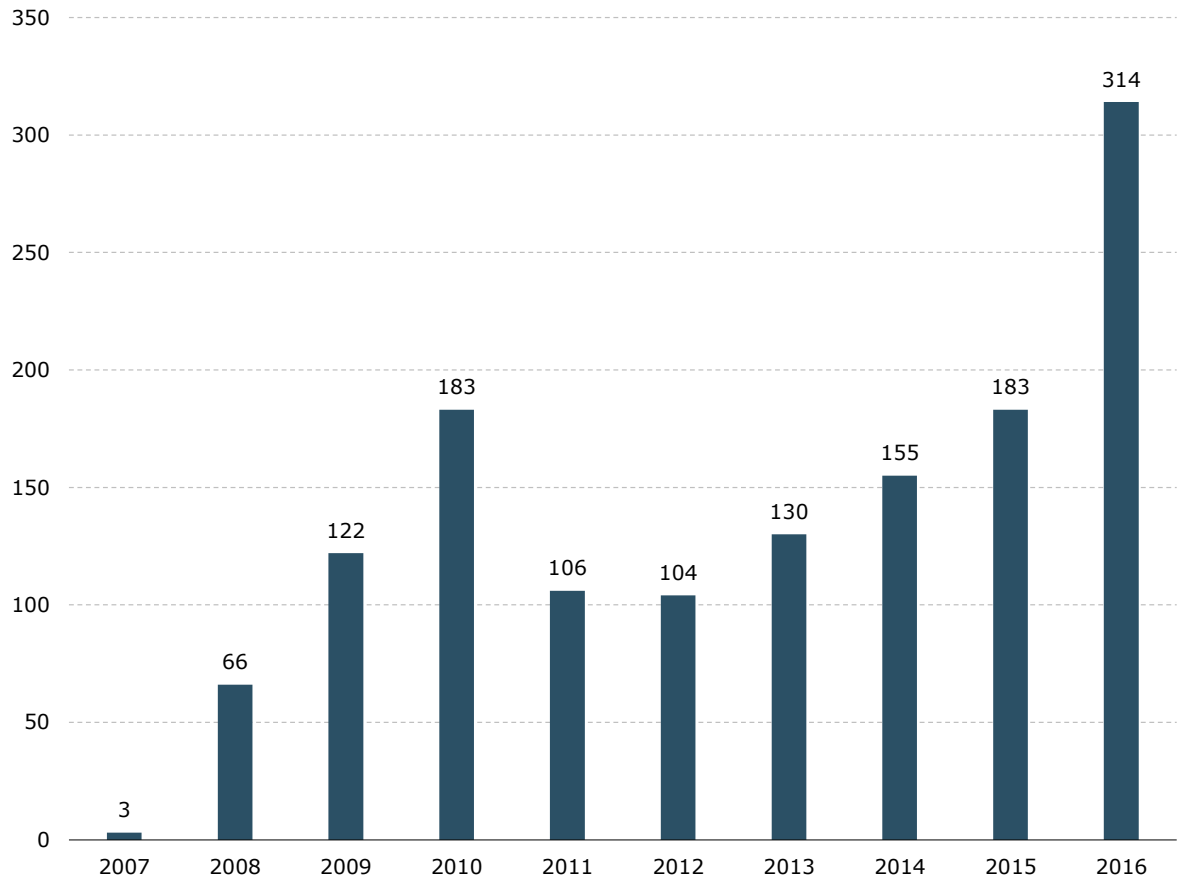
Since the introduction in 2006 by Regulation (EC) No 1901/2006, the number of decisions regarding paediatric investigation plans (PIPs) has increased, with an all-time high in the latest year, 2016.

At face-value, the increase signals a success in incentivising more studies undertaken to assess the use of medicinal products for children. The graph to the right covers all decisions regarding paediatric investigation plans. As such granting of waivers and deferrals are e.g. likewise included. The peak in 2016 thus reflects a peak in the total number of decisions regarding paediatric investigation plans.

A key driver behind the increase in PIPs is probably the fact that Article 7 of Regulation (EC) No 1901/2006 means that PIPs have to be agreed upon for most new medicinal products[1].

As can be seen later, only eight orphan products have obtained a positive PIP compliance check.

Number of decisions regarding paediatric investigation plans, 2007-2016



Note: Covers only centrally approved products. Covers all decisions regarding paediatric investigation plans; decision agreeing on a paediatric investigation plan, with or without partial waiver(s) or deferral(s), decision granting a waiver in all age groups for the listed condition(s), decision on the application for modification of an agreed paediatric investigation plan, decision referring to a refusal on a proposed paediatric investigation plan, decision referring to a refusal on a request for waiver in all age groups for the listed condition(s), decision referring to a refusal on the application for modification of an agreed paediatric investigation plan.
Source: Data from the European Medicines Agency website.

1 Another possibility is likewise for a deferral or waiver to be granted.

Increasing use of the orphan designation

The number of applications and the number of actual grants of orphan designations have risen significantly since the introduction of the orphan regulation in 2000[1].

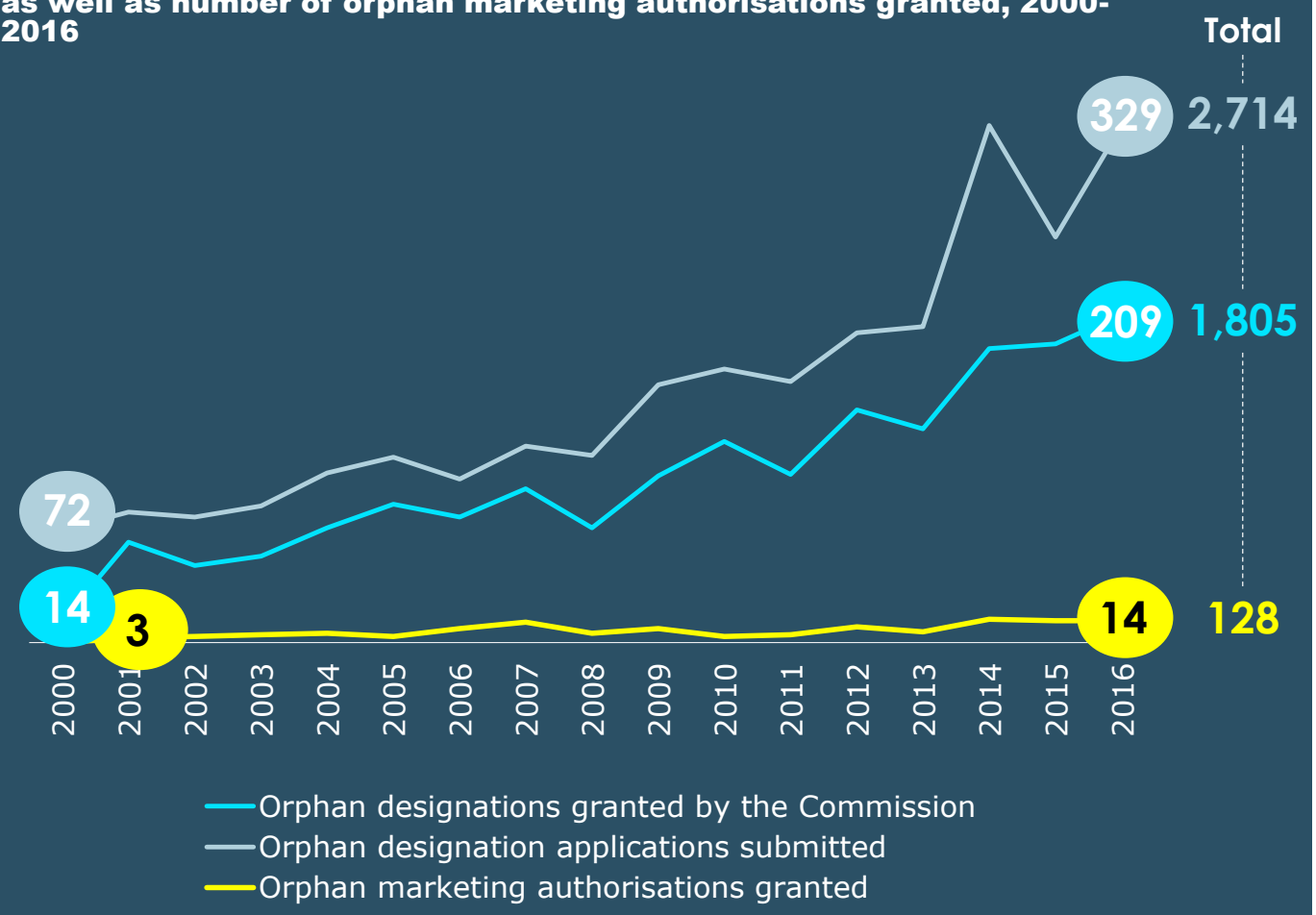
It is important to note, that the increase in orphan designations does not necessarily equal an increase in the number of orphan marketing authorisations granted. However, the number of orphan marketing authorisations have increased over the period.

The increase in the number of granted orphan marketing authorisations can by itself be seen as an indication that the orphan regulation has helped to promote the development of medicinal products for the treatment of rare diseases.

In the years from 2000 to 2016, 2,714 applications for orphan designation were submitted. Out of these, 1,805 had been granted by the Commission by the end of 2016. During the same period, 128 orphan marketing authorisations were granted.

As orphan designations are granted before marketing approval, there is a lag between designation and possible grant of marketing authorisation. As such, the fact that the yearly number of marketing authorisations granted for orphan medicinal products has not increased hugely since 2000 might to a great extend be due to said lag.

Number of applications for orphan designation submitted and granted, as well as number of orphan marketing authorisations granted, 2000-2016



Note: Graph showing the yearly number of submitted and granted applications for orphan designation as well as the number of orphan marketing authorisations granted from 2000 to 2016.
Source: European Commission, DG SANTE (2016), Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products and EMA (2017), Orphan Medicines Figures 2000-2016.

1 Regulation (EC) No 141/2000.

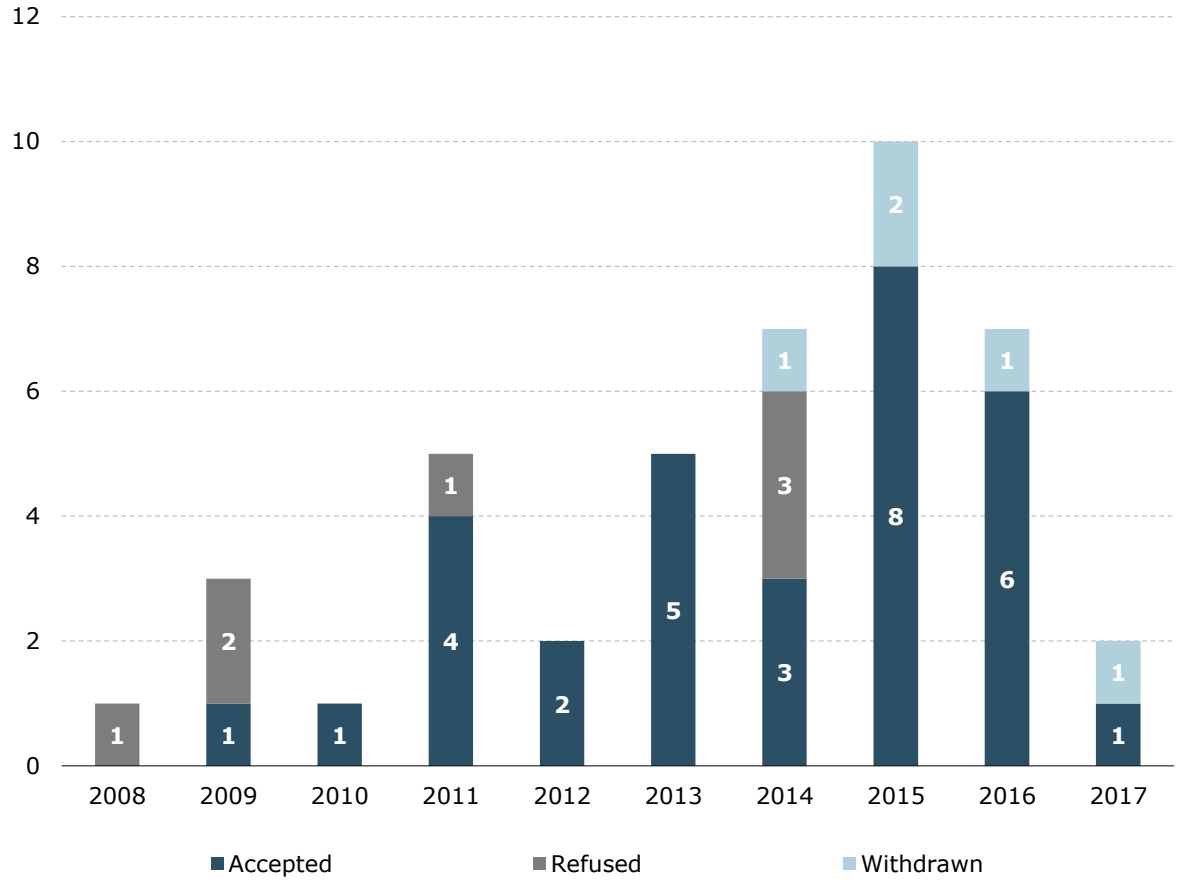
Increasing number of one-year extensions of market protection for new indications with significant clinical benefits

Under current regulation, it is possible to obtain a one-year extension of the 10-year regulatory market protection period[1]. The extension can be obtained if a given medicinal product is approved for a new therapeutic indication within the first 8 years of marketing authorisation being granted for the original indication[1]. Furthermore, the company must be able to show that the medicinal product has a significant clinical benefit for the new indication compared to existing therapies within the area.

Since 2008, there has been an increase in the use of this option, both in terms of the total number of applications and the number of applications accepted (i.e. products being granted the extension).

The data covers only centrally approved products, and as such there is the possibility that the increase could be driven by the increasing use of the centralised procedure during the same period.

Outcome of applications for one-year extensions of market protection, 2008-2017



Note: Covers all medicines which are centrally approved. Data provided before the end of 2017, hence final figures might be higher for this year. See Regulation (EC) No 726/2004 for the legal framework.
Source: Data provided by the European Medicines Agency.

1 Regulation (EC) No 726/2004, Article 14(11).

The use of certain incentives is sparse

Some incentives providing additional regulatory data protection or market protection have only been used sparsely. The extreme case is the one-year extension of data protection provided if a well-established substance (used for 10 years or more) is approved for a new therapeutic indication. This instrument has never been applied for for any centrally approved substance.

The table covers only centrally approved products, and as such the incentives might be used more often for products approved through the mutual recognition procedure or nationally.

Even if use of the incentives is sparse, they might have a large effect for the few individual medicinal products, which are eligible. This would be the case if the extra years of protection are decisive in turning the ex ante development decision from a negative business case into a positive business case.

Use of incentives from enactment year until June 2017

	Accepted	Refused
one-year data protection for well-established substance[1]	0	0
one-year data protection for classification change[2]	1	2
2-year market exclusivity for completion and compliance with a paediatric investigation plan[3]	5	0

Note: Covers all medicines which are centrally approved.
Source: Data provided by the European Medicines Agency.

1 Directive 2001/83/EC, Article 10(5). No such extensions have been granted.
2 Directive 2001/83/EC, Article 74a.
3 Regulation 1901/2006, Article 37. According to data from the EMA 8 orphan medicinal products had completed a PIP by 2016. Five of them obtained the 2-year extension of the market exclusivity period. The remaining three products no longer have orphan status.

1.4.2 THE COMBINED EFFECT OF INCENTIVES AT PRODUCT LEVEL

Effective protection and development time

PATENT-PROTECTED MEDICINES

Innovative medicinal products frequently require substantial up-front financial expenditures to fund their invention, development, testing and approval process[1]. The pharmaceutical innovation process involves numerous critical steps and can fail in any of the phases mentioned above.

Regulation (EC) No 469/2009(4) states that "*At the moment, the period that elapses between the filing of an application for a patent for a new medicinal product and authorisation to place the medicinal product on the market makes the period of effective protection under the patent insufficient to cover the investment put into the research*". As such, the introduction of SPCs seeks to remedy this.

EFFECTIVE PROTECTION

Counting patents, marketing exclusivities, supplementary protection certificates and further potential protection term extensions, a plethora of legal instruments are available to a pharmaceutical innovator wanting to obtain exclusive commercial exploitation rights. However, a newly developed medicinal product can only be launched commercially once the company trying to market the product has received approval to do so. The approval process is a time-consuming endeavour that requires time and resources to complete. However, it is needed to ensure the safety, quality and efficacy of medicinal products. As such, the period in which a product is both on the market and enjoying certain legal protection instruments is shorter than the total period of protection. The timeframe theoretically relevant to companies, and therefore also to the initial decision to pursue the innovation process, is the *effective period of legal protection*. This means that the cumulative nominal protection period of exclusive commercial exploitation net of the authorisation(s) to commence doing so by launching the developed product on the marketplace is the time period that innovators should consider in their decision-making process.

COMPUTING EFFECTIVE PROTECTION FOR MEDICINES

In principle, computing the effective period of protection for a medicinal product is relatively straightforward. To compute the protection period, one would subtract the date of grant of the authorisation to market a product in the country in question from the date of expiry of the last legal instrument establishing exclusive commercial exploitation privilege to the company holding the authorisation to market. From that point onward, the product would no longer be protected by exclusivity rights, and generic competition could ensue.

Due to their nominal protection period of 20 years, patents or legal instruments extending them – such as supplementary protection certificates or paediatric extensions – regularly constitute the last incentive scheme to provide protection to a product.

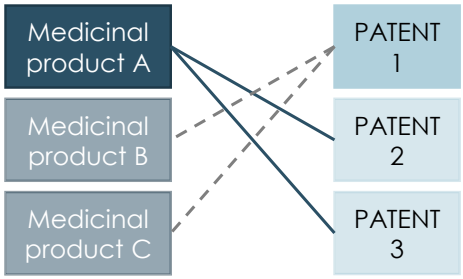
DATA AVAILABILITY

Calculating the effective period of protection therefore requires a mapping of medicinal products with the patents and additional protection schemes protecting them.

Unfortunately, a comparable mapping is not available for the European market as companies are not required to disclose the patents protecting their products. The situation is further complicated by the many-to-many nature of the relationship between medicinal products and patents in particular: a single medicine can be – and usually is – protected by numerous patents. However, using a novel technique, utilising the legally mandated linkage between medicinal product and patent(s) in the US and subsequently identifying European patents from this, it is possible to create a unique dataset containing products and their patents for the European Union, which is what we have done[2].

DEVELOPMENT TIME

Besides calculating the effective protection period, the information contained in the data allows us to calculate the development time for a given medicinal product. In this study, the development time is calculated as the period elapsed from first patent to first marketing authorisation in the EU.



The following pages analyse the development time and effective protection period.

1 The literature shows estimated costs of bringing a medicinal product from the lab to the market of between USD 648m and USD 2.6bn. See Prasad, V. and Mailankody, S. (2017), Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval and Di Masi, J. A., Grabowskib, H. G. and Hansen, R. W. (2016), Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs.

2 For a thorough description of the technique used to create the dataset and the dataset itself, see the appendices of chapter 1 and 2.

Calculation of development time

Development time is calculated as the period elapsed from first patent to first marketing authorisation in the EU. This can be seen in the 'illustrative example 1', depicted to the right.

This period is likewise called the 'patent period lost'. It is the period used when calculating whether an SPC is possible and what length it potentially should have.

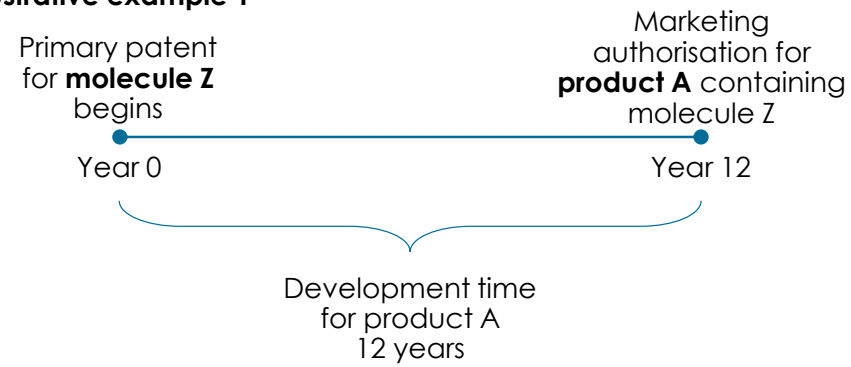
A result of the above definition is that secondary patents do not influence the development time.

As development time is calculated as the period elapsed from first patent (usually protecting the molecule) until marketing authorisation in the EU of a given product (identified by tradename), products which reuses 'old' molecules will have a longer development time, than the product in which the molecule originally was present. This can be seen in the 'illustrative example 2', depicted to the right.

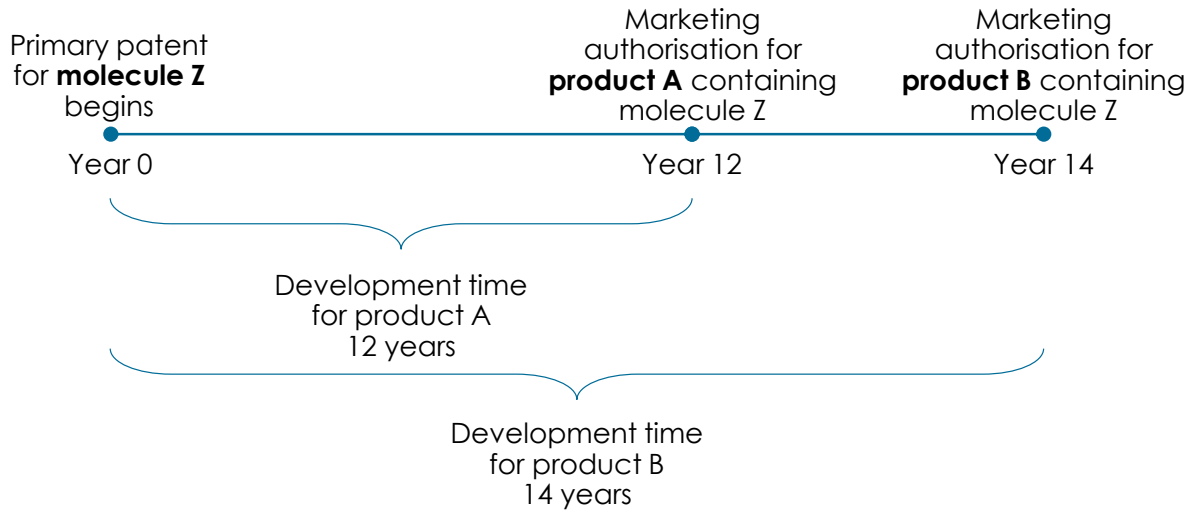
As such, if there has been an increase in the reuse of 'old' molecules over time, this will contribute to an increase in the calculated development time.

Illustrative examples of calculation of development time

Illustrative example 1



Illustrative example 2



The development time of pharmaceuticals seems to have increased over time (1/3)

In this study, the development time of a product is defined and calculated as the time elapsed from the time of the first patent protecting the product anywhere in the EU to the first marketing authorisation anywhere in the EU.

Development time
= date of first MA in the EU
– date of filing of corresponding patent

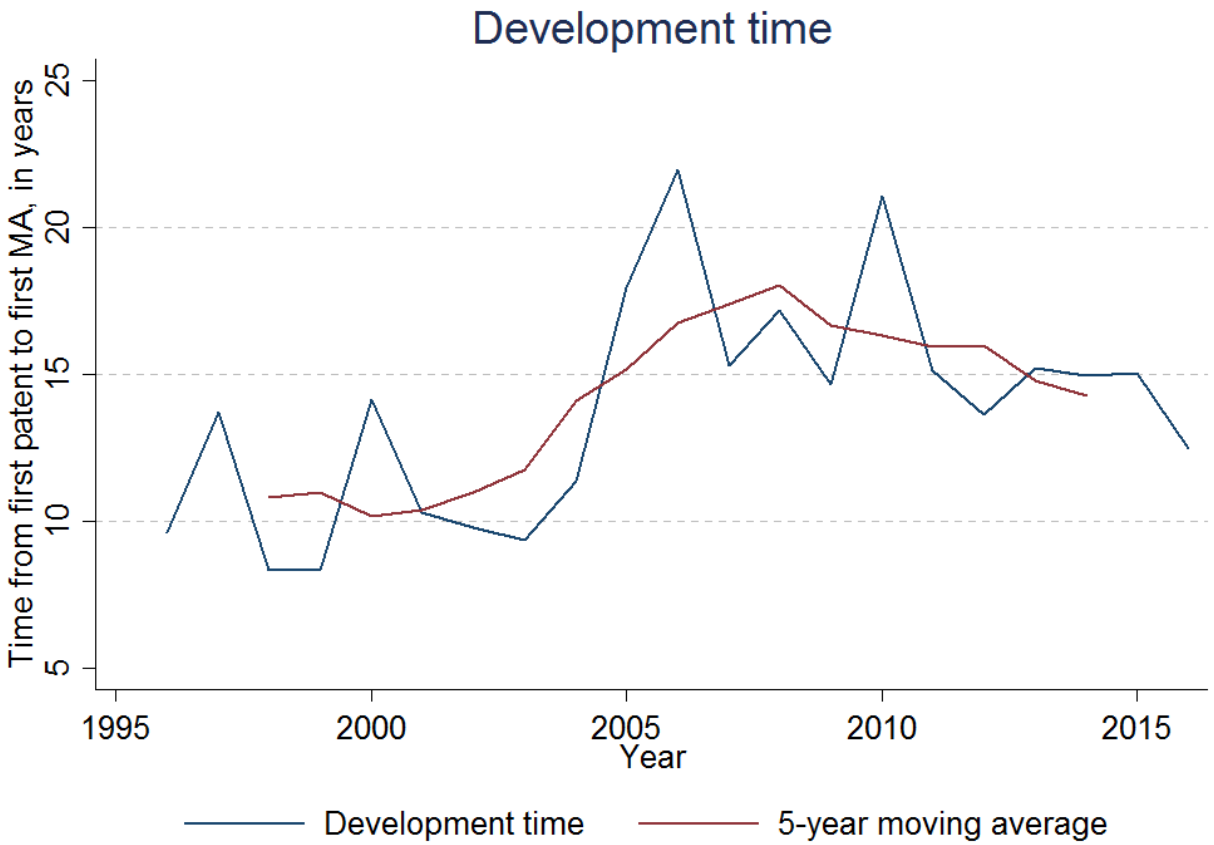
Thus, the definition of development time applied in this study focuses not on the number of years where the innovator was, in fact, directly engaged in developing the specific medicinal product, but on the 'patent time lost', which is an important factor in the commercial decision on whether or not to invest in R&D projects. It is likewise the period used to calculate the duration of any would be SPC.

From the graph to the right it seems that the development times of medicinal products have increased from around 10 years in the first half of the period, to around 15 in the last half of the period.

In a recent study, Kyle (2017) likewise analyses development time of new pharmaceuticals. However, there are several differences between this study and that of Kyle.

Firstly, the definition of development time is different. In the Kyle study, development time is defined as time elapsed from first patent, until first international launch. In the present study, development time is defined as time elapsed from first patent until first launch in the EU. In the case that a medicinal product is launched in the EU as the first place in the world, the two coincide, otherwise they will differ.

Average time from patent to marketing authorisation, 1996-2016



Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described above. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with development time below zero are not included in the figure. The development time is calculated from the date of the first patent anywhere in the EU, to the date of the first marketing authorisation anywhere in the EU. As such, there is one observation per medicinal product as identified by trade name. Development time is counted in the year the product obtains marketing authorisation. The 5-year moving average is calculated as the average of the two years before and after a given year as well as the value in that year.

Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI.

The development time of pharmaceuticals seems to have increased over time (2/3)

Secondly, the data sources differ. Kyle (2017) relies on data from IMS Health, while the present study uses a novel dataset, linking patents and products from a range of different sources[1].

Thirdly, the time period analysed in the two studies differ. Kyle (2017) studies the period 1990-2015, while the present study analyses the period 1996-2016.

As the calculation method, the sample and the time period differ between the two studies it is thus not surprising that the calculated development times do not completely coincide in absolute number.

In Kyle (2017), development times have increased from around 10 years in the period 1990-1994 to a little more than 12 years in the period 2010-2015. As such, even though the calculated years of development time differ, both Kyle (2017) and the present study find an increase in development time.

Looking at the graph, it is however difficult to draw a clear conclusion as to whether the development time has stabilised at a new stable level, will increase even further or follow the bend in 2016 decreasing again.

INCREASE IN DEVELOPMENT TIME

The visible historical increase in development time depicted by the graph on the previous page might have several explanations.

Over the period, there might have been an increase in the regulatory requirements for documentation when submitting an application for marketing authorisation, i.e. the clinical data needed to obtain a marketing authorisation might have increased. An increase in the requirements for showing efficacy and safety of a new medicinal product might e.g. prolong the clinical trial period as more extensive data needs collecting. It is reported that between 1999 and 2005 the median number of procedures per clinical trial protocol increased from 96 to 158, and the duration of clinical trials increased from 460 to 780 days[2].

Another possibility is that the approval time has increased. However, according to reports from the Centre for Innovation in Regulatory Science (CIRS), an independent research organisation, the median approval time in the EU fell slightly between 2004 and 2017, though with some variation between years[3,4].

In its reports, CIRS defines approval time as the time from the submission date until the granting of the marketing authorisation. The approval time thus includes time spent by both the EMA, the company in question and the European Commission.

Notably, the median approval time in Europe fell each year between 2004 and 2007[3]. This seems to indicate that changes in approval times cannot explain the increase in development time seen on the previous page. Rather, the decrease in median approval times should, all else being equal, indicate a decrease in development time in these years.

There might also have been an increase in repurposing of old molecules for new purposes during the period. In that case, the patent protecting the molecule might have been taken out long before the repurposed medicinal product enters the market. The new medicinal product with the repurposed molecule will appear to have had a very long development period, as it is calculated as the time elapsed from the first patent protecting the molecule until first marketing authorisation for a unique product[5]. The company has not necessarily spent all this time developing the new product, but rather undertaken additional R&D into the use of the molecule after the original product was placed on the market.

This means that if there is an increase in the use of old molecules, with old patents, in new products in our sample, this might entail an upward bias in the estimation of development time.

Another possibility might also be that the products on average are becoming more complex and hence take longer to develop. This could be the case with more biological medicines with complex research and manufacturing processes.

1 See pp. 82-87 for more information about the dataset.

2 Rollins, T. (2016), "How Europe's SPC regime works in practice" reports these figures provided by EFPIA. Getz, K. A., Campo, R. A. and Kaitin, K. I. (2011), Variability in Protocol Design Complexity by Phase and Therapeutic Area likewise reports an increase in procedures per clinical trial from 2000 to 2007.

3 Bujar M, McAuslane N. 2014. R&D Briefing 55: The impact of the changing regulatory environment on the approval of new medicines across six major authorities 2004-2013. Centre for Innovation in Regulatory Science.

4 Bujar M, McAuslane N, Liberti L. 2016. R&D Briefing 59: The impact of the evolving regulatory environment on the approval of new medicines across six major authorities 2006-2015. Centre for Innovation in Regulatory Science.

5 See e.g. the case studies on Revatio and Viagra in chapter 5. These two medicinal products contain the same molecule but are approved 7 years apart. This means that the development time as defined in this study for Revatio is 7 years longer than the development time for Viagra.

The development time of pharmaceuticals seems to have increased over time (3/3)

This might happen for two reasons. Firstly, it might be that many of the 'low-hanging' fruits within the medical sciences have already been picked. This would entail that as more treatments are being discovered, new and better treatments become more difficult and time-consuming to identify.

However, more knowledge and advances within the technological and medical sciences might conversely entail that the research community today has previously unseen potential for discovering new radical and beneficial medical innovations.

Secondly, it might be that the underlying structural consolidation of minimum protection periods has allowed pharmaceutical companies to pursue innovations that take longer, but perhaps likewise offer bigger benefits to patients.

The formalisation of a minimum protection period of 10 years for new innovative products in the EU through the market protection period might be an important parameter in this[1].

Being guaranteed a protection period of at least 10 years can be said to limit the downside to undertaking innovations with a potentially long development period. The protection period can never be completely lost as there is a guaranteed 'floor'.

At the same time, there is no established cap on the upside both in terms of benefits for patients and potential profit, and this might incentivise commencement of longer expected R&D projects[2].

It is not certain that one of the above explanations is the whole reason for the increase in development time. Rather, the increase could be ascribable to a combination of two or more of the above explanations.

Unfortunately, the available data does not allow us to conclude which of these explanations or combination of explanations might be the reason for the apparent increase in development time. As such, based on the currently available data, we cannot conclude which of the explanations reviewed above might have contributed to the increase in development time.

To sum up, from 1996 to 2016 there was an increase in development time, defined in this study as the time from first patent to first marketing authorisation, as identified in the available data material. An increase is also found in Kyle (2017).

CALCULATION METHOD

In the dataset utilised for the analysis, a medicinal product is identified by its tradename. Hence, if a product has different tradenames in different countries for e.g. linguistic reasons, the product will exist in the dataset as a unique observation for each tradename. If a product is launched in some EU countries under one name and later launched in other EU countries under another tradename, this would cause the calculated development time to be biased in an upward direction. However, according to the EMA this has only ever occurred twice for centrally approved products, as it can only happen in exceptional circumstances[3]. As such, we view any possible bias from this exception to be negligible.

If there has been an increase in the reuse of known molecules over time in new medicinal products, this would tend to increase the reported development time. This is so, as development time is calculated from first patent of the molecule until a product obtains marketing authorisation. If a known molecule is used in a new product, the development time will be calculated as the period elapsed from the first patent until launch of this new product[4]. This is thus parallel to the calculation method used when calculating the length of a possible SPC.

1 Market protection is enshrined in Regulation 726/2004, Article 14(11). Before this, 10 years of data protection existed for the centralised procedure and likewise in some EU member states.

2 There is, of course, a certain limit to what payers will be able to pay for a certain innovative pharmaceutical treatment. However, there is a relationship between the benefit to patients and the willingness to pay. In the extreme case that a company e.g. discovered a vaccine for all cancers, this would entail enormous value for patients, and most payers would probably be willing to pay a rather high price for such a treatment. This is what is meant when we say that there is no established cap on the upside.

3 See the EMA document "Guideline on the acceptability of names for human medicinal products processed through the centralised procedure".

4 See p. 65 for further elaboration on this.

Development times seem to be centred around 10 years

The development time determines the term of the SPC and is thus crucial to the impact of the SPC on the total period of protection from generic competition which a medicinal product can enjoy.

Development time
= date of first MA in the EU
– date of filing of corresponding patent

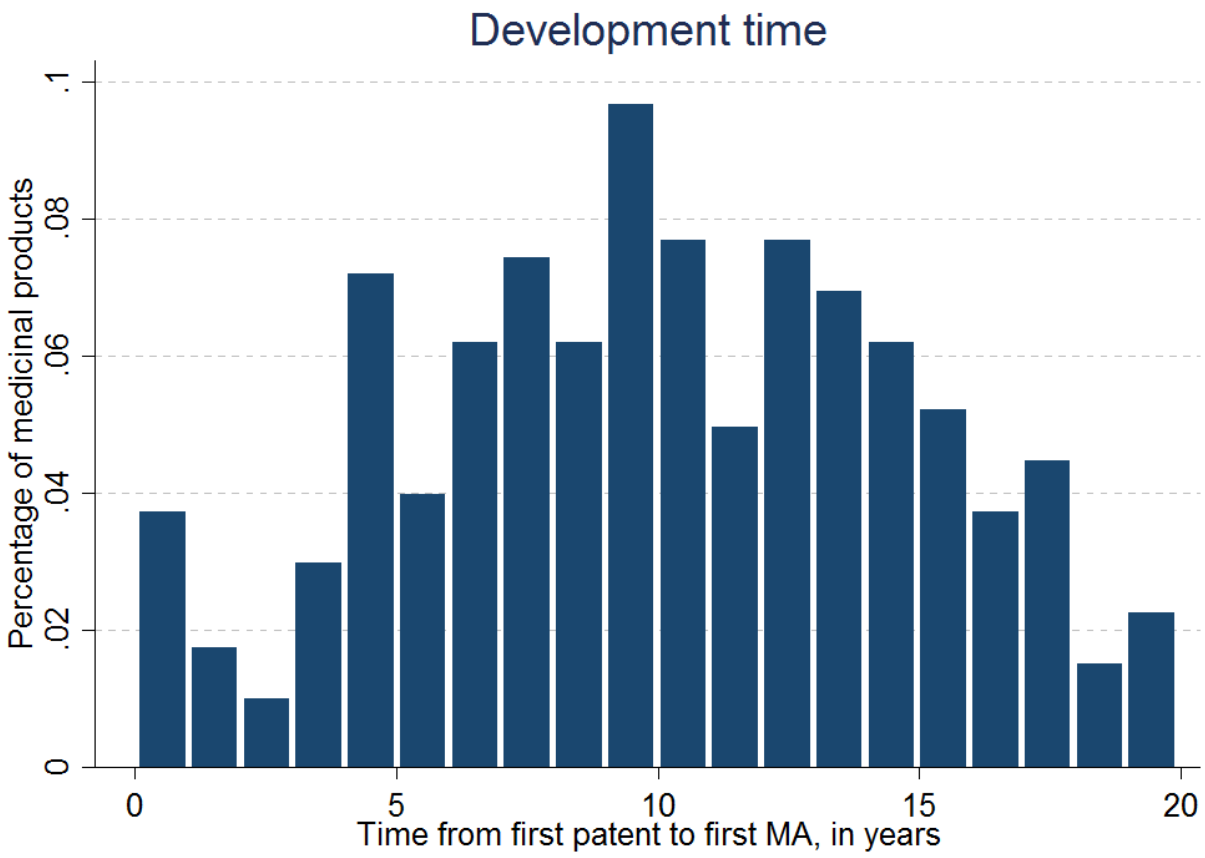
A development time of less than five years means that the SPC is not relevant (except in special cases), while a development time of ten years or more means that the pharmaceutical company can apply for the maximum of 5 years of SPC protection[1].

The figure to the right shows that the development times have a wide distribution ranging from close to zero to up to 20 years (where it is censored in this graph). In most cases, the development time is more than five years, meaning that a possible SPC can impact the total protection period.

The development times of the medicinal products in the sample seem to be centred around 10 years, but with common deviations from this.

In the graph to the right, all products in the sample are combined together regardless of the year of authorisation. As such, this is another way of viewing the data than in the graph on p. 62, where the average development times where distributed by years, instead of being consolidated.

Distribution of time from patent to marketing authorisation for medicinal products with development times of less than 20 years, 1996-2016



Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described above. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with development times below zero and above 20 years are not included in the figure. The development time is calculated from the date of the first patent anywhere in the EU, to the date of the first marketing authorisation anywhere in the EU. As such, there is one observation per medicinal product as identified by trade name. Development time is counted in the year the product obtains marketing authorisation.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI.

Some products in the sample seem to have a rather long development time

The sample includes a small number of products with a rather long development time. This can e.g. be the case if an already known molecule is repurposed for inclusion in a new medicinal product[1].

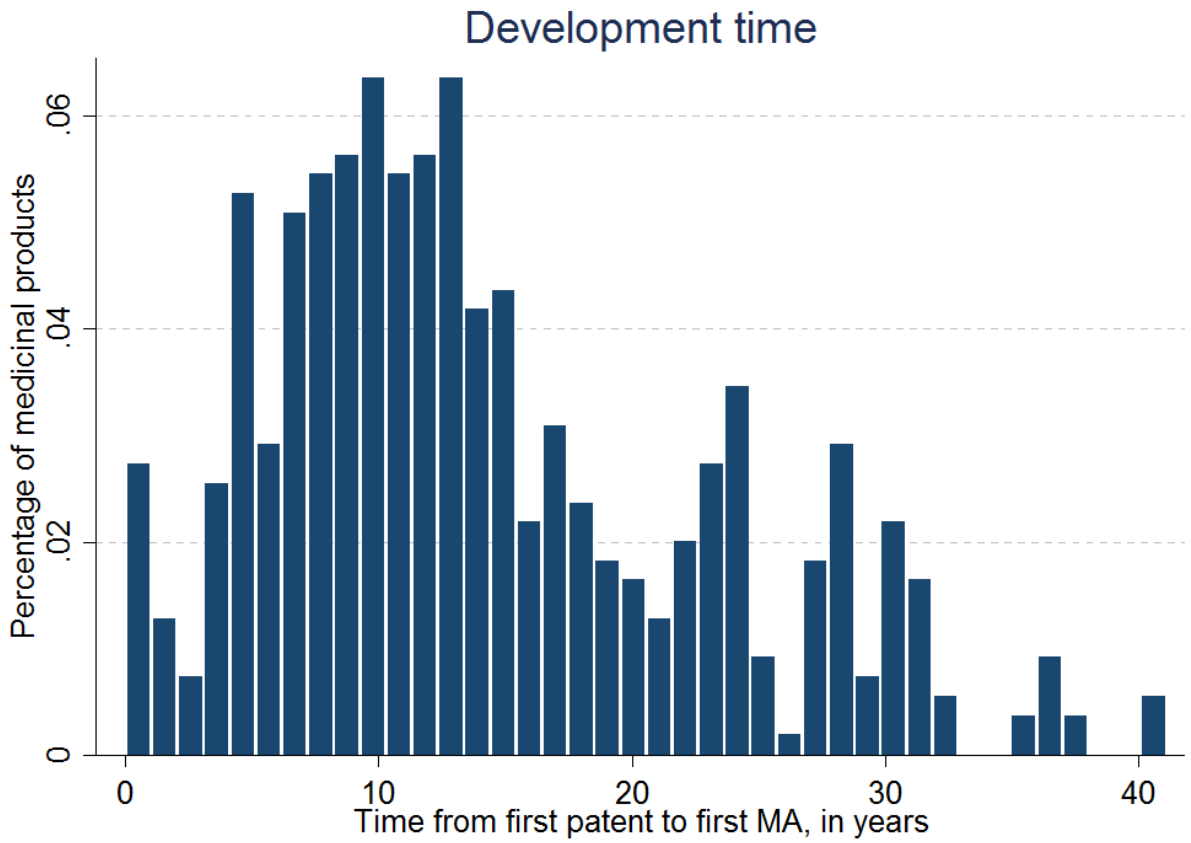
In these cases, it is likely that a patent would have been taken out when the molecule was first discovered. The development time from the patent to the first marketing authorisation for a product containing the molecule might be e.g. 10 years. However, if the molecule is later used in another medicinal product with a new trade name, the first patent will still protect the molecule. Hence, the time elapsing from the first patent to the marketing authorisation for the new product with the new trade name might be e.g. 20 years.

Development time
= date of first MA in the EU
– date of filing of corresponding patent

In the case of the above example, in our calculation this will be recorded as one product having a development time of 10 years and another product having a development time of 20 years.

In the dataset shown in the graph to the right, 50% of all products have a development time of between 5 and 15 years.

Distribution of time from patent to marketing authorisation, 1996-2016



Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described above. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with development time below zero are not included in the figure. The development time is calculated from the date of the first patent anywhere in the EU, to the date of the first marketing authorisation anywhere in the EU. As such, there is one observation per medicinal product as identified by trade name. Development time is counted in the year the product obtains marketing authorisation.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 See p. 65 for further elaboration on this.

Calculation of effective protection period (1/2)

EFFECTIVE PROTECTION PERIOD

For each product-country combination for which information has been obtained, we identify the last protection scheme to expire, i.e. taking account of the IP incentives patent, SPC and the regulatory incentives market protection (taking account of market exclusivity for orphan medicinal products and paediatric extensions) and data protection. From the EMA and MRI data on market authorisations through the centralised procedure as well as the mutual recognition process and decentralised procedure, we are able to obtain information on the date of marketing authorisation for each product, in each country.

The time elapsed from the identified marketing authorisation until the last IP protection scheme expires is designated to be the effective protection period.

Both patents and SPCs are granted at the national level. This means that a given medicinal product does not necessarily have the same amount of protection in all countries, where it is launched.

In this study, the effective protection period is calculated as the time elapsed from marketing authorisation until the last protection scheme expires, in each country, the product is launched in. A product is identified by its tradename.

In some countries an SPC might be granted, while in others it might not. To make sure that we capture all aspects of this, we calculate the effective protection period for each product, in each country in which it has been launched. If a product is launched in e.g. 20 countries, it counts 20 times in the calculation of the average effective protection period. This is so, as the protection period might differ for the same product, between countries.

For each country-year combination, we take the mean of all observations on effective protection periods. The effective protection period of a given medicinal product is recorded in the year it obtains marketing authorisation.

This provides us with a variable containing the average effective protection period for each country in the sample in each year.

This is one of the key measures utilised in the econometric studies undertaken in chapter 2. Where possible (depending on data availability), the effective protection period will likewise be reported in the case studies in chapter 5.

Note on effective protection period

During the lifetime of a patent, there is some uncertainty as to how long the effective protection period will be. The uncertainty is greatest at the start of the lifetime of the patent, when it is unknown when marketing authorisation will be obtained and whether any SPC or other extensions can be applied for. During the lifetime of the patent, this uncertainty is reduced. For example, on the date of granting of a marketing authorisation, it is known whether the product is orphan or not, and after obtaining a marketing authorisation, an application for SPC must be handed in within six months.

Paediatric extensions and extensions for e.g. new therapeutic indications for well-established substances and classification changes are not known until later.

Because of the above, calculating effective protection periods for the future can be subject to some uncertainty.

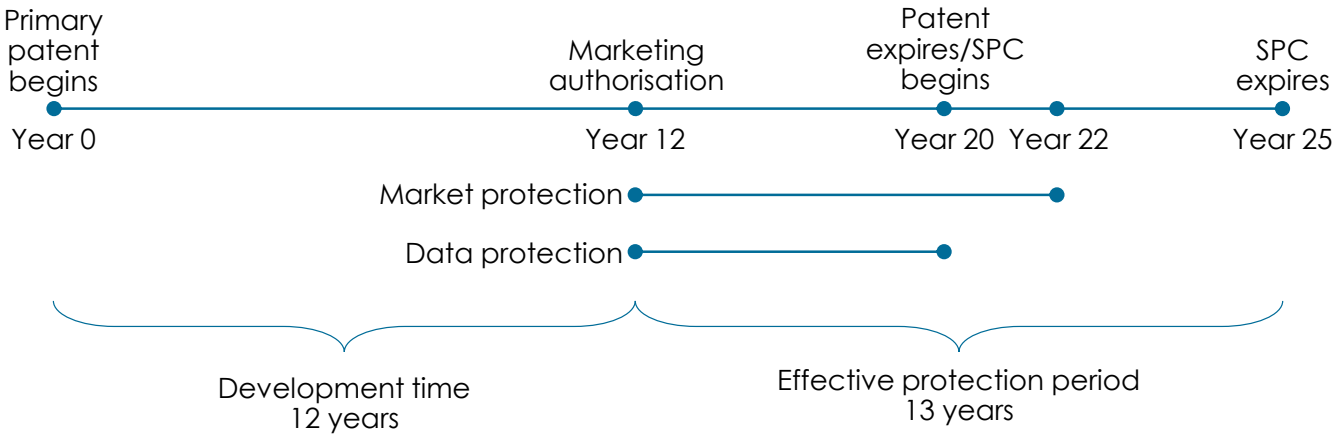
In the worst-case scenario, e.g. an orphan medicinal product obtains a paediatric extension after our sample period has ended, and hence our effective protection period calculation is off by two years (if a patent protecting the invention does not run for longer, in which case the calculation is still correct).

Calculation of effective protection period (2/2)

Illustrative examples of calculation of development time and effective protection period

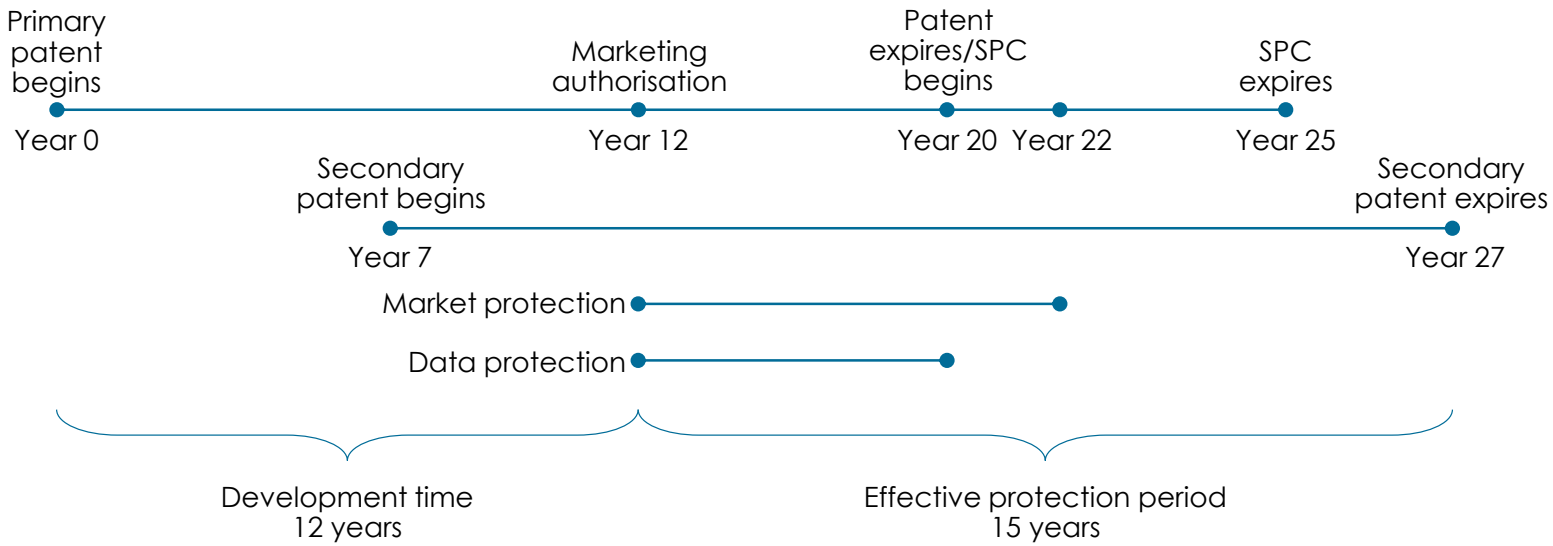
Example 1
In this illustrative example, marketing authorisation is granted 12 years after the primary patent begins. This gives a development time of 12 years.

An SPC of 5 years is granted and as such, the total effective protection period is 13 years.



Example 2
In this illustrative example, marketing authorisation is granted 12 years after the primary patent begins. This gives a development time of 12 years.

An SPC of 5 years is granted. 7 years after the primary patent, a secondary patent protecting the product is taken out. As such, the total effective protection period is 15 years.



Note: Graphic showing illustrative examples of how development time and effective protection period are calculated.
Source: Copenhagen Economics.

The effective protection period has decreased over time

The figure to the right shows that the duration of the effective protection period for medicinal products has been falling since the 1990s from a level of around 15 years down to around 13 years by the end of the sample period[1]. This result should be seen in the light of the increase in the development time in the same period, which despite the partial compensation through the SPC seems to have resulted in a decrease in the effective protection period offered to new medicinal products.

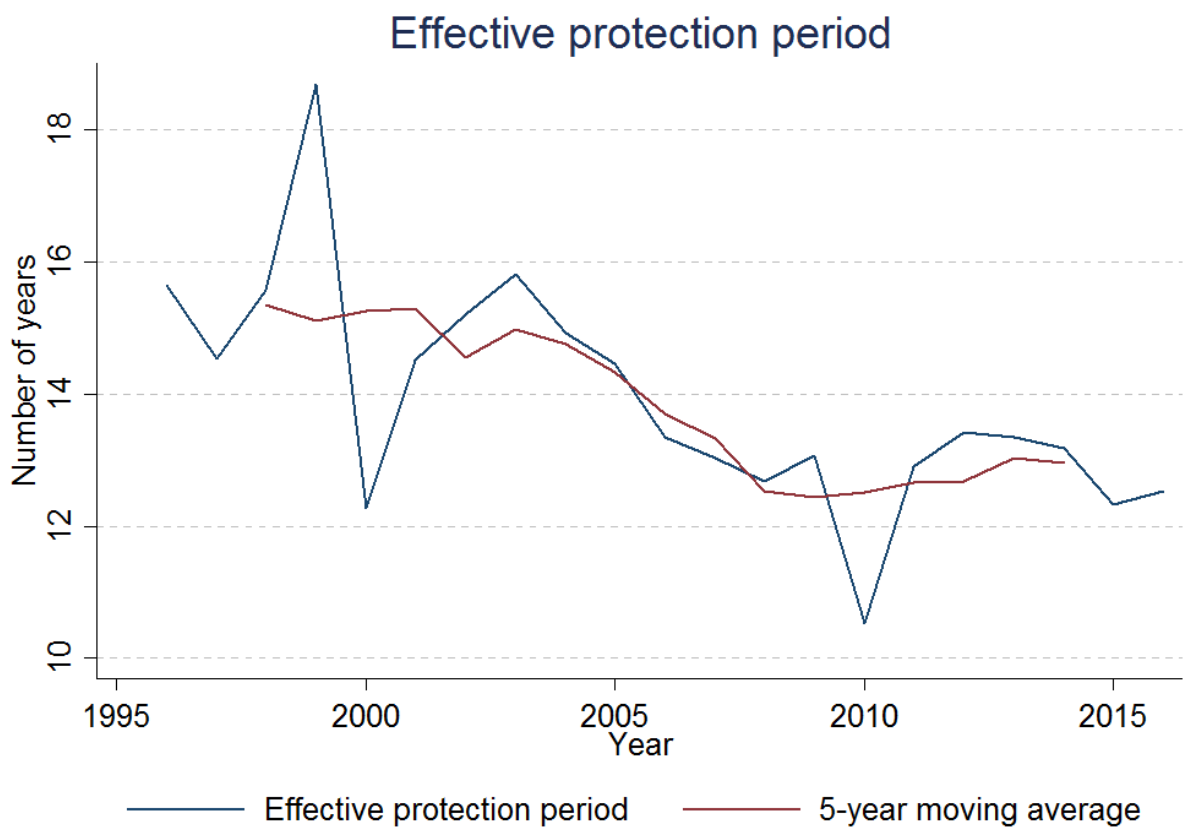
Effective protection period
= date of last protection to expire
– date of marketing authorisation

The findings are in line with the findings of Kyle (2017), where it is observed that for a sample of medicinal products which have been granted an SPC, the effective protection period fell from 13.8 years to 12.5 years between 1990 and present (2015). The difference between the Kyle (2017) study and the present analysis is that Kyle restricted her sample to only include products with an SPC, whereas the sample in the present study also includes medicinal products without an SPC.

This development in isolation could drive down the economic reward for developing new innovative medicinal products since the companies will have a shorter time period in which to recoup their investments. However, the prices charged and the patient base covered are likewise crucial elements in determining the profitability of developing new medicinal products. As such, when taking this into account, the fall in the effective protection period shown in the graph to the right does not necessarily mean that the motivation for developing new medicinal products has decreased.

The rather sharp drop in 2010 might, at least partly, be explained by a peak in development times for medicinal products approved in that year[2].

Average effective protection period in Europe 1996-2016



Note: Based on the unique dataset described in the appendix to chapter 1 and 2. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with a development time below zero years are not included in the figure. The sample consists of unique combinations of trade name and country, i.e. each product is present in the sample once for each EU member state in which it has obtained a marketing authorisation. This is imperative when analysing protection periods as the effective protection period might differ between countries because of differences in marketing authorisation dates, patents and SPCs. The 5-year moving average is calculated as the average of the two years before and after a given year as well as the value in that year. The overall conclusion of a decrease in the average effective protection period is robust to the exclusion of all secondary patents, however the size of the fall decreases slightly when secondary patents are excluded.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 The overall conclusion of a decrease in the average effective protection period is robust to the exclusion of all secondary patents, however the size of the fall decreases slightly when secondary patents are excluded. See the appendix to chapter 1 for more on this.

2 See previous graph of development times. Several robustness checks have been carried out to analyse the sharp drop. It can be concluded that it is due neither to a lower number of observations than in the other years, nor to extreme outliers.

Large spread in the distribution of effective protection period

As illustrated previously, the combined protection from generic competition yielded by both IP protection and pharmaceutical incentives is called the effective protection. This term does not distinguish between the types of protection as it only focuses on whether or not generics/biosimilars can enter the market.

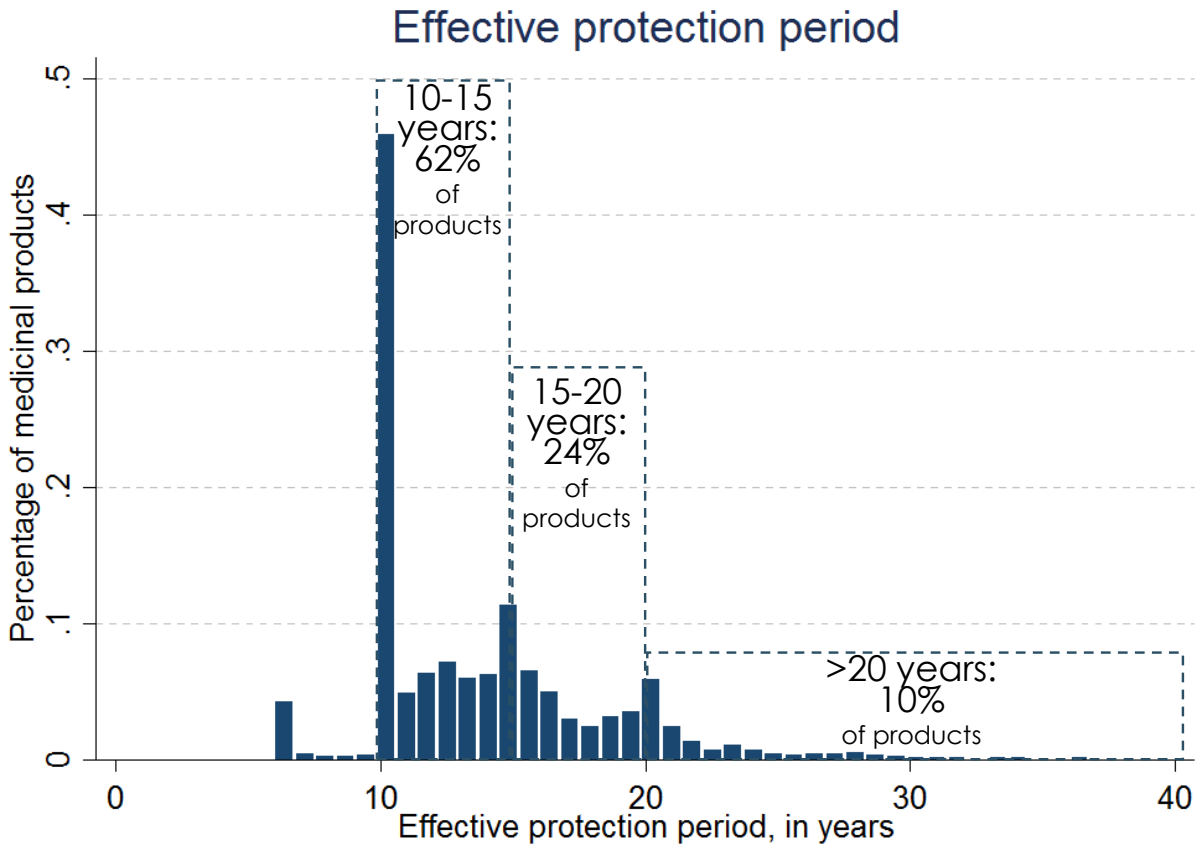
Effective protection period
= date of last protection to expire
– date of marketing authorisation

The figure to the right shows that the duration of the effective protection period is distributed from a minimum of less than 10 years, stemming from the market protection yielded by the marketing authorisation to all products, up to 30 years stemming from the combination of multiple types of IP protection, secondary patents and incentives.

The fact that some medicinal products enjoy up to 30 years of protection might seem rather surprising as a patent lasts 20 years. However, for some medicinal products pharmaceutical companies take out several patents protecting different inventions associated with the products. Some of these patents might be taken out later in the development process than others, and some maybe even after marketing authorisation is obtained[1].

Some of these might be more or less peripheral and as such could be difficult to defend in a patent court if challenged by e.g. a generic manufacturer. However, all patents have to live up to the same requirements when applied for, and in our sample we thus do not have a measure for the legal 'strength' of a patent, and as such the effective protection period is calculated on the basis of all patents taken out on a given product[2].

Total effective protection period in Europe from 1996-2016



Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described above. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with development times below zero, i.e. first identified patent is taken after first launch, are not included in the figure. Before 2005 the effective protection period could be shorter than 10 years due to some countries providing less regulatory protection, in the form of data protection, than currently. The sample consists of unique combinations of trade name and country, i.e. each product is present in the sample once for each EU member state in which it has obtained a marketing authorisation. This is imperative when analysing protection periods as the effective protection period might differ between countries because of differences in marketing authorisation dates, patents and SPCs.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 For examples of medicinal products with an average effective protection period across the European member states of more than 20 years see e.g. case studies on Humira and Herceptin in chapter 5. See also European Commission (2009) Pharmaceutical Sector Inquiry, figure 55, p. 175.
2 As all patents live up to the same requirements when applied for, the legal "strength" or enforceability of a patent can only be decided by a court of law.

CHAPTER 1 APPENDIX

Utilising US Regulatory Disclosure Requirements

A GLOBAL PHARMA MARKET

Big pharmaceutical companies developing new and patent-protected medicinal products operate and compete on a global scale. Many companies market their products not only in their home market, but also in other geographical regions of the world where consumers, governments and/or insurance companies are capable of paying a sufficiently high price for the medicinal products.

When trying to identify which patents cover which medicinal products in Europe, we are faced with one overarching problem; no such direct link exists in any readily available database.

As such, we need to create this link, through a cross-country approach.

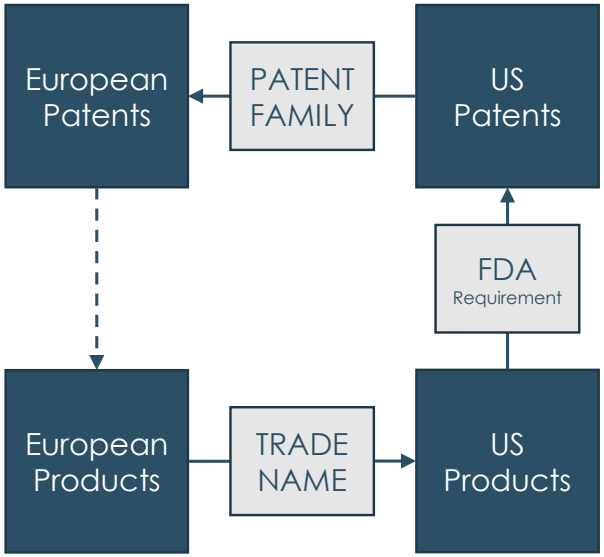
The US Food and Drug Administration authority (FDA) mandates that innovators disclose the key patents protecting their products in the so-called FDA Orange Book[1] when they apply for marketing authorisation of a newly developed medicine.

Hence, a link between medicinal product and patent exists in the US. The following section describes how we utilise this linking of information in the US to construct a unique dataset containing a similar link for the EU.

MEDICINAL PRODUCTS AND THE PATENTS PROTECTING THEM ARE LINKED IN THE US

A mapping of medicinal products and the patents and patent extension schemes protecting these products exists in the US. Moreover, due to the reporting requirements[1], the available data on patent protection in the US pharmaceuticals market extends to cover the many-to-many relationship between the products and the protection schemes.

Consequently, if a pharmaceutical company offering a medicinal product has decided to launch a particular product both in the European market and in the US market, and if the medicinal product in question can be identified in both European and US regulatory approval records, a European product can – through its US counterpart – be connected to a US patent protecting the US-approved version of the European product.



INTERNATIONAL PATENT SYSTEM

Once a European product has been linked to a US patent, one can use so-called patent family connections to identify international patents that protect the same technical invention as an identified US patent.

Using the European Patent Office's (EPO) worldwide patent information database PATSTAT[2], the US patent's family identification can be used to obtain and identify European patents that protect the same technical invention – and as such the same pharmaceutical or medicinal product. In this way, a mapping of products and patents can be created for European medicinal products that are launched in both the US and Europe and that are patent-protected.

ADDITIONAL PROTECTION SCHEMES

To compute effective protection periods, one has to account for additional protection schemes and term extensions that might be in force. Once the European patents covering a European medicinal product have been identified, supplementary protection certificates extending the terms of these patents can be identified in the EPO's PATSTAT database and can be factored into the effective protection period.

Further protection schemes granted, namely orphan medicinal product designations for rare diseases and exclusivity extensions for compliance with an paediatric investigation plan, can be identified via the medicinal product's trade name via the EMA website[3].

1 The Orange Book is the common name for the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations". It is a publication and an online database which identifies medicinal products and their related patents and exclusivity information in the US.
2 Spring 2017 online version. See https://www.epo.org/searching-for-patents/business/patstat.html#tab-1
3 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

Patent families and the international patent system

LINKS BETWEEN INVENTIONS ACROSS GEOGRAPHIES

Facing the lack of available links between medicinal products and patents in Europe, the US regulatory requirements for disclosure of such links when applying for marketing authorisation can be used to identify the respective connections at least for medicinal products that are launched in both Europe and the US under the same trade name.

Once a medicinal product launched in Europe has been identified in US records, the US patents protecting the medicinal product's US counterpart can be identified. Using the respective patent title's patent number, the patent can be identified in the EPO's PATSTAT database.

Each US patent can be identified by its unique patent number and patent application identifier. Moreover, each patent is connected to a so-called patent family. Generally, a patent family can be defined as "*a collection of related patent applications that is covering the same or similar technical content. The applications in a family are related to each other through priority claims.*"[1]

In essence, this means that a properly defined patent family[2] can be used to identify the worldwide population of patents protecting the same invention based on the fact that they refer to a joint initial 'priority' application. Hence, the European patent family members related to a US patent represent the patents protecting the very same invention in Europe – and thus also protect the medicinal products using said invention.

Priority claims[3]

When trying to protect a patentable invention in more than one country, applicants can make use of so-called priorities. Once an initial application has been filed with a patent office, subsequent applications with other patent offices can claim the first application as priority. If claimed validly, the applications will be linked and events occurring in the interval will not invalidate the second application.

International patent system

The Patent Corporation Treaty (PCT), ratified by 152 countries, and the Paris Convention scheme are the pillars of the international patent system that allows applicants to "*simultaneously seek protection for an invention*"[3] in its member countries.

Different paths are open to applicants:

- An applicant can use the Paris Convention system and file separate patent applications in different countries referring to the first of these as a priority filing.
- An applicant can use the PCT system and file a single application through the international system referencing an initial local application as the single priority.

PCT applications then enter a national phase, where local patent offices decide about grants based on an international patentability assessment.

DOCDB simple patent families

The definition of a patent family can be rather wide or narrow, depending on the extent of the direct or indirect priorities considered. The definition of a family might differ, for instance, based on whether applications are considered when they share any priority or only when they share all priorities.

The EPO maintains two definitions of patent families:

- INPADOC extended patent families covering similar technical content, and
- DOCDB simple patent families covering the same technical content.

This study uses the narrower definition of a DOCDB simple patent family to identify relevant patents. Patents belonging to such a family have the exact same priorities and are subject to expert quality control.[5]

European patents

As of spring 2017, a European patent is "*a 'bundle' of individual national patents. […] For the patent to retain its protective effect and be enforceable against infringers, it must be validated nationally*".[4] Currently, the EPO counts 38 member countries, meaning that a single US patent can have up to 38 different European counterparts in addition to corresponding national-level patents.

1 EPO (2017), *What is a patent family?*
2 Here: DOCDB simple patent families.
3 See for instance the WIPO's PCT FAQ at http://www.wipo.int/pct/en/faqs/faqs.html
4 EPO (2015), European Patents and the Grant Procedure.
5 Martinez (2010), Insight into different types of patent families.

Iterative matching procedures and compiling European data

ISSUES OF IDENTIFICATION

While medicinal products are frequently launched in different markets across the world, pharmaceutical companies often apply different trade names or specifications to the same medicinal product in different countries.

A medicinal product launched in both the US and in Europe might have the same name in both regions, a slightly amended name in one of the regions, a localised/translated name in one of the regions, or even completely different trade names in the two regions. The medicinal product called Regaine in Europe is e.g. marketed as Rogaine in the US, the medicinal product Champix is called Chantix in the US, while the medicinal product Glivec is called Gleevec in the US. In addition, the same pharmaceutical might be launched by different pharmaceutical companies (related or not). Different labelling and identification obligations might further differentiate the ways that one and the same pharmaceutical might be branded in various markets.

DATA ANALYSED

To nonetheless be able to match products from US and European records, iterative string-based matching procedures are applied to the different sets of records.
The data analysed to obtain the maximum number of product-level matches encompasses:

- 33,620 US FDA-approved new drug approval applications encompassing 6,572 different trade names
- 26,506 drug approval applications through the mutual recognition procedure within the EU, differentiated through variation on the trade name/product variation level
- 972 trade name-differentiated drug approval applications through the centralised marketing authorisation procedure steered by the European Medicines Agency (EMA)
- 1,497 paediatric investigation plan (PIP) proposals documented by the EMA
- 1,880 applications for rare disease (orphan medicinal product) designations documented by the EMA

European Medicines Agency (EMA) data
Since 1995, the EMA has been responsible for evaluating, supervising and ensuring the safety and high quality of medicinal products in the EU and the EEA.

This study uses the following EMA data:

- Applications for an authorisation to market a product, varying on the trade name level
- PIP applications for active substances, partly connected to trade names
- Orphan designation applications for active substances and indications, partly connected to trade name

DATA MATCHING APPROACH

Final data compilation is achieved using an iterative matching procedure. European applications for authorisation to market a product are matched to US authorisation applications using the European products' trade names and active ingredients.

In a first step, a product is matched to the trade name that constitutes the longest sequence of alphanumerical characters which in its entirety and exact order can be identified within the reciprocal trade name. This procedure is repeated for the active substances listed as ingredients in the medicinal product.

In a second step, the matching result is reviewed on a case-by-case basis. The combination of matched names and substances is then used as multi-item primary code to combine the product and patent databases. This approach has the advantage of identifying pairs of medicines even though the sequence of alphanumerical characters constituting their trade name in the records might include additional information (e.g. dosages or administration forms) or be subject to name extensions or modifications.

PATENT DATA

Once US patents have been linked to European products, the population of distinct US patents can be identified in the patent data available on PATSTAT. Subsequently, US patent numbers are matched with their corresponding DOCDB[1] simple patent family identifier. Finally, European patents are added by forming all pairwise combinations between all European regional and national patent family members and the DOCDB simple patent families protecting a medicinal product.

PIP and orphan designation data are matched to the data in an additional step. Here, only approved and compliant applications are kept. The link between an application and a medicine is completed using the medicinal product's trade name.

1 See previous page, Martinez (2010), Insight into different types of patent families and https://www.epo.org/searching-for-patents/technical/docdb.html#tab-1

Dataset description: levels of variation in effective protection data[1]

DATA SOURCES USED

The present study generally uses three distinct categories of data:

- Regulatory and medicinal data on medicinal products in Europe
- Patent protection and filing data (incl. SPCs) related to medicinal products in Europe
- Linked patent and medicinal product data (incl. exclusivities) on medicinal products in the US

EUROPEAN DATASET

Regulatory data on medicinal products in the European market mainly consist of authorisation data and exclusivity extension data. Data on the centralised marketing authorisation procedure, on rare disease designations, and on paediatric investigation plans are obtained from the EMA.

The EMA marketing authorisation data contains information on different medicines as identified by the trade name that the medicines are marketed under. Usually, the following information items are available per medicinal product:

- Trade name
- EMA product number
- Active substances and generic or common name
- ATC codes
- Authorisation applicant
- Application status
- Authorisation date (if applicable)
- Pharmaceutical indications of the medicine
- Flags for orphan, generic or biosimilar medicinal products and for exceptional circumstances.

EMA PIP data contains:

- Trade name (if applicable)
- Active substances
- Decision date, number and outcome
- Pharmaceutical form and route of administration
- Diseases/conditions targeted
- Therapeutic area
- Date and outcome of compliance assessment

The mutual recognition authorisation data encompasses the following information items:

- Trade name
- Application number
- Active substances
- Authorisation applicant
- Authorisation status
- Authorisation date (if applicable)

EMA orphan designation data contains:

- Active substances
- Diseases/conditions targeted
- Decision date and outcome
- Trade name (if applicable)

The relevant PATSTAT patent data contains:

- Patent filing and application identifiers
- Authority receiving the application filing
- Type of IP protection
- International application and phase flags
- Patent family numbers (DOCDB/INPADOC)
- First filing and priority dates
- Patent family size
- Patent and family-level citations
- Applicants and inventors
- SPC filings and legal events per patent application

Data	Source	Maintained by
European Marketing Authorisations (centralised)	European public assessment reports	EMA
Marketing Authorisations in Europe (mutual recognition)	MRI	HMA
European Exclusivity Extensions	Paediatrics, Rare disease designations	EMA
European Patents	PATSTAT	EPO
US Drug Approvals	DrugPatentWatch	Private
US Patents	DrugPatentWatch	Private

1 For further description of the dataset see appendix to chapter 2.

Strengths and weaknesses of the data compilation approach

A comprehensive dataset encompassing European medicinal products, patents and additional exclusivity rights is not feasibly available. The compilation of such a database by combining data from different sources therefore inherently comes with a set of caveats and drawbacks. This page illustrates some of these concerns.

RISK FACTOR: MISMATCHED DATA FRAGMENTS

The employed data matching approach relies on identifying medicinal products by their trade name in various databases. If names coincide only in part, or if products sold under the same name differ in their pharmaceutical usage and effect, mismatches can occur, e.g. linking a European product and a US product that do not actually belong together.

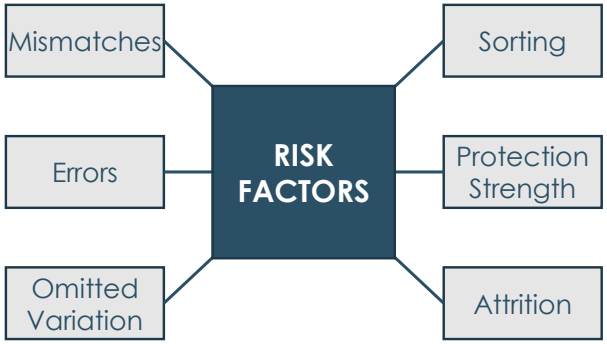
Case-by-case reviews and multi-key merges are used to mitigate this risk factor.

RISK FACTOR: REPORTING ERRORS AND MISSING VALUES (ESP. PATENT DATA)

The final dataset uses data that come from different and in part aggregated sources. The different source files use diverging formatting and coding practices and are subject to varying and at best limited amounts of quality control. Some information items vary across jurisdictions and within jurisdictions over time. Data is subject to publication lags, aggregation errors, and displays missing values.

RISK FACTOR: UNOBSERVED VARIATION

Exclusivity protection depends on the different IP protection schemes that are applied and connected to a specific product or patent. Unreported patents or patent term extensions would therefore lead to unobserved exclusivity that may bias the results of this study. In a worst-case scenario, differences in reporting regimes across time, countries or types of medicinal products might lead to clustered errors and skewed data that leaves important parameters unobserved.



RISK FACTOR: ATTRITION

While recursive and iterative matching may lead to mismatched, and in that sense additional but invalid observations on the one hand, the same procedure can also lead to superfluous attrition in the data-joining procedures. Narrow definitions of patent families and further constraints on data that is allowed to match can in some cases lead to the exclusion or non-reporting of observations that would actually qualify for inclusion. This means that in being conservative in our data matching procedure, we might exclude some observations due to doubt as to whether they are valid.

RISK FACTOR: SORTING

This study only includes medicinal products that are launched and identifiable in both Europe and the US. While this constraint is imposed for technical reasons, it might lead to a sorting bias among the pharmaceuticals considered. On the one hand, there may be sorting by profitability so that the medicines included in the sample are on average more successful than the ones excluded. This in turn might impact the exclusivity and patenting strategies employed by the respective companies. On the other hand, additional sorting factors, such as lifestyle, social security schemes, prominence of diseases etc., may impact the launch of medicinal products but also other aspects such as medicine naming practices that have a bearing on the matching outcome.

RISK FACTOR: PROTECTION STRENGTH AND INCENTIVES

Using economic theory, pharmaceutical companies can be expected to behave according to profit maximisation objectives. In consequence, they have incentives to extend legal exclusivity for as long as possible. To this end, they might take out additional patents protecting other inventions relating to the product or IP rights that may protect the product in question with a lower 'legal' strength[1]. These IP rights might be subject to invalidation proceedings or in other fashions cease to maintain effective protection. However, weaker titles cannot necessarily be separated from stronger ones. As such, exclusivity might no longer effectively be the case – even though nominal protection is still in place.

1 If the patent is challenged in court by e.g. a generic company, it might not hold up.

The effective protection period has decreased over time, when excluding secondary patents as well

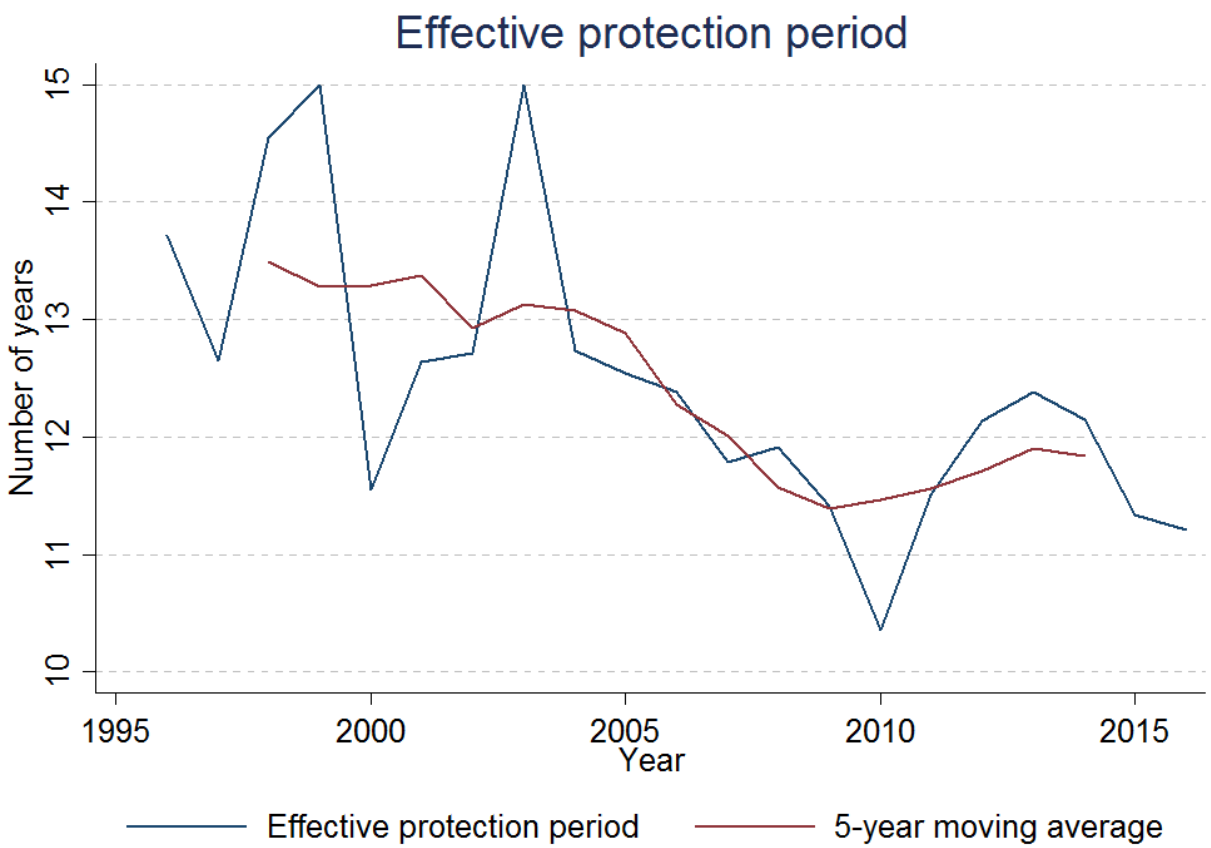
The figure to the right depicts the development of the effective protection period, when excluding secondary patents. The effective protection period has been falling since the 1990s from a level of around 13.5 years to around 12 years by the end of the sample period. A fall of around 1.5 years

Effective protection period
= date of last protection to expire
– date of marketing authorisation

Previously the effective protection period when *including* secondary patents was reported. It showed a drop from around 15 years to around 13 years. Hence, a fall of around 2 years.

As such, when excluding secondary patents the conclusion of a fall in the effective protection period stands, however the fall is slightly smaller. Not surprisingly, the effective protection period is shorter, when excluding secondary patents.

Average effective protection period in Europe, when excluding secondary patents, 1996-2016



Note: Based on the unique dataset described in the appendix to chapter 1 and 2. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with a development time below zero years are not included in the figure. The sample consists of unique combinations of trade name and country, i.e. each product is present in the sample once for each EU member state in which it has obtained a marketing authorisation. This is imperative when analysing protection periods as the effective protection period might differ between countries because of differences in marketing authorisation dates, patents and SPCs. The 5-year moving average is calculated as the average of the two years before and after a given year as well as the value in that year. Secondary patents are excluded.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI.

Datasets used in the report (1/2)

The following contains a description of the two datasets utilised in the present study.

IMS DATASET

One dataset stems from IMS and has been provided by the European Commission. The dataset contains all medicinal products sold in Europe. Variables included are e.g. drug name, launch date (both international and in a given country), sales volume and turnover as well as molecule of the drug. When using the IMS dataset analysis is mainly carried out on the molecule level[1].

The IMS dataset is used to undertake the econometric analysis of launch in section 2.2.

The unedited IMS dataset contains 310,590 observations. Each observation constitutes a product introduced in a country. The time period of product introductions present in the dataset is 1900 to 2006. However, scrutinising the data, the further back in time, the less reliable the data seems.

Keeping only unique molecule-country combinations for molecules having first international launch in the period from 1st January 1996 to 31st December 2015 leaves us with 8,102 unique observations. These cover a total of 907 unique molecules.

The pricing analysis in section 2.3 likewise utilises the IMS dataset. However, here the unit of interest is the product. Generic entry is identified by finding entry of new products, containing the same molecule as the first product[2].

The subset of the IMS dataset used for the econometric analysis in section 2.3 is highly restricted. This is the case, as analysis of the volumes sold and the revenue from sales revealed several problems and unexplainable variations across years.

As such, to ensure credibility of the data, the subset had to be restricted only to contain capsule products. The final dataset used in section 2.3 contained 3,500 observations covering around 600 medicinal products. The data on sales revenue and volume covers the quarters from 4th quarter 2013 to 3rd quarter 2016.

UNIQUE STUDY DATASET

The other dataset is a unique dataset compiled from several sources, by Copenhagen Economics. It contains information regarding specific products, their marketing authorisation date, patents and SPCs. When utilising this dataset analysis is mainly carried out on the product (and country) level.

The dataset contains products authorised either by the centralised procedure or the mutual recognition process with a marketing authorisation in the period spanning from 1996 to 2016.

The point of departure is the EMA dataset[3] on centrally approved products. This dataset is merged with the MRI dataset[4] on products approved through the mutual recognition procedure.

As there is no direct link between products and patents in the EU, it has been necessary to utilise an American database (Drug Patent Watch) to obtain patent information on the products in the combined dataset.

In the US, the Orange Book[5] contains information linking a product with the patents protecting the inventions utilised in it.

By identifying the product names found in the EMA dataset on centrally approved products and the MRI dataset on mutually recognised products, in the US Orange Book it has been possible to identify the patent families.

Through PATSTAT it was possible to use the patent families to identify European patents. This made it possible to create a dataset with products authorised in the European Union either centrally or through the mutual recognition procedure and their related patents and SPCs.

For a product to be included in the final dataset it must be the case that it was possible to identify the same product in the US dataset, as the US data is what links a product and its related patents.

In some instances a medicinal product might have a different name in the EU and the US. For some products these differences are small, while for others the names might be very different. The medicinal product called Regaine in Europe is e.g. marketed as Rogaine in the US, the medicinal product Champix is called Chantix in the US while the medicinal product Glivec is called Gleevec in the US.

1 For a further description of the IMS dataset and the molecule focus, see section 2.2.
2 See section 2.3.
3 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124
4 http://www.hma.eu/mriproductindex.html
5 The Orange Book is the common name for the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations". It is a publication and an online database which identifies medicinal products and their related patents and exclusivity information in the US.

Datasets used in the report (2/2)

To make sure the dataset includes as many products as possible, an iterative string-based matching algorithm is used. This procedure makes sure that in spite of small differences in names between the US and EU, the product can be included.

The data analysed to obtain the maximum amount of product level matches encompass:

- 33,620 US FDA approved new drug approval applications encompassing 6,572 different tradenames.
- 26,506 drug approval applications through the mutual recognition procedure within the EU, differentiated through variation on the tradename/product variation level.
- 972 tradename-differentiated drug approval applications through the centralised marketing authorisation procedure steered by the European medicines agency (EMA).
- 1,497 paediatric investigation plan (PIP) proposals documented by the EMA.
- 1,880 applications for rare disease (orphan medicinal product) designations documented by the EMA.

Conducting the above described matching procedure across sources creates the unique study data utilised in the present report. This dataset encompasses 558 unique products. When looking at the number of unique combinations of countries and products this gives a total of 7.130 combinations.

This is the information utilised when calculating the *effective protection period*[1].

The dataset containing information at the product level is used to create most graphs in chapter 1. It is likewise utilised to create the graphs in chapter 3.

For the econometric analysis in section 2.1 the data is consolidated at the country level. Here it is merged with information on GDP, spending on pharmaceutical R&D, etc.[2] The sources used to obtain information at the country level, besides the aforementioned data on medicinal products and patents, are OECD and the World Bank.

The dataset with countries as the unit of analysis is the dataset used to analyse the impact on innovation in section 2.1.

1 The period from marketing authorisation until the last protection scheme expires.
2 See section 2.1.

Details on the unique dataset compiled by Copenhagen Economics for this study

The table to the right reports information about the unique dataset compiled by Copenhagen Economics for this study.

The dataset contains 558 unique tradenames. This covers 465 unique molecules. As such there are some products which have different tradenames, but contain the same molecule. This is not uncommon for medicinal products[1].

Of the 558 unique tradenames, 45% have an SPC in at least one country.

Of the 465 unique molecules, 50% have an SPC in at least one country.

As patents and SPCs are granted at the national level, the unit of observation in the dataset used to calculate e.g. the effective protection period, is unique tradename/country combination. This means that a given product has an observation for each country in which it is launched. There are 7,130 unique tradename/country observations in the dataset. Of these 17% have an SPC.

Correspondingly, if focusing on molecules instead of tradenames, there are 6,280 unique molecule/country combinations in the dataset. Of these 18% have an SPC.

Number of observations in the unique dataset

Unit	Number
Unique tradenames	558
Unique tradenames with an SPC in at least one country	251 (45% of the above)
Unique molecules	465
Unique molecules with an SPC in at least one country	231 (50% of the above)
Unique tradename/country combinations	7,130
Unique tradename/country combinations with SPC	1,190 (17% of the above)
Unique molecule/country combinations	6,280
Unique molecule/country combinations with SPC	1,138 (18% of the above)

Note: Table reporting information on the unique dataset compiled and used in the study.
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA and MRI.

1 See e.g. case study on Cometriq/Cabometyx on pp. 336-337.

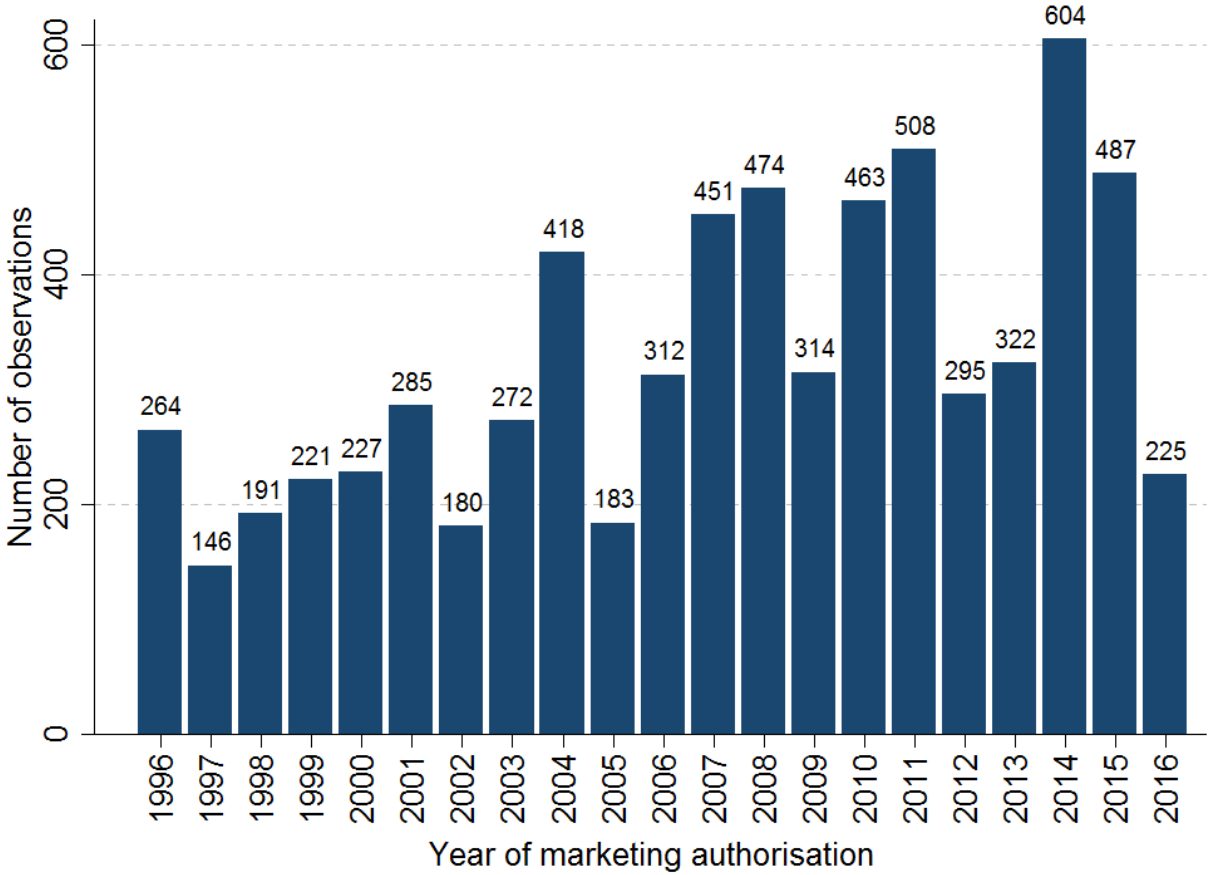
Number of observations per year in the unique dataset

The graph to the right depicts the number of tradenames by year, for the unique dataset, used for the calculation of development time and effective protection period.

A medicinal product is counted in the year it obtains marketing authorisation.

Not surprisingly, the number of observations vary between years. However, there is a tendency for more observations towards the end of the sample period.

Number of tradenames by year of marketing authorisation, 1996-2016



Note: Graph depicting the number of observations by year in the unique dataset, used for calculation of development time and effective protection period.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

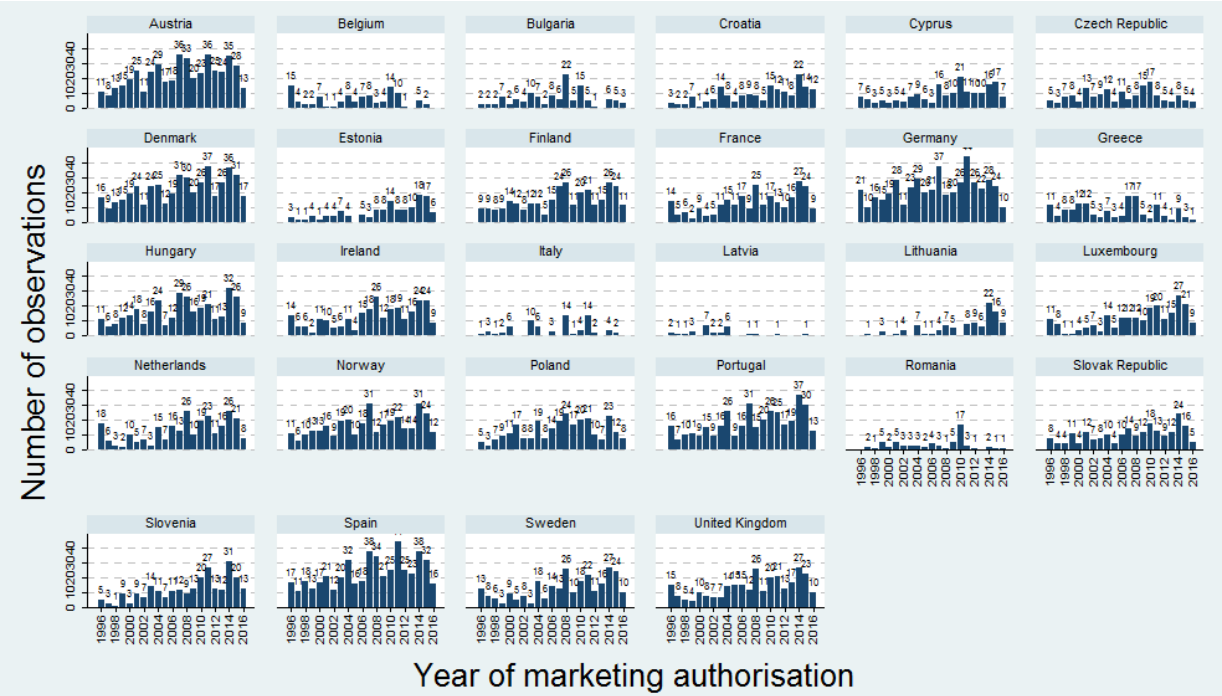
Number of observations per year and country in the unique dataset

The graph to the right depicts the number of unique tradenames identified in each country, in the sample period 1996-2016.

Some of the countries depicted in the graph, joined the EU during the sample period. However, as this information is used to analyse a general picture regarding development time and effective protection period, over time, they have been included in all years, where there are observations available. Norway has likewise been included as a member of the EEA.

In the analysis in chapter 2, only a subset of the countries depicted in the graph to the right is included. This is due to e.g. data availability of control variables[1].

Number of tradenames by year of marketing authorisation, for each country, 1996-2016



Note: Graph depicting the number of observations by year and country in the unique dataset, used for calculation of development time and effective protection period.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 See chapter 2 appendix for more information on this.

Details on the IMS dataset used for the availability analysis

The IMS dataset is used for the availability analysis in section 2.2. It contains 907 unique molecules having first international launch in the period from 1st January 1996 to 31st December 2015. When including the country dimension, this gives 8,102 unique molecule/country observations.

Unit	Number
Unique molecules	907
Unique molecule/country combinations	8,102

The table to the right reports the number of unique molecules by ATC code for the molecules in the sample with only one ATC code.

The dataset contains most molecules with the ATC code 'Antineoplastic and immunomodulating agents' and fewest molecules with the ATC code 'Systemic hormonal prep, excluding sex hormones'

Number of observations in the IMS dataset by ATC code

ATC code	Number of unique molecules*
Alimentary tract and metabolism	105
Blood and blood forming organs	38
Cardiovascular system	50
Dermatologicals	56
Genito urinary system and sex hormones	37
Systemic hormonal prep, excluding sex hormones	11
General antiinfectives for systemic use	93
Antineoplastic and immunomodulating agents	117
Musculo-skelatal system	39
Nervous system	88
Antiparasitic products	16
Respiratory system	41
Sensory organs	34
Various ATC structures	42

*Note: Table reporting information on the IMS dataset used in the study. * Includes only the 767 molecules which only has one ATC code in the dataset.*
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

* For molecules with only one ATC1 code.

Copenhagen Economics CE

CHAPTER 2

Analysis of the overall economic effects of incentives and rewards and their impact on innovation, availability and accessibility of medicinal products

Outline of Chapter 2

2.1 Impact on innovation

2.2 Impact on availability

2.3 Impact on accessibility

2.4 Pricing drivers

2.5 Effect on generic medicines and fiscal sustainability of health systems

Chapter 2 – Main conclusions

INNOVATION

Using a dynamical panel data model for the years 1996 to 2014 the impact of changes in the effective protection period on pharmaceutical innovation in the European Union is analysed. Three main conclusions are drawn from the econometric model.

1. The average effective protection period that medicinal products enjoy in a country is found not to have a statistically significant effect on the level of spending on pharmaceutical R&D in that country.

2. The average effective protection period for medicinal products in the other EU countries with which a given country trades the most in pharmaceuticals is found to have a positive and statistically significant effect on the level of spending on pharmaceutical R&D in that country; i.e. the protection period provided in foreign markets where companies sell their products seems to have a positive impact on domestic spending on pharmaceutical R&D.

3. The wealth of the other EU countries with which a given country trades the most in pharmaceuticals seems to have a positive impact on domestic spending on pharmaceutical R&D; i.e. the wealth of the foreign nations in which companies sell their medicinal products seems to have a positive impact on domestic spending on pharmaceutical R&D.

AVAILABILITY

To assess the availability of pharmaceuticals, the launch delay of new innovative molecules is analysed by estimating duration models.

In general, new molecules are only launched in half of the EU member states within 20 years from the first international launch. There is large variation in the launch delay across the EU Member States.

The time until 25% of new molecules are launched varies from 0.8 to 6.4 years across Member States, while the time until 50% of new molecules are launched varies from 2.6 years to more than 20 years for some countries.

Cancer medicines are generally launched earlier and in more countries than medicines for any other kind of illness.

We do not identify a statistically significant effect of the domestic effective protection period on the probability of product launch.

We do find that countries with a large GDP and population have more launches of new pharmaceutical molecules and have them earlier, than countries with smaller GDP and population. This suggests that, launch decisions to a certain degree are guided by market attractiveness.

ACCESSIBILITY

For a medicinal product to be accessible to a given patient, it not only has to be available in the given country, it likewise has to be affordable to the payer. Hence, accessibility is analysed using a price perspective. The section analyses the prices of originator and generic products, before and after the first generic entry into the market.

Prices for generic medicinal products entering the market after the original medicinal product loses exclusivity are on average around 50% of the price of the original medicinal product over the first five quarters after the generic entry.

On average, the prices of originator medicinal products decrease by 40% during the period six quarters prior to and five quarters after the loss of exclusivity.

HEALTH BUDGETS

Scenarios for a change in spending between originator and generic pharmaceuticals are explored. As an illustrative example, we find that if it is possible to change 10% of total spending on pharmaceuticals within the European Union, from originator products to the corresponding quantity of generics, it will yield savings of approximately USD 12.4bn. This corresponds to 0.7% of the total expenditure on healthcare within the EU. This example can be extrapolated further, according to the percentage change in spending from originator products to corresponding generics.

This insight is based on scenario analysis relying on a number of assumptions to counter the very complex nature of such a scenario.

2.1 IMPACT ON INNOVATION

The effects of IP rights and incentives on R&D levels in pharma (1/4)

EXISTING EVIDENCE

There is a vast body of literature studying the relationship between pharmaceutical incentives (as well as IP rights) and stimulation of domestic innovation. However, the results are ambiguous, as the following literature review will demonstrate.

Qian (2007) exploits cross-country variation in the IP framework over time and matching techniques to study whether national patent protection spurs domestic innovation.

The study utilises information on citation-weighted US patent awards, domestic pharmaceutical R&D and pharmaceutical industry exports as proxies for domestic innovation within the pharmaceutical industry.

The data used covers the period from 1978 to 2002 for 26 countries. To study the effect of the IP regime, the paper analyses the effect of a country going from no pharmaceutical patents to the implementation of national laws providing this form of IP protection. To circumvent the issue of different countries implementing national IP regulation that is different in scope, the author matches countries that implement a certain extent of IP regulation with countries where regulation to this extent is already implemented. A fixed-effects analysis is then carried out for these country pairs.

The author finds that, in itself, national patent protection does not stimulate domestic innovation. This conclusion is robust across model formulations. However, in countries with higher levels of education, economic development and economic freedom, patent protection seems to accelerate domestic innovation – i.e. pharmaceutical patents have more effect on innovation the more developed the country is.

Furthermore, the author finds that there seems to be an optimal level of IP rights beyond which further bolstering is detrimental to domestic innovation. This optimal level relates to the period of the patent protection period. However, the author does not report what the optimal period seems to be, as this depends on other factors such as development, educational level and market freedom in the given country.

Sakakibara and Branstetter (1999) use the extensive Japanese patent reforms of 1988 to study how the R&D decisions of companies respond to changing R&D regime. The study utilises interviews and a sample of 307 Japanese firms.

On the basis of the interviews the authors find that companies recognise that the reforms expanded the patent scope in Japan.

Studying both companies' R&D spending and innovative output, measured as claims per patent, the authors are unable to decisively identify a statistically significant effect of the patent reforms.

The effect on R&D expenditure is close to or equal to zero, while it does appear that the patents taken after the reforms have more claims per patent and hence can be said to be more "idea-rich" than cohorts before the reforms.

Pazderka (1999) studies two reforms undertaken in Canada in 1987 and 1992. The two reforms reinstated full IP protection for medicinal products, after almost two decades of compulsory licensing.

Comparing interindustry trends within Canada, intercountry trends within the pharmaceutical industry as well as Canada's share of foreign R&D spending of US-owned multinationals, the author finds that the reform of 1987 had a significant positive effect on pharmaceutical R&D spending. The reform of 1992 was too close to the end of the study for any conclusion to be drawn.

In a study with a somewhat different but still related aim, **Kumar (1996)** examines the determinants of overseas R&D activities by US multinational enterprises. The author finds that larger markets, technological resources and infrastructure influence the choice of R&D placement.

As such, it seems to be the case for much of the literature in this field that it has proven difficult to show a direct relationship between the protection offered by IP rights and incentives in a country and the measures of innovation in the country (e.g. R&D spending levels).

The effects of IP rights and incentives on R&D levels in pharma (2/4)

IP PROTECTION AND SPENDING ON R&D

As the literature study in the previous section shows, detecting a direct empirical relationship between the extent of IP protection and the amount of innovation undertaken in a given country has proven difficult.

In theory, the effect of IP protection is likewise difficult to predict. The IP rights conferred by a patent prevent others from using the protected innovation without the consent of the patent owner. Seen in isolation, that might deter or postpone innovation, because a certain time period has to elapse before others can use the new knowledge protected by the patent (for instance, in areas where innovation is cumulative, i.e. built directly on previous innovations).

However, without any rights to protect an innovation against uncontrolled use by others, innovators will be reluctant to invest in R&D in the first place, as the expected return on investment will be very uncertain and probably quite small or even negative if it is easy to copy the innovation.

On the other hand, an innovator applying for a patent must describe the innovation in great detail in the patent application. If the patent is granted, this document becomes publicly available. Hence, the patenting scheme has a built-in mechanism of knowledge-sharing through full disclosure. This mechanism may be conducive to innovation, as it entails everybody having access to all new knowledge created and patented.

This brief discussion has highlighted just a few aspects of the many opposing elements in IP protection and the incentives for investing in R&D.

In compiling the knowledge obtained from our literature review and the previous discussion, we believe that a range of econometric specifications can help to shed more light on the many nuances of the impact of IP protection and incentives on innovation.

R&D IN THE PHARMACEUTICAL SECTOR

The pharmaceutical industry is the most R&D-intensive sector in the world. In 2016, the sector's global spend on new R&D equalled 15% of sales[1].

R&D within the sector is highly risky and as a consequence some of the successful projects are highly profitable[2].

Several things have an influence on companies incentives' to undertake R&D. One of these is the profitability of the products that the inventions eventually lead to. The more profitable the products are expected to be, the better sense it makes to spend on the R&D process while still preserving a satisfactory return on investment.

The profitability of new medicinal products is likewise influenced by a broad range of elements. Among these is the period of protection from generic competition that new products enjoy.

During the period that a new medicinal product enjoys protection against competition from generics, the company is freer to set the price it prefers than it would have been had there been multiple generics with which to compete in the market.

This means that the longer the protection period a new product enjoys, the more profitable that product is likely to be to the company.[3]

According to this line of reasoning, a longer protection period for new products should have a positive effect on the R&D investments made by firms.

EFFECTIVE PROTECTION PERIOD

Following the reasoning in the previous section, when making their R&D decisions pharmaceutical companies should, among other things, be concerned with the period of protection from generic competition their new products can expect to enjoy.

The IP rights, incentives and rewards in the pharmaceutical sector consist of an extensive range of legal rights, extensions and schemes running in parallel. For instance, patents and SPCs run in parallel to, and independently of, market exclusivity (for orphan medicinal products) and data protection. These schemes have different periods, scopes and starting points.

The patent protection period begins when the company applies for a patent,[4] typically quite early in the development process. An SPC begins when the patent ends, while market exclusivity and data protection begin when a marketing authorisation is obtained and the product is ready for launch. This means that the scheme that protects the product at a given time depends on a combination of a wide range of factors.

1 European Commission, Industrial Research and Innovation, The 2016 EU Industrial R&D Investment Scoreboard, table 3.2 p. 57.
2 According to BIO, Biomedtracker and Amplion (2016), Clinical Development Success Rates 2006-2015, only 1 out of 10 products entering phase 1 of clinical trials makes it all the way to approval.
3 Unless the company seeks to earn back a fixed amount of profit on the product, in which case a longer protection period will not change profits but instead mean a lower price during that period. This is, however, in contrast to profit-maximising behaviour.
4 Or more specifically on the priority date of the patent.

The effects of IP rights and incentives on R&D levels in pharma (3/4)

However, continuing in the mind-set of understanding pharmaceutical companies as profit-maximising entities, what ultimately matters is whether the company can recoup their initial R&D investment and earn a return on investment. At the extreme, the period in which this can be done can be said to be the time running from marketing authorisation being granted until the last protection scheme runs out and generics can enter the market.[1]

The period from marketing authorisation being granted until the expiration of the last protection scheme, whatever the form, is known in the literature as the *effective protection period*.[2]

Effective protection period
The time from marketing authorisation is obtained until the last protection scheme expires and generics can enter the market.

The notion of the effective protection period being the term of interest is exceedingly important as this captures the interaction between all protection schemes as well as regulatory processes and authorisation procedures. This means that even though two member states have the same protection schemes on paper and running for the same period of time, the effective protection period may differ due to e.g. the propensity to grant SPCs and marketing authorisations.

Accordingly, in order to gain the most relevant insights into what matters in the R&D decision-making of pharmaceutical companies, we have examined the effect of the effective protection period on innovation.

Difference in protection across schemes
It is important to note here that the schemes for data protection and market protection protect against competition from generics in the sense that other companies cannot obtain a marketing authorisation using the data of the innovator when these schemes are in effect.

However, companies willing to undertake their own clinical testing to obtain their own dossier of data with which to seek marketing authorisation of the same medicinal product can lawfully do so if they do not infringe on any patents or SPCs.

This means that the market protection and data protection schemes do not protect against competition in the same way as a patent or SPC.

DIFFERENCES IN EFFECTIVE PROTECTION PERIODS

Most pharmaceutical companies sell their products in many countries around the world. In the EU there is a European agency for the evaluation of medicinal products, the European Medicines Agency (EMA). Applications for union-wide marketing authorisations can be handed in to the EMA, which forms an opinion on the basis of which the Commission decides whether or not to grant authorisation.

Much of the regulation governing the pharmaceutical sector is undertaken at the EU level. However, pricing legislation and reimbursement policies are still member state competences.[3] Moreover, a unitary patent does not yet exist within the union[4] and the granting of SPCs is likewise done at the national level.

This means that the previously mentioned *effective protection period* may differ between countries, even within the European Union, due to a range of factors, including institutional and regulatory differences.

EFFECTIVE PROTECTION PERIODS IN PARTNER TRADE COUNTRIES

As many medicinal products are sold in multiple countries worldwide, it is not only the characteristics of a single market that matter for the profitability of pharmaceutical companies, but rather the different characteristics of all the various markets in which they sell their products.[5]

As such, one might assert that what matters to pharmaceutical companies is not necessarily the extent of IP protection in their home country or the countries where their R&D and manufacturing activities are situated, but rather the IP protection schemes in the countries where they sell most of their products; i.e. the interaction between the extent of IP protection and market size in export markets may play a crucial role in influencing the R&D decision (the IP protection in the country where their R&D is situated, for example, may however be important, if, say, most of their competitors are situated in the same country).

There are two main pivotal observations which go to support this hypothesis.

1 When generics enter the market they usually do so at a price well below that of the innovator medicinal product. This creates competition pressure for the innovator, often resulting in a decrease in price or market share or both.

2 In the general literature regarding the subject effective patent life is often mentioned, but this applies only to the time that a pharmaceutical is protected by a patent (or SPC) and does not take regulatory protection periods into account.

3 See the Treaty on the Functioning of the European Union, Article 168(7) and Directive 2001/83/EC, Article 4(3).

4 Much work has been undertaken in this area, but ratification has not yet been obtained in all required countries and as such it is still unknown when or whether a unitary patent will come into effect.

5 Characteristics of markets in which the companies do not yet sell their products may also affect their future investment decisions if they have plans to expand their sales to more markets.

The effects of IP rights and incentives on R&D levels in pharma (4/4)

Firstly, through the findings in the existing literature, it can be seen that a relationship between domestic IP rights and innovation has not been clearly identified. At the same time, in several studies market size has been found to be a significant determinant of pharmaceutical companies' R&D activities. Combined with the economic theory that firms are profit-maximising entities, it follows that IP rights in some form should influence the R&D decision, as they effectively confer a period when higher profits can be obtained.

Secondly, the literature shows the estimated costs of bringing a medicinal product from the lab to the market of between USD 648m[1] and USD 2.6bn.[2] This means that for a pharmaceutical company to undertake the initial investment, the management must expect that, by bringing the product to the market, they can recoup the initial investment plus the costs of e.g. marketing and distribution, as well as ensure a satisfactory return on investment.

Bringing matters to a head, the profit a company can earn on a product depends on the interaction between the price obtained and the number of products sold. As such, to recoup a large investment, it takes either a lot of patients paying a small price, a few patients paying a high price, or some combination of the two.

The number of patients reached by entering the market of a given country depends on many factors. Two of the more important ones are the size of the population and market share.

The price a company can charge likewise depends on a range of things, one of these being the period of the effective protection period.

In such a situation, changing the protection period in a market where a company sells very few products may not improve profit enough to change the firm's investment decision, while changes in the protection period in markets where a company sells a lot of products may be more pivotal in driving the decision.[3]

Following this line of thinking, an element that should matter in a firm's R&D decision is the extent and period of IP protection in the countries where they sell the majority of their products. It thus necessarily follows that what might actually influence strategic decisions on pharmaceutical companies' R&D activities is market size and IP rights in combination.

WEIGHTED EFFECTIVE PROTECTION PERIOD

To study whether the assertion presented in the previous section can be found to have empirical merit, we construct a composite measure for each country in an attempt to describe the effective protection period in the other EU countries with which a given country trades the most.

We do this by weighting the mean effective protection period in a given year for the other EU countries with which a given country trades, by the fraction of total pharmaceutical exports that country received from the country of interest. We call this the composite variable.

Illustrative example: This means that if Germany sold 40% of its pharmaceutical exports to France and 60% to the UK in 2002, and the mean effective protection period was 14 in France and 16 in the UK, the weighted effective protection period variable would be 15.2 for the UK in 2002.[4]

It should be noted that, as we have data on the mean effective protection periods only for EU member states and the US, the trade weights are calculated based on the exports going to these countries.

The constructed composite measure is meant to capture changes in the mean effective protection period in the countries where most of the pharmaceutical exports from a given country are flowing.

The discussions in the previous sections would indicate that if the measure correctly identifies[5] and gives the most weight to the mean effective protection period in countries with the most important markets for the domestic pharmaceutical industry, there should be a positive relationship between the composite measure and the spending on pharmaceutical R&D.

However, the variable likewise provides interesting information on the effect of the changing size of pharmaceutical exports to the other EU countries with which a given country trades the most. This intricacy will be discussed at length in a later section.

1 Prasad, V. and Mailankody, S. (2017), Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval.
2 Di Masi, J. A., Grabowskib, H. G. and Hansen, R. W. (2016), Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs.
3 Provided that prices do not differ hugely between the two markets.
4 0.4*14+0.6*16
5 See Chapter 2 appendix for further discussion of this.

Data for the econometric model (1/2)

INNOVATION

The variable of interest in this section on innovation is the expenditure on pharmaceutical research and development in the EU member states. The variable is collected from the OECD database and reported in constant 2010 US dollars at Purchasing Power Parity (PPP).

Using the spending on pharmaceutical R&D as a measure of the innovation in a given country has its caveats. An important characteristic is that it is an input measure; i.e. it describes what is put into the R&D effort. The amount of money spent on R&D is, however, not necessarily linearly correlated with the amount of actual innovation happening in a given country. Some countries may be better or worse at utilising the resources spent.

In an attempt to utilise an output measure, previous studies have used measures such as citation-weighted publications and pharmaceutical exports. These likewise are not perfect measures of innovation, as a scientific publication and the citations thereof do not necessarily reveal whether the innovation is valuable, nor do changes in exports necessarily convey more than just information about changes in relative prices.

Finding the right measure of innovation can easily boil down to a rather philosophical discussion on what innovation really is. Is it the number of inventions, for instance, or the value of these inventions from a private or societal perspective?

We have chosen the input measure of spending on pharmaceutical R&D as the variable of interest when studying innovation. The preceding discussion is meant to highlight the fact that this choice is not straightforward and may influence the results of the final model.

COVARIATES

To control for confounding variables, we obtain information on a wide range of covariates.

Total expenditure on R&D is collected from the OECD database.[1] This covers both public and private spending. This is important, as in many countries the public sector is responsible for a large part of the R&D undertaken, mainly at universities and, in the case of pharmaceuticals, at hospitals. The variable is reported in constant 2010 US dollars at PPP. Using the information on spending on pharmaceutical R&D and total expenditure on R&D, we can calculate the amount spent on R&D in all sectors besides pharmaceuticals. This variable controls for whether the country is research intensive in general.

To work as a proxy for the educational level of the population, we use tertiary school enrolment as a percentage of the population, taken from the World Development Indicators. An educational variable with a more direct linkage to the pharmaceutical sector would have been preferred, but sufficient data coverage was not attainable. Nevertheless, the percentage of the population enrolled in tertiary education still provides us with valuable information as a proxy for the current educational level and not least for the future expected educational attainment level of the population.

Data on pharmaceutical exports is obtained from the United Nations Commodity Trade Statistics Database (UN Comtrade). The Comtrade database contains information on imports and exports as reported by statistical authorities in close to 200 countries or areas. It is the most comprehensive trade database available. From Comtrade we obtain information on the value of trade flows of physical goods between countries. Our area of interest is the trade flows of medicinal products; i.e. for each country we can identify by year which countries the pharmaceutical exports have gone to and their value.

1 The OECD data on expenditure on R&D is distributed by the International Standard Industrial Classification, Revision 4. The pharmaceutical industry is classified as D21: Pharmaceuticals, medicinal, chemical and botanical products and includes both public and private spending on any activity related to R&D within the pharmaceutical sector.

Data for the econometric model (2/2)

DATA COVERAGE

The final model, to be utilised later, relies on total expenditure on pharmaceutical R&D as the dependent variable and the control variables described in the previous section.

For the model to be able to make use of an observation for a country in a given year, data is needed for all included variables. If a variable has no value because of a missing observation, that observation is not used in the model for that particular country.

The information on pharmaceutical R&D is more sparse than e.g. information on trade flows. This puts some restrictions on the quantity of observations the model can successfully utilise (see the Chapter 2 appendix).

As for the data on the period of effective protection, this is available only for EU countries and the US. This means that other markets which are important to pharmaceutical firms, such as Japan, are not a part of the analysis.[1]

However, even though one country may have a missing value for a variable in one year, other countries may not. This means that the time period we observe differs between countries.

The issue of missing observations restricting the information in the model makes it more difficult to identify the effect of the independent variables. For a further review of the data, see the Chapter 2 appendix.

Purchasing Power Parity (PPP)
Using a variable reported in PPP corrects for the fact that the costs of goods and services in two countries are different.

In the hands of consumers, money is not worth more than what they can buy. Thus, if a banana cost USD 2 in country X and USD 4 in country Y, citizens in country Y need to hold twice the amount of wealth measured in dollars to be as rich as citizens in country X.[2]

PPP corrects prices between countries for this fact by comparing a "basket of goods".

This effectively makes e.g. GDP comparable across countries.

Constant prices
The growth rate of a variable measured in its nominal currency value over time is influenced by price inflation. In the case of GDP, this would mean that one would observe an artificially high growth rate if the series were not corrected for price inflation.

Using constant prices normalises amounts reported in nominal currency values in a given year to the same base year.

This effectively makes e.g. GDP comparable across time.

1 The data on effective protection periods is calculated from the unique dataset created for the purpose of this study. For more information on the dataset and its creation, see section 1.4.2 and the appendix for chapter 2.
2 Provided there is no trade.

The dynamic panel data model (1/2)

PANEL DATA

A panel data model exploits the fact that the data present is longitudinal. A longitudinal dataset tracks the same type of information for subjects over multiple time periods. In our case, the subjects are countries and the time period is years. The information we track is e.g. educational level, effective protection period and R&D (see previous data description).

One strength of panel data models using longitudinal data is that as we follow the same subjects over time, all so-called unobserved effects which are fixed across time (do not change over time) can be controlled for. In the case of countries, this could be e.g. inherent culture or historical and institutional factors.

This means that we are able to model individual dynamics across time. This is a unique capability of panel data models.

Due to the data restrictions of some of the included variables, the time period over which we can follow the countries varies. This means that we have a so-called unbalanced panel. This is important, as unless we choose a model that can incorporate this, we risk losing valuable information.

In many cases the current value of a variable depends on past realisations of that variable. In the case of a country, if one is e.g. setting up a model to explain GDP, the current value is of course heavily dependent on the value of GDP in past years. This means that in many cases it is pivotal to be able to include past values of e.g. the dependent variable among the control variables.

PERSISTENCE OVER TIME

In our case, where we are modelling the spending on pharmaceutical R&D in a given country based on a range of covariates, it likewise makes theoretical sense to include at least one lag of the dependent variable among the control variables.

When a company decides to undertake R&D in a country, certain investments must be made. The R&D must take place in some sort of location, a building or a lab, and the employees are in need of certain equipment. In the case of pharmaceutical R&D, this equipment can be quite specialised and rather expensive. Furthermore, employees, likewise often highly skilled in specific areas, must be hired. These individuals can sometimes be difficult to recruit and are very valuable once in the company. In addition, the R&D currently being undertaken is often the result of many years of previous investment in R&D. All of these facts taken together make it rather difficult, impractical and in many cases economically unsound to make large changes in R&D investment in the very short run.

As such, the decisions regarding spending on pharmaceutical R&D may exhibit some persistence over time, and the inclusion of at least one lag in the model thus has theoretical merit (see appendix).

DYNAMIC PANEL DATA MODELS

One of the pivotal but very technical requirements for regular panel data models is that the explanatory variables included in the model are all uncorrelated with the error terms across time. This is a rather technical explanation, but what it means for the model in practical terms is that it is not possible to include one or more lags of the dependent variable among the control variables. Hence, in a regular panel data model it would not be possible for us to include the lagged value of spending on pharmaceutical R&D as a control variable to control for persistence.

Instead of the regular panel data models, one can use so-called dynamic panel data models. These models allow for the inclusion of lags of the dependent variables.

In our case we utilise an augmented version of the Arellano-Bond (1991) model[1], outlined by Arellano and Bover (1995)[2] and later further developed by Blundell and Bond (1998)[3]. This model is also known as the system generalised method of moments (GMM) model.

Technique of the SYS GMM model

As a technical note, the model utilises the lagged first differences as instruments for the variables in levels included in the regression. In any given time period the model uses all available lags of first differences as instruments. This means that the model uses a different number of instruments in each time period, without loss of observation.

As such, this model utilises all available information in any given period, while preserving the number of observations utilised.

1 Arellano, M. and Bond, S. (1991), Some Tests of Specification for Panel Data: Monte Carlo Evidence and an Application to Employment Equations.
2 Arellano, M. and Bover, O. (1995), Another Look at the Instrumental Variable Estimation of Error-Components Models
3 Blundell, R. and Bond, S. (1998), Initial Conditions and Moment Restrictions in Dynamic Panel Data Models.

The dynamic panel data model (2/2)

SHORT- AND LONG-RUN EFFECTS

When working with dynamic panel data models, where one or more lags of the dependent variable are included as explanatory variables, care must be taken when interpreting the estimated coefficients.

When no lags are included, the estimated coefficient for a control variable is simply the effect on the dependent variable of changing the value of the control variable by one unit.[1]

However, if the model includes e.g. one lag of the dependent variable, a change in a control variable will have both a short-run (immediate) effect and a long-run effect on the size of the dependent variable.

The easiest way to think about this intuitively is by way of an example. If one is trying to model GDP, and in the regression one is controlling for e.g. education, the value of GDP in the previous period and a range of other things, there will be both a short- and a long-run effect from changing the educational level.

Increasing the value of the variable "education" will have the immediate effect of changing GDP in the same time period.[2] However, as GDP depends on the level of GDP in the previous time period, there will be a feedback mechanism in the next period through the lagged value of GDP.

This means that one must take the size of the coefficient of the lagged value of the dependent variable into account when interpreting the long-run effect of a change in a control variable.

The long-run multiplier

The long-run multiplier describes how much larger the cumulative long-run effect is compared to the short-run effect.

If the model includes one lag of the dependent variable and the coefficient of this is called α, the long-run multiplier is given by:

$$\frac{1}{1-\alpha}$$

This means that the closer the coefficient of the lagged dependent variable is to 1 (i.e. the more persistent the variable is), the higher the long-run multiplier will be.

The long-run effect of a change in a control variable with an estimated coefficient of β is thus given by:

$$\frac{\beta}{1-\alpha}$$

If the change in the control variable is permanent, the long-run effect can be interpreted as the expected permanent long-run increase in the dependent variable from a one-unit increase in the control variable.

LOG TRANSFORMATION

In the final regression model utilised in the next section, we have log-transformed the dependent variable, which is spending on pharmaceutical R&D. This is done both to normalise it and to reduce the issue of outliers.

When the dependent variable is log-transformed, the interpretation of the coefficients of the control variables changes. Because of the log transformation they signify so-called semi-elasticities. This means that the coefficient of a control variable signifies the percentage change in the dependent variable from a one-unit increase in the control variable. This goes both for the short- and long-run effects.

The long-run effect as semi-elasticity

Using the same notation as before, where α is the coefficient of the lagged dependent variable and β is the coefficient of the control variable, the long-run effect of a one-unit change in the control variable is calculated as

$$exp\left(\frac{\beta}{1-\alpha}\right)-1$$

and signifies long-run semi-elasticity.

1 There are various subtleties to this statement if either the dependent or the control variable (or both) is given in logs.
2 This is an illustrative example and thus does not necessarily have any empirical merit.

The dynamic panel data model provides three main insights

Using the dynamic approach described in the previous section it is possible to obtain a well-specified model for the period 1996 to 2014 using information for 20 EU member states.[1]

THE DATA

The results reported in the following sections are subject to the complexities and caveats encountered when creating the dataset. These primarily occurred when linking patent data with product data within the EU.

As described in section 1.4.2 and the appendix for chapter 2 this was possible through the link between products and patents which exists in the US. However, this likewise entails the products for which it was possible to find a link being only those with sufficiently similar names in the US and the EU.

Moreover, patents are linked through patent families shared on US and EU databases. As such, the accuracy of the calculated effective protection period reflects the degree to which patent families can be successfully linked and, similarly, include all relevant patents.

Only products approved through the centralised procedure or mutual recognition process could be included. Hence, the sample used to calculate the effective protection period across countries does not contain all medicinal products available in the EU.

The dataset is, however, a unique coupling of product and patent information and, as far as we are aware, the first of its kind within the EU.

MAIN RESULTS

The empirical model provides us with three main insights:

1 Domestic protection

The average domestic effective protection period cannot be found to have a statistical significant effect on the level of domestic spending on pharmaceutical R&D; i.e. the protection period in a given country does not seem to determine the spending on pharmaceutical R&D in said country.

2 Trade country protection

The average effective protection period for medicinal products in the EU countries with which a given country trades the most seems to have a positive significant effect on the level of domestic spending on pharmaceutical R&D; i.e. the protection period provided in markets where companies sell their products seems to have a positive impact on domestic spending on pharmaceutical R&D.

3 Trade country wealth

The wealth of the EU countries with which a given country trades the most seems to have a positive impact on domestic spending on pharmaceutical R&D; i.e. the wealth of the nations in which companies sell their medicinal products seems to have a positive impact on domestic spending on pharmaceutical R&D.

NUANCES AND ASSUMPTIONS

As is the case with all empirical studies utilising econometric models, the above-presented conclusions are based on some central assumptions.

Furthermore, the conclusions are not without nuances and further analysis undertaken has expanded the range of implications and insights derived beyond the main three reported here.

On the following pages, the further nuances, implications, insights and assumptions will be discussed in turn and at length.

1 The countries included are Austria, Belgium, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, the Netherlands, Poland, Portugal, Romania, the Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom. The remaining EU member states have not been included due to data coverage issues.

Main regression of the relationship between domestic spending on pharmaceutical R&D and the mean effective protection period (1/3)

DOMESTIC PROTECTION

That the average domestic effective protection period cannot be found to have a statistically significant effect on domestic spending on pharmaceutical R&D can be seen from the coefficient of the variable "mean effective protection period" in the table to the right. The variable is positive but miniscule and does not have statistical significance.

One possible explanation for this is that the individual home markets for pharmaceutical companies constitute a rather small share of their total sales.

For example, the company Novo Nordisk is based in Denmark, where it has its headquarters and where much of its R&D is still undertaken. However, Denmark constitutes only 0.4% of Novo Nordisk's total sales worldwide[1]. This exemplifies the fact that pharmaceutical companies are rather globalised and that home markets in many instances make up only a small share of total revenue.

As such, changing the protection period in Denmark and possibly increasing the value of the products sold there will have only a miniscule effect on the total revenue of Novo Nordisk. Changing the effective protection period in the other EU countries with which the given country trades the will have a far more pronounced effect.

System-generalised method of moments regression with spending on pharmaceutical R&D as the dependent variable, 1996-2014

Variable	Coefficient estimate[2]
Pharmaceutical R&D in the previous period	0.414***
	(0.155)
Education	0.433**
	(0.182)
Mean effective protection period	0.00156
	(0.0135)
Weighted mean effective protection period (composite variable)	0.0697**
	(0.0278)
Other R&D	0.437***
	(0.122)
Constant	-0.870
	(0.890)
Observations	187
Number of id	20
Standard errors in parentheses	
*** p<0.01, ** p<0.05, * p<0.1	

Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described in section 1.4.2. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with a negative development time are not included. Standard errors are in parenthesis. The 20 EU countries for which adequate data could be found are included in the regression. The overall conclusions are robust to the exclusion of all secondary patents.

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA and MRI.

1 Novo Nordisk Annual report 2017.

2 When interpreting the coefficient estimates it is important to note that the immediate numeric value cannot be compared directly across variables, as this is dependent on the unit in which the variable is recorded. For a further explanation on how to interpret the coefficients, see p. 171.

Main regression of the relationship between domestic spending on pharmaceutical R&D and the mean effective protection period (2/3)

Another possible explanation is that as we are analysing only European countries, the variation in the effective protection period may be limited. Many of the rules governing IP protection of pharmaceuticals are rather standardised across EU countries and have become so to a greater degree over time. As such, the lack of significance may reflect too little variation between countries to identify a significant effect. This is further explored by including the US, which is a very important market for pharmaceuticals, in the regression in a later section.

The fact that the home country effective protection period does not seem to have a significant effect in explaining the level of spending on pharmaceutical R&D within that country naturally leaves the question of what then does have an influence on the level of R&D spending.

It is outside the scope of the present study to independently analyse this issue. However, the regression presented on the previous page, as well as the results from the literature, can help to shed some light on it.

In the regression on the previous page, it can be seen that the education variable has a statistically significant influence on the amount of pharmaceutical spending within a country.

The variable "Other R&D" depicts the amount of spending on R&D in industries other than pharmaceuticals. This variable can be said to identify whether the general conditions are conducive to undertaking R&D in a given country. The better the general conditions (e.g. taxes, infrastructure, public-private partnerships etc.) support the undertaking and placing of R&D in a given country, the higher the spending on pharmaceutical R&D is likely to be.

These results are supported by results from the literature, which e.g. points to factors such as education, infrastructure, political stability and taxation as important drivers of the placement of R&D across industries.[2]

TRADE COUNTRY PROTECTION

That the average effective protection period for medicinal products in the other EU countries with which a given country trades the most seems to have a positive significant effect on the level of domestic spending on pharmaceutical R&D can be seen from the composite variable "Weighted mean effective protection period". The sign of the variable is positive and significant.

This indicates that, when making their R&D decision, companies are concerned with the amount of protection their medicinal products can enjoy in the countries to which they export the largest share of their products.

This suggests that the current amount of protection provided in their main markets influences the companies' expectations of future protection. Current R&D decisions made by the firm will not influence the actual stock of products for another 10 to 15 years.[1]

Following the example given above of Novo Nordisk, which had 99.6% of its total sales outside its home market of Denmark, the assertion that companies are more concerned with the protection period in the other EU countries with which a given country trades more than they are with this period in their home market has economic theoretical merit.

The numerical value of the composite variable entails a one-unit increase in the variable giving rise to a 7% increase in domestic spending on pharmaceutical R&D in the short run.

Using the calculation method presented in previous pages, the long-run effect can be calculated to be 12.6%. A one-unit increase in the composite variable will thus entail a long-run effect on domestic spending on pharmaceutical R&D of 12.6%.

The above increases of 7% in the short run and 12.6% in the long run are rather large. However, obtaining a one-unit increase in the composite measure would entail the mean effective protection period in all the other EU countries with which a given country trades the most increasing by one year.

Conversely, a one-unit increase may happen if there is a very large composition change in the EU countries to which a given country exports most of its medicinal products. If such a change happens from countries with very low effective protection to countries with very high protection, it is theoretically conceivable that such a change could produce a one-unit increase in the composite variable.

1 Depending on the development period.

2 See e.g. Demirbag, M. and Glaister, K. W. (2010) Factors Determining Offshore Location Choice for R&D Projects: A Comparative Study of Developed and Emerging Regions.

Main regression of the relationship between domestic spending on pharmaceutical R&D and the mean effective protection period (3/3)

However, as we are analysing European countries, the difference between countries in the mean effective protection period is diminishing over time.[1] Hence, for a change in the trade weights to drive a one-unit increase in the composite variable, the change would have to be rather drastic. As the amount of trade between EU countries does not in general vary immensely from year to year, this may also be an empirically unrealistic scenario.

The above-reviewed results pertain to EU countries. However, to the extent that companies outside the EU are equally globalised in their sales, the identified relationship will most likely hold for them. This would mean that a common change in protection within the EU would have an effect on the amount of pharmaceutical R&D undertaken within the EU. However it would equally affect the amount of R&D undertaken in countries exporting medicinal products to the EU.

For a change in protection to disproportionately influence the amount of pharmaceutical R&D undertaken in Europe as compared to the rest of the world, the EU countries would have to have a larger share of exports flowing to other EU countries than countries outside the EU have. This seems to be supported in the literature; e.g. in Ludivine (2015), where it is found that "*...the distance between the EU and importing countries has a negative impact on the trade in pharmaceuticals*".[2]

This means that if the effective protection period were to decrease in the EU, the amount of pharmaceutical R&D in the world would likely decrease. However, the reduction in R&D would disproportionately hit the European countries as an effect of the trade patterns.

TRADE COUNTRY WEALTH

That the wealth of the other EU countries with which a given country trades the most seems to matter to the R&D decision of companies cannot be seen directly from the regression on the previous page. The explanation for this assertion will be given on a following page.

CONTROL VARIABLES

Besides the two variables depicting the relationship between effective protection period domestically and abroad and the spending on pharmaceutical R&D, the regression contains three control variables.

These are: the spending on pharmaceutical R&D in the previous period, the level of education and the spending on other R&D.

Including the spending on pharmaceutical R&D in the previous period captures the idea that the spending is not completely scalable from year to year; i.e. it is quite unlikely that it would be attractive for a company to have very high spending on R&D in one year and spend almost nothing in the next year in a given country. It is to be expected that the spending will be somewhat dependent on the investments made in previous years. This may e.g. be because of investment in building, machinery etc. It may likewise be due to the fact that pharmaceutical R&D is a lengthy process and hence the R&D projects started today will take 10-15 years before they reach the market.[3] This means that the R&D pipeline today is greatly dependent upon decisions made in the past.
The positive significant coefficient of the variable depicting the spending on pharmaceutical R&D in the previous period supports the above-given assertion.

The level of education can be seen as an important variable for depicting the available stock of possible employees. To undertake pharmaceutical R&D, specialised and well-educated individuals are needed. The higher the stock of such individuals in a given country, the higher the possible amount of R&D. This is supported by the positive significant coefficient of the variable in the regression.

Finally, the level of spending on R&D in other industries besides pharmaceuticals has been included. This has been done as a so-called "proxy variable" to control for the general framework conditions for undertaking R&D.

The literature points to a range of factors influencing the level of R&D undertaken in a given country.[4] Instead of including each of these factors as separate variables and possibly flooding the regression with a wide range of variables, the level of spending on R&D in industries besides pharmaceuticals incorporates the framework in one variable. If the framework conditions in general are good, spending in other sectors should be high as well. If framework conditions generally are less favourable, spending on R&D in other industries can be expected to be low as well. Hence, the size of spending on R&D in other sectors functions as a proxy for general R&D framework conditions. The positive significant coefficient of the variable supports this assertion.

1 See appendix.
2 Blanc, Ludivine (2015), The European Pharmaceutical Industry in a Global Economy: What drives EU exports of pharmaceuticals?. Bruges European Economic Research Papers (BEER) 31/2015 [Policy Paper].
3 See p. 66.
4 See e.g. Demirbag and Glaister (2010) Factors Determining Offshore Location Choice for R&D Projects: A Comparative Study of Developed and Emerging Regions.

Including the US in the main regression changes the significance of the effective protection period in the country itself (1/2)

The table to the right reports the result of running the main regression reviewed on the previous pages, but now including the United States. As such, the table to the right reports the results when both the countries of the EU and the US are included in the analysis.

The US makes up almost half[1,2] of the total pharmaceutical sales in the world, which makes the US market a main driver for profitability in the sector and hence of interest to include in the analysis. It can be seen that the coefficient of "Mean effective protection period" is still positive but now it is significant. This means that by using this formulation one obtains the result that the domestic protection period seems to have a statistically significant impact on domestic spending on pharmaceutical R&D.

This could be due to the fact that, as previously mentioned, the US market constitutes almost half of the total value of the world market for medicinal products. At the same time, R&D spending in the US accounts for 54% of the world's R&D within pharmaceuticals.[3]

This means that for companies in the US, the domestic market is rather important. At the same time, most of their R&D is likewise undertaken domestically. Thus, if the protection period in the US increases, it is conceivable that the profitability of these pharmaceutical firms will increase to a large extent. This would make more R&D projects profitable and thus increase pharmaceutical R&D. As the R&D is likewise primarily undertaken in the US, domestic changes in protection will be found to have an effect on domestic spending on pharmaceutical R&D.

System generalised method of moments regression with spending on pharmaceutical R&D as the dependent variable and including the US, 1996-2014

Variable	Coefficient estimate[4]
Pharmaceutical R&D in the previous period	0.513***
	(0.144)
Education	0.496**
	(0.204)
Mean effective protection period	0.0285**
	(0.0127)
Weighted mean effective protection period (composite variable)	0.0548**
	(0.0261)
Other R&D	0.424***
	(0.128)
Constant	-2.901**
	(1.167)
Observations	204
Number of id	21
Standard errors in parentheses	
*** p<0.01, ** p<0.05, * p<0.1	

Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described in section 1.4.2. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with a negative development time are not included. Standard errors in parenthesis. Both the 20 EU countries for which adequate data could be found and the US are included in the regression.
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA and MRI.

1 https://www.statista.com/statistics/272181/world-pharmaceutical-sales-by-region/
2 https://www.efpia.eu/media/25055/the-pharmaceutical-industry-in-figures-june-2016.pdf
3 Own calculations based on OECD (2015), "Research and development in the pharmaceutical sector", in *Health at a Glance 2015: OECD Indicators*, OECD Publishing, Paris p. 188. It is reported that world industry spending on pharmaceutical R&D was USD 92bn and that in the US alone spending on pharmaceutical R&D was close to USD 50bn.
4 When interpreting the coefficient estimates it is important to note that the immediate numeric value cannot directly be compared across variables, as this is dependent on the unit in which the variable is recorded. For a further explanation of how to interpret the coefficients, see p. 171.

Including the US in the main regression changes the significance of the effective protection period in the country itself (2/2)

This supports the hypothesis that what matters to pharmaceutical companies is the protection period in the markets in which they sell most of their products. In the case of the US, the domestic market is a large part of the global market.

The change in significance of the domestic protection variable when including the US can, however, also be seen as an indication that the estimation of this variable should be interpreted with caution in both regressions. As such, on the basis of the existing data material we are not able to firmly conclude whether the domestic protection period has an impact on the level of domestic spending on pharmaceutical R&D.

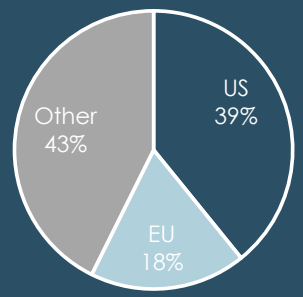
The coefficient estimate of the composite variable "Weighted mean effective protection period" is still significant and has not changed much in numerical value. This can be interpreted as signifying that the estimate of this coefficient is fairly robust across formulations. This is quite interesting, especially in light of the change of significance of the domestic protection variable when including the US.

Hence, even when including the US, which evidently makes the domestic market an important driver of domestic spending on pharmaceutical R&D, foreign trade markets still seem to be important. This could point to the assertion that exports to foreign countries are immensely important to pharmaceutical companies across countries.

The global pharmaceutical market

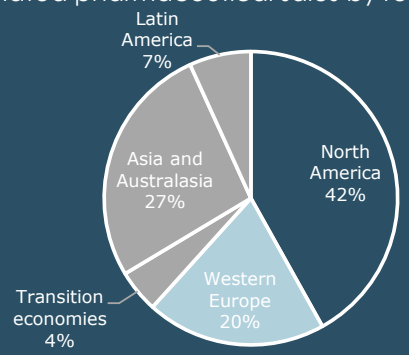
The global pharmaceutical market is still concentrated in the developed countries, which accounted for approximately 70% of world pharmaceutical sales in 2015.[1] Notably, as can be seen from the figures below, the US features prominently in the global pharmaceutical sector, in terms of both sales and R&D expenditure.

Pharmaceutical R&D by region 2014:



Sources: OECD: Health at a Glance 2017 and Evaluate Pharma: World Preview 2017, Outlook to 2022.

Estimated pharmaceutical sales by region 2014:



Source: Deloitte 2015 Global Life Sciences Outlook.

1 International Federation of Pharmaceutical Manufacturers & Associations (2017) The Pharmaceutical Industry and Global Health.

Trade country wealth seems to be an important driver of the size of the individual trade weights (1/2)

IDENTIFICATION

The correct identification of the composite variable, which depicts the importance of the effective protection period in the other EU countries with which a given country trades the most, is important to the interpretation of the coefficient estimate reported.

The variable is a weighted average of the effective protection period in the other EU countries with which a given country trades the most. The utilised weights are the fraction of total pharmaceutical exports (trade weight) shipped from the given country to the other EU countries with which the country trades.

As such, the composite variable may vary over time, either because the trade weight changes or because the effective protection period in the other EU countries with which the country trades the most changes.

ENDOGENEITY

The trade weight can change because e.g. total exports from a country increase but exports to another EU country do not. In this case the fraction of total exports shipped to a given country decreases. Likewise, it may change if the customs duties of the EU countries with which a country trades the most are increased. This will likewise decrease the fraction of total exports shipped to the given country.

The estimation of the variable is robust with respect to the above-mentioned changes as long as the changes are exogenous;[1] they do however imply certain intricacies in the interpretation of the estimated coefficient of the variable.

However, if the changes in the trade weights are affected by a variable not included in the regression, which likewise influences the amount of pharmaceutical R&D, there may be a so-called endogeneity problem. This would entail both the level of domestic R&D and the trade weights being determined by a third unobserved variable. In this case the coefficient estimate of the composite variable may be biased.

One such variable may be the wealth of the other EU countries with which a given country trades the most.

WEALTH OF THE OTHER EU COUNTRIES WITH WHICH A GIVEN COUNTRY TRADES THE MOST

If a country with which another EU country trades becomes relatively more affluent than the other EU countries, the expected profitability of investing in more pharmaceutical R&D may increase in a given country. This would increase the incentive for spending resources on pharmaceutical R&D. As such, an increase in the wealth of the other EU countries with which a given country trades the most may increase the spending on pharmaceutical R&D in a given country.

At the same time, if another EU country with which a country trades becomes relatively more affluent than the other EU countries, it may become more profitable to ship a larger fraction of total pharmaceutical exports to said country. If this happens, it would increase the trade weight on said country. A likely mechanism ensuring this would be the demand effect, whereby nations obtaining a higher amount of wealth in turn demand more medicinal products. Similarly, they may demand better and more expensive products, with the outcome that exports to this country increase.

The two possible chains of effects discussed entail that the wealth of the other EU countries with which a given country trades the most may influence both the amount of pharmaceutical R&D and the trade weight. To analyse the latter of these assertions, it is possible to undertake an auxiliary regression.

AUXILIARY REGRESSION

The auxiliary regression tests whether there is a relationship between the average trade weight of other countries on their EU export countries and the level of GDP per capita in said countries. To do this, the average of the other countries' trade weights on a given country for each year is calculated.

An illustrative example where there are only three countries in the sample: Germany, the UK and France. If Germany e.g. sells 40% of its pharmaceutical exports to France and the UK sells 60% of its pharmaceutical exports to France, the average trade weight for France would be 50%; i.e. on average, the other countries ship 50% of their pharmaceutical exports to France.

The relationship between this measure and the GDP per capita in the receiving country (France in the example above) is then analysed.

This auxiliary analysis helps in shedding some light on the issue of whether the wealth of a given country with which another country trades has an influence on the trade weight on the former.

The following page presents the results of the auxiliary regression analysing the issue.

1 The changes are exogenous if they are not influenced by e.g. variables not included in the regression, which likewise has an influence on the level of spending on pharmaceutical R&D.

Trade country wealth seems to be an important driver of the size of the individual trade weights (2/2)

The result of the auxiliary regression described on the previous page can be seen in the table to the right.

From the positive and significant coefficient of the variable "GDP per capita" it can be seen that the wealth in the other EU countries with which a given country trades the most seems to be an important factor in explaining the fraction of pharmaceutical exports that these countries receive.

There are two main takeaways from this result.

The first is, as described above, that it seems that the wealth of an EU country that another country trades with is an important factor in deciding what fraction of pharmaceutical exports the former country will receive. This resonates nicely with economic theory, implying that more products will be sold in more affluent markets (likely as an effect of higher demand). Furthermore, this result is supported by some of the results shown in the next chapter on availability. Here, GDP per capita is likewise found to be a statistically significant driver in determining the launch strategy.

The other key result is that this potentially has implications for the interpretation of the coefficient of the composite variable in the main regression.

This is analysed further on the following pages.

System generalised method of moments regression with average export trade weight from other countries as the dependent variable, 1996-2014

Variable	Coefficient estimate
GDP per capita	0.734***
	(0.0415)
Constant	-5.951***
	(0.142)
Observations	368
Number of id	20
Standard errors in parentheses	
*** p<0.01, ** p<0.05, * p<0.1	

Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described in section 1.4.2. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with a negative development time are not included. Standard errors in parenthesis. The dependent variable is the average fraction of other countries' pharmaceutical exports the given country receives.
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA and MRI.

Analysing the trade country weights (1/3)

In the previous section it was shown that the wealth of the other EU countries with which a given country trades the most, measured by GDP per capita, is a significant variable in determining the trade fraction for said countries.

To analyse this further, and identify whether this has an implication for the interpretation of the coefficient of the composite measure in the main regression, it is possible to run the regression with fixed trade weights.

Fixing the trade weights removes any time variation. This is done by calculating the trade weights as an average across the whole observed time period. Only countries with observations during the whole period are included. To maximise the number of countries, the time period is slightly shortened to 1998-2014.

Keeping the trade weights fixed means that they can be said to be approximately exogenous. Hence, all remaining variation in the composite variable will stem from variation in the effective protection period in the countries to which medicinal products are exported.

The following regression thus explores whether the dynamically changing weights which are influenced by the wealth of the other EU countries with which a given country trades the most can be found to bias the conclusion in the main regression to a degree that invalidates the results.

Analysing the trade country weights (2/3)

The results from running the main regression but utilising fixed trade weights can be seen in the table to the right.

The main finding from the results reported is that the composite variable still has a positive significant coefficient. Hence, even if there is a possible endogeneity bias from the dynamically changing trade weights in the main regression, this does not seem to influence the overall conclusion. The weighted effective protection in the other EU countries with which a given country trades the most has a significant effect in explaining the amount of spending on pharmaceutical R&D.

Keeping the trade weights fixed at their average value during the sample period does not have any direct empirical meaning. It is merely a theoretical abstraction, to analyse whether there is an endogeneity problem. As such, the size of the coefficient of the composite variable in the table to the right cannot directly be concluded upon. However, the sign and significance support the conclusion drawn from the main regression.

System-generalised method of moments regression with spending on pharmaceutical R&D as the dependent variable and using trade weights fixed over time, 1998-2014

Variable	Coefficient estimate
Pharmaceutical R&D in the previous period	0.454***
	(0.163)
Education	0.533**
	(0.235)
Mean effective protection period	0.00122
	(0.0163)
Weighted mean effective protection period (composite variable)	0.0944**
	(0.0382)
Other R&D	0.395***
	(0.126)
Constant	-1.531
	(1.120)
Observations	168
Number of id	19
Standard errors in parentheses	
*** p<0.01, ** p<0.05, * p<0.1	

Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described in section 1.4.2. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with a negative development time are not included. Standard errors in parenthesis. The 19 EU countries for which adequate data could be found are included in the regression. The calculation of fixed trade weights puts limits on the number of countries used and the time period.

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA and MRI.

Analysing the trade country weights (3/3)

One way of remedying the potential for an endogeneity bias would be to include the GDP per capita of the other EU countries with which a given country trades the most in the main regression.

The reason for not directly including this variable in the regression is that it would entail having one variable for each included country. As the system GMM method utilised in this section employs an instrumental approach to dynamic panel data modelling, the inclusion of 20 new country-specific variables would quickly diminish the degrees of freedom. This would reduce the explanatory power of the model and the estimates may become less reliable.

In order to preserve the ease of interpretation, and because the potential endogeneity issue cannot be found to change the conclusions, it is deemed best to not further complicate the main regression. However, the main results and conclusions should be seen in the light of the above caveats and nuances.

Considerations as to the effective protection period as well as the co-location of pharmaceutical manufacturing and R&D

THE AVERAGE EFFECTIVE PROTECTION PERIOD

The above analyses and conclusions are centred around the measure of the average effective protection period that medicinal products obtain in a given country. Hence, the validity of the results is built upon the assumption that this measure is a relevant measure for the IP protection of medicinal products.

It has already been pointed out that there are certain data challenges and that the results are valid to the degree that these have successfully been overcome. However, using the average effective protection period as the central measure likewise assumes that this variable is important to the companies when they are making their R&D decisions.

A risk is that the average effective protection period is biased across countries as an effect of decisions made by the pharmaceutical companies.

It may e.g. be that companies launch products with very short protection periods only in the large countries, because only here is the patient base large enough to recoup the investment and earn a return. This would entail products in the large markets being biased towards having a shorter protection period.

It may, however, likewise be the case that companies tend to seek SPCs and secondary patents most rigorously in the large countries where keeping competition at bay as long as possible is most profitable. This would entail products in the large markets being biased towards having a longer protection period.

The key takeaway is that the size of the effective protection period may be correlated with e.g. the size of the markets. However, it is difficult to speculate as to whether the net bias is positive or negative. It is, however, important to keep in mind when interpreting the results reported in the previous sections.

CO-LOCATION OF PHARMACEUTICAL R&D AND MANUFACTURING

The present analysis studies the relationship between the average effective protection period, trade flows and spending on pharmaceutical R&D. For this to have empirical merit, it must, at least to a certain degree, be some form of co-location between manufacturing and R&D within the pharmaceutical sector.

When e.g. the relationship between protection in the other EU countries with which a given country trades the most and R&D in the given country is analysed, there must be some level of co-location of manufacturing and R&D for the analysis to have empirical merit.

If manufacturing and R&D within the pharmaceutical sector were completely decoupled, theoretically there would not be a link between how much a given country exports to another country, the protection in the country which receives the export and the spending on pharmaceutical R&D within the given country.

This assertion is best described with an example. The present analysis assumes that, at least to some degree, the following example of a chain of events holds.

Illustrative example: A country increases its effective protection. The expected profit from exporting to this country now becomes higher. This incentivises companies to invest more in R&D. The extra investment in R&D is placed in the same country as the exports come from. If the R&D were placed in another country, it would not be possible to see an increase in the spending on R&D when the effective protection in another EU country with which a country trades increases.

The fact that there is a significant effect on the composite measure supports this assumption. Furthermore, an analysis undertaken to map the location of 13 of the top 20 largest pharmaceutical companies' manufacturing and R&D activities has revealed that there is a certain degree of co-location.[1]

The regression describes the historical relationship between the included variables. To the extent that e.g. further globalisation of the pharmaceutical sector dilutes the amount of co-location between manufacturing and R&D, the results may not hold to the same degree in the future.

1 See appendix p. 166.

2.2 IMPACT ON AVAILABILITY

The economics of medicinal product launches (1/3)

THE COST OF MARKET ENTRY

When a company is deciding whether or not to enter a new market *after* having developed a new medicinal product, standard economic theory would suggest that the preceding expenditure on R&D should not be factored in – only the future costs of entering the market should be of importance.

Once money has been spent on developing a new innovative medicinal product, the R&D investment is a so-called sunk cost. This means that the investment cannot be reversed to have the money refunded. This is the case for R&D investments, as the money is spent on obtaining new knowledge and knowledge in general cannot be returned.[1]

However, *before* making the R&D decision, the cost of the ex ante investment compared to the expected ex post profits needs to be favourable.

This means that there is a large difference in the factors influencing the decision whether or not to undertake R&D and the decision whether or not to launch a medicinal product in a given country *after* development.

In the section on innovation we study the effect of the IP framework on the expected ex post profits and hence the R&D decision of the company.

In this section we study the decision on entry and the timing of entry into a given market once a new medicinal product has been developed and is ready for the market.

DETERMINANTS OF MARKET ENTRY

When a company makes the decision to enter a market with a new medicinal product, the condition upon which the company bases its decision is that *ex ante profit* (i.e. expected profits after entry) needs to be large enough to justify *ex ante costs* related to launch (i.e. expected entry costs).

For market entry to occur and hence for a medicinal product to become available to patients, at least one company must experience the following condition being fulfilled:

$$\textit{Ex ante profit} - \textit{ex ante costs} > 0$$

Ex ante costs are driven by a range of factors. These are e.g. costs of authorisation, product registration and regulatory approval, obtaining import licences, developing distribution channels, and marketing the medicinal product as well as educating health-care providers and possibly patients about the appropriate use of the medicinal product. Some of these may entail a large market access cost.

When studying the EU, it is important to note that with the centralised procedure for marketing authorisation, some of the regulatory costs may only have to be incurred once, possibly facilitating a lower cost per country if launching in many countries.

Ex ante profits are driven by market size and price. Market size and price include e.g. the characteristics of competition, the regulatory environment in the country, the size of the population and its demographics, disease incidence, cultural characteristics influencing the attitude towards medicinal products and the economic wealth of the country.

The characteristics of competition depend to a large extent on the regulatory environment present in the country. The regulatory framework encompasses the IP protection regime in the country, whether there is price regulation and price referencing and the structure of the reimbursement system. If the reimbursement system is public, it is likewise important whether or not there is a centralised buyer and whether the pricing agreements are conveyed through tenders.

The IP protection regime is important to the extent that it determines whether and when generic companies can enter the market. This can have an effect on both the feasible prices and the investment made into marketing and education.

If no (or weak) IP protection exists, generics can quickly enter the market. Besides driving prices down, as they have not incurred the same R&D investment costs as the originator firm, the generic companies can benefit from the marketing and educational efforts of the originator company. Once patients and doctors learn how to utilise a new medicinal product and what its effect is, they do not care whether it comes with a brand name on the package or from a generic firm.[2]

1 There is of course the possibility of selling the invention to another company. This would entail a scrap-value of the invention and may only partly recoup the initial R&D investment. Successfully progressing through the different R&D phases may likewise increase the value of the company and attract investors and possible buyers.

2 Unless, of course, there is a difference in clinical value. This should, however, not be the case within the EU, as generics have to adhere to certain quality requirements. There is evidence pointing to some consumers caring about this, but in the case of an insurance company or the public sector reimbursing the costs, often the cheapest alternative is chosen. Furthermore, as we are looking at first launch, there is no alternative.

The economics of medicinal product launches (2/3)

Thus, there is the possibility of free riding at other companies' expense. Free riding theoretically leads to less investment in marketing and educational effort than is optimal from a societal point of view. There is evidence that originator firms invest more in stimulating demand (i.e. reaching more patients) when they have exclusivity rights.[1] This means that potentially more people will receive and benefit from the medicine. However, marketing efforts may also make some patients/doctors choose the expensive brand version over the generic.

PRICE REFERENCING AND PARALLEL IMPORT

If price regulation and price referencing successfully achieve the objective of lowering prices, seen in isolation they make the market less attractive from a company's point of view but more attractive from the buyer's point of view. However, for the buyer there could be the detrimental effect of the launch of products being delayed or even completely deferred.

From a company's viewpoint, price referencing potentially introduces pivotal considerations as to the launch order of countries. If a high-price country references the prices of a low-price country, it may be more profitable for the pharmaceutical company to delay (or completely abstain from) launch in the low-price country.

This is easiest to imagine in cases where large high-price countries reference small low-price countries. In this case, if the company launches in both countries, it will have to do so at the same price because of price referencing. It can then either set a high price in both countries, a low price in both countries or something in between.

If it sets a high price in both countries, the low-price country may not be able to afford the product and sales will be zero in that country. If it sets a price anywhere below what the high-price country is willing to pay, the company will lose revenue in the high-price country. The question then becomes whether increased sales because of a lower price in the low-price country can compensate for this. Depending on the size of the countries and the differences in wealth, this may not always be the case. In these cases the most profitable action for the company may be to enter the high-price country with a high price and completely abstain from entering the low-price country.

Further evidence on external price referencing can be found in a survey carried out for the European Commission in 2014.[2] Here stakeholders were asked to rank 16 different policy measures by their effectiveness in achieving seven different policy objectives.[3]

Stakeholders were first asked to assign weights to each policy objective according to their perceived importance and thereafter rank a range of policy measures according to how good they were at achieving the objectives.

Across all stakeholders, who may reasonably be expected to place different emphases on the various policy objectives, external reference pricing was seen as among the least effective policy measures.[4]

Notably, external reference pricing was given the lowest rank by both the pharmaceutical industry (generic and research-based, n=30) and the authorities and payers (n=27). The only stakeholders in the survey viewing external reference pricing as among the most effective policy measures were doctors. However, only one doctor responded to the survey, which brings its representativeness into question.

Naturally, such a survey is limited by the fact that only a sample of all stakeholders respond. Nonetheless the study contributes to shedding some light on the issue.

Considerations about parallel import likewise have an effect on the launch and price decision. If a product needs to be marketed and sold at a low price in one country, while the prices set in other countries are much higher, the company risks the higher-price countries starting to parallel import the medicinal product from the low-price country. As such, this has much the same effect as a price referencing system.

This means that for the pharmaceutical companies, considerations as to price referencing and parallel import are pivotal in the launch decision.

The matters of price referencing and parallel import imply that the launch sequence and decision in European countries are far from independent. This complicates the econometric analysis of availability.

1 See Kyle and Qian (2014), Intellectual Property Rights and Access to Innovation: Evidence from TRIPS.
2 European Commission (2014), Study of the policy mix for the reimbursement of medicinal products.
3 The selected policy objectives were *timely access to medicines, equitable access to medicines, reward for innovation, cost-containment/ control of pharmaceutical expenditure/budget, long-term sustainability (for the health-care system), promotion of more rational use of medicines* and *increased competition.*
4 See European Commission (2014), Study of the policy mix for the reimbursement of medicinal products for further elaboration and nuances regarding the different stakeholders' ranking of the policy measures in the survey.

The economics of medicinal product launches (3/3)

SECRET DISCOUNTS

There is likewise the nuance that for some medicinal products there is a great deal of difference between the list price and the actual price paid by e.g. hospitals (and hence in the end the reimbursements systems, insurance companies or payers). In many cases secret discounts are given by companies to e.g. the central buying authorities of countries. The fact that the discounts are secret makes it impossible to use the actual price in any price referencing system and greatly complicates any comparison of medicinal product prices across countries.

In a price referencing system where all prices are visible to all parties and where all countries referenced all other countries, the prices of medicinal products would converge towards the prices in the lowest-price country in the long run. However due to e.g. secret discounts and the delay or absence of product launch in some countries, this is currently not the case. In practice, countries often refer to a limited number of other countries, also known as a "basket".

MANY STRATEGIC CONSIDERATIONS

All of the above implies that there are a multitude of strategic considerations to be taken into account when a pharmaceutical company is deciding which markets to enter and when.

However, it is important to understand that the launch strategy of a firm is driven to a great extent by an economic cost-benefit analysis of which markets can be expected to be most profitable.

In this respect, the expected number of products sold and the expected obtainable price per product are two pivotal elements essentially deciding what size of profit the company can expect to obtain by entering the country in question.

THE PARAMETER OF INTEREST: AVAILABILITY

In this section we study the determinants of availability. Our main interest is how various characteristics of a given country affect the availability of new innovative medicine.

Availability is to be understood as whether or not a product is available on the market, to the patients.

Availability

In this study a product is defined as being available if it has undergone development, received marketing authorisation and subsequently been placed on the market (i.e. products that have obtained a marketing authorisation *without* physically having been placed on the market are not defined as being available).

MOLECULE FOCUS

An important distinction here is that we will study the availability of a given molecule and not the exact medicinal product. Studying the availability of the molecule means that we make sure not to distinguish between whether it is available through a brand name or a generic manufacturer. From a patient's point of view, what should matter is the availability of the molecule that confers a given effect and not the name on the package.

This means that in our model, we look for the first time a product containing a given molecule is launched in a given country, whether the molecule is found in an originator product or a generic product.

For simplicity we shall interchangeably use molecule and medicinal product in the following text.

Existing literature (1/2)

IP RIGHTS AND AVAILABILITY OF MEDICINAL PRODUCTS

The relationship between intellectual property rights and availability of medicinal products has been studied extensively in the literature. A popular approach is using the change in patent laws following the enactment of TRIPS,[1] especially in developing countries. This makes it possible to study how a rather drastic change in IP protection affects the availability of medicinal products. Other approaches have also been utilised, such as exploiting cross-country variation in IP protection.

Kyle and Qian (2014) study the effect of changes in IP rights stemming from the enactment of TRIPS.[2] The authors analyse the effect on speed of medicinal product launch, price and quantity in 60 countries covering the period from 2000 to 2013. The speed of medicinal product launch is estimated using a discrete-time hazard model.

The most interesting result on availability is that across all the different specifications used, the authors find that new products are launched faster in the presence of patents. The income of a country has a large effect on medicinal product launch and the study shows that poor countries are more likely to receive older medicinal products.

In their study the authors use the existence of an active patent as the measure of patent protection. Hence, the analysis does not consider the interaction with other protection schemes, such as market exclusivity and data protection. Furthermore, using the existence of an active patent provides information only on the principled legal right and not the actual empirical period of patent protection.

Danzon and Epstein (2008) study the effect of price regulation and competition on medicinal product launches in 15 countries covering the period from 1992 to 2003.

Using the prices of established products in the countries studied, the authors find that launch timing depends on these. Thus, to the extent that e.g. price regulation decreases prices in a given country, the policy will contribute to a longer launch delay for a new innovative medicine.

What is perhaps even more striking is that the authors find that the availability of new medicine in low-price countries is also affected by price referencing in high-price countries, especially within the EU. The consequence is that if a high-price country uses a low-price country for price referencing, the high-price country imposes a welfare loss on the low-price country due to the longer delay time for the new medicine. This finding is consistent with pharmaceutical companies delaying launch in low-price countries to avoid having their prices in high-price markets undermined by a price referencing policy.

Berndt and Cockburn (2014) examine the availability of new medicinal products in India compared to Germany and the United States. The data used contains 184 new medicinal products approved by the FDA in the years 2000-2009.

Focusing on India can highlight the importance of patent protection, as India did not have patents for medicinal products from 1971 to 2005. Patent protection is still weak in India today and the generic sector is substantial. This combination means that competition is fierce and that innovator companies cannot be sure of obtaining sufficient IP protection to obtain a satisfactory profit when entering the country.

The authors find substantial launch delays in India as compared to Germany and the United States. In India it took more than five years before 50% of the medicinal products became available while in Germany and the United States this took less than a year. Furthermore, the distribution of launch delays in India exhibits a longer right tail, with more innovations taking a very long time to reach market.

In combination with this, the authors likewise find that the number of sellers of a given medicinal product is much larger in India (and takes a very short time to reach this number) than in Germany and the United States.

Based on these findings, the authors conclude that India has succeeded in keeping prices for pharmaceuticals low and hence ensures the accessibility of medicinal products for their citizens. The caveat, however, is that this has come at the expense of availability. The fierce generic competition spurred by weak patent protection causes severe delays in the launch of new innovative medicines in India compared to Germany and the United States.

1 The Trade-Related Aspects of Intellectual Property Rights (TRIPS) sets forth a range of minimum requirements for IP protection in countries which are a member of the World Trade Organisation.
2 See p. 25 for a description of TRIPS.

Existing literature (2/2)

As such, this paper highlights the seeming trade-off between policies enhancing accessibility and the availability of new innovative pharmaceuticals.

Cockburn et al. (2016) study the timing of the launch of new innovative medicine using information on 642 medicinal products in 76 countries for the period 1983-2002. The launch delays are modelled using a so-called parametric hazard model.

In the study, medicinal products are understood as molecules (active moiety) and not directly as a physical product. This is important, as one molecule may be available through multiple products; e.g., innovator and generic versions. The clinical value of a molecule does not depend on whether it is available in a package with a brand name or generic name on it. What matters clinically is that the molecule which confers the desired effect is available. Hence this too is the matter of focus in the study.

In line with other literature, the study shows that price regulation delays the launch of new medicinal products.

Furthermore, the study shows that longer and more extensive patent rights are associated with the faster launch of new medicine. A striking result in this regard is that in many countries some medicinal products do not become available until more than 10 years have passed since their first international launch. Moreover, many medicinal products are never launched in more than a handful of wealthier countries. In the sample, less than 50 percent of possible country launches of new medicinal products had taken place within 20 years of the first international launch. This means that in many countries, especially poor countries, patients never have the same options regarding available medicine as do patients in rich countries. This highlights the need for insight into this area, as low prices and thus high accessibility are a main concern insofar as the medicine is actually available to patients.

The effect on launch delay of the legal patent regime is quite pronounced. The authors find that moving from a no patent policy to a regime with a long patent protection[1] period entails a 55% decrease in launch delay. This effect is robust in respect to the wealth of countries.

Besides patent protection regimes and price controls, the authors find that launch delays are highly dependent on income, as measured by GDP per capita. On average, it takes nine years for a medicinal product to be launched in the low-income countries, while it only takes two years in the high-income countries.[2]

1 A long patent protection period is defined as equal to or greater than 18 years. This e.g. includes all countries adhering to the TRIPS agreement in WHO, as this states that the minimum patent protection period can be no shorter than 20 years.
2 The classification of low-, middle- and high-income countries is based on the income categories of the World Bank.

Our approach following the literature study on existing evidence (1/2)

The main finding of the existing literature examined on the previous pages regarding the subject of availability is that a longer and more extensive patent regime decreases launch delay. This means that the literature suggests that the longer the patent protection period is in a country, the earlier that new innovative medicine becomes available in the country.[1]

Taking these findings at face value, together with the fact that legally an SPC increases the IP protection period for pharmaceuticals, SPCs should have contributed to decreasing launch lags of new medicine in Europe.

This assertion, however, does not take into account the interaction between SPC and other IP protection schemes which play a role in giving a complete picture of the effect of the IP regime.

As described at the beginning of section 2.1, the protection of individual IP rights and incentives conveyed on paper are one thing, while the empirical protection period actually enjoyed when the different schemes work in combination is something else.

For example, the protection period conferred by a patent is 20 years "on paper" and the protection period conferred by marketing protection is 10 years. If a product is authorised 11 years after the priority date of the patent, nine years of protection are left before expiry of the patent. However, the market protection scheme will provide 10 years of protection. Furthermore, it is possible for the company to apply for an SPC, which if granted will last for five years. As such, the protection the product can enjoy while authorised on the market is 14 years when all the protection periods are taken into account.[2]

Hence, as was the case when we studied innovation, we will utilise the *effective protection period* as the measure of patent protection in a given country. This ensures that we will catch the interaction between the legal framework, the workings of the authorities and other factors having an effect on the actual period of time a medicinal product is protected by IP rights or incentives.

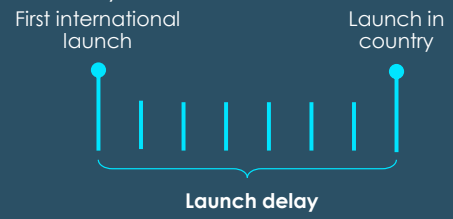
LAUNCH DELAY

It is one thing to study whether or not new innovative medicine becomes available on the market; the time that elapses before this happens is another thing. If two countries both experience that the same new medicinal product becoming available, but it happens immediately in one country, whereas the other country has to wait several years before the medicine becomes available there, then depending on the price, the country with the earlier launch may be better off than the other country from a welfare perspective.

As such, when studying the availability of medicinal products in countries, launch delay is of at least as much interest as assessing whether the product becomes available or not.

Launch delay

The launch delay or lag of a medicinal product in a country is the time elapsed from when the medicinal product first becomes available anywhere in the world until it is launched in the given country.



NOT ALL ABSENCE OF LAUNCH IS EQUIVALENT TO WELFARE LOSS

It is important to note that if a certain medicinal product is not launched in a given country in a given year, from a theoretical standpoint it does not necessarily equate to a loss of welfare in this country. It may be that some medicinal products become obsolete because of new innovations before they are launched in all countries, and some medicinal products may treat diseases mostly prevalent in certain countries (e.g. malaria or the Zika virus).

Moreover, if a medicinal product is launched at a very high price, and the clinical effect is relatively low, reimbursing it may actually entail a welfare loss from a societal point of view, especially in low-income countries.

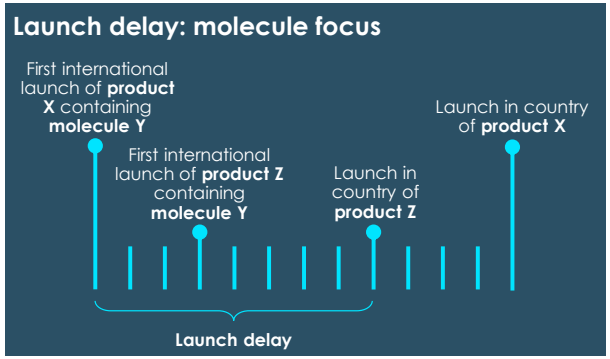
1 See e.g. Kyle and Qian (2014), Berndt and Cockburn (2014) and Cockburn et al. (2016).
2 This is notwithstanding additional patents besides the patent which the SPC is "attached" to.

Our approach following the literature study on existing evidence (2/2)

MOLECULE FOCUS

As is the case in previous literature (see e.g. Cockburn et al. (2016), Berndt and Cockburn (2014) and Danzon and Epstein (2008)), we are studying availability at the molecule level and not at the product level. We do this as, when studying availability, it is not clinically important whether the package which the product comes in bears a brand name or the name of a generic manufacturer. What matters clinically is whether the molecule which confers a given effect is available no matter who the manufacturer is.

This means that in the data we identify the first time a molecule becomes available anywhere in the world through any company, and the time at which it becomes available in the given country through any company.



DURATION MODELS

Following Cockburn et al. (2016), Berndt and Cockburn (2014) and Kyle and Qian (2014), we use so-called duration models to study the launch delay of new medicinal products.

This type of model is often used in epidemiological studies to analyse e.g. whether a new clinical medicinal product can extend the life of terminally ill patients.

In our case we will use the duration model framework to model the time that elapses from a new molecule first becomes availably anywhere in the world until it is launched in a given country. This time spell is what we call the launch delay.

The duration models estimate the probability of transitioning from a given state into another state. In our case this means estimating the probability of a new molecule transitioning from having been launched somewhere in the world but not in a given country to being launched in the country.

The evidence from duration analysis can be presented in a variety of ways. The two main categories of results are parametric and non-parametric.

Non-parametric results are basically descriptive statistics. However, it is possible to present quite informative evidence, such as the hazard function and Kaplan-Meier failure function.

The hazard function describes the unconditional instantaneous probability of leaving the initial state at any given point in time; i.e. the probability of a molecule that is internationally available being launched in the country.

The Kaplan-Meier failure function estimates the probability, in the sample, of the event having happened at a certain point in time. In our case the Kaplan-Meier function gives us a non-parametric function describing how many of the possible country-molecule combinations have been utilised at a given point in time after the international introduction of the molecule; i.e. in how many of the EU member states has the new molecule been launched.

The Kaplan-Meier function is quite informative, and as it can be estimated and compared for categorical variables, we can easily gauge how separate variables influence the probability of launch.

Using a parametric estimation technique, we can do a more thorough investigation of which variables have an effect on the probability of launch. This is equivalent to regular econometric model analysis such as e.g. OLS.[2] The difference is that here, the covariates serve to translate the hazard function and hence give an estimate of how the probability of launch is affected by a change in the control variable.[3]

COVARIATES

Launch delay may be driven by more than merely the period of patent protection. To control for this we include time-varying covariates in the parametric hazard function. These include

- GDP
- Population size
- Whether the medicinal product is biologic or not
- GDP per capita
- Various interaction terms

1 For more technical specification of the hazard model, see appendix.

2 Ordinary Least Squares (OLS) is a technique for estimating linear econometric models. See e.g. Verbeek, M. (2012), A Guide to Modern Econometrics.

3 This is true for the proportional hazard functions, whereas for an accelerated failure time model, the covariates influence the shape of the hazard function as well.

Data for the availability model (1/2)

IMS DATA ON PRODUCTS IN EUROPEAN COUNTRIES

The point of departure is a dataset from IMS, provided by the European Commission on a third-party basis to Copenhagen Economics.

The data covers all medicinal products in the retail and hospital sectors in European countries launched from 1900 to 2016.[1] Malta, Cyprus, Denmark, Greece and Slovenia are not covered in the data. For Estonia, Latvia and Luxembourg there is only retail data. The data includes products on the market during at least one quarter from the last quarter of 2013 and the third quarter of 2016.

In line with Cockburn et al. (2016), we are looking at a 20-year period. We have much more recent data, however, so our period of interest is 1996 to 2015. We have not included 2016 as our control variables do not cover this year.

The data is included in the dataset on a product-country basis and contains e.g. information on:

- Date of first launch anywhere in the world
- Date of launch in each EU member state
- Molecule
- Company
- Manufacturer
- Whether the molecule is biologic or not
- Whether the product is generic or not
- Chemical salt
- Physical form
- Package
- Quantity sold
- Sales

The dataset contains information only on products that have been launched in at least one EU member state.

What interests us, however, is not the distinct product and its launch, but rather the molecule in the product. This is because it is not which company introduces a given product in a country or what they call it that interests us but merely that the product, in any form and by any name, is available to the patient.

As such, we need to recalibrate our data so that the molecule is the focal point.

Below we focus on the hospital sector.

The original IMS dataset contains 310,590 observations. This is a fairly large number of observations due to the fact that each product has one observation per country it has been introduced in. Hence, in a molecule sense, many of these observations are identical where products offered contain the same molecule. The time period is similarly rather long, including products introduced between 1900 and 2016 (uncertainty about data quality increases the further back in time one goes; hence we only use data from 1996 onwards).

We begin by identifying the date when each molecule was first introduced anywhere in the world. Here we use the international launch date, but we also check whether a domestic launch date precedes it. The earliest date when the molecule is recorded as being launched, whether internationally or domestically, is used as the first international launch date.[2]

The first international launch date is crucial to our analysis, as in principle it is from this date that the molecule is capable of being launched in all countries; i.e. the molecule cannot be launched before its international launch date, whereas in each subsequent year there is a positive probability of the molecule being launched in each EU member state.

Retaining only unique molecule-country combinations for molecules with a first international launch in the period from 1 January 1996 to 31 December 2015 leaves us with 8,102 unique observations, as the time dimension is not at work here. These observations cover 907 unique molecules.

This compares to 17,189 molecule-country observations in Cockburn et al. (2016), corresponding to 642 unique molecules for a 20-year period spanning 1983 to 2002. The big difference is that the number of countries covered in Cockburn et al. (2016) ranges from 45 in the beginning of the period to 76 by the end of their sample period. As our focus is the EU, our sample contains 18 countries.[3] Despite the smaller sample of countries, our dataset covers more molecules.

1 The older the data is, the less reliable it is. As such, it is doubtful whether the data actually goes back as far as 1900. However, as we use data from 1996 onwards, we are not impaired by this.

2 Each unique molecule or unique combination of molecules in one product counts as a unique observation. Hence if two molecules are introduced in a country in two separate products and then are subsequently introduced in a combination, the molecules count by themselves and in the combination as unique observations.

3 Malta, Cyprus, Denmark, Greece and Slovenia are not covered at all by the sample, whereas Estonia, Latvia and Luxembourg only have retail data included. Norway is included as a member of the EEA. Bulgaria, Croatia and Lithuania are excluded as control variables could not be found for these countries.

Data for the availability model (2/2)

Our dataset now contains only one observation per molecule-country combination and only for countries where the molecule is introduced during our sample period.

The next step is to expand the dataset to have one observation for each year for each molecule-country combination, from international launch until domestic launch. This allows us to include time-varying covariates in the analysis.

Furthermore, we must include observations for all molecule-country combinations where the molecule is not introduced during our sample period. We do this as the molecule could have been introduced during the sample period but was not. If we did not do this, all our results would be *conditional* on actual domestic launch. By including these observations, we ensure that our results are widely applicable.

For certain country-molecule combinations we will experience so-called right-censoring. This means, that by the end of the sample period, 31 December 2015, a given molecule will not have been launched in a given country. However, it may still be launched *after* our sample period ends. If we did not include these, our results would be biased, as these molecules would then (incorrectly) not be counted as part of the sample. Our econometric estimation method corrects for these right-censored observations.

This leaves us with a final dataset where each molecule-country combination has a yearly observation from the first international launch of the molecule until domestic launch or the end of the sample period on 31 December 2015. The final dataset has 119,176 observations.

ONLY EU DATA AVAILABLE

An important point is that the dataset used for this analysis contains data only on products and hence molecules which at some point have been launched in at least one EU member state. As such, the analysis does not contain information on new molecules that are launched outside the EU and do not reach any EU member state market before the end of the sample period.

PRICE REFERENCING AND PARALLEL IMPORT

As we have seen in the literature and also touched upon in the discussion on the economics of medicinal product launch, price referencing and parallel import seem to play a pivotal role in firms' launch decisions.

As such it would have been optimal to include measures for this in the model. With the available data material, however, this was not possible. The results of the following analysis allow several interesting points to be made, but they should also be seen in the light of what was possible given the available data material.

Unless right censoring is taken into account, results may be biased towards overrepresentation of medicinal products introduced in only a few countries

THE MODEL TAKES RIGHT CENSORING INTO ACCOUNT

The table to the right describes the number of countries each medicinal product is launched in *during* our sample period. As we do not observe whether any medicinal products are introduced after the end of our sample period, the table shows an overrepresentation of medicinal products launched in only a few countries. This is the consequence of right censoring.

By using non-parametric estimation, in the form of Kaplan-Meier estimates, and appropriate duration models we can account for the right censoring in the following analysis. This means that the model takes exactly into account the picture we see in the table to the right, where many molecules appear to be introduced in only one or a few countries. However, many of these products are introduced towards the end of the sample period. As such, at the end of our sample period they may not yet have had enough time to disseminate to many countries.

One of the strengths of duration analysis is precisely that any right censoring is factored into the model when the coefficients or functions are estimated. This ensures that we take full account of all available data and not just the products launched in the countries within our sample period.

Number of countries in which new medicinal products are launched, not taking account of right censoring

Count	Frequency	Percent	Cumulative percentage
1	238	28.03	28.03
2	65	7.66	35.69
3	41	4.83	40.52
4	19	2.24	42.76
5	23	2.71	45.47
6	15	1.77	47.23
7	23	2.71	49.94
8	14	1.65	51.59
9	20	2.36	53.95
10	22	2.59	56.54
11	11	1.30	57.83
12	25	2.94	60.78
13	39	4.59	65.37
14	29	3.42	68.79
15	37	4.36	73.14
16	45	5.30	78.45
17	64	7.54	85.98
18	119	14.02	100.00
Total	**849**	**100**	

Note: Table showing the number of countries each molecule in the sample is introduced in during the years 1995-2015, conditional on the molecule being launched in at least one EU member state. Not corrected for right censoring.
Source: Copenhagen Economics, based on IMS data.

The non-parametric Kaplan-Meier estimation technique allows for right censoring and incorporates this in the likelihood function to establish non-biased results

ANALYSING DURATION OF LAUNCH DELAY

Note that as we analyse the so-called duration of launch delay (how long it takes from international launch until launch in the EU member states), the exact distribution of observations across our sample period is not important.[1] What matters is the length of the launch delay regardless of whether the medicinal product is introduced in e.g. 2001 or 2010.

What we are modelling is hence the length of launch delay running from "0" if launched domestically in the same year as the first international launch to "20" if launched internationally in 1996 but not launched domestically by the end of our sample period in 2015. Thus our sample has launch delays falling in the interval from 0 to 20.

An observed molecule can have a launch delay equal to a certain time either because it is introduced domestically at that time or because our sample period ends at that time. For example, a medicinal product introduced internationally in 2002 and domestically in 2004 will have a launch delay of 2. Likewise, a medicinal product introduced internationally in 2014 but not introduced domestically by the end of the sample period (2015) will similarly have a launch delay of 2.

However, the estimation techniques used to identify the *hazard function* in the following analysis take this right censoring into account by estimating the probability of a molecule being introduced at any given time based on the number of molecules actually being introduced compared to those *at risk* of introduction.

HAZARD FUNCTION

The hazard function at a certain point in time describes the probability that a medicinal product will be introduced at a given time, conditional upon not having been introduced before that time.

The estimation method utilised in the following analysis allows for right censoring by comparing the number of medicinal products being introduced at any given time with the number of medicinal products *at risk* of being introduced at any given time.

The number of medicinal products at risk of being introduced at any given time are those that are introduced at that time plus all those that are introduced at future times in the sample, as well as those medicinal products that are censored in the interval between that time and the next year and those censored in any future interval.

1 Unless fundamental conditions in the market not captured by the model have changed.

Over time, the probability of introduction of a given medicinal product decreases

The hazard function, shown to the right, describes the probability of a molecule being introduced in a country at any given time, conditional upon it not having been introduced up until that time.

Thus, if a medicinal product has not been introduced in a given country within five years of its first international launch, there is a 4% chance that it will be introduced in that given year, as illustrated by the dotted line in the graph to the right.

The hazard function shown to the right decreases for the whole time period. This means that the underlying probability of launch decreases as time passes.

This can be explained by the fact that the years of IP protection diminish as time passes and the expected profit of launching in a given country hence decreases over time.

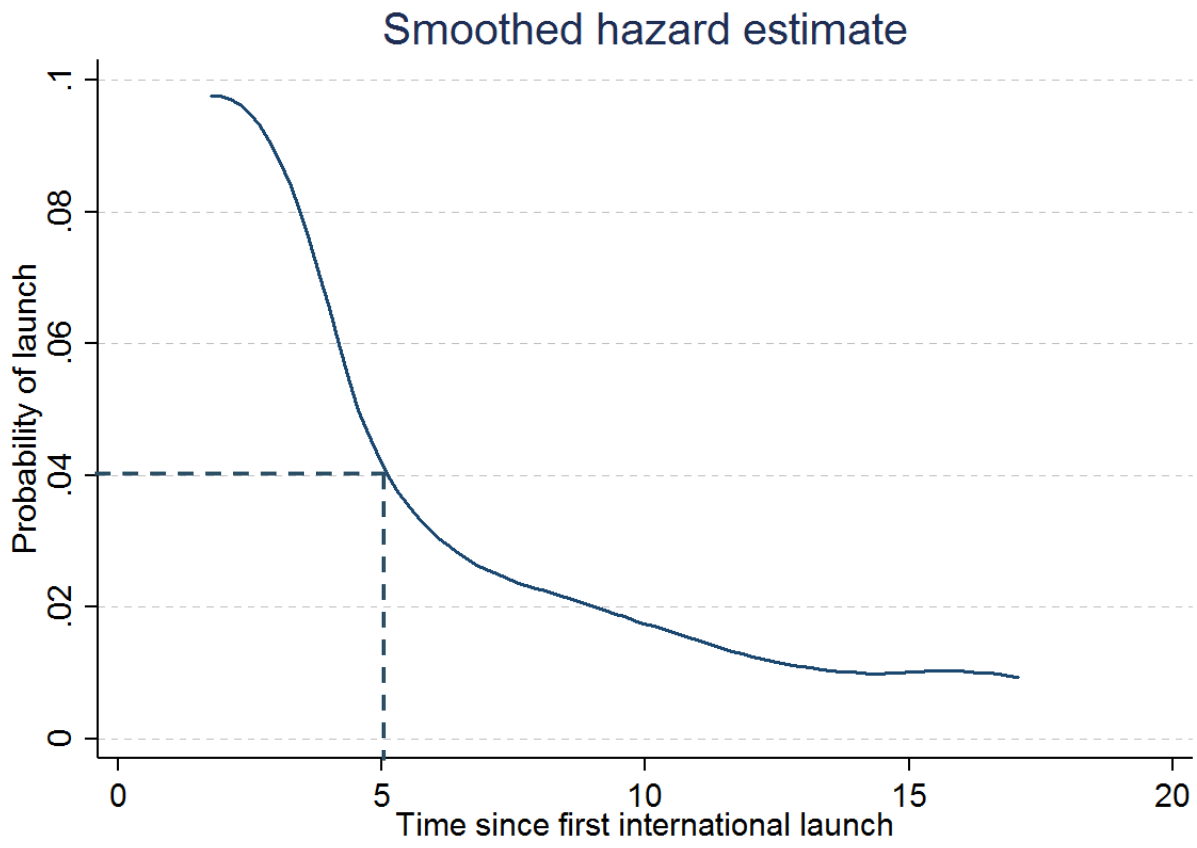
PARAMETRIC ESTIMATION

Using the general estimation technique, one cannot estimate both the baseline hazard function and the effect of explanatory variables at the same time. Thus, when making a parametric estimation, a function form of the baseline hazard must be chosen, and then a shape parameter is estimated along with the coefficients of the control variables.

In our case, the non-parametric estimation of the hazard function bears a resemblance to a Weibull distribution. This is in line with Cockburn et al. (2016). We have used this to guide our choice of the Weibull hazard function as the baseline hazard when undertaking the parametric estimation.

When carrying out the parametric analysis a proportional hazard function is used. This means that the model estimates a common shape of the hazard function for all observations, and the explanatory variables serve to "move" this hazard function up or down.

Non-parametric estimation of the hazard function for the EU member states, 1996-2014



Notes: Graph showing the probability of launch at any given time since first international launch, conditional upon the medicinal product not having been introduced before said time.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

Even twenty years after their first international launch, new medicinal products have been introduced in only half of EU member states

By using the same way of accounting for right censoring, a so-called *failure function* can be estimated.

The failure function estimates the number of EU member states that new molecules are launched in over time after the first international launch. It thus describes the probability of a new molecule being launched before a given time.

Thus, 1.5 years after their first international launch, new molecules were introduced in 25% of the EU member states in our sample.

ONLY LAUNCH IN 50% OF MEMBER STATES

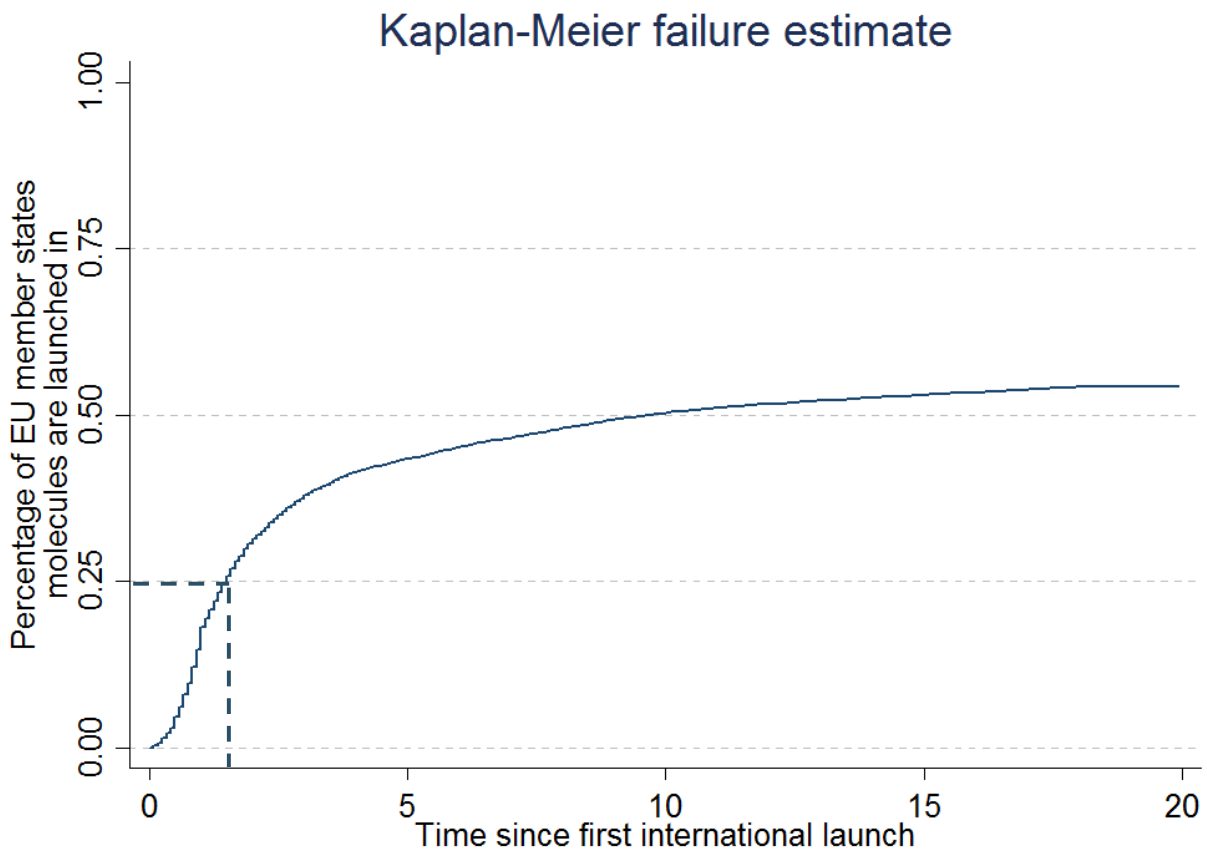
Across the EU, new molecules are launched in only a little more than 50% of EU member states within 20 years of a new molecule's first international launch.[1]

As a launch occurs on a country basis, this means that, on average, only half of EU countries will have a new molecule available on the market within 20 years of it being introduced anywhere in the world.

The median medicinal product launch anywhere in the included European countries is 4.2 years. This means that half of the molecules in the sample are launched in at least one of the member states within 4.2 years of international launch. Correspondingly, half of the molecules are launched later than 4.2 years after first international launch, in at least one of the member states included in the analysis.

The failure functions for each country are available in the appendix.

Fraction of EU member states where molecules are launched, 1996-2014



Note: Graph showing the estimated fraction of EU member states where new molecules are launched over time following their first international launch.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

1 In Creativ-Ceutical for European Commission (2014), External Reference Pricing of Medicinal Products: Simulation-based Considerations for Cross-Country Coordination, the authors find that the application of external price referencing to drive prices down may have the effect that lower-income (and hence price) countries are de-prioritised when new medicinal product launches are taking place, to minimise the effect on prices in other more important markets. This may in part help to explain why after 20 years only a little more than 50% of medicinal product launch opportunities are taken within the EU.

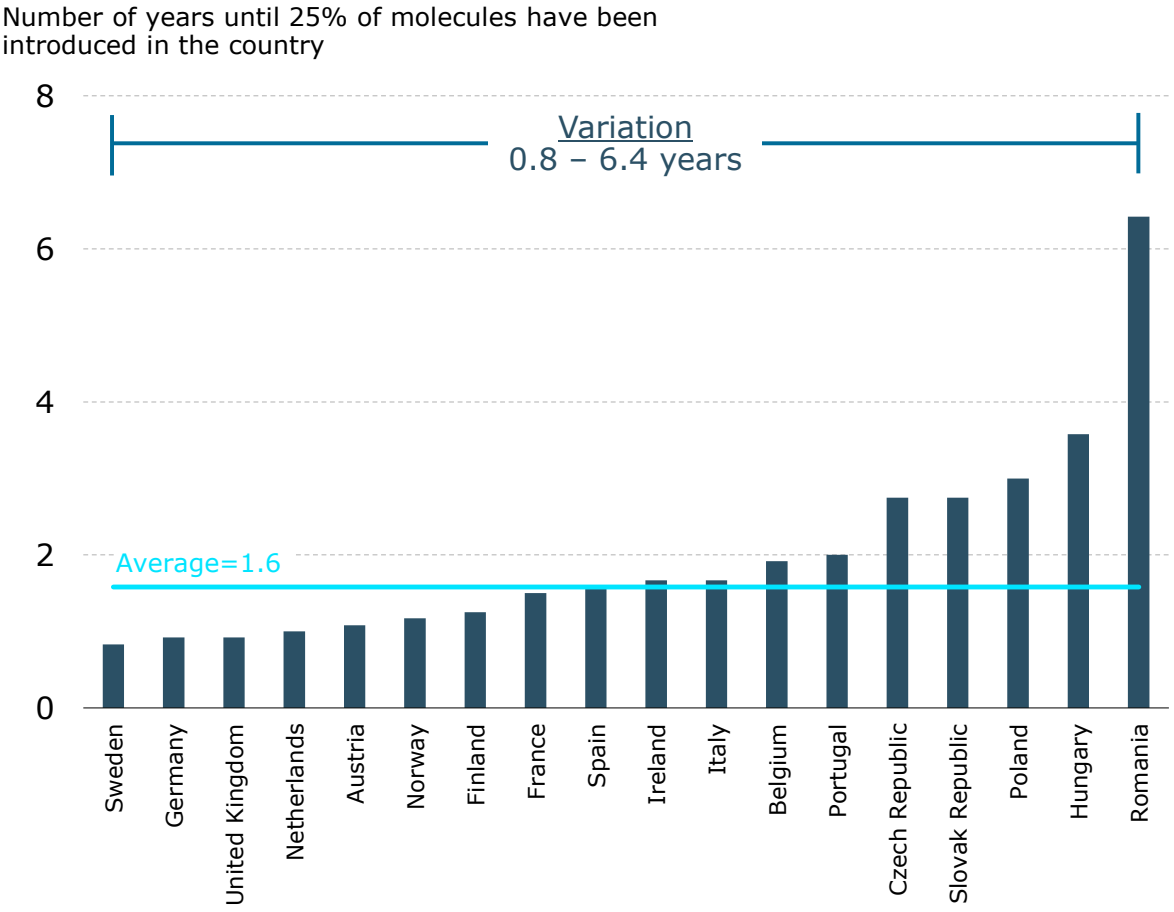
Launch delay from first international launch until 25% of molecules have been launched in member states is relatively low for most countries

The statistical tools allow an analysis of the average time it takes from molecules being launched for the first time internationally until 25% have been launched in the European member states present in the sample.

From the graph to the right it can be seen that for most member states this launch delay period is relatively low.

For Sweden, Germany and the UK it is less than one year and the average is just 1.6. However, for Hungary the launch delay until 25% of internationally available molecules are launched is around 3.5 years, while the delay is more than six years in Romania. This shows that there is much variation among the European member states.

Time from first international launch until 25% of molecules in the sample are launched in the given countries, 1996-2014



Note: Graph showing the average time from first international launch of molecules until 25% are available in the given country.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

Launch delay from first international launch until 50% of molecules have been launched in member states differs fundamentally between countries

The statistical tools allow an analysis of the average time it takes from molecules being launched internationally for the first time until 50% have been launched in the European member states present in the sample.

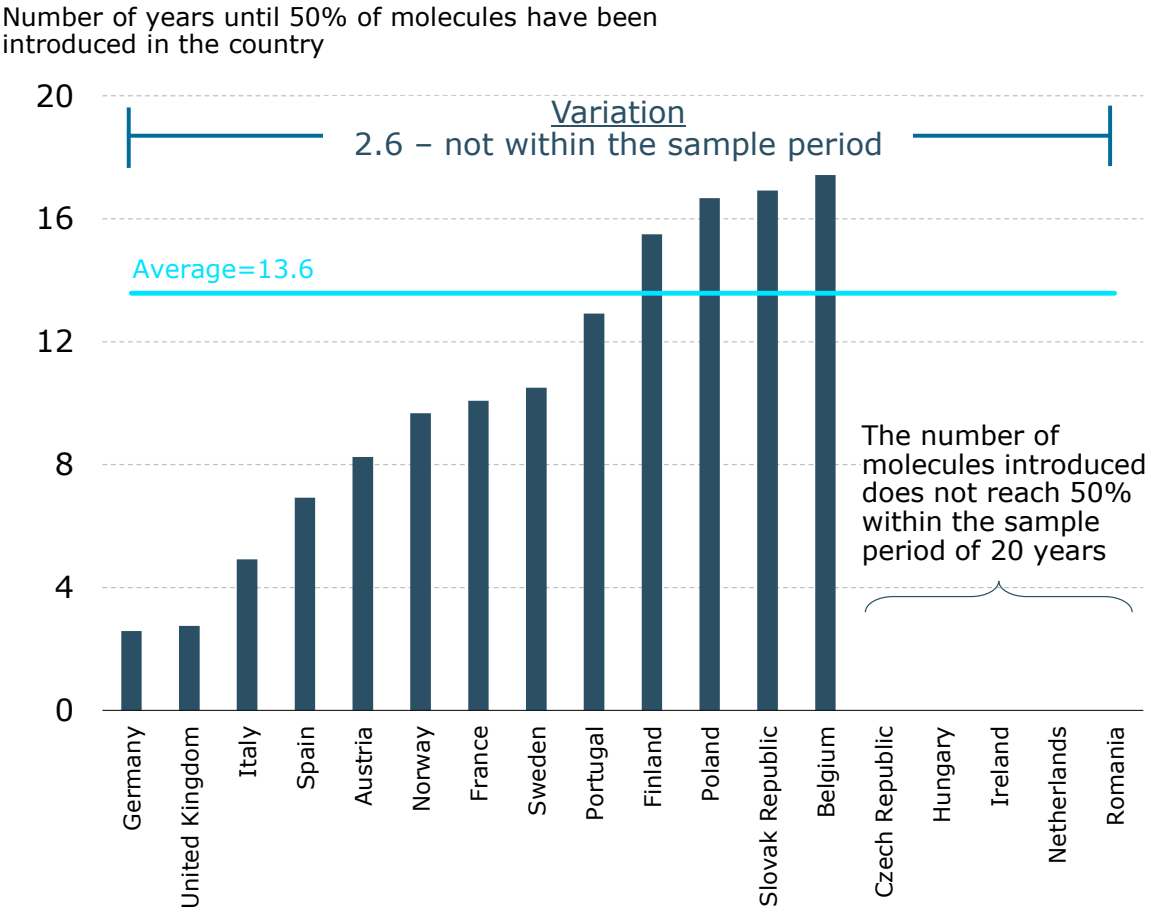
From the graph to the right it can be seen that there is variation in this delay time among member states.

For Germany and the UK the launch delay until 50% of internationally available molecules are launched is less than three years. These two countries also have very low launch delay periods until 25% of internationally available molecules are launched.

Looking at e.g. the Netherlands, the picture is quite different. The Netherlands has a launch delay of just one year until 25% of internationally available molecules are launched. However, during the sample period of 20 years, the Netherlands do not reach the point where 50% of internationally available molecules are launched.

It can thus be seen that the variation in delay times until 50% of internationally available products are launched is bigger than for the 25% mark shown on the previous page.

Time from first international launch until 50% of molecules in the sample are launched in the given countries, 1996-2014



Note: Graph showing the average time from first international launch of molecules until 50% are available in a given country.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

Higher GDP increases the speed and number of new medicinal product launches

The variable *income* is coded as low if GDP per capita is less than USD 30,000 (constant USD, PPP) and high otherwise.[1]

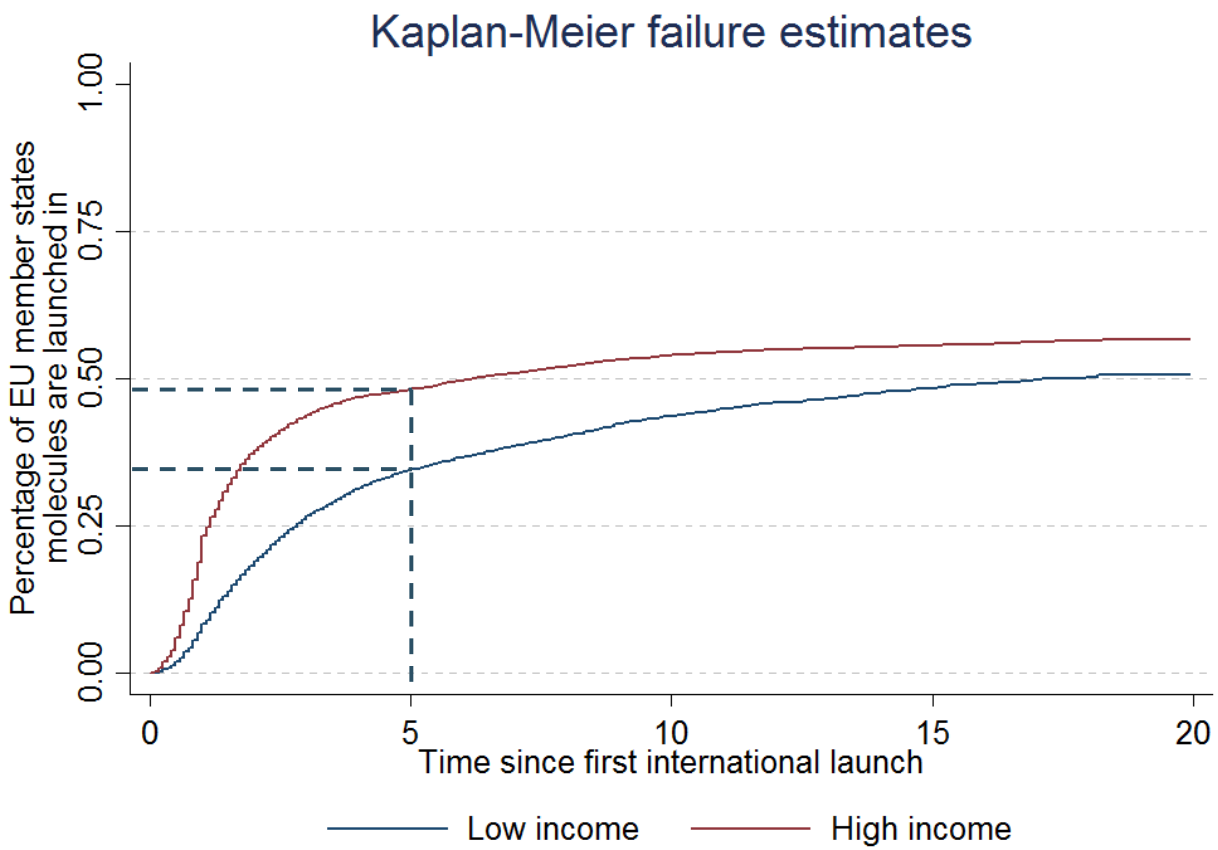
Thus, after five years, around 30% of medicinal product launch opportunities are taken in low-income countries while around 45% are taken in high-income countries.

The gap between high- and low-income countries is most pronounced after around 2.5 years, when it is around 16%. Over time the gap decreases but never fully ceases to exist. After 20 years the gap decreases to around 7%.

This result is perhaps not surprising, but from an EU community perspective it may be concerning nevertheless. The implication of the result is that some countries receive new medicinal products much faster than others, while some medicinal products never become available outside a range of more affluent countries.

To fully reveal the ramifications of and reasons for this result, further research is needed. Apart from the rather one-sided measure of GDP per capita, it would be interesting to see whether institutional factors, the political system, infrastructure etc. explain some of the difference captured in the graph to the right.

Fraction of EU member states where molecules are launched classified by GDP per capita, 1996-2014



Note: Graph showing the estimated fraction of EU member states where new molecules are launched over time following the first international launch. Classified by high and low income. Low income is given as GDP per capita of less than USD 30,000 (in constant USD, PPP). As GDP per capita changes over time, some countries change from the low category to the high category over time. However, generally the following countries fall in the low category: Czech Republic, Hungary, Poland, Portugal, Romania, Slovak Republic. Generally the following countries fall in the high category: Austria, Belgium, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

1 This threshold is the mean across countries and thus ensures an adequate number of observations both above and below it to allow for the statistical analysis.

No difference in launch based on effective protection period

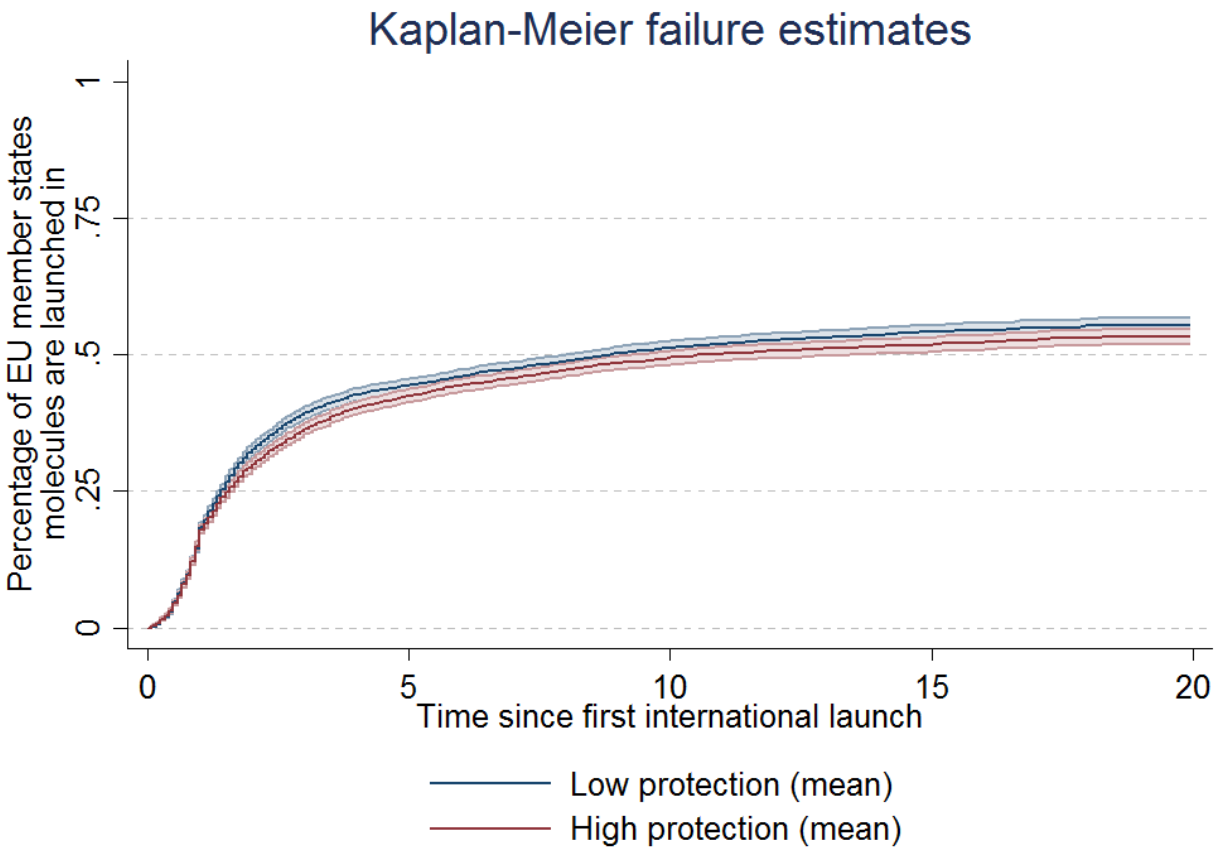
The variable *protection* is coded as low if the effective protection period is less than the mean effective protection period in the given year and as high otherwise.

The two lines in the graph to the right are depicted with 95% confidence intervals. The confidence interval accommodates the fact that these lines are statistical estimates and hence have inherent statistical uncertainty. The confidence interval describes the interval in which the line falls with 95% certainty. If the two confidence intervals overlap, it cannot be concluded that statistically the two lines differ in their estimates.

When looking at the overlapping confidence intervals there does not seem to be a difference in the estimated failure functions of the two categories.

The picture is the same if one uses the median effective protection period as the divider between low and high protection.

Fraction of EU member states where molecules are launched classified by patent protection period, with the mean moving over the years, 1996-2014



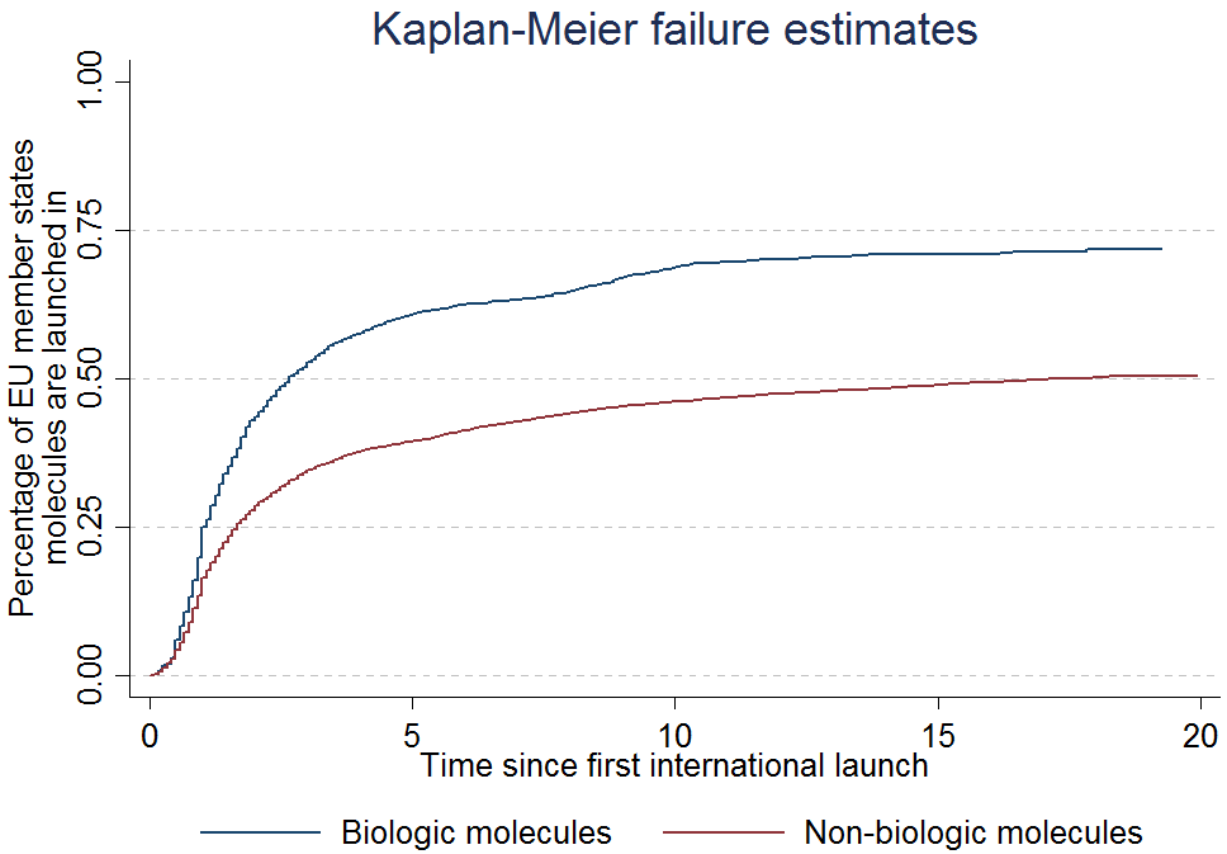
Note: Graph showing the fraction of launch opportunities for molecule-country combinations filed over time from the first international launch of a given molecule.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

Biologic medicinal products are introduced faster and in more countries than non-biologic medicinal products

Biologic medicinal products are introduced much faster and to a much higher degree than non-biologic molecules. This can perhaps be explained by an economic incentive, as biologic medicinal products generally have high prices[1] and thus there are more countries where entry is profitable than is the case for less profitable non-biologic products.

Furthermore, as biologic medicinal products are more complex than regular small-molecule medicinal products, biosimilars are in general harder to make than generics are for chemical products. As such, competition may be less fierce for biologics, adding to the attractiveness of more markets.[1]

Fraction of EU member states where molecules are launched classified by biologic or non-biologic medicinal product, 1996-2014



Note: Graph showing the fraction of launch opportunities for molecule-country combinations filed over time from the first international launch of a given molecule. Medicinal products developed using biotechnological processes as described in the Annex (point 1) of Regulation (EC) No 726/2004 must be authorised through the centralised procedure. In practice this means that most biologic products in the EU are approved through the centralised procedure. However, many vaccines do not fall within the scope of the mandatory centralised approval.[2]

Source: Copenhagen Economics based on IMS data provided by the European Commission.

1 https://www.thebalance.com/top-biologic-drugs-2663233, https://www.forbes.com/2009/12/03/kramer-health-care-intelligent-investing-pharmaceuticals.html, http://health.usnews.com/health-news/health-wellness/articles/2015/02/06/why-are-biologic-drugs-so-costly, http://www.health24.com/Natural/News/why-are-biologics-so-expensive-20170623

2 Wang, W. and Singh, M. (2013), Biologic Drug Products: Development and Strategies.

Large difference in launch speed and number of countries for different ATC codes

Using the present data it is possible to analyse the speed with which new molecules are launched and diffused across the EU member states based on Anatomical Therapeutic Chemical (ATC) codes.

ATC codes are a classification system for classifying different medicinal products based on the "*organ or system on which they act and their therapeutic, pharmacological and chemical properties*".[1] There are five different levels of ATC codes.

If a given molecule is authorised for the treatment of several indications, it may be that it has more than one ATC code. Using the highest level (ATC1, 1st level, anatomical main group), which has 14 codes, in the present sample 59% of the molecules have only one ATC code.

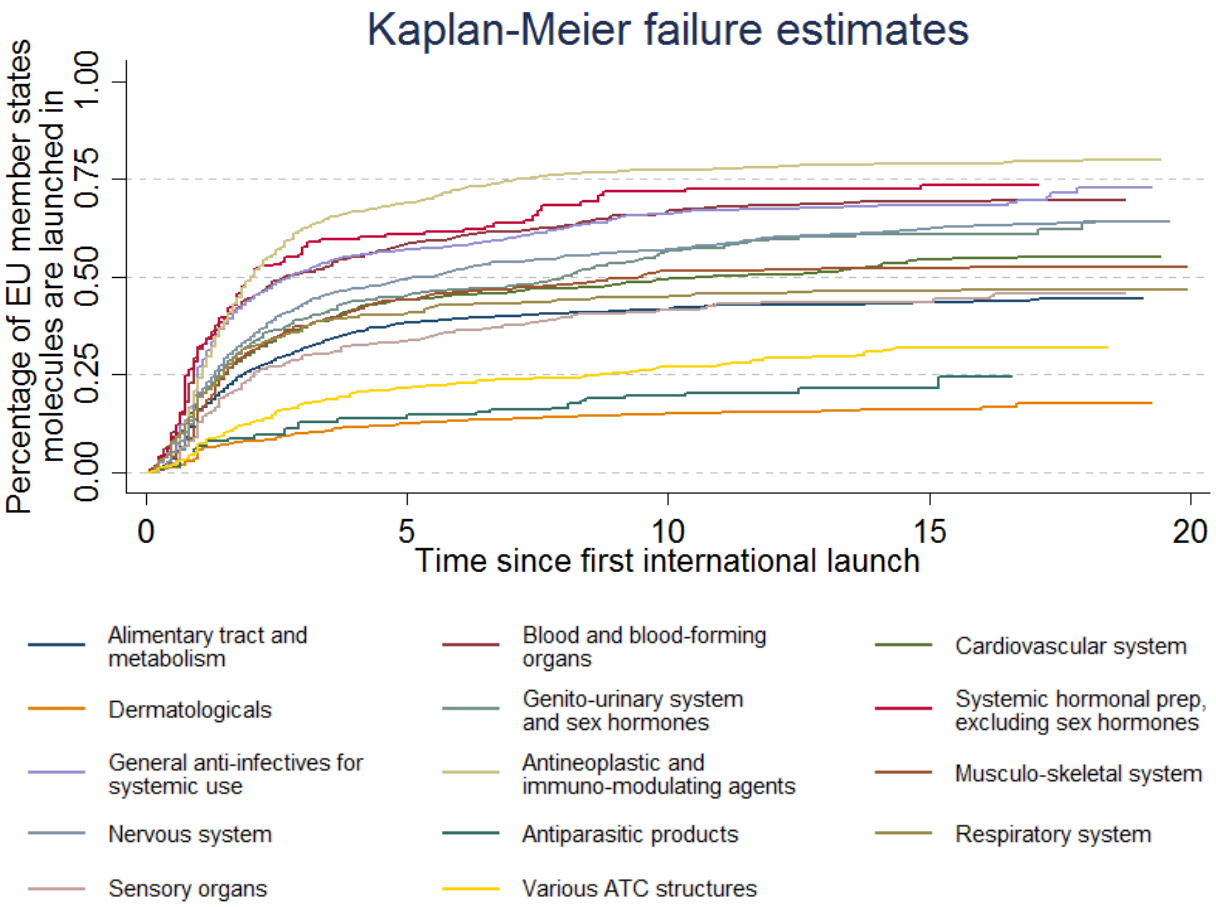
To ensure the analysis is not confounded by molecules with several different ATC codes, these are excluded from the launch analysis to the right. As such, the graph depicts the estimated percentage of EU member states in which the 59% of molecules with only one ATC1 code are launched.[2]

As such, the graph to the right depicts the estimated launch speed and launch extent across EU member states and categorised by ATC code.

The medicinal products with the highest estimated launch are products belonging to the ATC1 category of "Antineoplastic and immuno-modulating agents". This category contains many cancer medicines.

The medicinal products with the lowest estimated launch are products belonging to the ATC1 category of "Dermatologicals".

Fraction of EU member states where molecules are launched classified by ATC-code, 1996-2014



Note: Graph showing the estimated fraction of EU member states where new molecules are launched over time after first international launch. Classified by ATC code at the broadest level.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

1 WHO Collaborating Centre for Drug Statistics Methodology (www.whocc.no).

2 Non-randomly excluding molecules opens up the estimation to possible bias, if the excluded molecules systematically differ from the included ones. However, assigning only one ATC1 code to a molecule with several ATC1 codes would likewise entail a possible bias depending on the allocation mechanism used. As such, the exclusion strategy has been deemed the most implementable approach.

The econometric modelling of the availability of pharmaceuticals shows a range of interesting points (1/2)

MARKET SIZE AND WEALTH

The process behind a pharmaceutical firm's decision to launch a medicinal product is an intricate procedure and involves many considerations. Among these is the attractiveness of the market (and possibly strategic, political and ethical considerations; i.e. ensuring that as many patients as possible have access to a given treatment).

The overall attractiveness of a given market is based on a combination of a range of elements. These include e.g. market size (i.e. number of patients), willingness to pay for pharmaceuticals, pricing structure, structure of the healthcare system, culture and more.

Across model formulations it can be seen that an increase in the size of the population has a negative effect on the probability of launch. This may partly be explained by the fact that without an accompanying increase in the wealth of a country, population increase makes GDP per capita fall. As such, this leaves fewer resources to be spent on new innovative medicine for each individual citizen.

Likewise, it can be seen across formulations that the wealth of a country as measured by GDP has a positive effect on the probability of launch. This may be explained by more wealth enabling people to spend more money on treating different diseases through the use of e.g. pharmaceuticals.

This may happen through an increase in both the scope of diseases treated with pharmaceuticals and the propensity to spend money on pharmaceuticals. An increase in the scope of diseases treated could happen e.g. through people buying medicinal products to treat a disease instead of waiting for it to go away or using various household remedies.

An increase in the propensity to spend money on medicinal products may e.g. manifest itself in people having enough purchasing power to buy the newest, most innovative medicine to treat their specific disease.[1]

INTERACTION OF MARKET SIZE AND WEALTH

Expected profit, which is a main driver behind a pharmaceutical company's launch decision, is determined by both the quantity sold and the price obtained per unit.

In a very simplified way and with certain limitations and caveats, GDP and population size can be used as proxies for expected profit.

GDP per capita can be seen as a willingness-to-pay estimate and can therefore represent the possible price[2] and the population size can stand in for the number of possible patients.

The caveats are that GDP per capita may not be an accurate measure for willingness-to-pay for medicinal products. This also depends on e.g. the way individuals plan their consumption. One consumer may be willing to spend a large part of her income on medicinal products, while another consumer, perhaps with an even larger income, may not be willing to spend as much as the individual with a lower income. As such, personal preferences matter as well.

Population size may not accurately track the size of the market as some diseases may be more prevalent in some countries than in others. This may be due to e.g. geography (malaria in the tropics) or the demography of the population (some diseases are e.g. more prevalent in the elderly part of the population).

To analyse whether the joint presence of both a large potential market and a possibly high willingness to pay for pharmaceuticals has a combined effect on the probability of launch of pharmaceuticals, an interaction term between GDP and population can be included in the model. GDP per capita is also used.

Including an interaction term between these two variables in model 2 reveals a positive and statistically significant effect. This signifies that for countries with a large population, an increase in GDP has a larger positive effect on the probability of launch than for countries with a small population.

This seems to suggest that the joint presence of a large potential market and a potentially high willingness-to-pay plays at least a part in the launch decision of new pharmaceuticals. A possible explanation may be that the higher the willingness-to-pay is in a given country, the higher the price that companies can charge. Hence, these markets are more profitable and the launch is undertaken first here.

1 In countries where the patient does not directly pay for pharmaceuticals themselves, this may manifest itself through an upward pressure on the government to provide more expensive innovative treatments or on the insurance companies to offer more extensive coverage, including expensive new medicine.

2 Many other elements play a role here as well. Among these are price control mechanisms and price referencing. Using GDP as a measure for willingness-to-pay is a valid method, regardless of whether the consumer or private or public health insurance pays for the medicinal products, as GDP measures the wealth of the country as a whole.

The econometric modelling of the availability of pharmaceuticals shows a range of interesting points (2/2)

NO APPARENT EFFECT OF THE EFFECTIVE PROTECTION PERIOD

Common to the different formulations of the model presented here is the finding that by using the available data material it is not possible to identify a statistically significant effect of the effective protection period on the probability of launch.

It is important to note that this is not necessarily equivalent to the effective protection period pharmaceuticals face in a given country not having an effect on the probability of launch. It could also be that there is a high degree of correlation between market attractiveness and the effective protection period. If this is the case, it may be difficult to separate the two effects, making it difficult to statistically identify a significant effect of the effective protection period.[1] This does not necessarily mean that it is not important; it may be a result of its being correlated with other similarly pivotal variables.

As with all statistical methods there are caveats that one must be aware of. The above-mentioned is one such point.

EFFECTIVE PROTECTION PERIOD IN COMBINATION WITH MARKET SIZE AND WEALTH

Using the same line of thinking as in the previous section it may be that even though it is not possible given the data material and econometric models utilised to identify an isolated effect of the effective protection period (see model 1), it may play a role in an interaction with e.g. the population size and the wealth of the countries.

This assertion can be checked by including an interaction term between the effective protection period and population (see model 3) and an interaction term between the effective protection period and GDP (see model 4).

However, in neither of the two model formulations is there a statistically significant effect of the included interaction term. This does not necessarily mean that there is no joint effect of the variables; it may rather come down to a low level of variation in the effective protection period data.[1]

USING GDP PER CAPITA

In models 1 through 4, the absolute values of the population and GDP are included. This is done following the assertion that these represent two important elements when assessing the attractiveness of a market; i.e. they are proxies for the absolute size of a market and willingness-to-pay.

However, a large GDP spread among many people does not necessarily constitute an attractive market, nor does a low GDP necessarily constitute an unattractive market if it is spread among only a few people.

The fact that the interaction between GDP and population in model 1 is significant suggests that the interplay between the variables is important.

Another way of gauging this relationship is to include GDP per capita as a control variable. This variable serves as an international measure of the wealth of a country. The higher GDP per capita is, the more affluent a country is.[2]

When GDP per capita is included in the model instead of GDP and population, a statistically positive effect can be identified. This shows that regardless of the absolute size of the market, the probability of launch is larger in rich countries than in less affluent countries.

THE FOLLOWING SECTION

In the following page a table with output from each model is presented. The following pages delve deeper into each model and provide insights beyond those already provided here.

1 This point will be elaborated upon with an auxiliary regression on p. 136.
2 The GDP measure used in the regressions is in constant prices and adjusted for purchasing power parity.

Five different model formulations are utilised to analyse the elements affecting the availability of pharmaceuticals

Duration models with Weibull baseline hazard function

On the following pages each model is examined in turn. In addition to the regressions listed here, the last section features a regression including ATC codes as independent variables.

	Model				
Variable	1	2	3	4	5
Effective protection period	0.9995	1.0005	1.0169	1.0018	0.9949
Population	0.7115***	0.7759***	0.6750**	0.7123***	
GDP	1.6193***	2.2719***	1.6239***	1.5654***	
Non-biologic molecule	0.4963***	0.4959***	0.4963***	0.4963***	0.4997***
Constant	0.0891***	0.1094***	0.0709***	0.0870***	0.0668***
GDP * Population interaction		1.1047**			
Effective protection period * Population interaction			1.0039		
Effective protection period * GDP interaction				1.0026	
GDP per capita					1.5124***
p	0.6357***	0.6378***	0.6359***	0.6358***	0.6339***
Log pseudo-likelihood	-21,318.38	-21,300.43	-21,318.08	-21,318.27	-21,385.14
Subjects	16,300	16,300	16,300	16,300	16,300
Observations	119,176	119,176	119,176	119,176	119,176

*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Coefficient reported in hazard ratios. Population is given in natural log and billion people, GDP is given in natural log and trillion international 2011 dollars at PPP, GDP per capita is given in natural log and thousand international 2011 dollars at PPP. The variable p is the estimated shape parameter of the Weibull baseline hazard function. Medicinal products with a negative development time are not included when calculating the effective protection period.*
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

Market size and willingness-to-pay for pharmaceuticals are two important factors in a firm's launch decision

In this simple model controlling for population size, GDP and whether the medicinal product is biologic or not, the effective protection period cannot be found to have a statistically significant effect on the probability of launch.

As previously touched upon, this may however be due to a correlation between market attractiveness and the effective protection period (see next page).

Increasing the size of the population by 1% decreases the probability of launch at any given time by 0.34%.[1] One reason for this may be that increasing population size without increasing the wealth of the country decreases the per capita amount available for spending on pharmaceuticals. Market size does indeed increase, but as purchasing power does not follow suit, the coefficient suggests that the overall effect on the attractiveness of the market is negative.

Increasing the GDP of a country by 1% increases the probability of launch by 0.48%.[2] One explanation for this may be that when the country's GDP increases, the amount available for spending on pharmaceuticals increases. As such, the positive sign of the coefficient seems to suggest that this increases the attractiveness of the market.

The coefficient of "non-biologic molecule" signifies that the probability of launch for regular small molecule medicinal products is only half that of biologic medicinal products.

Duration model with Weibull baseline hazard function of molecule launch probability, 1996-2015

Variable	Estimated coefficient
Effective protection period	0.9996
Population	0.7114***
GDP	1.6193***
Non-biologic molecule	0.4963***
Constant	0.0891***
P	0.6357***
Log pseudo-likelihood	-21,318.38
Subjects	16,300
Observations	119,176

*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Coefficient reported in hazard ratios. Population is given in natural log and billions of people, GDP is given in natural log and trillions of international 2011 dollars at PPP, and GDP per capita is given in natural log and thousands of international 2011 dollars at PPP. The variable p is the estimated shape parameter of the Weibull baseline hazard function. Medicinal products with a negative development time are not included when calculating the effective protection period.*

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

1 ln(0.71167)=0.34
2 ln(1.61931)=0.48

The effective protection period is correlated with market attractiveness, making identification of a separate effect difficult (1/2)

As was shown in chapter 1, there seems to be a correlation that more SPCs are sought in larger countries. If this entails the effective protection period being higher in countries with larger populations, we may not be able to identify a separate effect of the effective protection period, as it is correlated with population size.

To further analyse this, an auxiliary regression can be utilised. The auxiliary regression can give us an idea as to whether any correlation exists between population and effective protection period. However, as it is auxiliary in nature, no conclusions can be directly inferred from the size of the coefficients.

By using a panel data model with a fixed effect it is possible to analyse whether there is a statistically significant relationship between market attractiveness and the effective protection period.

From the regression reported to the right it can be seen that there is indeed a relationship over time between the effective protection period and population size and GDP.

A bigger population is correlated with a longer effective protection period. However, at face value, the regression suggests that a higher GDP is correlated with a shorter effective protection period.

Fixed effects estimation using the effective protection period as a dependent variable, 1996-2015

Variable	Estimated coefficient
Population	13.48***
GDP	-9.950***
Constant	62.16***
Observations	352
Number of countries	18
R-squared	0.319

*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Population is given in natural log and billions of people, GDP is given in natural log and trillions of international 2011 dollars at PPP, and GDP per capita is given in natural log and thousands of international 2011 dollars at PPP. Medicinal products with a negative development time are not included when calculating the effective protection period.*
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

The effective protection period is correlated with market attractiveness, making identification of a separate effect difficult (2/2)

The negative relationship between GDP and effective protection period may be explained to some extent at least by the launch strategy of firms.

If a medicinal product has taken a very long time to develop and has only a short protection period left when it is ready for market, the cost-benefit analysis may reveal that the only countries where a positive profit post-launch can be expected are countries with a high willingness to pay, measured here as GDP. This is built on the fact that the potential for earning a profit is higher if launching in a high-income country than if launching in a low-income country. As such, by launching in a rich country, it may be possible to earn a higher revenue in a shorter period than by launching in a less affluent country.

This may entail more medicinal products with short protection periods being launched in high GDP countries than in low GDP countries. This would be consistent with the results reported on the previous page.

Having both a high willingness-to-pay and a large market increases the probability of launch even further. This underscores how both parameters are important for the attractiveness of a market

Including an interaction term between GDP and population can reveal whether these two variables have an additional effect when jointly high (or low).

When including an interaction term, the overall effect of e.g. GDP depends on both the coefficient of the individual GDP variable, the coefficient of the interaction term and the size of the population. The next page presents evidence on the effect of a change in GDP.

At face value, the coefficient of the interaction term suggests that in a country with a large population, an increase in GDP has a more positive effect on the probability of launch of a new medicinal product than in a country with a small population. Vice versa, an increase in population size seems to have a more positive effect in a country with a high GDP than in a country with a low GDP. A more precise interpretation is given on the next page.

The significance of the effective protection period does not change.

Duration model with Weibull baseline hazard function of molecule launch probability, 1996-2015

Variable	Estimated coefficient
Effective protection period	1.0005
Population	0.7759***
GDP	2.2719***
Non-biologic molecule	0.4959***
Constant	0.1094***
GDP * Population interaction	1.1047**
P	0.6378***
Log pseudo-likelihood	-21,300.43
Subjects	16,300
Observations	119,176

*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Coefficient reported in hazard ratios. Population is given in natural log and billions of people, GDP is given in natural log and trillions of international 2011 dollars at PPP, and GDP per capita is given in natural log and thousands of international 2011 dollars at PPP. The variable p is the estimated shape parameter of the Weibull baseline hazard function. Medicinal products with a negative development time are not included when calculating the effective protection period.*

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

Wealthier countries have more launches and have them earlier

The previous model formulations focused on the absolute size of the market as represented by total population and the willingness-to-pay for pharmaceuticals as represented by GDP. The positive interaction term between the two suggests that the joint presence of both a large potential market and a potentially high willingness-to-pay has a positive significant effect on the launch decision.

In model 5, GDP per capita is included instead of population and GDP.

It can be seen that the variable is statistically significant and positive. The coefficient signifies that increasing GDP per capita by 1.000 dollar[1] increases the probability of launch by 51%.

As such, here it is likewise found that greater wealth increases the probability of launch. This underscores the previous findings and adds to the robustness of the results.

Duration model with Weibull baseline hazard function of molecule launch probability, 1996-2015

Variable	Estimated coefficient
Effective protection period	0.9949
Non-biologic molecule	0.4997***
Constant	0.0668***
GDP per capita	1.5124***
P	0.6339***
Log pseudo-likelihood	-21,38.14
Subjects	16,300
Observations	119,176

*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Coefficient reported in hazard ratios. Population is given in natural log and billions of people, GDP is given in natural log and trillions of international 2011 dollars at PPP, and GDP per capita is given in natural log and thousands of international 2011 dollars at PPP. The variable p is the estimated shape parameter of the Weibull baseline hazard function. Medicinal products with a negative development time are not included when calculating the effective protection period.*
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

1 Measured in 2011 international dollars at PPP.

The ATC code is a significant determinant of launch speed and diffusion across EU member states

The table to the right reports the duration model estimates when the ATC1 codes are included as explanatory variables.

It is important to remember that this entails restricting the sample, as some molecules have more than one ATC1 code. Consequently, the regression to the right is restricted to the 85% of molecules in the full sample which have only one ATC1 code.

For the regression method to work, one ATC1 group has to be left out as a reference. The reference ATC1 code is "Alimentary tract and metabolism". A coefficient larger than one for the included ATC1 codes thus means that molecules within this category have a greater probability of launch than molecules belonging to the reference group. A coefficient smaller than one signifies that molecules within this group are less likely to launch than molecules within the reference group.

The coefficient estimates mimic to a high degree the estimated launch speed and diffusion shown previously in this chapter. "Antineoplastic and immuno-modulating agents" has a launch probability more than twice as great as that of the reference group. At the other end of the spectrum, the launch probability of "Dermatologicals" is on average only 30% of that of the reference group.

This generally means that many of the molecules used for treating e.g. cancer are launched faster and to a higher degree across Europe than are molecules used for treating dermatological conditions.

Nearly all of the estimated coefficients for the different ATC1 codes are significant. As such, the ATC1 code seems to be a significant predictor of launch speed and diffusion across EU member states.

Duration model with Weibull baseline hazard function of molecule launch probability, 1996-2015

Variable	Estimated coefficient
Effective protection period	0.9971
ATC1 code	
Blood and blood-forming organs	1.9267***
Cardiovascular system	1.3315***
Dermatologicals	0.3032***
Genito-urinary system and sex hormones	1.4960***
Systemic hormonal prep, excluding sex hormones	2.0750***
General anti-infectives for systemic use	1.9900***
Antineoplastic and immuno-modulating agents	2.6780***
Musculo-skeletal system	1.2363***
Nervous system	1.6754***
Antiparasitic products	0.4273***
Respiratory system	1.1096*
Sensory organs	1.0287
Various ATC structures	0.5789***
Population	0.7218***
GDP	2.5481***
GDP * Population interaction	1.1172***
Non-biologic molecule	0.8168***
Constant	0.0452***
p	0.6709
Log pseudo-likelihood	-17,990.20
Subjects	13,785
Observations	93,903

*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Coefficient reported in hazard ratios. Population is given in natural log and billions of people, GDP is given in natural log and trillions of international 2011 dollars at PPP, and GDP per capita is given in natural log and thousands of international 2011 dollars at PPP. The variable p is the estimated shape parameter of the Weibull baseline hazard function. Medicinal products with a negative development time are not included when calculating the effective protection period. The reference ATC1 code is "Alimentary tract and metabolism". Molecules with more than one ATC1 code are excluded. This restricts the sample to 85% of the molecules in the full sample.*

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

2.3 IMPACT ON ACCESSIBILITY

Existing literature (1/2)

Berndt and Aitken (2010) use IMS prescription data to study the US pharma market for prescription drugs following regulation in 1984 (i.e. the so-called Hatch-Waxman Act). One important finding from the paper is that the generic share of retail prescriptions in the US has grown substantially, from approx. 19% in 1984 to 75% in 2009.

Furthermore, the authors construct a generic price index for the top 25 generic molecules launched between 2005 and 2009. They find that the generic price index falls from 100 to 68 in the first 12 months following generic entry, and to 27 after the first 24 months. The corresponding average number of generic entrants is 12.

The index is comparable to a similar index constructed in 1996 concerning data from 1994. In 1994, the index fell to 80 in the first 12 months and to 65 in the first 24 months.

To conclude, the key results in the paper are, firstly, that the generic share of retail prescriptions has risen substantially and, secondly, that the effect on price of generic entry has become more rapid.

Wouters and Kanavos (2017) calculate commonly used price indices for generics using 2013 IMS Health data. This is done for seven European countries, and the study encompasses 3,156 generic medicinal products.

In general, the authors conclude that there are large differences in generic drug prices across countries. However, the results are sensitive to the choice of index, base country, unit of volume, therapeutic category etc.

On this basis, the authors conclude that although price indices can be a useful statistical approach to comparing drug prices across countries, researchers and policymakers have to be cautious when using them given their limitations.

Frank and Salkever (1992) investigate the development of pricing following generic entry. The authors use a market segmentation model which delineates a price sensitive market and a price insensitive market segment. Using this method, the study finds that generic entry can lead to increased prices for originator products. Furthermore, it is found that originator companies respond to generic entry by decreasing their spending on marketing.

Frank and Salkever (1995) use the theoretical model developed in Frank and Salkever (1992) as the point of departure for an empirical analysis.

In the paper, the authors observe a substantial increase in the share of generic products sold by prescription in retail pharmacies in the US since the 1980s. This is comparable to the result found in Berndt and Aitken (2010), although this paper is naturally concerned with a shorter time period.

The data used in the empirical analysis comes from IMS America.

By studying a sample of 32 drugs post-patent expiry, the authors find that branded products increase in price after generic entry, while more competition among generic producers results in substantial price reductions for those drugs. The net effect of these price changes is a reduction in the average price of a prescription for the off-patent drug.

Pammolli, Magazzinni and Orsenigo (2002) study the intensity of competition within pharmaceuticals after a patent expires. The authors show country-level variation in relationships between prices, patent expiry and competition. They differentiate between market-based competition regimes in the US and price administration systems in the EU. Quarterly data from the IMS MIDAS database covering the years 1987-1998 is utilised. The main findings are that in the US, prices increase over time, before and after patent expiry, while European prices decline when patent expiry is approaching and continue to either decline or stagnate after expiry.

The authors conduct a multivariate analysis. For the US, the key results concerning the average price of the original products are that:

- The average price of the original products increases over time.
- An indicator-term for patent-expiry is statistically insignificant.
- However, an interaction term between patent expiry and time is significantly negative, implying that patent expiry slows the price increase.
- Generic entry negatively affects prices and over time slows price increases.

Existing literature (2/2)

In the European countries considered, the average prices of original products decrease over time, even before patent expiry. This result is the opposite of the result for the US, where prices increase over time.

Germany is the only country considered in the study where patent expiry itself significantly affects prices (negatively). Over time, patent expiry significantly slows the decrease of prices in France and Italy, meaning that the average price of the original product decreases more rapidly prior to patent expiry than afterwards.

Generic entry significantly magnifies price decreases in France and Italy while slowing the fall of prices in the UK.

A similar estimation was done for the average prices of generics. This showed that a more concentrated market will have higher prices for generics in the US and France and conversely have lower prices in Italy. In the UK and Germany, the effect is statistically insignificant.

Over time, the average price of generic drugs decreases significantly in all countries except Italy, where the effect is positive but insignificant.

The results of the paper are consistent with the observation that prices tend to fall with age in Europe. Conversely, US original producers seem firstly to practice penetration pricing to some extent (setting lower prices initially to win market shares), and secondly to succeed in segmenting the market after patent expiry in order to continue charging premium prices on their branded drugs.

Using the IMS Health database Midas covering the market for angiotensin-converting enzyme[1] (ACE) inhibitors for a range of European countries in the period 1991 to 2006, **Von der Schulenburg, Vandoros and Kanavos (2011)** study the effect of drug market regulation on originator pharmaceutical prices. The authors find that while generic entry does not have an immediate effect on originator prices, subsequent changes in generic prices do. It is likewise found that an increasing number of competitors leads to decreasing originator prices. Thus, in the case of ACE inhibitors in Europe, originator prices are responsive to generic entry and competition.

Furthermore, the study shows that mandatory generic substitution and regressive pharmacist mark-ups have a strong negative effect on originator prices.

The results are not as pronounced for demand-side measures. Profit controls and the use of cost-effectiveness analysis appear to have a negative effect on prices, while the results of price referencing are inconclusive.

In relation to this study, it should be noted that the data exclusively covers ACE inhibitors (drugs used to treat hypertension).

1 ACE inhibitors are e.g. used for treating hypertension and congestive heart failure.

Declining prices after generic entry (1/2)

RESULTS

Our analysis shows that the price of the original medicinal product decreases around the time period when exclusivity is lost. On average, original medicinal product prices steadily decrease by 40% during the period six quarters prior to and five quarters after the loss of exclusivity.[1] This is contrary to some of the results from the literature presented on the previous page.

Prices for generic medicinal products entering the market after the original medicinal product loses exclusivity are on average around 50% of the price of the original medicinal product over the first five quarters.

Interestingly, however, there does not seem to be a sharp drop in originator prices immediately after generic entry, even though generic prices are 50% that of the originator price. Furthermore, even five quarters after generic entry, there still seems to be a price gap between originator and generic prices. This is comparable to the findings in the Sector Inquiry.[2]

The above suggests that e.g. brand value and/or switching costs may play a role in the pricing strategy. If there were no brand value/loyalty and patients could immediately switch to the generic medicinal product post generic entry, nobody would buy the originator medicinal product when a cheaper, identical product is available.

Another potentially important point is that there may be inertia in the market whereby doctors and patients only later learn about a new generic. This may be especially important for medicinal products, as in many EU countries, the cost is paid by either the government or private health insurance companies.[3] This means that, in many cases, neither the person writing the prescription nor the person using it has the same monetary interest in finding the cheapest product available as they would have, had they themselves paid for the treatment. However, it should be noted that this is not necessarily the case for all countries and all medicinal products, and as such, it should not be seen as a generalised point but rather as a contributing factor in some instances.

Another potentially important point when it comes to switching patients from an originator product to a cheaper alternative is that the propensity to switch may differ depending on whether the product in question is a chemical compound or biological. Many biologics are relatively new and hence the body of knowledge surrounding this area is limited. Recent studies point to no difference in outcomes for patients switching from an originator biologic to the biosimilar version.[4] However, the aforementioned study still concludes that switching should remain a "case-by-case" decision.

That the originator medicinal product begins its price reduction even before entry of the generic medicinal product suggests that the pricing strategy of the originator firm is influenced even before generic entry. This could be e.g. to increase market share before competition enters.[5] If the patient's course of treatment is very long (for example, if a disease is chronic and switching during treatment is very infrequent), a profit-maximising strategy by the originator firm may be to decrease price prior to the entry of generics to increase market share. After the entry of generics, increasing prices may actually be the most rational strategy, as this "cash-in" action makes only a few patients switch. The alternative is to try to compete with the price of the generic, which may be an unfeasible strategy for the originator firm. Another factor in a price decrease prior to generic entry may be competition from other originator companies. Unfortunately, we cannot identify this kind of competition in the data.

The important point here is that insofar as the SPC delays the time when generics can enter the market, the time when the fall in prices found in this section takes place is delayed.

METHOD

This analysis is based on medicinal product-specific data from the IMS on quarterly revenue and sales volumes in hospitals in 21 European countries for the period 2013Q4-2016Q3 (i.e. 12 quarters). Hence, the dataset is a panel dataset in which we have sales revenue and volumes of specific medicinal products (identified by country, manufacturing corporation and acting molecule) over the period.

We have used this data to analyse what happens to medicinal product prices when original medicinal products lose market exclusivity and generic medicinal products (copies with the same acting molecule) enter the market. We have done this by comparing medicinal product prices for the same molecule in the same country.

1 See graph on p. 146.
2 European Commission (2009), Sector Inquiry – Final Report, p. 83.
3 See the section on pricing drivers for a more thorough review of pharmaceutical firms' pricing strategies.
4 Moots et al. (2017), Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology and dermatology inflammatory conditions: considerations for the clinician.
5 Market share considerations are relevant, of course, only if the company is not the market's sole supplier; i.e. if there are other originator companies offering medicinal products with the same effect.

Declining prices after generic entry (2/2)

To do this, first we have to specify which medicinal products are original and which are copies. For all medicinal products the dataset includes information on the launch date (which may be prior to the first quarter in the dataset 2013Q4). We therefore label the medicinal product which was launched first as the original medicinal product. Medicinal products introduced later are labelled as copies. This is done for each molecule and each country.

As we know the launch date of all medicinal products, we can also extract information about whether the original medicinal product is the only one in the market at any given time. Further, we can specify the time when the first generic medicinal product enters the market. We therefore create a time variable for each molecule and country which specifies the number of quarters before and after the first generic medicinal product is introduced into the market. This variable is shown on the horizontal axis in the figure on the following page.

Medicinal product prices are calculated by dividing sales revenue by sales volumes. For each molecule in each country we normalise the prices so that the price of the original medicinal product in the quarter before exclusivity is lost is 1. Thereby we can compare the prices of different medicinal products with different price levels. Lastly, the normalised prices are averaged for both original and generic medicinal products. The result is shown in the figure on the following page.

RESTRICTION ON DATA

A number of data corrections had to be carried out to make the prices comparable. The IMS data includes three different volume measures: units, standard units and kg. However, volumes in units and kg seem to be flawed as implausibly large variations can occur over time for the same product. This analysis was therefore restricted to the use of standard units. With the standard unit, it should be possible to compare products whose package sizes differ. However, we found that in a large number of cases this cannot be done. We therefore manually adjusted the standard units according to the number of milligrams in each package. The information on milligrams was available and feasible only for a subset of the data. We have therefore restricted the data to only look at capsule products. The IMS documentation did not contain enough detail to confirm this method, and this is a potential cause of error.

The result is a very restricted data sample of the original dataset. The final dataset used had 3,500 observations representing around 600 different medicinal products. If more information about the reasons behind the irregularities in the data can be obtained, the current analysis can be greatly expanded.

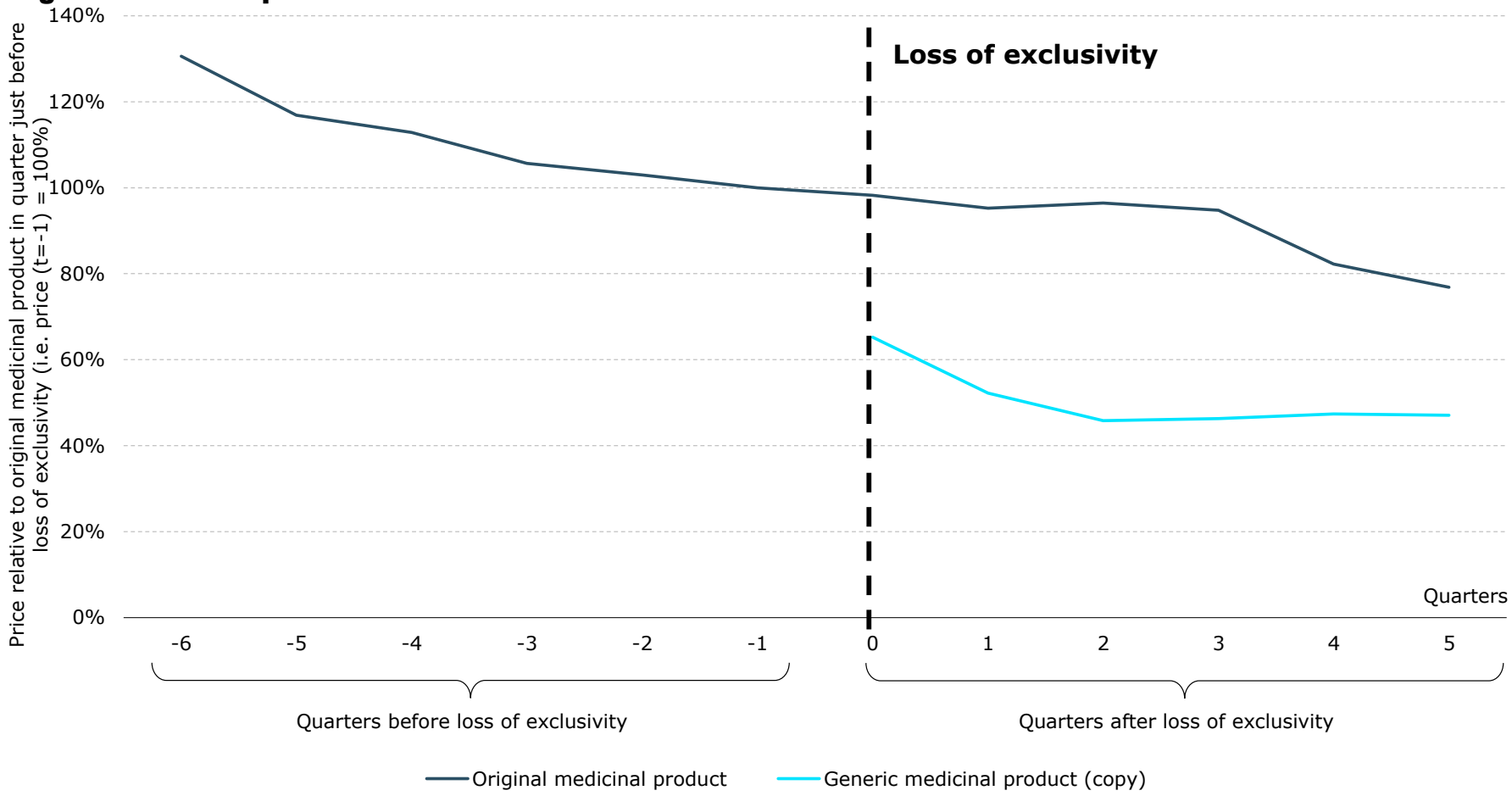
Note that we compare prices of medicinal products with the same acting molecule. However, a given molecule can be used for several treatments/indications and possibly be priced based on the intended use. This is not taken into account in the current analysis as we do not have information on which molecules can be used for which treatments.

The data present does however include ATC codes.[1] Using ATC1 codes would allow the analysis to determine whether the price difference and change are different for medicines used in different therapeutic areas. Unfortunately, the previously described restrictions put on the sample do not allow individual analysis of ATC1 codes as there are too few observations within each category.

1 ATC codes are a system for classifying different medicinal products based on the "*organ or system on which they act and their therapeutic, pharmacological and chemical properties*". See WHO Collaborating Centre for Drug Statistics Methodology (www.whocc.no).

Analysis of the effect of exclusivity on medicinal product prices (1/2)

Average price development of original and generic medicinal products before and after loss of exclusivity of original medicinal product



Source: Copenhagen Economics analysis based on IMS data provided by the European Commission.

Analysis of the effect of exclusivity on medicinal product prices (2/2)

From the graph on the previous page it can be seen that generic products enter the market at a price around 40% below that of the originator one quarter prior to entry. Over the following quarters the price of generics decreases to around 40-50% of the originator price prior to generic entry.

Furthermore, the price of the originator product also falls after generic entry. However, the price decrease is not immediately observable. By the fifth quarter after generic entry, the price of the originator product decreases to around 80% of the price prior to generic entry.

An interesting observation is that the prices of originator products also fall in the quarters before the entry of generics. Whether this is due to an anticipatory effect priming the market before competition or whether it is due to e.g. competition from other originators the data unfortunately cannot show us.

Again it should be mentioned that the sample is rather restricted due to data availability issues.

SECTOR INQUIRY

In the sector inquiry of 2009 carried out by the European Commission, a graph similar to the one reported on the previous page was presented.[1] The graph is reproduced to the right for ease of comparison.

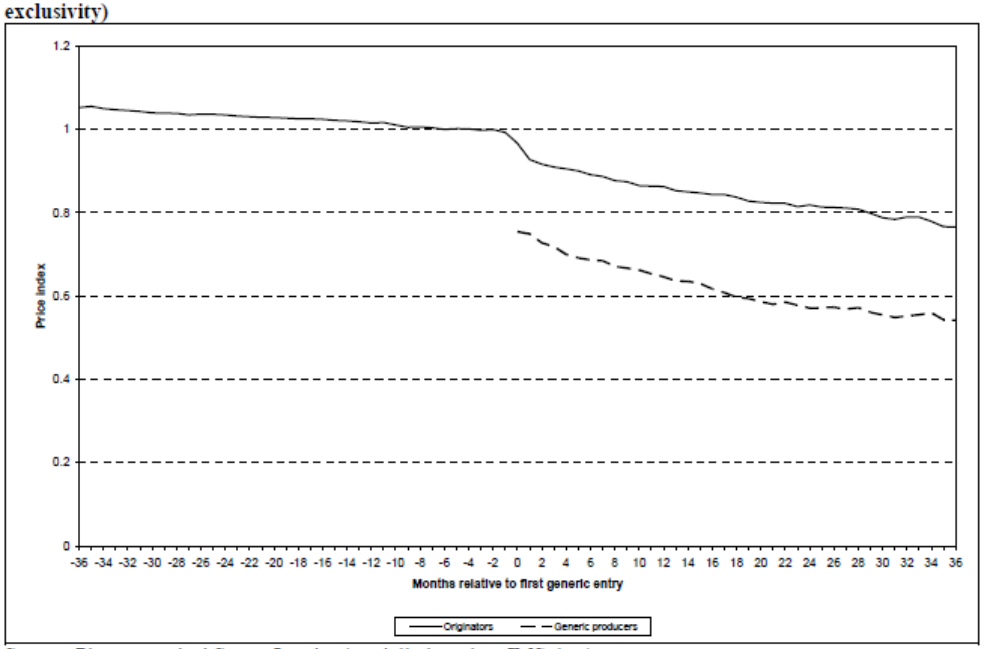
In the graph from the sector inquiry, the drop in originator prices is more pronounced at generic entry. However, the decrease after the initial drop seems to mimic the graph on the previous page quite closely. In the graph from the sector inquiry, originator prices also fall prior to generic entry, albeit not as much as what can be seen in the graph on the previous page.

Generics enter at a price level around 25% lower than the originator price in the graph from the sector inquiry. After entry, prices fall further but do not reach 50% before the end of the observed period. As such, prices for generic products reported on the previous page seem to be lower than that found in the sector inquiry.

A reasonable explanation for this may be the limiting restrictions we are forced to impose on our data sample. In the graph we present, only products in tablet form can be used due to problems with the reported prices for other products. As the sector inquiry is built on a larger sample dataset, it is not surprising that there is some difference in the results.

However, when comparing the two graphs, the available data material for the present study appears to give results in line with those of the sector inquiry.

Figure 25: Development of originator and generic price indices for INNs with generic entry (sample: E75 list, all INNs with entry; weighted by INN; month 0 = entry; index = 1 for price six months before loss of exclusivity)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

1 European Commission (2009), Sector Inquiry – Final Report, p. 83.

Robustness check: Restricted sample

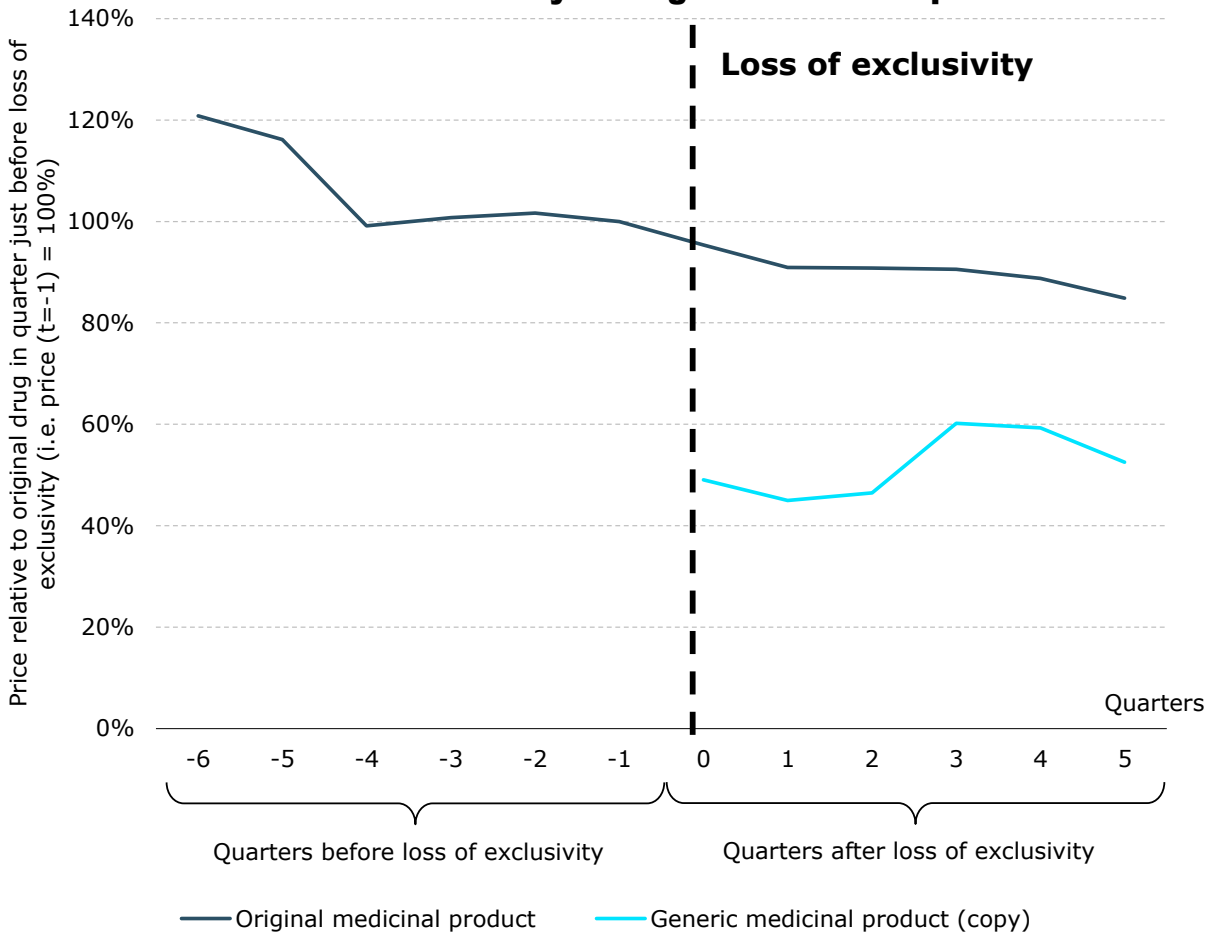
The unit of comparison in each country is the molecule; i.e. the products competing in this analysis are identified by the molecule in the product. As mentioned, a molecule can treat multiple diseases and thus can have very different prices.

In our data we often have multiple original products for a molecule. Such products are often the same molecule but with a different package. One package may be of 100 mg capsules, another of 200 mg capsules. When adjusting prices for the quantity of mg, different prices (per mg) are sometime experienced. If these prices are very different, it may be because these product treat different diseases.

We have therefore conducted a robustness check in which we have restricted the dataset to include only competing products for which the different forms of original medicinal products have roughly the same price per mg (+/- 5%).

The result is shown in the graph to the right. In this restricted sample we also see a decreasing trend for the original medicinal product, and the generic medicinal products enter the market at almost half the price of the original medicinal product. We therefore conclude that the results are fairly robust.

Average price development of original and generic medicinal products before and after loss of exclusivity of original medicinal product



Source: Copenhagen Economics analysis based on IMS data provided by the European Commission.

2.4 PRICING DRIVERS

Introduction to pricing

Gross profit is given by the margin per unit, multiplied by the number of units sold. According to economic theory, firms as a rule will always attempt to set a price which maximises their gross profit.

In this regard, firms generally face a trade-off. They can either set a high price and make a large margin on fewer units (because demand is lower in response to the high price) or set a low price and make a small margin on more units (because demand is higher in response to the low price).

The optimal price will depend on the strength of the demand response to price changes. This varies depending on the characteristics of the market in question.

In our case, we are especially interested in understanding how pharmaceutical companies attempt to maximise their gross profit by setting the price of their medicinal products.

There are a few characteristics which make the market for medicinal products unusual:

- Marginal costs are often negligible, meaning that firms will make a positive gross profit at any positive price[1]. This is not necessarily irreconcilable with strategic launch, as this also depends on e.g. reference pricing and the cost of marketing in a new market.
- Investing in the development of a pharmaceutical is expensive and time-consuming, which means that market entry in response to high short-run market prices is implausible.
- Competing products are in some cases (small molecule) exactly homogeneous (apart from e.g. packaging).
- Usually prices are not updated regularly but often set simultaneously by all firms for a certain period of time; e.g., a tender period.
- Market share has persistence due to patient treatment programmes from which patients cannot always immediately deviate. Firms may thus be able to set a high price and profit from their existing patient base without risking those customers substituting away.
- Consumers of medicinal products (patients) are generally not very price responsive since large parts of their bill are typically covered by public institutions or insurance companies. Nor do the prescribers of the good (doctors) have direct monetary incentives.
- Besides IP protection through patents, regulatory protection schemes exist that protect medicinal products.

ECONOMIC THEORY

The following pages are written from a purely economic viewpoint. This means that there is an underlying assumption that companies are profit-maximising entities. As such, the following sections defer any ethical, political or other considerations which may also have an effect on the strategic decisions of pharmaceutical companies.

This does not mean that pharmaceutical companies do not take ethical, political or other concerns into consideration when making decisions regarding their pricing.

However, to distinguish the range of differing considerations from purely economic incentives, the next section focuses strictly on the latter.

1 This might not necessarily be the case for all pharmaceuticals, e.g. biologics might have another cost-profile.

Market structure

RANGE OF MEDICINAL CATEGORY / NUMBER OF COMPETITORS

The higher the number of competing firms whose medicines are placed in the same tender or treatment category by a public institution, the more intense will be the price competition that arises. Thus a broader definition of medicinal category which places more firms within each category will imply lower prices, as firms must fight to underbid each other and capture market share.

If there are only a few competing firms, it may be possible for the firms to engage in tacit collusion whereby the competing firms implicitly coordinate to establish a high-price equilibrium that is profitable to all firms. However, as the number of competing firms increases, such an equilibrium becomes less sustainable due to the risk of deviation by a single firm.

MARKET SHARE AND SWITCHING

A firm's market share entering the tender period determines the size of the firm's existing patient base on which the firm can profit. This group's demand is likely to be relatively unresponsive to price changes (given that there are some frictions deterring pre-existing patients from switching away immediately or completely).

Firms that have a large stock of current patients will be incentivised to price high in order to profit from their existing customer base if competition intensifies. By setting higher prices, these firms also place less competitive pressure on their competitors, as a result of which price competition in the market may abate.

This means that an uneven distribution of patients between firms, where at least one firm has a very high market share, is likely to give higher prices in general.

SIZE OF CONTESTABLE MARKET SHARE

In some pharmaceutical markets there may be two or more comparable medicinal products which can treat the same illness. However, it will sometimes be the case that specific medicines are recommended to certain patient groups, irrespective of price, if those patients respond most favourably to only that specific medicine.

Patients that will be prescribed the same medicine regardless of price are essentially non-contestable since their demand is ensured to the producer of the specific medicine.

If the share of non-contestable patients in the market is high overall, then firms will, ceteris paribus, set higher prices to profit from those customers. The market will be characterised by less competitive pressure, and all firms can thus set higher prices, even those firms that do not themselves have a non-contestable base.

LENGTH OF AVERAGE PATIENT TREATMENT PERIOD

The degree of persistence in market share will depend partly on the potential degree of switching behaviour in patients and partly on the length of treatment periods.

If the length of average treatment periods is short, market share persistence may be low and competition for new patients will be constant. This incentivises companies to bid low since they cannot effectively exploit their current market share with a high price.

LENGTH OF TENDER PERIODS

If the pricing or tender periods are long, then the cheapest medicine will accumulate all new patients over a very long period.[1] This will incentivise firms to bid lower initially in order to ensure long-run market share.

REGULARITY OF TENDERS

The regularity of price updates or tenders can also impact the pricing decision of pharmaceutical firms, although the impact of this parameter is not unambiguous.

On the one hand, competitive iterative pricing patterns can be sped up such that competing firms quickly enter a downwards spiral of pricing towards marginal costs. This is likely if there are many competitors on the market.

On the other hand, however, regular price-setting can also allow competing pharmaceutical firms to exchange more regular signals on pricing strategy. With few competitors, such signalling could enable such firms to potentially establish a high-price bidding pattern that is profitable to all firms.

A combination of the two aforementioned effects may also arise and can be observed in so-called Edgeworth pricing cycles.[2]

1 Unless doctors and patients are unresponsive to price competition.

2 "*Edgeworth pricing cycles refers to an asymmetric pattern of prices that results from a dynamic pricing equilibrium among competing oligopolists*"; see http://www.noeleconomics.com/research/articles/NOEL_palgrave.pdf.

Tender impact and future perspectives

TENDER IMPACT

Structure of competing companies
Regional branches of pharmaceutical firms may not experience full autonomy when setting their local medicine prices. Often, an international headquarters may dictate the pricing strategy for all of its regional branches by setting general pricing guidelines, such as price floors, from which individual countries are not permitted to deviate.[1] The head office will thus prompt regional offices to set higher prices, despite the potential isolated disadvantages of losing individual tenders.

Such firm constellations are most likely to be observed when the medicine in question is produced by large international pharmaceutical companies and competed for in many countries.

Guidelines
State agencies and/or insurance companies will often produce medicine guidelines on the basis of medicine prices. Such guidelines will advise doctors and patients which medicine to use in which cases.

The nature of such guidelines varies from country to country and from medicine to medicine. For example, the guidelines may state that doctors are obliged to prescribe the cheapest medicine in at least e.g. 80% of treatment cases. The guidelines may also be of a more flexible nature whereby the cheaper medicine is simply recommended.

Many countries employ lowest price reimbursement, whereby individual patients are compensated by an amount corresponding to the cheapest available medicine that treats the given disease.

The nature of the resulting guidelines will impact the pricing decision of firms. Hard guidelines for a large proportion of the market will ensure that the contestable market is as large as possible, which will incentivise low bids. Soft guidelines, on the other hand, can allow firms to compete using marketing, research and other channels, thereby enabling more differentiation and higher prices.

Guideline conformity
Doctors and patients may be given some flexibility to deviate from guidelines in individual cases; e.g., in relation to specific symptoms. Doctors and patients may also deviate from the guidelines due to personal preference or for other reasons.

If guidelines resulting from medicine prices are not enforced and/or doctors are explicitly afforded flexibility, then setting the lowest price will not be as important. In this case, firms are more likely to set a higher price and then differentiate their product via research and marketing.

FUTURE PERSPECTIVES

Length of patents and pipeline
Firms will also consider the future perspectives of the market when setting their price. If all of the competing medicinal products on the market have patents which extend far beyond the upcoming pricing or tender period and no new medicines are in the pipeline, then the current market structure will be likely to persist and firms will care about maintaining their future market share. This will, ceteris paribus, incentivise firms to bid lower.

If, on the other hand, the current market is soon to be disrupted by generic medicinal products or a new and improved medicine, then it may make more sense for firms to simply cash in on the existing customer base by setting a higher price.

1 OECD (2008), Pharmaceutical Pricing Policies in a Global Market.

Switching rates in pharmaceutical markets

MEDICINE PROCUREMENT

Medicine is often paid for by the public sector or insurance companies, which wish to provide cost-effective solutions to their citizens/customers. This means that in pharmaceutical markets, as in most other markets, demand will depend somewhat on the prices of different goods, even though the consumer is not necessarily the same as the entity paying for a treatment.

Procurement entities such as the public sector will often create guidelines that specify their purchasing policies. For example, if there are several somewhat comparable medicines that treat the same illness or disease, they may specify that patients should always be prescribed the cheapest available option (or they may specify that they will provide compensation corresponding only to the cheapest option).[1]

Thus, the cheapest medicine among several comparable options is likely to experience the highest level of demand and may capture a large market share.

However, a distinction must be made between two different sources of demand for medicine.

For new patients who are to be prescribed a treatment for the first time, the choice of several different medicines may be relatively inconsequential given that they have not yet committed to a certain treatment programme. These patients can potentially be assigned flexibly to the cheapest available option (depending on their symptoms etc.).

Existing patients, on the other hand, will have already commenced a treatment programme with a specific medicine and may therefore be committed to continuing to use that specific medicine. It is not necessarily straightforward to simply shift an existing patient to a different medicine if another option becomes cheaper during their treatment programme.

While procurement guidelines may clearly specify conditions for the prescription of medicine for new patients, there may be more variability regarding the conditions under which existing patients are switched to cheaper options.

SWITCHING RATE

The switching rate of a pharmaceutical market describes the degree to which existing patients can or do switch their treatment programme to a different medicine, particularly in response to price changes.

The switching rate of a specific pharmaceutical market will depend on many factors. It will depend upon the characteristics of the illness and the treatment process, the similarities between the different medicines on the market, the regulation that is imposed on that market and so on.

For example, if there are several comparable medicines that provide a similar treatment experience and are somewhat interchangeable, then the procurement body (e.g., the public sector) may specify that patients should always switch treatment to the cheapest current option, as this may not be detrimental to patients and health outcomes.

1 For example, a policy requiring that the cheapest generic product be prescribed instead of a more expensive originator product.

Simulation: The impact of switching on pricing

THE IMPACT OF SWITCHING ON PRICING

The switching rate associated with a pharmaceutical market will impact the responsiveness of demand to pricing. This will in turn impact the pricing strategy of pharmaceutical firms.

In particular, the switching rate impacts whether firms must continually provide an attractive offer to their current patients in order to maintain their business, or whether they can rely on their current patients continuing to purchase their medicine regardless of its price.

If the switching rate in a market is low, then pharmaceutical firms will, in the short term, be incentivised to set higher prices, since they can earn higher revenues by charging their current patient base a higher price. This is because these patients cannot or do not switch to alternatives in response to a price increase.

If, on the other hand, the switching rate associated with a pharmaceutical market is high, then pharmaceutical firms will instead be incentivised to set lower prices, as they must constantly set more aggressive prices in order to maintain the revenue stream from their current patient base, who can simply switch to alternatives if faced with higher prices. A higher switching rate also means that it is easier to capture patients from competitors, which again increases the profitability of setting a low price.

PRICING SIMULATION

We have run a simulation of a simple market for pharmaceuticals in order to illustrate the impact of switching rates on pricing strategy.

We have simulated a firm that is about to set its price for a period of a set length; e.g., a year. The firm considers two illustrative pricing strategies for their medicine: a low price of EUR 50 per patient-month or a high price of EUR 150 per patient-month. For simplification, we have ignored all other pricing options.

In the simulation, the firm is interested only in maximising its gross profit; i.e. its revenue per patient-month multiplied by the number of patient-months. For this reason, it does not consider, for example, the consumer backlash it could experience in response to a tremendous price increase.

In scenario A, the firm acts in a market in which patients have a relatively low switching rate of 20%. This means that only 20% of the patients are eligible to switch or capable of switching to a different medicine if it becomes cheaper. The remaining 80% of patients will stick to their current treatment programme regardless of the prices that are set in the new period.

In scenario B, the same firm acts in a different market in which patients have a relatively high switching rate of 70%. This means that 70% of patients are eligible to switch or capable of switching to a different medicine if it becomes cheaper. Only 30% are incapable of switching or unwilling to switch medicine in response to new prices.

All other parameters are held equal between the two scenarios. This allows us to isolate the effect of the switching rate on optimal pricing strategy and profitability.

For simplicity, we have assumed that the firm can be certain of setting the lowest price in the market by setting the low price of EUR 50. By setting the lowest price in the market, it is ensured that the firm will capture 80% of new patient volumes.

READING THE SIMULATION RESULTS

On the following pages we present the results of several simulation scenarios. The results are presented as gross profit in Euros. However, as these are simulations, the exact size of the gross profit does not bear a meaning in itself. What is interesting is how the gross profit when using one strategy compares to the gross profit when using another strategy. In a given scenario, the strategy with the highest gross profit will be the strategy that best optimises the profit of the firm.

Result: A higher switching rate encourages a lower pricing strategy

In scenario A, in which there is a low switching rate, the high-price strategy is more profitable than the low-price strategy. This is because the firm can accrue high revenues from its current patient base, losing only 20% of its current customers to switching. While setting a low price in this scenario does allow the firm to capture a large majority of new customers, it is still unable to attract many of the competitors' patients – again, due to the low switching rate. Thus, although the low price attracts higher volumes, this is insufficient to compensate for the higher revenues per unit of the high-price strategy.

In scenario B, in which there is a high switching rate, the low-price strategy becomes more profitable. This is because the low-price strategy captures not only a majority of new patients but also 70% of the patients of competitors. In comparison, the high-price strategy is less profitable, since 70% of patients will switch away from the medicine in response to its higher price.

It should be noted that this simulation does not account for the risk associated with setting a low price, which may still end up being more expensive than that of the competitor. This would result in the least profitable strategy overall (low volumes and low revenues per unit). Thus, it is not necessarily a given that a firm should set a low price if it is not able to accurately observe or predict the prices of competitors. The simulation indicates that, in the short term, a higher switching rate incentivises firms to set lower prices.

Scenario A: Low switching (20%)

Strategy	Price	Competition outcome	Resulting market share of new customers (patient months)	Gross profit	Conclusion
Low price	EUR 50	Lowest price	80%	EUR 2.5 mn	
High price	EUR 150	Highest price	20%	**EUR 3.75 mn**	**Optimal strategy: High price**

Scenario B: High switching (70%)

Strategy	Price	Competition outcome	Resulting market share of new customers (patient months)	Gross profit	Conclusion
Low price	EUR 50	Lowest price	80%	**EUR 3.13 mn**	**Optimal strategy: Low price**
High price	EUR 150	Highest price	20%	EUR 1.88 mn	

Note: The two scenarios are based on identical assumptions, apart from the switching rate, which are:

- *The firm has an initial market share of 50% in a market with two firms.*
- *Prices are set for a certain length of time (e.g., one year).*
- *Marginal costs are EUR 0.*
- *The existing patient base will generate 50,000 patient months during the upcoming pricing period.*
- *All existing patients are currently associated with a specific medicine, although these patients may switch treatment during the pricing period to the new lowest-priced medicine, to a degree dependent on the switching rate.*
- *New patients will generate 25,000 patient months during the upcoming pricing period.*
- *80% of new patients will become associated with the lowest-priced medicine; the remaining 20% will become associated with the more expensive medicine regardless (e.g., because of specific symptoms, preferences or similar).*

Source: Copenhagen Economics pricing simulation.

Result: Low switching rate can still encourage low prices

In the long term, the impact of switching rates on pricing strategy is less clear cut. This is because low switching rates also imply the importance of establishing a long-run market share.

This follows from the fact that, if a pharmaceutical company first manages to capture a patient (by setting a low price) in a low switching rate scenario, then that patient is very likely to remain as a customer, regardless of future pricing. It thus becomes very important to capture patients in a low-switching scenario, and this is only possible by setting lower prices.[1]

In practice, the weight which pharmaceutical companies assign to the two counteracting incentives will depend on the extent to which they expect the current market structure to continue; i.e. the importance of establishing a sizeable existing patient base.

We have also run a simulation of Scenario A, with the low switching rate, for two pricing rounds in order to investigate what happens when firms consider the longer-term consequences of their pricing strategies. In the simulation, the price which is set in the first round impacts the market share entering into the second round and thus the size of the existing patient base in the second round.

In this simulation, it becomes most optimal to set a low price in the first round, even with a low switching rate, as this gives a larger patient base in the second round. The firm then sets a high price in the second round.

Scenario A: Low switching (20%)

Strategy	Price	Competition outcome	Resulting market share of new customers (patient months)	Gross profit	Conclusion
Low price, low price	EUR 50, EUR 50	Lowest price, lowest price	80%, 80%	5.50 mn	
High price, high price	EUR 150, EUR 150	Highest price, highest price	20%, 20%	6.00 mn	
Low price, high price	EUR 50, EUR 150	Lowest price, highest price	80%, 20%	**7.75 mn**	**Optimal strategy: Low price, high price**
High price, low price	EUR 150, EUR 50	Highest price, lowest price	20%, 80%	5.75 mn	

Note: The two scenarios are based on identical assumptions, apart from the switching rate, which are:

- *The firm has an initial market share of 50% in a market with two firms.*
- *Prices are set for a certain length of time (e.g., one year) in both periods.*
- *Marginal costs are EUR 0.*
- *The pre-existing patient base will generate 50,000 patient months during both upcoming pricing periods.*
- *All existing patients are currently associated with a specific medicine, although these patients may switch treatment during the pricing period to the new lowest-priced medicine, to a degree dependent on the switching rate.*
- *New patients will generate 25,000 patient months during both upcoming pricing periods.*
- *80% of new patients will become associated with the lowest-priced medicine; the remaining 20% will become associated with the more expensive medicine regardless (e.g., because of specific symptoms, preferences or similar).*
- *The market share of a firm which has set a low price will be 75% at the end of the first period. The market share of a firm which has set a high price will be 25%.*

Source: Copenhagen Economics pricing simulation.

1 This conclusion pertains to the given scenario under analysis.

Generic policies vary greatly between countries

Policies regarding generic products vary across the EU Member States.

Some EU Member States have mandatory *generic prescribing*. This entails that prescriptions are filled with an international non-proprietary name instead of an distinct brand name. This policy gives the pharmacy the freedom to provide the costumer holding the prescription with any suitable medicinal product containing the active ingredient, instead of a particular brand-named product.

Other EU Member States have mandatory *generic substitution*. This entails that no matter what medicinal name is written on a prescription, the pharmacy can provide the costumer with the generic version, containing the same active ingredient, if available.

Both policies are aimed at making sure that the cheapest available medicine, containing the prescribed active ingredient is given to the costumer whenever possible.

Generic policies for the European Union member states

Country	Generic prescribing	Generic substitution
Austria	Forbidden	Forbidden
Belgium	Voluntary	Forbidden
Bulgaria	Voluntary	Forbidden
Croatia	Voluntary	Voluntary
Cyprus	Mandatory	Mandatory
Czech Republic	Voluntary	Voluntary
Denmark	Voluntary	Mandatory
Estonia	Mandatory	Voluntary
Finland	Voluntary	Mandatory
France	Mandatory	Mandatory
Germany	Voluntary	Mandatory
Greece	Mandatory	Mandatory
Hungary	Voluntary	Voluntary
Ireland	Voluntary	Voluntary
Italy	Mandatory	Mandatory
Latvia	Voluntary	Voluntary
Lithuania	Mandatory	Voluntary
Luxembourg	Voluntary	Forbidden
Netherlands	Mandatory	Mandatory
Poland	Voluntary	Voluntary
Portugal	Mandatory	Mandatory
Romania	Mandatory	Voluntary
Slovakia	Mandatory	Voluntary
Slovenia	Voluntary	Voluntary
Spain	Mandatory	Mandatory
Sweden	Voluntary	Mandatory
United Kingdom	Voluntary	Forbidden

Note: Table showing whether the individual EU member states have mandatory, voluntary or forbidden generic prescribing and generic substitution for nonhospital pharmacies. Generic prescribing entails prescribing a medicinal products by its international non-proprietary name. Generic substitution entails that pharmacies substitute a prescribed branded medicinal product for a generic version of the same active substance. Information regarding Malta is missing.
Source: Wouters et al. (2017), Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending, p. 566, Figure 3

2.5 EFFECT ON GENERIC MEDICINES AND FISCAL SUSTAINABILITY OF HEALTH SYSTEMS

Many uncertainties exist when analysing the possible saving from changing the IP protection period (1/2)

ORIGINATOR AND GENERIC PRODUCTS

Each year patents or other types of protection schemes expire for a number of medicinal products. This exposes these products to generic competition. If the average protection period for medicinal products were decreased, generic products would have the opportunity to enter the market earlier than is the case today. This is, of course, based on the assumption that there will be generics ready to enter the market.[1]

In the market for medicinal products some of the products used are protected by patents or other types of protection, while some are not. This entails total spending on pharmaceuticals being split between these two product categories.

Generally, generic products cost less than originator products. This is at least partly due to the fact that originator companies bear the expense of R&D, while generic producers replicate originator products when protection expires.

Currently generic products' share of total expenditure on pharmaceuticals is around 24%, while their share of total volume is around 52% in Europe.[2]

CHANGE IN THE SPLIT

If e.g. the protection period for medicinal products were decreased, originator products would enjoy a shorter period of protection before generic companies could enter the market. This would entail originator products being exposed to generic competition at an earlier stage of their life cycle.

If generic companies were to enter the market now, with protection expiring for originator products at an earlier stage, it would entail more of the stock of available originator products being available in a generic, less expensive version. This means that the same kind of products would be available, but on average at a lower price.[3]

Assuming that the above holds and that there are no behavioural changes among the concerned parties, and especially no decrease in innovation, this hypothetical reduction of protection would entail the same amount of medicine being sold and bought but at a total lower cost.

This would in turn cause the split between how much of total expenditure is spent on originator and generic products to change. The share spent on originator products would decrease, while the share spent on generics would increase.

As generics generally are priced lower than originator products, total expenditure on medicinal products would fall.

It is imperative to underscore that the above-given hypothetical example is dependent on none of the agents in the ecosystem changing their current behaviour.

IMPACT ON INNOVATION

It is, however, quite conceivable that a change in the protection period would entail behavioural changes for some or all of the concerned agents.

It may e.g. be that originator companies would change their R&D effort. We showed in Chapter 2 that there is a positive relationship between the effective protection period and spending on pharmaceutical R&D within EU countries.

If the effective protection period in the EU as a whole were to fall, the results from Chapter 2 would entail total spending on pharmaceutical R&D decreasing. Exactly what consequences this would have is difficult to say. It may be that development times will increase if fewer resources were put into each development opportunity. This would entail products taking a longer time to get to market, which would delay the time when patients could benefit from the new innovation. In effect, this would slow the pace of innovation within the pharmaceutical industry. It may also be the case that the number of development projects would decrease. This would entail fewer products reaching the market, which again would be to the disadvantage of patients.

1This depends on the profit generics can expect to earn in the market, compared to the costs of entering the market.
2 OECD (2016), Health at a glance 2016.
3 Assuming that the same amount of products would be developed by the originator companies. This is a major assumption, as this means that taken to the extreme, completely abolishing IP protection and letting generic companies enter the market at once would not change the R&D effort of originator companies. However, this example is for illustrative purposes.

Many uncertainties exist when analysing the possible saving from changing the IP protection period (2/2)

A decrease in the originator R&D effort would mean that fewer generic products would be available over time. This is the case as a generic version of a medicinal product can be made only if an originator has developed it in the first place. As such, if there are fewer innovative products on the market or the pace of new innovation is decreased, there will be fewer products for generic producers to make their less expensive versions of.

A change in the time when generics can enter the market may also change the behaviour of buyers of medicinal products. It may be e.g. that the possible saving from using more generics would be spent on buying a larger amount of more expensive originator products which are currently unavailable due to budget constraints.

That budget constraints prevent authorities, insurance companies or individuals from buying or reimbursing the purchase of certain medicinal products means that there is limited money within current budgets to be spent.

It is thus conceivable that if a budget for pharmaceuticals is fully spent, there may be certain products which the buyer would like to purchase but simply cannot. If the price of medicinal products currently being purchased were to decrease, the same quantity of products could be purchased but without spending the whole budget. It is quite conceivable that the newly recovered saving in the budget would be spent on purchasing products which were previously unavailable due to the budget being fully spent.

The brief discussion in this section is meant to highlight the fact that a new split between how much is spent on originator and generic products following a change in the effective protection period would depend on a wide range of factors. This would entail a change in e.g. the IP protection period leading to a new equilibrium situation for the split between spending on originator products and generics. An equilibrium situation is a situation in which the different factors and variables in a system find their stable value and do not change unless something new such as a policy change occurs.

Furthermore, the adjustment to the new equilibrium situation would be dynamic and hence happen over time. An effect on the R&D effort of companies, may not be visible in the market for 10-15 years, which is when many new products are ready for marketing based on R&D decisions made now.

All of the arguments given above mean that a possible model analysing the exact total effect on health budgets of changing the IP protection period would need to include a wide range of intricate possibilities of behavioural changes for a variety of agents as well as combining these with a very long time horizon. Taken as a whole, any such model would inherently be associated with a substantial amount of uncertainty.

Furthermore, when taking these considerations into account it is conceivable that any such model would have to be build on a vast number of assumptions. This would likely entail any conclusions drawn from the end result being subject to a degree of uncertainty that would make it impossible to say anything meaningful about the precise trajectory of the spending split between originator and generic products.

As such, building such a model is not deemed to be a productive endeavour. It is, however, possible to produce a scenario analysis of a range of possible outcomes for health care budgets from changing the effective protection period. A scenario analysis will enable us to identify types of outcomes and the most decisive factors governing them.

In order for the scenario analysis to be viable, behavioural effects are not included. This means that neither changes in e.g. innovation efforts by originator companies nor spending patterns by buyers of medicinal products are included.

Changing 10% of total spending from originator products to buying corresponding generics would generate a possible saving of USD 12.4bn

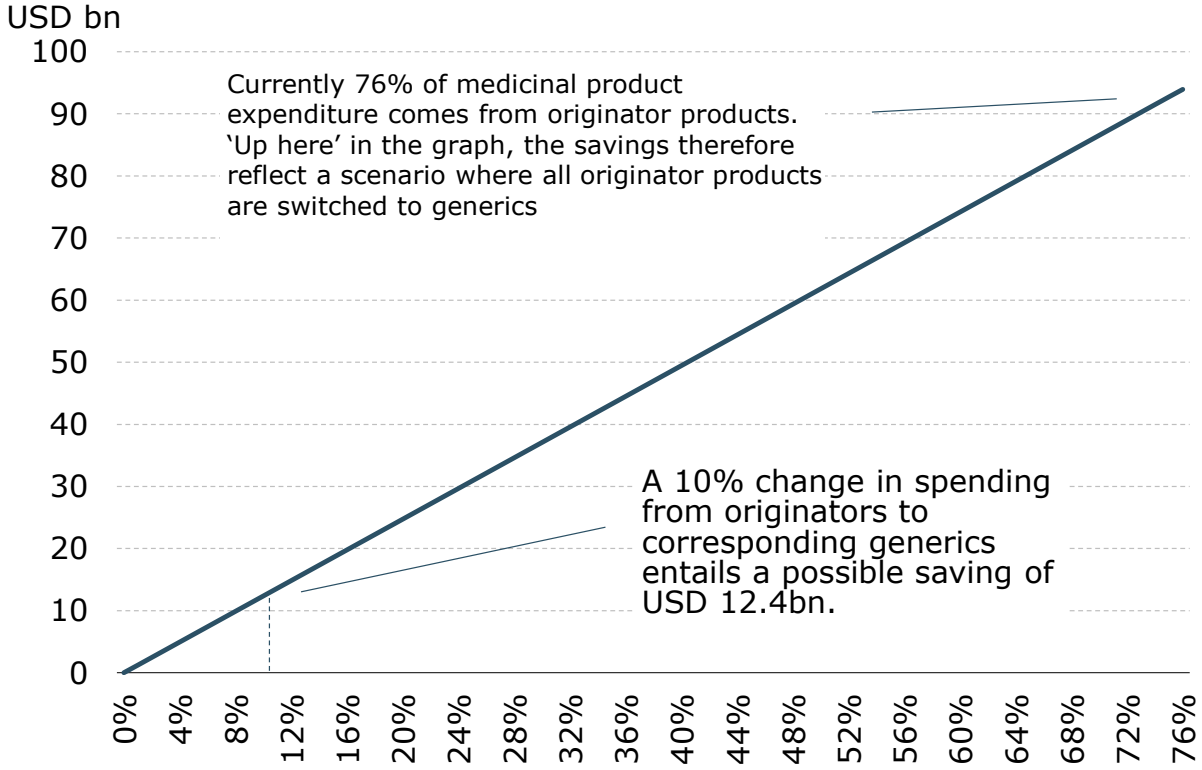
In a hypothetical scenario where the effective protection period is decreased, it would be possible for generic companies to enter the market at an earlier stage. This would lead to more generic competition and the accompanying price saving being realised at an earlier stage for medicinal products.

In the hypothetical scenario situation presented here, this change in the competitive situation is assumed not to change the behaviour of any agents affected by the change. This means that the innovation effort of originator companies stays the same so that the same quantity of new products are introduced. Furthermore, buyers do not change the 'basket'[1] of medicinal products they buy except to shift a given percentage of total spending on originator products to corresponding generic products, as these are now available at an earlier stage of originator products' lifetime.

In Chapter 2 we estimated that on average generic products are available at a price 50% below that of originator products.[2] Applying this to our scenario analysis means that if it is possible to change 10% of total spending on medicinal products from originator products to buying corresponding generic products, this would entail a saving of 50% of this 10% of total spending.

Total spending on medicinal products in the EU is USD 247bn.[3] Hence a 10% change of total spending on medicinal products from originator products to generic products would entail a possible saving of USD 12.4bn (=247 x 0.5 x 0.1).

Possible saving on pharmaceutical spending depending on the percentage of spending which can be shifted from originator products to generic products, in 2010 USD



Note: Graph showing the possible saving on pharmaceutical spending in the EU member states, based on changing a percentage of spending from originator products to corresponding generic medicinal products. Total spending on medicinal products is USD 247bn as reported by the OECD in the dataset "Health expenditure and financing". These statistics do not include spending in Bulgaria, Croatia, Cyprus, Lithuania, Malta or Romania. The spending split between originator and generics is 76%-24% as reported for EU18 in OECD (2016), Health at a Glance 2016. Generics are set to cost 50% of originator prices, as was the case in the analysis in Chapter 2. Behavioural effects are excluded as these can be ambiguous.

Source: Copenhagen Economics, based on numbers from OECD (2016), Health at a Glance: Europe 2016, OECD health expenditure and financing dataset and econometric analysis on accessibility undertaken in Chapter 2.

1 If buyers purchase only two medicinal products before the change, product X and Y, they likewise purchase these two products in the same amount after the change. They do, however, shift a given percentage of the total spending from originator product X and Y to generic versions of product X and Y.

2 Our estimates suggest around 50-60% below depending on the period of measurement. In the literature there are many different estimates of the price difference. Furthermore, this is complicated by the fact that the price difference changes over time. As the current scenario analysis is of a static nature, a given permanent price difference must be chosen. The choice of 50% is supported by findings in e.g. Frank and Salkever (1995). In the appendix we show the significance of using different levels of price saving for generic products.

3 Reported in the OECD dataset "Health expenditure and financing" and is thus in USD. We have kept this currency to preserve source numbers. These statistics do not include spending in Bulgaria, Croatia, Cyprus, Lithuania, Malta or Romania

There are many matters to be aware of when interpreting the scenario analysis

ANALYSIS BASED ON THE AVERAGE PRODUCT

The scenario analysis presented on the previous page is an analysis of the average product in the sense that the price difference between generic and originator products of 50% comes from an analysis of different kinds of products.

This is in line with the view of what would happen if the mean effective protection period for all products were reduced by a given period.

However, if e.g. there were to be a change in the protection period of the SPC, this would mostly affect products eligible for this scheme.[1] If there are certain characteristics for these products, which separate them from the average medicinal product (e.g. number of generic producers entering the market after protection expiry), these specificities must be taken into account.

At the same time, changing the protection period provided by the SPC would affect the generic competitive situation for fewer products than would changing the mean effective protection period for all products. This would entail the possible saving from changing the protection period provided by the SPC probably being lower than the saving from changing the mean effective protection period for all products.

Furthermore, as this is an average view, the possible saving shown in the scenario on the previous page is seen over the long run. In some years some very successful blockbuster products will come off patent and the saving from having generics enter at an earlier stage may be very high.

MAXIMUM SAVING

The absolute maximum shift depicted in the graph on the previous page is 76%, as this is currently the fraction of total pharmaceutical costs spent on originator products. As such, shifting 76% of total spending from originator to corresponding generic products would entail no originator products being purchased and all medical needs being met by generic products.

In turn this would entail originator companies earning no revenue within the EU. There would be no premium for inventing new pharmaceuticals within the EU. As such, this is the ultimate free-rider situation, where the EU would not contribute to new pharmaceutical R&D by rewarding innovation but would merely reap the benefits of other countries paying a premium for originator products in order for new medicine to be developed.

As the EU is a very large market within the worldwide pharmaceutical industry, it is inconceivable that this would not have consequences for innovation within the field, as well as conceivably creating an international uproar.

As such, the most extreme situation in which 76% of total spending shifts from originator products to corresponding generics is an unrealistic scenario and has been included merely as a maximum theoretical upper limit.

TOTAL HEALTH BUDGET

Spending on medicinal products is a piece of the puzzle for treating EU citizens for various conditions. As such, spending on medicinal products cannot be seen completely independently of the total health care budget.

One crucial consideration is that a possible saving on spending on medicinal products may have detrimental effects elsewhere in the health system.

This could be the case if e.g. a decrease in the effective protection period as depicted in the scenario on the previous page has an effect on the R&D effort of pharmaceutical companies. If a decrease in the effective protection period decreases the amount or pace of innovation of new and better pharmaceuticals, this may entail higher costs elsewhere in the health-care system. It may be e.g. that more people are sick for a longer time and hence require more care. Some may be admitted to a hospital for a longer period than would have been necessary had the pace of innovation been more rapid.

As such, a decrease in the effective protection period may entail a saving on spending on medicinal products, as depicted on the previous page. This, however, may come at the expense of an increase in costs elsewhere in the health-care budget. These two effects are opposites and whether the net result will be negative, positive or zero depends on such a broad range of factors that it is not possible to pinpoint them. However, this is an important consideration to take into account when interpreting the scenario analysis.

1 As will be elaborated upon in later sections, changing the protection regime may have an ex ante effect on more products than just those that ex post are eligible for the protection or have that protection scheme as the last protection to expire.

Changing 10% of total spending from originator products to corresponding generics would entail a possible saving of 0.7% of expenditure on health care

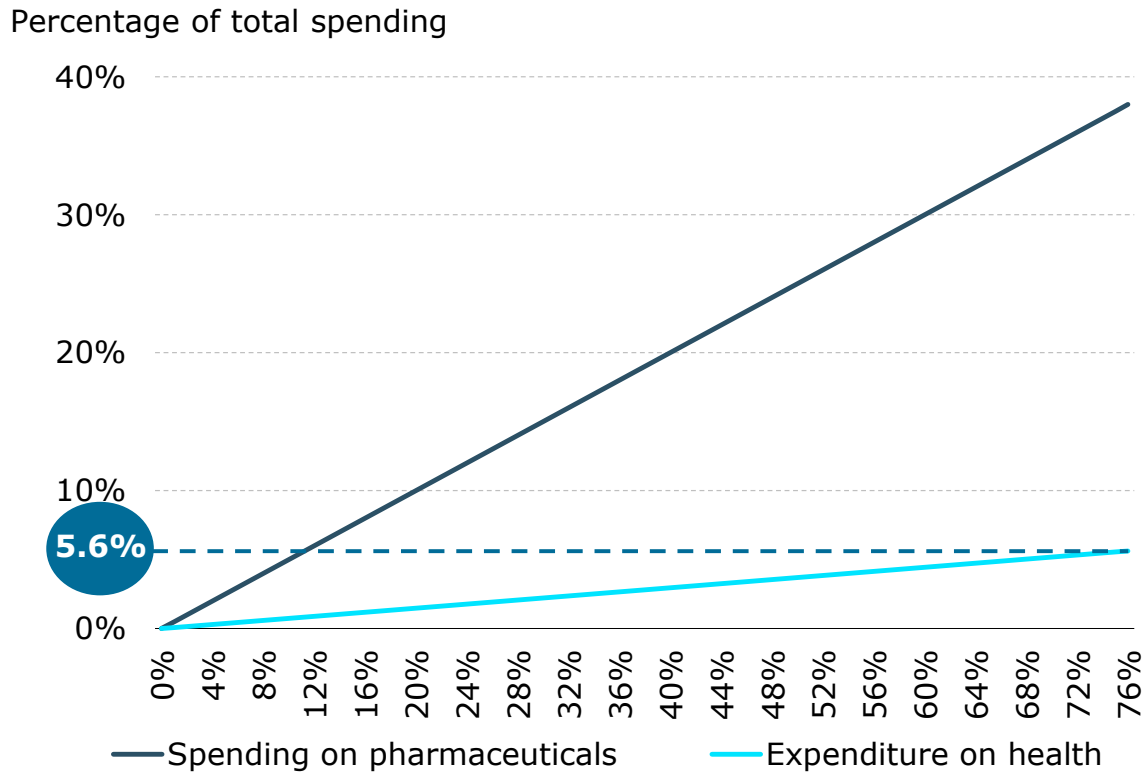
Spending on medicinal products is part of an effort to improve the health of EU citizens. As such, spending on medicinal products should be seen in relation to total spending on health care within the EU.

Total spending on health care services within the EU is USD 1,671bn.[1] Of this, 14.8% is spent on medicinal products. Of the 14.8% spent on medicinal products, 76% is spent on originator products.[2] We use previous results to assume that generics on average are priced at 50% of originator prices.

In combination, the numbers above mean that a 10% change in total spending on pharmaceuticals from originator to corresponding generic products would entail a total saving of 0.7% of the total expenditure on health within the EU.[3]

In the extreme case, where there is spending only on generic products and no spending on originator products, the possible saving on total health-care spending in the EU would be 5.6%.[4] As was elaborated upon on the previous page, this is conceivably a theoretical hypothetical situation.

Possible saving on pharmaceutical and health-care spending depending on the percentage of spending which can be shifted from originator products to generic products, in 2010 USD



Note: Graph showing the possible saving on pharmaceutical spending in the EU member states, based on changing a percentage of spending from originator products to corresponding generic medicinal products. Total spending on medicinal products was USD 247bn in 2015 as reported by the OECD in the dataset "Health expenditure and financing". These statistics do not include spending in Bulgaria, Croatia, Cyprus, Lithuania, Malta or Romania. The spending split between originator and generic products is 76%-24% as reported for the EU18 in OECD (2016), Health at a Glance 2016. Generics are set to cost 50% of originator prices, as was the case in the analysis in Chapter 2. Total spending on health care in the EU was USD 1,671bn in 2015 as reported by the OECD in the dataset "Health expenditure and financing". Behavioural effects are excluded as these can be ambiguous.
Source: Copenhagen Economics, based on numbers from OECD (2016), Health at a Glance: Europe 2016, OECD health expenditure and financing dataset and econometric analysis on accessibility undertaken in Chapter 2.

1 OECD health expenditure and financing dataset, 2015. Available at http://stats.oecd.org/index.aspx?DataSetCode=SHA
2 OECD (2016), Health at a glance 2016.
3 On p. 161 it is calculated that a 10% shift in total spending on pharmaceuticals from originator to corresponding generic products would entail a saving of USD 12.4bn. Out of the total spending on pharmaceuticals of USD 1,671bn, 12.4bn is equivalent to 0.7%.
4 Out of the total spending of USD 247bn on pharmaceuticals, 76% of the products would be 50% cheaper. This amounts to USD 93.9bn. Out of the total spending on healthcare in the EU of USD 1,671bn this amounts to 5.6%.

CHAPTER 2 APPENDIX

Caveats with the weighted effective protection period measure

LOCATION OF MANUFACTURING AND R&D

We are using pharma trade flows from a given country to other countries as a proxy for the markets that are important pharma export markets for companies in the country of interest. Our outcome variable is likewise pharma R&D spending in the country of interest. Hence, if a company fractionally collocates its production and R&D functions, our model will correctly depict the real world.

Illustrative theoretical example: Imagine that there is a large export of pharmaceuticals from Denmark to Sweden. Then Sweden increases its effective protection period. We would then expect R&D in Denmark to increase, because Sweden is an important market for Denmark. However, if the R&D of all firms producing pharmaceuticals in Denmark is located in Germany, German pharma R&D would increase as a result of this instead of Danish.

For R&D to increase when protection in the most important market increases, each firm needs to collocate their manufacturing and R&D activities proportionally. If a company produces/sells 10% of its global sales in/from Denmark, 10% of its R&D needs to be located in Denmark as well.

The above is of course an extreme assumption and if there is a reasonable correlation between manufacturing and R&D, the model should show an effect of the effective protection period in relevant markets on the R&D intensity of the domestic pharmaceutical sector.

FIRM LEVEL DATA

As we expect responses to market changes to happen at the firm level, the optimal dataset would be one with the firm as the subject. This would, however, entail having sales at the product level, geographically distributed across the years for all pharmaceutical firms in the world. We know of no such dataset in existence and by its sheer size it seems it would be quite unlikely for it to be possible to collect.

RESTRICTIVE SAMPLE

The weighted effective protection period can be calculated only for countries for which we have information on the mean effective protection period. This means that the measure is based on information about the EU member states and the US.

The total pharmaceutical exports on which the weights are based, e.g. for Germany, are thus the sum of pharmaceutical exports to the other EU countries and the US.

TIMING OF THE VARIABLES

It should be noted that the actual value of any of the included variables in a given year is not observable until the end of the year at the earliest.

Combined with the fact that most R&D efforts take quite a long time, the decision on how much to spend on R&D in any given year is probably not taken in that given year.

When we use the simultaneous value of a covariate, we are using information that the company did not have available at the time it made its R&D decision. This suggests that including lags of the covariates in the model could be a fruitful strategy. However, the next consideration would then pertain to which lags and how many to include. Which year is the information the company is basing its R&D decision on from? It may be that it is an average of several years. Or it may be the company's expectations of the realisation of future values of the variable. These are complicated questions for which it is difficult to find a precise answer.

In the interest of not drowning the conclusions in intricate econometric considerations, we have chosen a rather parsimonious (simple) model as the main way of modelling the effect on innovation.

Collocation of manufacturing and R&D within the pharmaceutical sector

To analyse the amount of collocation of manufacturing and R&D within the pharmaceutical sector, 13 global companies were studied. The companies are among the top 20 pharmaceutical companies with the highest sales in 2015.[1] The 13 companies constitute the companies in the top 20 where it was possible to find the necessary information.

The companies included are Pfizer, Novartis, Roche, Sanofi, Merck & Co., Johnson & Johnson, AbbVie, Novo Nordisk, Bayer, Takeda, Bristol-Myers Squibb, Bohringer Ingelheim and Astellas Pharma. Together they make up approximately 50% of the total sales of medicinal products in 2015.[2]

For each company information was found as to where they had placed their R&D facilities and manufacturing activities. It was possible only to find country locations and not how large the facilities were. This is a factor to be aware of, as what we essentially are looking for is the collocation in spending on R&D and the value of exports of the manufactured medicinal products. This, however, requires intimate knowledge of each company, which in most cases is not publicly available.

The correlation between the share of companies' R&D centres located in a given country and the share of the companies' production plants located in the same country was found to be 0.66. This means that 66% of the variation in the location of the companies' R&D centres can be explained by the location of their manufacturing plants (or vice versa, as correlations do not say anything about causality).

The degree of collocation is deemed to be fairly high. However, it does signify that, in some cases, R&D centres and production activities are not collocated in the same markets. This is a factor to be aware of when interpreting the results of the regression analysis.

1 See e.g. https://scrip.pharmaintelligence.informa.com/-/media/marketing/scrip-100/pdf/Scrip100_LeagueTables.pdf?la=en
2 Own calculations based on https://scrip.pharmaintelligence.informa.com/-/media/marketing/scrip-100/pdf/Scrip100_LeagueTables.pdf?la=en

Data coverage differing between countries for dependent variable

For some countries, there is no data on the dependent variable "spending on pharmaceutical R&D" for all of the years in the sample period. This means that for the given countries these years cannot be utilised as observations in the econometric model.

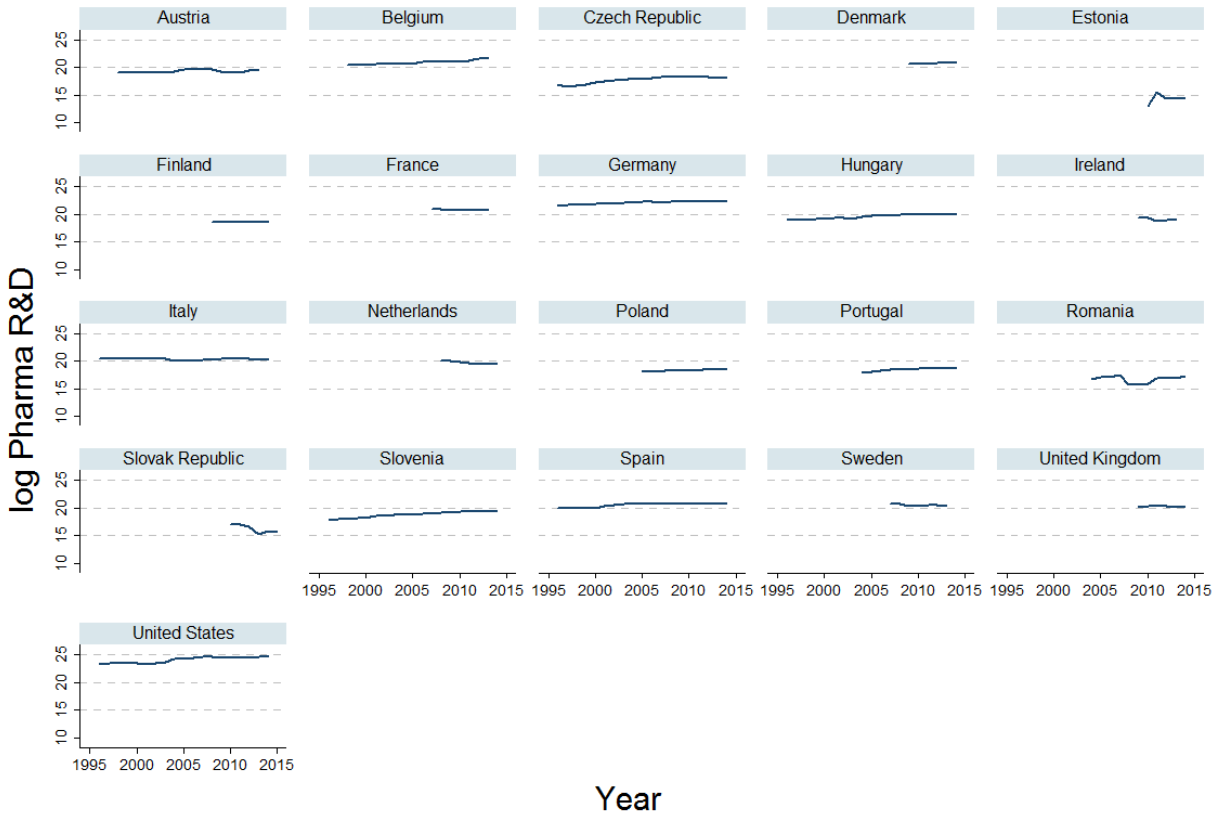
The closer the sample is to the present day, the more thorough the data coverage is. This is quite typical of empirical data for statistical analysis.

Some of the explanatory variables are also missing data for some years. Again, this is almost impossible to avoid when working with a large sample of countries tracked over many years. The different authorities may collect data in different ways and the series may experience breaks or changes in the exact content recorded in the variable.

The effect is that the study relies on a limited, unbalanced panel of countries. Having an unbalanced panel dataset means that the dataset tracks the same entities over time (in this case countries), but that the time period for which there are observations differs between countries. This is due to data availability.

In the graph to the right, the y-axis depicts the logarithmic transformation of spending on pharmaceutical R&D, while the x-axis depicts the year.

The logarithm of spending on pharmaceutical R&D across countries



Note: Graph showing the number of years for each country in the sample, where data on spending on pharmaceutical R&D is available.
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA and MRI.

Data for the econometric model (1/2)

DECREASING EFFECTIVE PROTECTION PERIOD OVER TIME

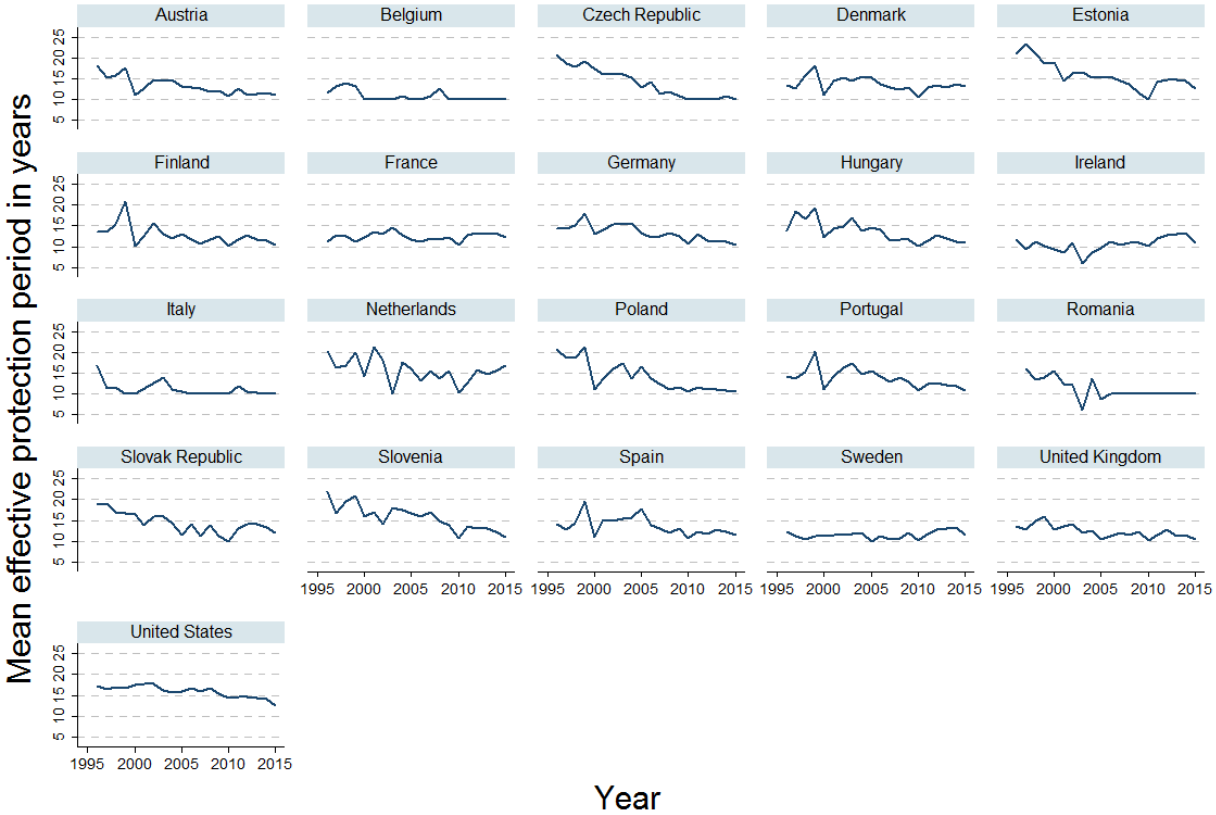
There is a general tendency for the mean effective protection period to decrease over time for most countries.

There is likewise a fair amount of variation across time and between countries.

Furthermore, there seems to be a tendency for most of the countries to approach a more common level by the end of the period, than the levels observed at the beginning of the period. This seems to reflect the standardisation of the rules within the EU[1].

Common for most of the countries in the sample is that the mean effective protection period is well below the 20 years of patent protection, which is also to be expected, as many pharmaceuticals have a rather long development period[2].

Mean effective protection period by country over time, 1996-2015



Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described above. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process.

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, EMA and MRI.

1 See e.g. Regulation (EC) No 726/2004, Article 14(11).
2 See e.g. graphs on p. 66 and 70.

Data for the econometric model (2/2)

PROTECTION IN THE OTHER EU COUNTRIES WITH WHICH A GIVEN COUNTRY TRADES THE MOST

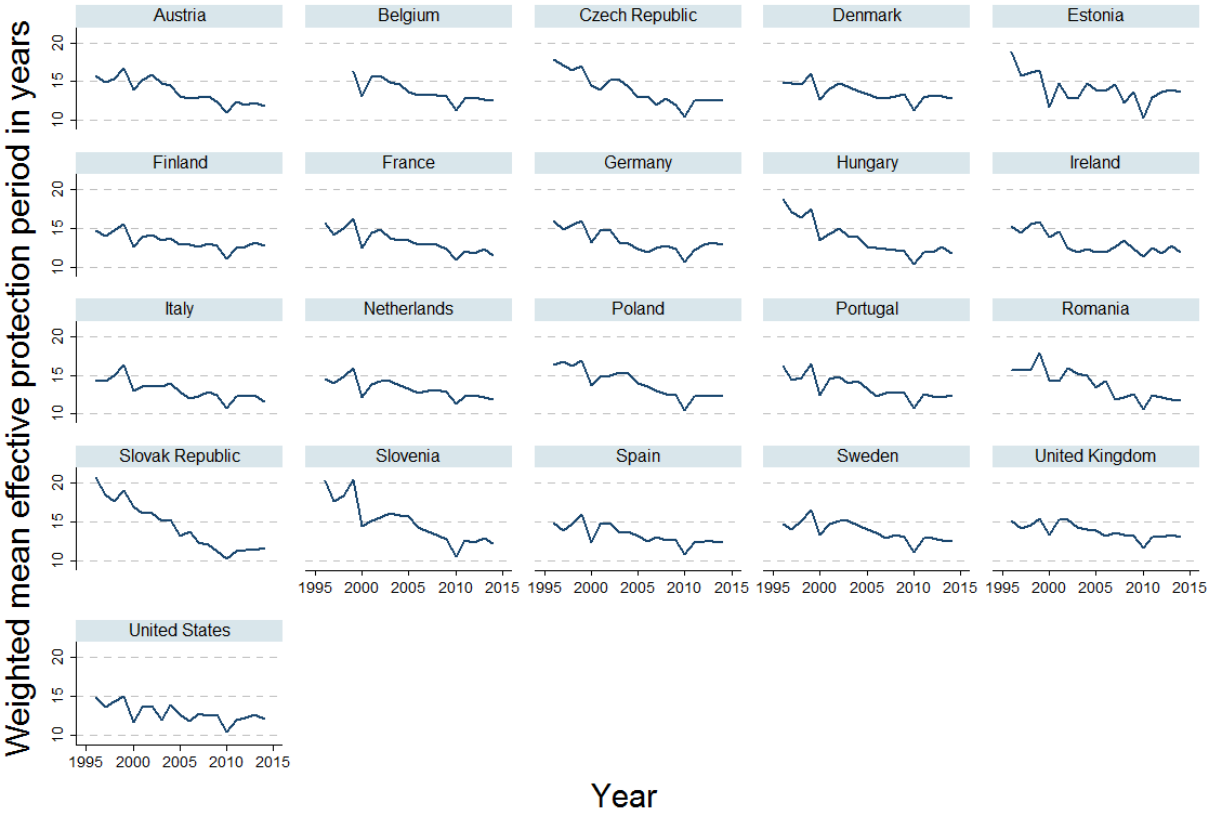
As elaborated upon in the theoretical discussion, most pharmaceutical companies sell their products in more than just one country.[1] As such, what should matter to profitability is not necessarily the mean effective protection period in the country where they locate their R&D but the effective protection period in the markets where they sell their products as well.

The graph to the right depicts the trade-weighted average effective protection period across the EU countries a given country trades with.

Across countries and across years we see a fair amount of variation in the effective protection of the other EU countries weighted by the share of pharmaceutical exports that go to that specific country.

As was the case with the effective protection period, the weighted effective protection period exhibits a downward trend in all countries.

Effective protection period in other EU countries weighed by pharmaceutical exports, 1996-2014



Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation as described above. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process.

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, EMA and MRI.

1 See section 2.1.

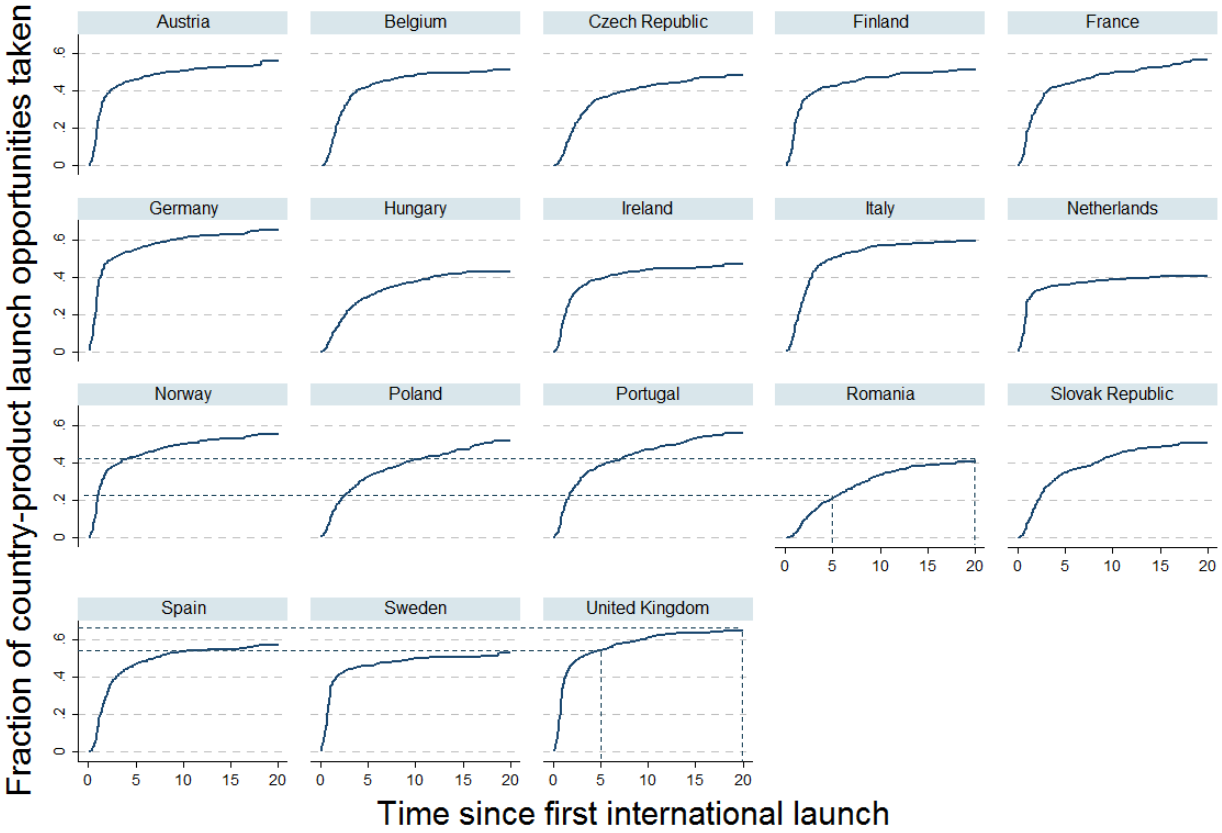
There is a large difference in the number and speed of new medicinal product launches across EU member states, with the largest countries having earlier access to more medicinal products

The graphs to the right shows the *failure functions* for each individual country in the sample.

An interesting result of the analysis of launch delay is that there seems to be quite a large difference between countries.

As can be seen in the graph from the steep slope of the estimated line for the United Kingdom, many of the products launched within the country are launched in the first five years of a product's lifetime. In e.g. Romania the number of products launched during their lifetime are more evenly distributed over the sample. Combined with the fact that more than 60% of products are launched in the UK while the comparable number is only around 40% in Romania, this means that the availability of medicinal products in Romania is lower than in the UK and that new products on average take a longer time to reach Romania than the UK.[1]

Speed of launch and share of new products launched in each country, 1996-2014



Note: Graph showing the fraction of launch opportunities taken for molecule-country combinations over time, from first international launch of the given molecule. Norway is not an EU country but is member of the EEA and as such has been included.
Source: Copenhagen Economics, based on IMS data provided by the European Commission.

1 Whether this entails an actual welfare loss in Romania does however depend on other factors such as e.g. prices..

How to interpret coefficient estimates and the assumptions behind the regressions

INTERPRETING HAZARD RATIOS

The coefficients in the duration models in section 2.2 are given in so-called hazard ratios. Hazard ratios signify how the variable influences the probability of launch, given the baseline hazard. Due to the multiplicative nature of the chosen parameterisation, a hazard rate of less than one signifies a negative effect on launch probability, while a hazard rate of greater than one signifies a positive effect on the probability of launch.

The deviation of the coefficients from one is the percentage influence on launch probability of a one-unit increase in the variable. For a continuous variable this means that e.g. a coefficient of 0.95 signifies that a one-unit increase in this variable decreases the probability of launch by 5%.

For a categorical variable the interpretation is that a coefficient of e.g. 1.05 signifies that products in this category have a 5% higher probability of launch than the baseline group.

COEFFICIENT ESTIMATES

Care should be taken when interpreting the size of the coefficient estimates. As some of the variables are of a rather large magnitude in their original level unit, they have been rescaled for tractability.

Some variables are included in the natural logarithmic transformation rather than their level value. This has both been done for interpretational reasons as well as rescaling purposes. Including logs in the regression gives elasticities, meaning the coefficient conveys the exponential percentage change in the probability of launch given a one-percent increase in the independent variable. For example, a coefficient of a variable, which is included in a natural logarithmic transformation, of 1.3 is interpreted as "a one-percent increase in this variable increases the probability of launch by 0.26 percent" (exp(1.3)=0.26).

GDP, for instance, has been rescaled in trillions and recalculated in the natural logarithm. This means that the interpretation of the coefficient of this variable is the exponential percentage change in the probability of launch given a one-percent increase in GDP in trillions.

Likewise, interpreting the size of the coefficients of the interaction terms requires a great deal of caution.

INTERACTION TERMS

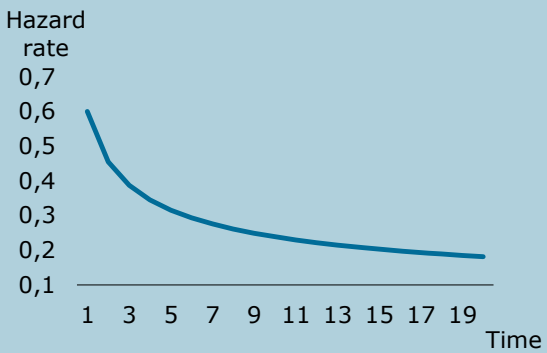
Including interaction terms in an econometric analysis serves to shed light on what the combined effect of the two variables is. For example, a positive coefficient of an interaction term between GDP and population signifies that for countries with a large population, an increase in GDP has a larger effect than for countries with a small population, or vice versa in that for countries with a high GDP, an increase in population has a larger effect than for countries with a low GDP.

When including interaction terms, the variables concerned are also included by themselves to separate their independent effects. However, when concluding what the overall effect is of e.g. GDP or population, the joint coefficient of the variable itself combined with the coefficient of the interaction term must be taken into account. As the interaction term features two variables, the partial effect of one variable will then depend on the value of the other variable. Thus, to conclude what the effect is of GDP, a value for population must be chosen. Usually mean values are used for this; however, values such as the quartiles or the median can be interesting to explore.

DISTRIBUTION

For all estimations, the Weibull distribution is used for the baseline hazard.[1]

The Weibull baseline hazard function is one of the most frequently used in the literature, and Cockburn et al. (2016) deploy it as well. Furthermore, our non-parametric estimation of the smoothed hazard shows a clear resemblance to a Weibull hazard function.



Note: Illustrative hazard function with p=0.6.
Source: Copenhagen Economics.

1 For the duration model used in section 2.2 to be able to estimate coefficients, an underlying baseline hazard function must be assumed. Different choices can be made, depending on the variable of interest. In the case of the present study a Weibull distribution is used to model the underlying hazard function of product launches. For more detail see e.g. Verbeek, M. (2012), A Guide to Modern Econometrics.

Having both a large market and a high effective protection period does not increase the probability of launch further

The interaction between effective protection period and population is included to unveil whether any joint effect of these two variables can be found. The theoretical reasoning would be that for a country with a large population, having a longer protection period is more valuable than it is for a country with a small population, as the higher the population, the larger the quantity of sales affected by the longer protection period.

The statistical insignificance suggests that in the available data material it is not possible to identify a statistically significant effect of the interaction term.

Again, this is not necessarily tantamount to there being no joint effect, but it could be an indication that in the present data material there is not enough variation to identify a distinct effect.

Duration model with Weibull baseline hazard function of molecule launch probability, 1996-2015

	Model 3
Effective protection period	1.0169
Population	0.6750**
GDP	1.6239***
Non-biologic molecule	0.4963***
Constant	0.0709***
Effective protection period * Population interaction	1.0039
p	0.6359***
Log pseudo-likelihood	-21,318.08
Subjects	16,300
Observations	119,176

*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Coefficient reported in hazard ratios. Population is given in natural log and billions of people, GDP is given in natural log and trillions of international 2011 dollars at PPP, and GDP per capita is given in natural log and thousands of international 2011 dollars at PPP. The variable p is the estimated shape parameter of the Weibull baseline hazard function. Medicinal products with a negative development time are not included when calculating the effective protection period.*

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

Having both a high willingness-to-pay and a high effective protection period does not increase the probability of launch further

The interaction between effective protection period and GDP is included to unveil whether any joint effect of these two variables can be found. The theoretical reasoning would be that for a country with a large GDP, the willingness-to-pay for pharmaceuticals may be higher; hence the prices charged may be higher, and the portfolio of marketed products may have a higher value than in countries with a lower GDP. An increase in the effective protection period could then be more attractive in countries with a high GDP than in countries with a low GDP.

The statistical insignificance suggests that in the available data material it is not possible to identify a statistically significant effect of the interaction term.

Again, this is not necessarily tantamount to there being no joint effect, but it could also be an indication that there is not enough variation in the present data to identify a distinct effect.

Duration model with Weibull baseline hazard function of molecule launch probability, 1996-2015

	Model 4
Effective protection period	1.0018
Population	0.7123***
GDP	1.5654***
Non-biologic molecule	0.4963***
Constant	0.0870***
Effective protection period * GDP interaction	1.0026
P	0.6358***
Log pseudo-likelihood	-21,318.27
Subjects	16,300
Observations	119,176

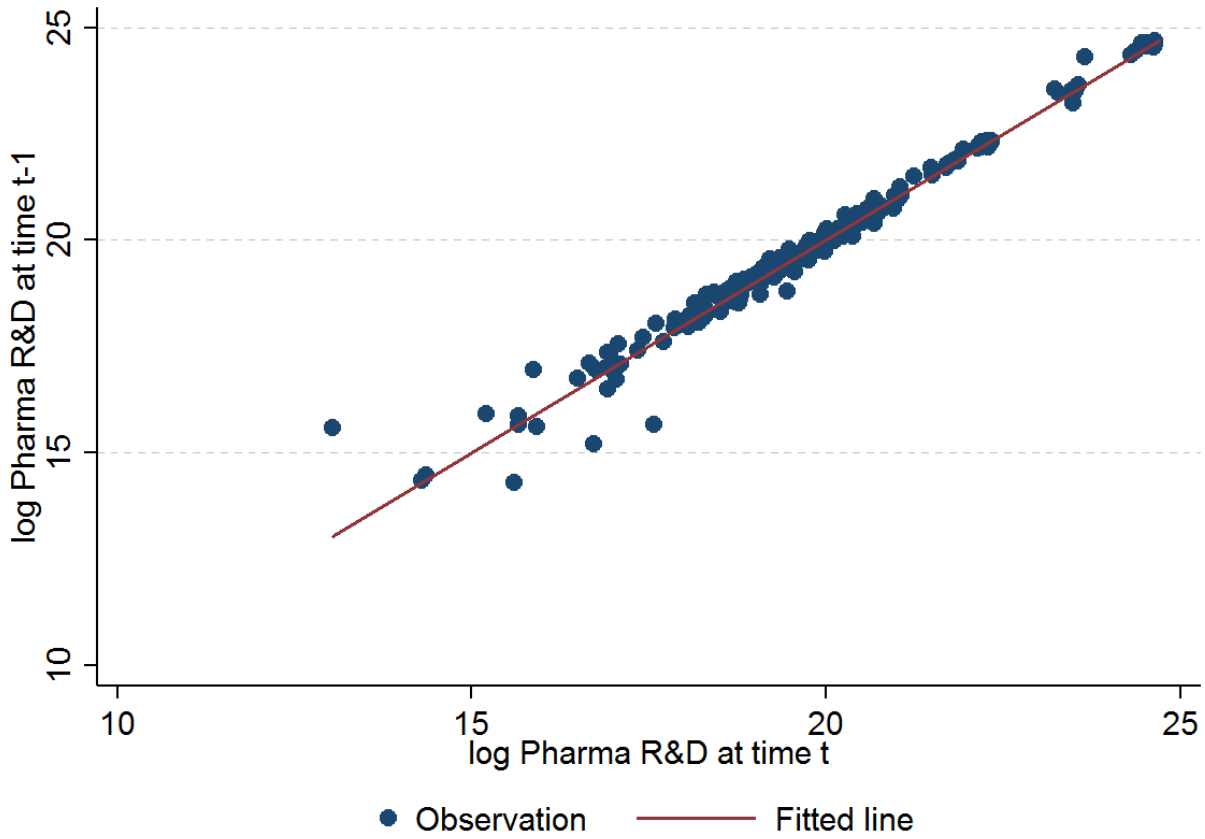
*Note: *** significant at 1%, ** significant at 5%, * significant at 10%. Coefficient reported in hazard ratios. Population is given in natural log and billions of people, GDP is given in natural log and trillions of international 2011 dollars at PPP, and GDP per capita is given in natural log and thousands of international 2011 dollars at PPP. The variable p is the estimated shape parameter of the Weibull baseline hazard function. Medicinal products with a negative development time are not included when calculating the effective protection period.*

Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA, MRI and IMS.

Persistence of pharmaceutical R&D over time

From the graph on the right it can be seen that there is quite a high level of persistence between spending on pharmaceutical R&D in one year and the year before. This endows our utilisation of a dynamic panel data model with empirical merit.

Correlation of spending on pharmaceutical R&D over time, 1996-2015



Note: Graph showing the correlation between spending on pharmaceutical R&D in one year and in the year before.
Source: Copenhagen Economics, based on a unique dataset created from Drug Patent Watch, PATSTAT, OECD, World Bank, EMA and MRI.

The possible saving in a new scenario with more generic competition and no change in innovation effort depends on the price difference between originator and generic products

The graph to the right depicts three different possible saving scenarios based on the price difference between generic and originator products.

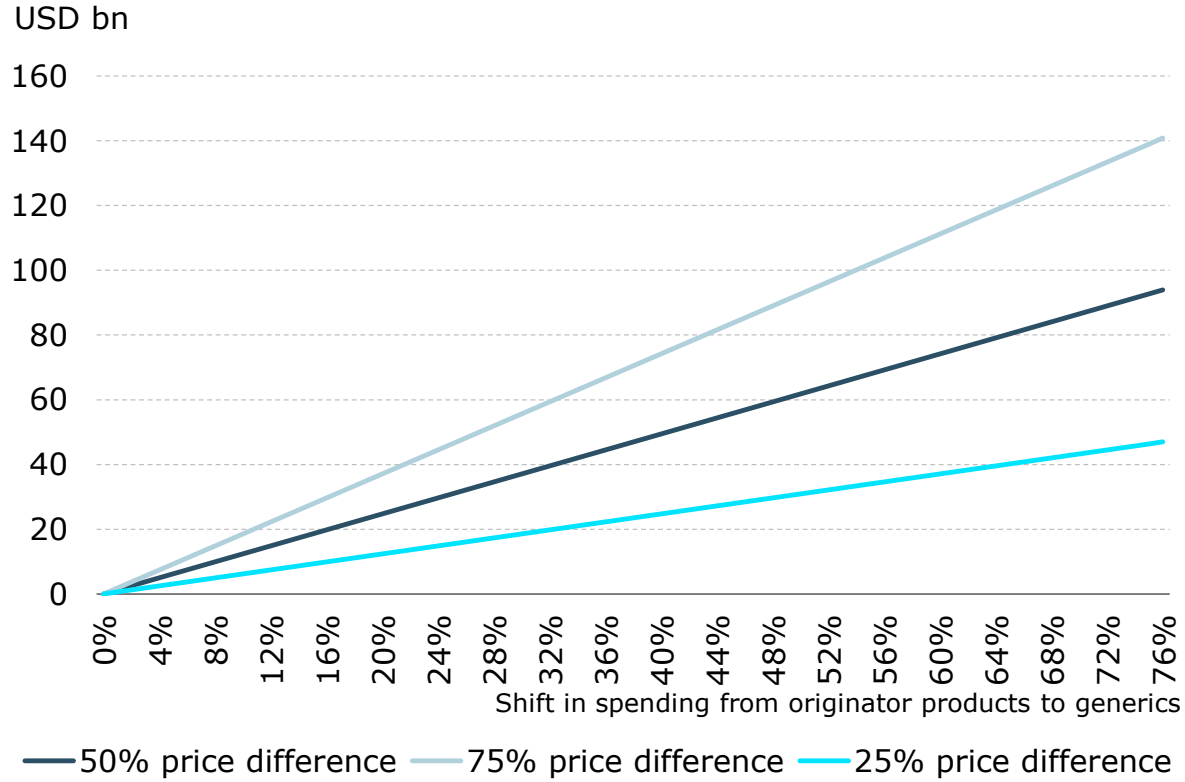
The background and the assumptions for the baseline scenario with a 50% price difference are the same as the those in section 2.5.

However, here two additional situations are depicted. In one there is a 75% price difference and in the other there is a 25% price difference.

The situation where there is a price difference of 25% is equivalent to the price at which generics are found to enter the market in the Pharmaceutical Sector Inquiry from 2009.

The situation where there is a price difference of 75% is equivalent to a situation where there are between 6 and 13 generic producers on the market, as depicted by an FDA analysis of retail sales data from IMS Health. This has been chosen so as to show a situation at the other end of the saving spectrum, as compared to that of the Sector Inquiry.

Sensitivity analysis of the possible saving on pharmaceutical spending depending on the percentage of spending which can be shifted from originator products to generic products, in 2010 USD



Note: Graph showing the possible saving on pharmaceutical spending in the EU member states on the basis of changing a percentage of spending from originator products to corresponding generic medicinal products. Total spending on medicinal products is USD 247bn as reported by the OECD in the dataset "Health expenditure and financing". These statistics do not include spending in Bulgaria, Croatia, Cyprus, Lithuania, Malta or Romania. The spending split between originator and generic products is 76%-24% as reported for the EU18 in OECD (2016), Health at a Glance 2016. Generics are set to cost either 75%, 50% or 25% of originator prices. These numbers come from respectively the Pharmaceutical Sector Inquiry, the econometric results in Chapter 2 and an FDA analysis of retail sales data from IMS Health on between 6 and 13 generic manufacturers in the market. Behavioural effects are excluded as these can be ambiguous.

Source: Copenhagen Economics, based on numbers from OECD (2016), Health at a Glance: Europe 2016, OECD health expenditure and financing dataset and econometric analysis on accessibility undertaken in Chapter 2.

Copenhagen Economics CE

CHAPTER 3

Analysis of the SPC framework

Outline of chapter 3

3.1 Objectives of the SPC regulation

3.2 SPC scope

3.3 Term of SPC protection

3.4 Impact of SPC fragmentation

3.5 SPC for plant protection products

Chapter 3 – Main conclusions (1/2)

SPC

Undertaking e.g. clinical trials, to ensure existence of sufficient data to show the efficacy, safety and quality of new medicinal products takes time. The SPC regulation[1] seeks to compensate pharmaceutical companies for effective protection time lost due to regulatory obligations. From 1992 to 2015, the average length of all granted SPCs has been 3.5 years[3].

When analysing the composition of the effective protection period for pharmaceuticals products we find that over time, the average extra effective protection period provided by the SPC has increased. However, the analysis also shows that the regulatory instrument of market protection has increased to a large degree in importance for the size of the average effective protection period.

The analysis of SPCs across countries reveals that the system is highly fragmented. The share of rejected and pending SPC applications differ to a large degree between countries. Moreover, a given product might have obtained an SPC in some countries, while having had the application rejected in other countries. It is rarely the case that SPCs for a given product is applied for in all EU countries.

LAST PROTECTION SCHEME TO EXPIRE

In our dataset 45% of the 558 unique products have obtained an SPC in at least one country[2]. The SPC is the last protection scheme to expire for 10% of all medicinal products in the sample across countries. That 10% of products have an SPC as the last protection to expire, is a combination of the fact that the products obtaining at least one SPC, not necessarily have an SPC in all countries where they are launched, not all products have an SPC and even when an SPC is present it might not be the last protection to expire, e.g. because of secondary patents. For the products, where the SPC is the last protection scheme to expire, the SPC on average increases the effective protection period by 2.6 years in the more recent period 2010 to 2016[2].

OBJECTIVES OF THE SPC REGULATION

Overall the objectives of the SPC regulation[1] can be divided into three distinct groups. These groups are supply-side objectives, demand-side objectives and market impact objectives. In general, the analysis studying to which extend the objectives of the SPC regulation[1] have been met paints a mixed picture.

Supply-side objectives

By making R&D investments in the pharmaceutical industry more attractive in general (inside and outside of the EU) the SPC has supported the objectives focusing on attracting and retaining innovation in the EU and ensuring sufficient protection to recoup investments. The supported increase in innovation has stimulated competition through innovation globally.

We do not find evidence that the SPC has supported the objective focusing on a fall in prices after the expiry of the SPC nor the objective focusing on the encouragement of innovation demanded and needed by consumers. Furthermore, we do not find theoretical arguments for why the SPC would support these objectives.

Demand-side objectives

Through the increased innovation described above, the SPC has supported the objective of better availability of generic medicinal products by stimulating the development of more medicinal products, many of which will at some point become available in a generic version, but at the cost of this availability occurring later, due to the longer exclusivity. The objective of preventing supply shortages has been supported by the SPC as these are less likely to occur during the period without generic competition, which is prolonged by the SPC.

We do not find evidence that the SPC has supported the objective of better accessibility and diffusion of innovative products across the internal market, the objective of preventing limits to innovative products amenability through industry pricing strategies or the objective of preventing missed or deferred market launches. Furthermore, we do not find convincing theoretical arguments as to why the SPC would support these objectives.

Market impact objectives

By making the European pharmaceuticals market more attractive, the SPC has supported innovation in all regions, but disproportionally more in the EU as European pharmaceutical companies have a larger market share here. In this way the SPC has most likely supported the objective of closing the gap between the European pharmaceutical industry and major competitors in the international market. However, we do not find clear empirical evidence that a gap existed before the enactment of the SPC or that such a gap has been closed.

1 Regulation (EC) No 469/2009.
2 See p. 84.
3 The 3.5 years is the formal length of the SPC. The effective protection period they add is on average 2.6 years. The difference between the two measures is that the effective protection period takes other forms of protection into account and hence only measure the period of protection the SPCs add, after expiration of all other protection schemes.

Chapter 3 – Main conclusions (2/2)

We do not find evidence that the SPC has supported the objectives of causing a fall in prices of SPC-protected products relative to products without an SPC or the objective of giving extended protection that is justified by revenues and profits. Furthermore, we do not find theoretical arguments as to why the SPC would support these objectives.

PLANT PROTECTION PRODUCTS

In addition to medicinal products, SPCs are also available for plant protection products. However, data on SPCs within the plant protection sector is very scarce.

The analysis of this sector reveals that the number of ingredients introduced or in development has decreased from 123 in the years 1980-1989 to 73 in the years 2005-2014. Furthermore, the focus of these products have changed. In 1980-1989, 33.3% of active ingredients introduced or in development focused on Europe. In the period 2005-2014 this had decreased to only 16.4%.

Contrary to the pharmaceutical sector, there is no research exemption[1] for plant protection products.

1 Also called the Bolar exemption within pharmaceuticals.

The economic impact of SPCs is widely unchartered territory

25 YEARS OF SPC REGULATION

The relatively short period of time which has passed since the introduction of the original regulation creating supplementary protection certificates in the EU may account for the apparent scarcity of desk research and academic literature that investigates the impact this regulation has had on pharmaceutical markets.

In the European Union, the observed time from invention to commercialisation of a medicinal product can at times exceed 12 years (as evidenced by e.g. Kyle 2017 and the data compiled for analysis in the scope of this study[1]). Often, medicinal products remain relevant on the market for decades and companies use the plethora of available legal and registration strategies to maximise the time period in which commercialised products yield profits. As such, the 25 years the SPC regulation has existed remains a relatively short period of time relative to the lifecycle of the average medicinal product.

Given the issues of data availability combined with the challenge of ensuring compatibility of the data that is available, the lack of insightful research within the area is understandable.

CASE LAW AND INTERPRETATIONS

While little is known about the *a posteriori* impact of the introduction of supplementary protection certificates in the EU, a large amount of literature exists on the specifics of application, grant, validity and legal impact of an SPC.

Realising the impact of being able to gain additional patent-like protection, firms and other stakeholders have shown plenty of engagement in challenging the interpretation of the SPC regulations in both national and European courts. As a result, the competent authorities as well as legal researchers and experts have created a sizable volume of case law and literature defining, challenging, harmonising and documenting the prevailing interpretations of the relevant national and Community law[2].

These interpretations and readings of the relevant regulations certainly have a bearing on the economic application and effect that the adoption of the SPC regime has had on the European community. For instance, where they change and clarify the scope of patent claims and market authorisations that can give rise to the right to supplementary protection as in the *Medeva* and *Georgetown* decisions of the European Court of Justice (Joshi, Roy & Janodia 2014).

These and comparable rulings should impact firms' decisions regarding where and how to apply for supplementary protection, as well as when and where to challenge such protection granted to competitors. In consequence, legal proceedings and changes to 'the rules of the game' could also have a tangible impact on the economic manifestation of SPC protection in the EU.

However, as this report analyses the economic effect of the SPC framework, a legal review of the current case law is outside the scope of this study, insofar as it does not have a direct bearing on the economic impact of the regulation.

SCOPE OF INVESTIGATION

Using the scarce literature available, as well as the data sourced for the purpose of this study and the insights from other countries allowing similar patent term extension provisions (e.g. US), this chapter aims to investigate the following:

1. Achievement of the objectives of the SPC regulations.
2. Analysis of potential extensions or reductions in the scope of SPCs in the EU.
3. Investigation of the terms of protection granted by SPCs in the EU.
4. Analysis of the impact of SPC fragmentation.
5. Analysis of SPCs for plant protection products.

1 See p. 66.

2 See e.g. Papadopoulou, F. (2016), Supplementary protection certificates: still a grey area for a recent review of case law within the area.

The number of countries having enacted the SPC legislation has increased over time

Chapter 1 of this report includes a graphical depiction of the number of supplementary protection certificates granted between 1992 and 2016. The number of grants increased slightly over time.

As highlighted in Mejer (2017), the SPC regulation's entry into force followed a gradual scheme throughout the European Economic Area. However, once the regulation entered into force, all marketing authorisations obtained in a multi-year time frame prior to entry into force became eligible for SPC application. Assuming that the 1992/1993 and 2007 peaks are largely attributable to an eligibility backlog, the number of SPCs granted can be interpreted as having risen slightly from an average of 500 per year between 1994 and 2004, to an average of 700 per year from 2004 onwards.

A similar picture prevails when looking at SPC application data. Mejer (2017)[1] notes a relatively stable period of ca. 500 applications per year from 1993 to 2004 followed by a sizeable increase in both volumes and year-on-year variation from 2004 to 2013. The author names geographical enlargement, development of more complex medicines and multiple SPCs per product as potential reasons for the observed increase.

The latter point is reiterated by Kyle (2017), who additionally sees an increase in the number of SPC applications per medicinal product innovation over time, including multiple SPCs per patent and SPCs for non-basic patents.

Mejer 2017: SPC regulations in the EEA

Group	EU SPC In Force	Year of First Eligible MA	EEA Member States
1	1993	1982	BE, IT
2	1993	1985	FR, UK, IE, LU, NL
3	1993	1988	DE, DK
4	1994	1982	AT
5	1994	1985	SE
6	1994	1988	FI, IS, NO
7	1998	1998	GR, PT, ES
8	2004	1999	CZ
9	2004	2000	HU, SK, PL
10	2004	n/a	CY, EE, LT, LV, MT, SI
11	2007	2000	BG, RO
12	2013	2003	HR

Source: Adapted from Mejer (2017), Table 1, "SPC provisions and transition".
Note: According to Mejer (2017), group 7 covers countries that did not allow pharmaceutical patents prior to the SPC regime and therefore entered the scheme 5 years later (1998 instead of 1993).

1 Mejer, M. (2017) "25 Years of SPC Protection for medical products in Europe: Insights and challenges".

Approval times and average length of granted SPCs

As can be seen from the graph to the right, the average length of granted SPCs across the EU member states has remained fairly consistent over the years, albeit with some yearly fluctuations.

From 2004 to 2015 the median approval times for the European Medicinal Agency, including the time spent by the European Commission, has been slightly decreasing. In 2015 the median approval time for the EMA was 417 days. As a comparison, the median approval time for the FDA was 351 in the same year[1].

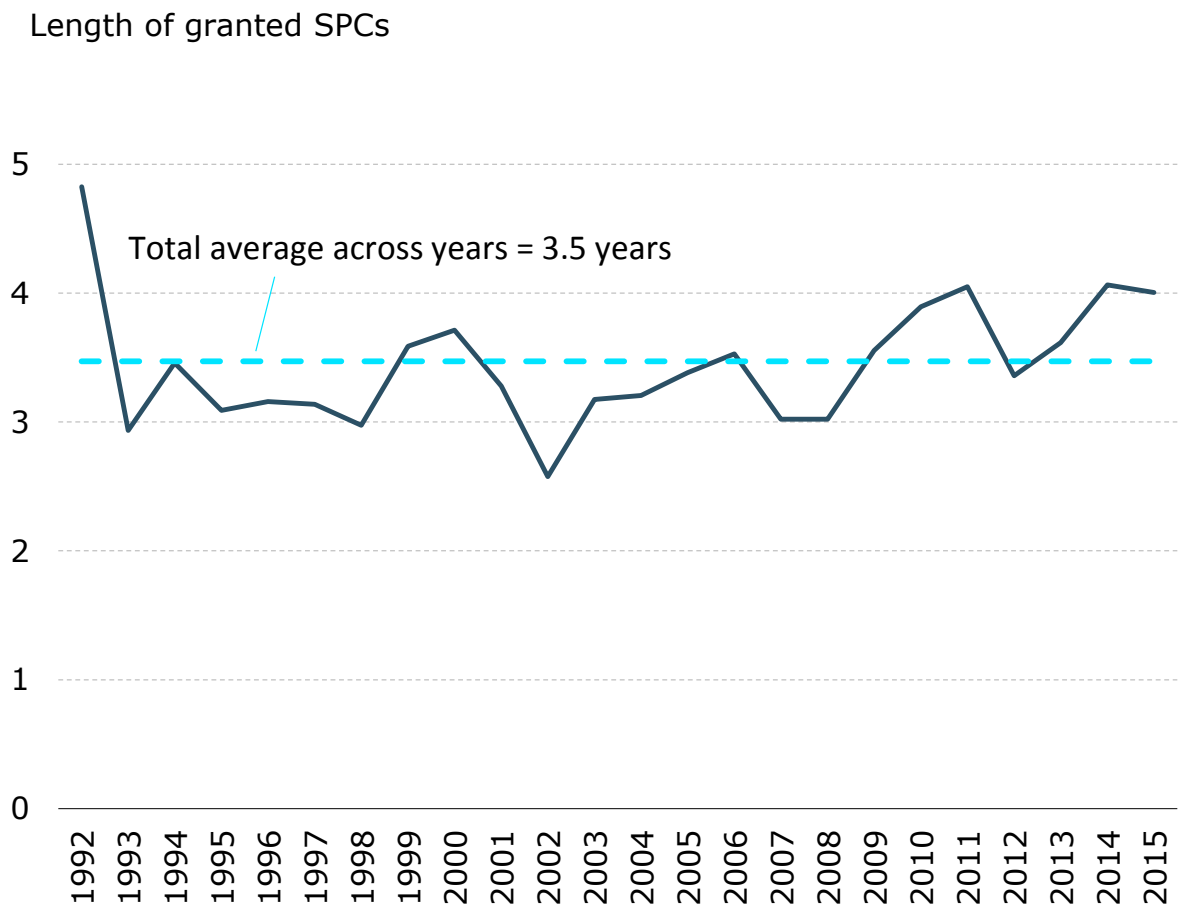
At face value, the decrease in approval time should contribute to increasing the time a medicinal product is on the market and protected by IP rights.

However, even though the regulatory approval process time has been slightly decreasing, there is other evidence pointing towards an increase in the regulatory requirements for applying for marketing authorisation.

Between 1999 and 2005 the median number of procedures per clinical trial protocol increased from 96 to 158. Furthermore the length of clinical trials increased from 460 to 780 days during the same period[2].

This points to the fact that even though the regulatory process has shortened, the regulatory requirements for approval of an application for marketing authorisation have increased, causing the development of new medicines to take a longer time.

Average length of all granted SPCs across EU, 1992-2015



Note: Graph showing the average length of all SPCs granted in the given year.
Source: Copenhagen Economics based on Alice de Pastors dataset on SPCs.

1 Bujar M, McAuslane N. 2014. R&D Briefing 55: The impact of the changing regulatory environment on the approval of new medicines across six major authorities 2004-2013. Centre for Innovation in Regulatory Science, Bujar M, McAuslane N, Liberti L. 2016. R&D Briefing 59: The impact of the evolving regulatory environment on the approval of new medicines across six major authorities 2006-2015. Centre for Innovation in Regulatory Science.

2 Rollins, T. (2016), "How Europe's SPC regime works in practice" reports these numbers provided by EFPIA. Getz, K. A., Campo, R. A. and Kaitin, K. I. (2011), Variability in Protocol Design Complexity by Phase and Therapeutic Area likewise reports an increase in procedures per clinical trial from 2000 to 2007.

SPCs increasingly relevant

SPCs IN THE CONTEXT OF IP PROTECTION SCHEMES

As noted in chapter 1, a supplementary protection certificate is an IP protection right designed to restore patent protection lost due to prolonged development time, where development time can be understood as the time from invention (first patent) to commercialisation (first authorisation to market) in Europe.

Due to the way additional protection granted by an SPC is calculated, this kind of protection right is relevant only where development time falls in the range of 5 to 15 years (abstracting from a case where an SPC might be relevant beyond 15 years due to its protection being qualitatively better than an overlapping market exclusivity but not quantitatively, i.e. for a longer period of time)[1]. In our dataset 45% of the unique products have obtained an SPC in at least one country[2].

CHANGES TO DEVELOPMENT TIME

As found in chapter 1 of this report and as depicted on the lower right hand side, average development time for medicinal products has increased over time for a sample covering medicinal products that obtained an authorisation to be marketed in the EU between 1996 and 2016. As noted before, this development is in line with the findings reported by Kyle (2017) covering a sample ranging from 1990 to 2015.

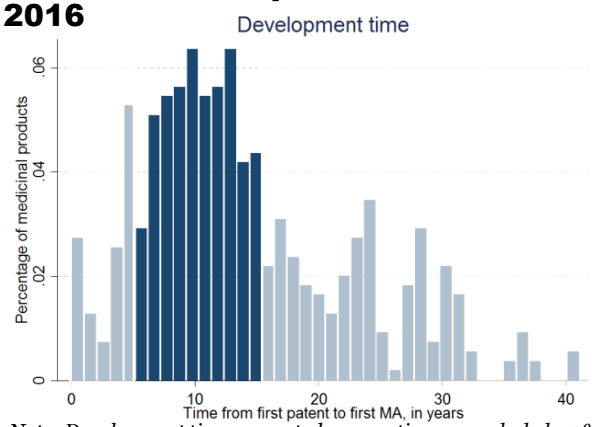
THE DISTRIBUTION OF DEVELOPMENT TIME

As can be seen on the upper right hand side, the majority of medicinal products that reach the market in the EU now fall into the SPC-relevant range of development times of between 5 and 15 years.

Besides a general increase in average development times, Kyle (2017) also observes a change in the distribution of development times around this range. Since 1990, the distribution of medicinal product development times has increasingly concentrated in the relevant time frame of 5 to 15 years. The proportion of development times within the relevant range has increased from just over 40% in the early 1990s to more than 65% in the 2010s. At the same time, the proportion of development times both below and above the relevancy threshold has fallen over time.

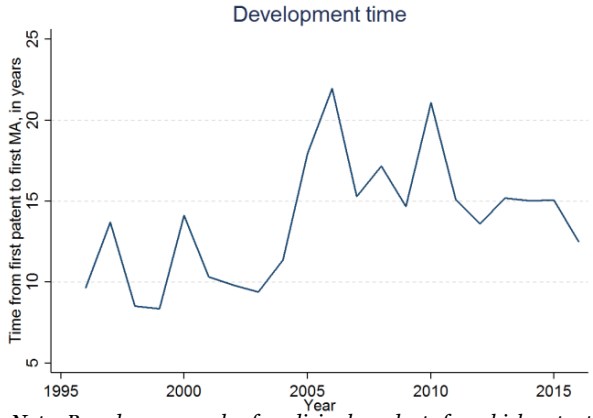
Kyle (2017) further observes an increase in the proportion of medicinal product innovations that apply for an SPC at all, as well as the proportion of SPCs that, being granted for non-first patents, provide a marginal effective protection gain larger than the 5-year maximum set by the regulator.

Relevant Development Time 1996-2016



Note: Development times reported as negative are excluded. 50% of observations have development time within the interval of five to fifteen years.
Source: Copenhagen Economics

Avg. Development Time 1996 – 2016



Note: Based on a sample of medicinal products for which patent data could be linked with the marketing authorisation. The sample consists of medicinal products which are either centrally approved or approved through the mutual recognition process. Medicinal products with negative development times are not included in the figure.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI

1 For products with a development time of between 5 and 15 years, a possible SPC would prolong the effective protection period. See e.g. pp. 28-30 and 42.
2 See p. 84.

SPCs increase effective protection when they are the last IPR to expire

The graph to the right depicts the effect of SPCs on the average effective protection period for products where an SPC is the last IP right to expire[1].

The red line depicts the effective protection period if patent, SPC, data protection and market protection are taken into account. The green line depicts what the effective protection period would have been, had there been no SPC for these products where the SPC is last to expire. In that sense, the difference between the two lines can be understood as the average marginal protection extension conditional on an SPC being the last protection scheme to expire.

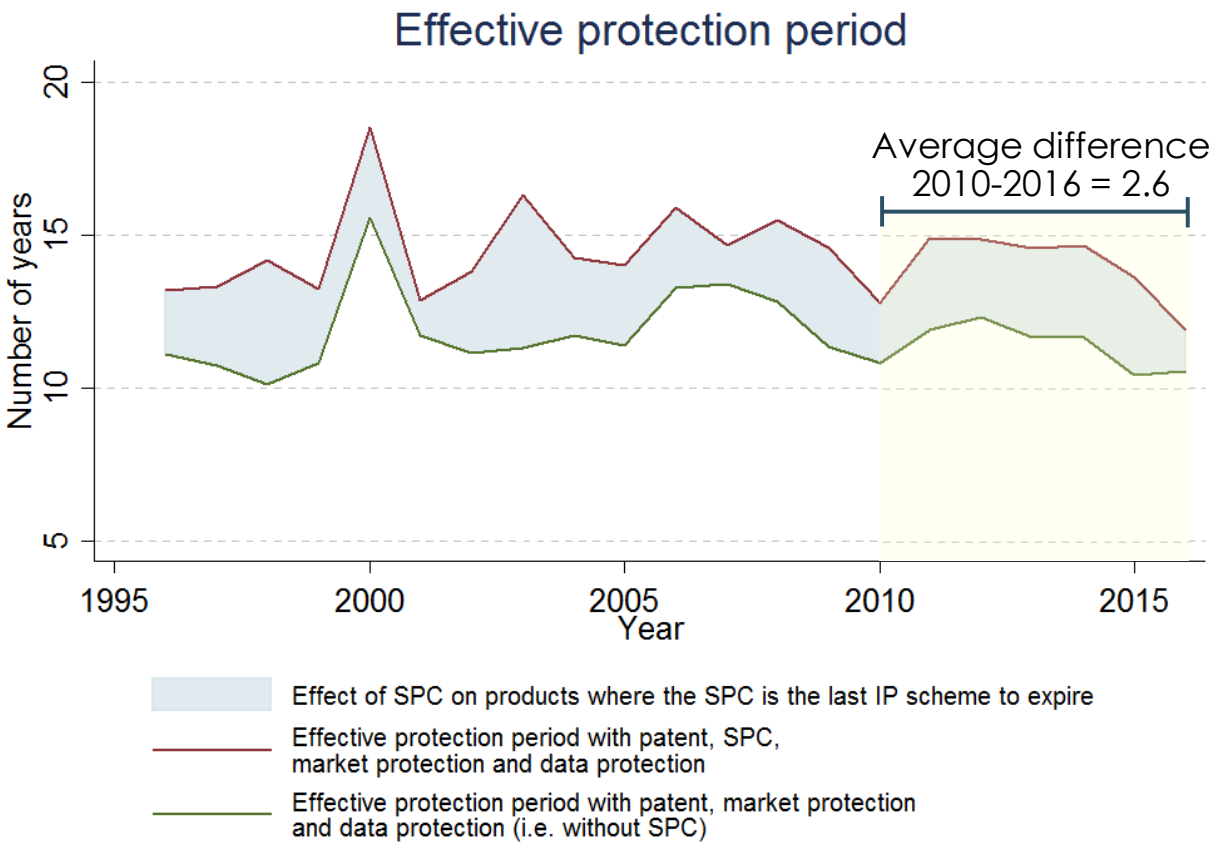
In our dataset, 45% of the unique products have obtained an SPC in at least one country[2]. From the table on the following page, it can be seen that, in our sample, an SPC is the last protection scheme to expire for 10% of products across countries.

In recent years, the SPC has had the effect of prolonging the effective protection period by approx. 2.6 years for products were the SPC is the last IP protection scheme to expire.

Even with the possibility of filing for an SPC, a patent is still predominantly the last protection scheme to expire. However, when controlling for whether medicinal products are actually subject to an SPC application, the picture is quite different.

When only looking at the medicinal products where an SPC is filed, the certificate is the last IPR to expire in more than 61% of cases.

Effective protection period for products where an SPC is the last IP scheme to expire, 1996-2016



Notes: Graph showing the effective protection period based on which protection instruments are used in the calculation. The graph only includes medicinal product-country combinations where an SPC is the last IP scheme to expire. As such, the difference between the lines depicted signifies the average increase in protection for products where SPCs actually extend the protection period. Given that the observation-level is unique medicinal product-country combinations means that a specific medicinal product is used in the calculation of the average as many times as it has an SPC in a member state.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 See chapter 3 appendix for the same graph, when excluding secondary patents.
2 See p. 84.
3 See pp. 215-216 for a further discussion of this.

SPCs across country observations

SPCs ACROSS COUNTRIES

We have previously shown that 251 (45% of 558) unique products in the dataset have obtained an SPC in at least one country. However, to analyse the last protection scheme to expire, we need to utilise the dataset where each product has an observation in each country where it is launched, as protection might differ between countries. When using this dataset, the 251 unique products with an SPC in at least one country corresponds to 1,190 observations with a granted SPC across all countries in the table to the right[1].

Out of these 1,190 observations 720 corresponding to 61%, have their SPC as the last protection scheme to expire.

EX ANTE BUSINESS CASE

A main effect of SPCs is that they change the *ex ante* investment considerations of pharmaceutical companies. As such, while *ex post* SPCs are the last IPR to expire for only 10% of the observations in the dataset, they may have affected the (pre-development) valuation process for a larger number of projects.

OBSERVED SAMPLE LIMITATIONS

The reported numbers in the table to the right reflects the information contained in the unique dataset, constructed for this study. For more information on the dataset see appendix to chapter 1.

Last protection scheme to expire, 1996-2016

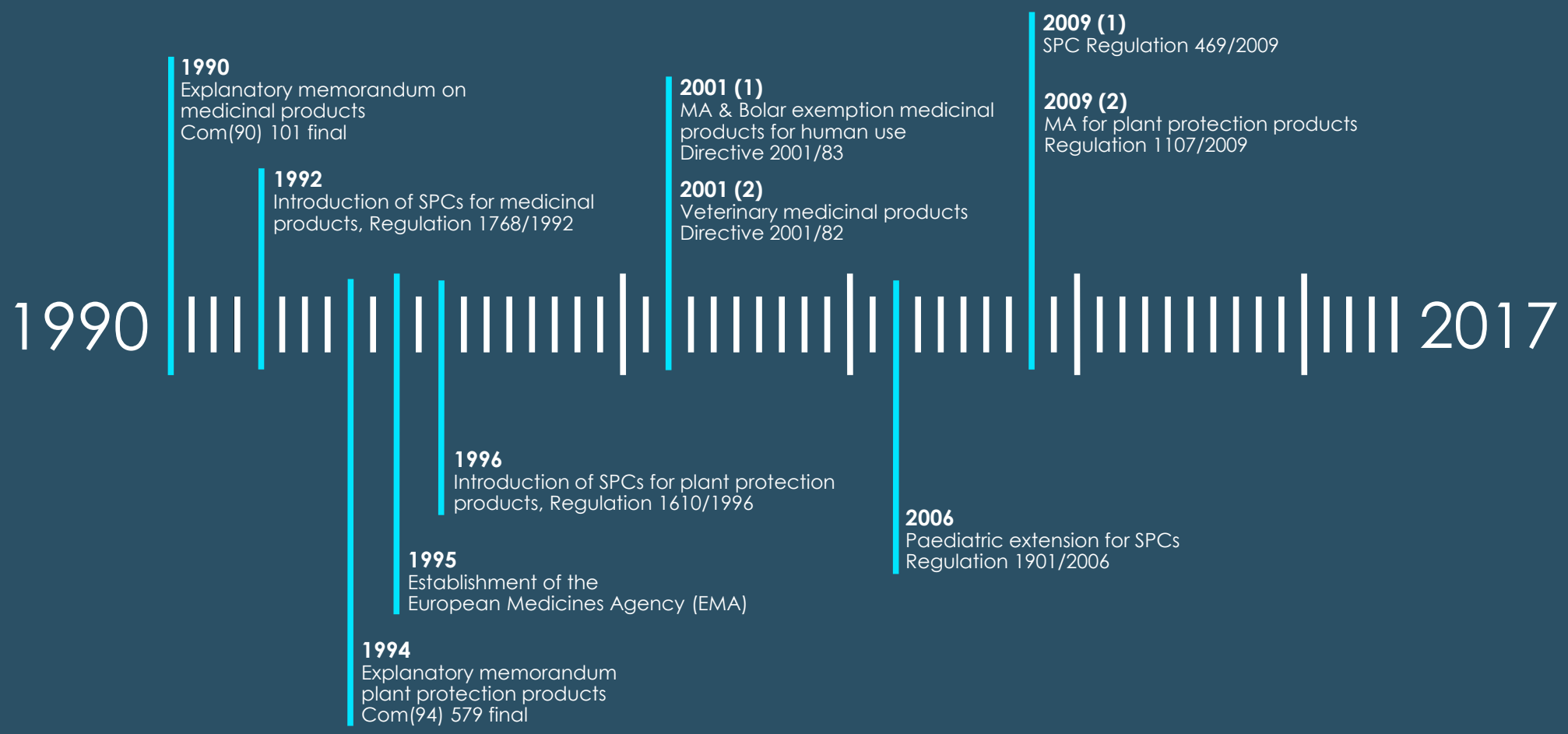
	Full sample		Observations with granted SPC	
Last IP scheme to expire	N	(%)	N	(%)
Patent	3,634	51	263	22
Supplementary Protection Certificate	720	10	720	61
Market protection*	2,294	32	188	16
Data protection**	482	7	19	2
Total	**7,130**	**100**	**1,190**	**100**

Note: Table showing the last protection scheme to expire for the unique dataset created for the analysis. The cases where data protection is the last protection scheme to expire are all before enactment of the 8+2(+1) system in 2005, as market protection under this regime is always longer than data protection.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

* Market exclusivity for orphan medicinal products are counted in this category.
** For certain observations before the 2005 changes to the 8+2+1-scheme, data protection is the last IPR to expire.
1 See chapter 3 appendix for the same graph, when excluding secondary patents.

3.1 OBJECTIVES OF THE SPC REGULATIONS

SPC and SPC-relevant EU regulation over time



The objectives are outlined in the explanatory memoranda accompanying the relevant regulations

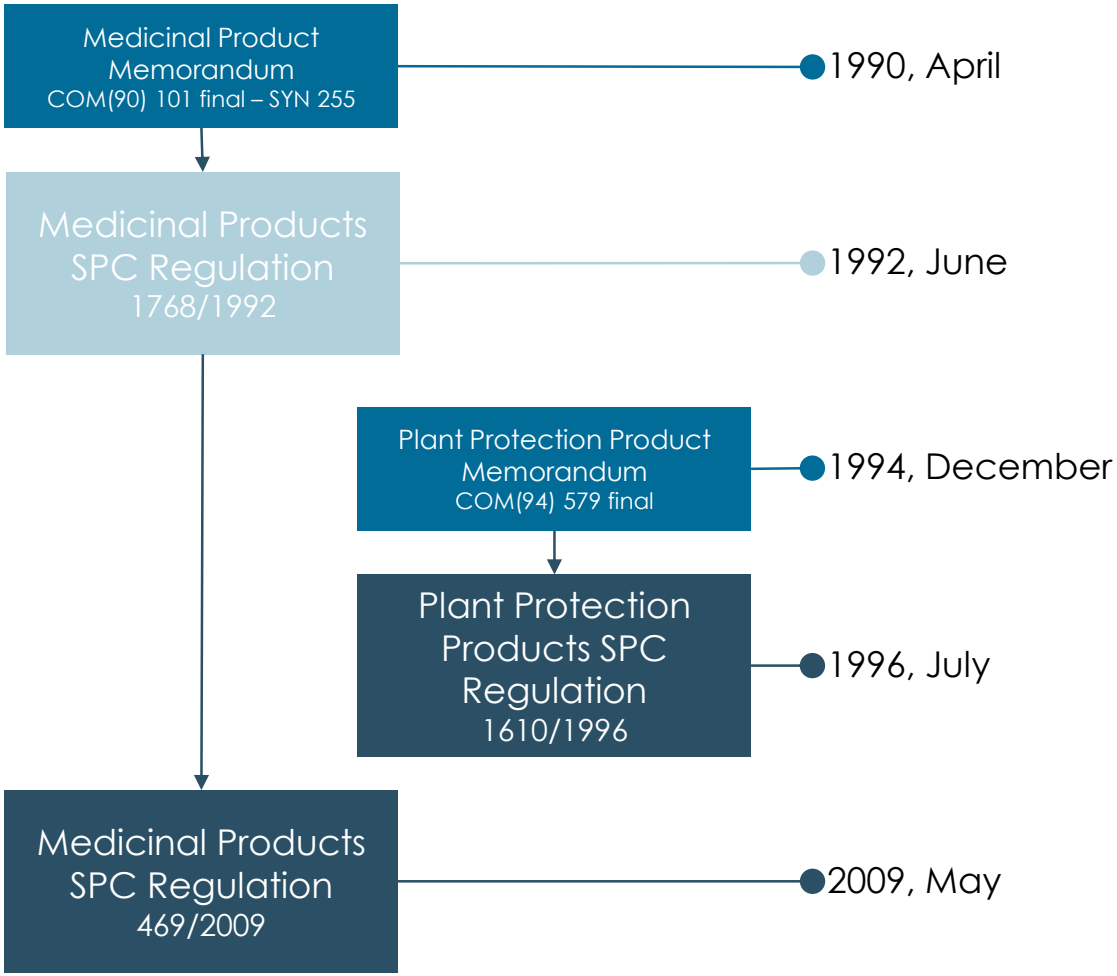
OBJECTIVES OF REGULATIONS 1768/92 AND 1610/96

The SPC regulation for medicinal products was published in the European Commission's Official Journal in July 1992 and the regulation for plant protection products was published in August 1996.[1]

Jointly, these regulations form the background of the regulatory objectives that the Commission aspired to achieve when designing the regulatory proposal. While the 1992 and 1996 regulations provide the technical regulations and the rules by which stakeholders have to abide, they only refer to the objectives indirectly.

The recitals leading the regulations summarise the main arguments but in order to understand and analyse the full scope of objectives underlying the adopted regulatory proposal creating SPCs, one has to refer to the respective explanatory memoranda referenced by the Commission.[2]

These memoranda, cited by the Commission proposal referenced in the regulations, introduce the proposed provisions and further provide an account of the context and aims that the proposal is designed to work towards achieving.



1 See OJ No L 182/1, 02.07.1992 for medicinal products and OJ No L 198/30, 08.08.1996 for plant protection products.
2 See COM(90) 101 final – SYN 255, 11.04.1990, Brussels for medicinal products and COM(94) 579 final, 09.12.1994, Brussels for plant protection products.

Achievement of the objectives of Regulations 1768/92 and 1610/96 (1/2)

OBJECTIVES OF SPC REGULATIONS

The objectives of the supplementary protection certificate framework were introduced in the explanatory memoranda Com(90)101[1] and Com(94)579[1] that predated the regulation on the introduction of SPCs for medicinal products and plant protection products, respectively.

The objectives are included in the recitals of the relevant regulations 1768/1992 for human and veterinary medicinal products and 1610/1996 for plant protection products and agrochemicals.

In general, three categories of regulatory objectives can be distinguished: *supply-side objectives*, *demand-side objectives* and *market impact objectives*.

The supply-side objectives focus on the stimulation of research and development within the Community, while demand-side objectives stress the provision and accessibility of innovative products to consumers across the internal market.

In addition, this study will investigate the market impact of introducing SPCs. On the following pages, we investigate the economic rationale implied by the regulator's formulation of the SPC objectives. We then analyse the achievability and achievement of these objectives using the evidence produced in our own analyses and the insights provided by the relevant literature.

Categories of regulatory objectives included in the SPC framework

1 Supply-side objectives	Regulatory objectives aimed at the creation of a market environment where companies within the medicinal products and plant protection products industries are able to provide the desired product innovation and development.
2 Demand-side objectives	Regulatory objectives aimed at the provision of required and demanded medicinal products, plant protection products and product innovations to consumers throughout the internal market in due time and at fair prices.
3 Market impact objectives	Regulatory aspirations of achieving supply and demand-side objectives while avoiding undesired or excessively adverse market consequences for producers and consumers. Catching up and closing gaps to other industrialised countries.

1 See http://thespcblog.blogspot.dk/2011/12/that-elusive-explanatory-mermorandum.html for links to both memoranda.

Achievement of the objectives of Regulations 1768/92 and 1610/96 (2/2)

In the following we analyse each identified objective in turn. Firstly the basis for the objective is reported, in the instances where this is directly identified in published documents. Secondly the economic rationale is analysed. Thirdly any available empirical evidence is reviewed.

For each objective we identify how relevant characteristics and points of the SPC regulation[1] works to either support achievement of the objective, is counterproductive to achieving the objective or whether there is no clear relationship between achieving the objective and the SPC regulation[1].

A consolidated overview of the effect of the characteristics of the SPC regulation[1] is given in easily discernible boxes for each objective.

Characteristics that work to support achievement of the objective are marked with a '+'. Characteristics that are counterproductive to achieving the objective are marked with a '-'. In cases where it is difficult to see the link between the SPC regulation[1] and the achievement of the objective, the given characteristic or point is marked with a '?'.

1 Regulation (EC) No 469/2009.

Supply-side objectives

Producers and innovators of medicinal, veterinary and plant protection products that want to market their innovations in the European Community's internal market are naturally subject to regulatory scrutiny and authorisation procedures before being allowed to do so.

The combination of research, product development, clinical testing and administrative authorisation procedures can take several years. A period of time elapses before products are brought to the market.

At the same time, the economic characteristics of the required research and development activities and the crucial role of intellectual property in the affected industries force actors to apply for patent protection early on in the product lifecycle. Often, a patent is obtained years before the patentee is granted the authorisation to market the protected product.

As a consequence, the effective protection period of patent protection is shorter than the period a patent protects the IP.

To compensate patentees for the shortened effective protection period[1], supplementary protection certificates (SPCs) can be granted as an extension to a patent right[2]. SPCs were designed to incentivise pharmaceutical and agrochemical innovation and to strengthen the affected industries' capability to recover investments.

Supply-side objectives

SPC objectives: R&D stimulation and innovation	**1 Attraction of pharmaceutical and agrochemical innovation to the EU** COM(90) 101 final Rec. 8
	2 Prevention of delocalisation of pharmaceutical and agrochemical innovation and manufacturing COM(90) 101 final Rec. 7
	3 Ensure that research-based industry has market protection of sufficient length to permit recovery of investments COM(90) 101 final Rec. 5, Rec. 25
	4 Fall in prices of medicines and agrochemicals following SPC expiry, or whether the setting of those prices have reflected the longer exclusivity period for recuperation of investments provided for by the rules COM(90) 101 final Rec. 24
	5 Promotion of competition through innovation COM(90) 101 final Rec. 25
	6 Encourage innovation demanded and needed by consumers, patients and stakeholders COM(90) 101 final Rec. 7

1 See pp. 28-30.

2 See https://ec.europa.eu/growth/industry/intellectual-property/patents/supplementary-protection-certificates_en [last accessed 29/01-2018].

Supply-side objective 1: Attraction of pharmaceutical and agrochemical innovation to the EU (1/3)

THE OBJECTIVE IN THE REGULATION

Objective no. 1: Attraction of pharmaceutical and agrochemical innovation to the EU
"The basic objectives of this proposal for a Regulation therefore concern the requirements relating to the proper functioning of the internal market, improvement of our competitiveness as compared with that of our trade partners and the encouragement of research and development in the health field."
- COM(90) 101 final, Recital 8

ECONOMIC RATIONALE

The introduction of a patent term restoration scheme in the European Union aims at increasing pharmaceutical companies' innovation incentives by prolonging the period of protection granted to the inventor behind a patented novelty[1].

In this context, the objective of attracting innovation to the European Union can be understood as creating the proper incentives and market structures for companies to be willing to carry out their research and development activities within the Community[2].

As discussed in section 2.1, the main driver determining firms' decisions to engage in R&D activities conducive to pharmaceutical innovation is the availability to reap the profits of successfully developing a product. As such, the time period over which a company is granted exclusive commercial exploitation of its innovative product, the effective protection period, is a key factor in driving R&D spending[3].

The effective protection period encompasses the time from filing of the first to expiry of the last intellectual property right providing meaningful protection[4], net of the time it takes the innovator to develop the product up to marketing authorisation.

Supplementary protection certificates are designed to compensate pharmaceutical companies for lost effective protection period, i.e. should increase effective protection time. The presence of an SPC can thus be compared to the effect of a conditional increase in effective protection time.

EVIDENCE

During their exclusive commercial exploitation period, firms can be expected to be able to obtain higher profits on the respective product market. If companies' decisions of whether and where to engage in R&D activities is mainly driven by expected profits, the presence of an SPC extending this exclusivity period could thus provide a positive incentive.

At the same time, an innovator's capability to recover sufficient profits to make up for initial fixed cost investment depends on the product's market size and profitability (i.e. number of patients and price per treatment).

On the other hand, studies of the placement of R&D have pointed out that decisive factors are e.g. education, infrastructure, political stability, taxation regulation and access to the right talent[5].

Furthermore the evidence as to whether domestic patent protection is important for the placement and investment in R&D is ambiguous. E.g. Qian (2007) and Sakakibara and Branstetter (1999) find that no direct relationship between domestic patent protection and placement/investment in R&D can be identified. On the other hand e.g. Pazderka (1999) does find that there is a connection.

Thus, we are cautious in concluding that domestic patent protection in itself should attract innovation.

However, as far as the results of the dynamic panel data estimation methodology described in section 2.1 hold, some interesting conclusions can be drawn from this.

It can be inferred that e.g. the mean effective protection period within the EU countries with which the given country trades the most have a positive and significant effect on domestic pharmaceutical R&D spending.

In general, two conclusions can be drawn from this result:

1. An increase of general effective protection period within the EU leads to an increase in R&D within the EU (and outside the Union).
2. As SPCs increase the effective protection through patent restoration, they lead to increased innovative activity within the individual Member States.

1 See Regulation (EC) No 469/2009 (4).
2 See Regulation (EC) No 469/2009 (3).
3 See Regulation (EC) No 469/2009 (9).
4 The 'quality' of protection provided by intellectual property rights varies across the type of IPR. The term 'meaningful protection' in this context refers to protection, such as patents and SPCs, that cannot be circumvented without infringing on the original right holder's right. Data protection, for instance, can technically be circumvented if a company is willing to compile their own data.
5 See e.g. Demirbag, M. and Glaister, K. W. (2010) Factors Determining Offshore Location Choice for R&D Projects: A Comparative Study of Developed and Emerging Regions, Reddy, P. and Sigurdson, J. (1997), Strategic location of R&D and emerging patterns of globalisation: the case of Astra Research Centre India, Kumar, N. (2001), Determinants of location of overseas R&D activity of multinational enterprises: the case of US and Japanese corporations.

Supply-side objective 1: Attraction of pharmaceutical and agrochemical innovation to the EU (2/3)

THE OBJECTIVE IN THE REGULATION

Objective no. 1: Attraction of pharmaceutical and agrochemical innovation to the EU
"The basic objectives of this proposal for a Regulation therefore concern the requirements relating to the proper functioning of the internal market, improvement of our competitiveness as compared with that of our trade partners and the encouragement of research and development in the health field."
- COM(90) 101 final, Recital 8

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These results are however dependent on the developed model used in section 2.1 being able to correctly identify and capture the relationship between patent protection and investment in R&D.

As was previously mentioned, an SPC is the last protection to expire in 10% of cases in the present data material. For these 10% of cases, the SPC extends the effective protection by approx. 2.6 years. Furthermore, 45% of the unique products in our sample have obtained an SPC[1]. As such, this would point to SPCs having contributed to increased spending on pharmaceutical R&D within Europe.

However, reviewing the literature, the most important determinants for the placement of R&D seems to be the before-mentioned factors such as education, infrastructure, political stability, taxation regulation and access to the right talent[1].
As such, if the attraction of innovation to the EU is the goal, the ease with which these factors can be enhanced needs to be weighed against their respective effect as well as the cost and effect of changing e.g. the protection regime.

The effect of the SPC in increasing the effective protection period might be dampened if firms apply for fewer certificates in non-home markets due to negative impacts of SPC fragmentation.

Effect of SPCs on effective protection period

Effect of trade-weighted foreign effective protection period on domestic R&D spending

1 See p. 84.
2 See e.g. Demirbag, M. and Glaister, K. W. (2010) Factors Determining Offshore Location Choice for R&D Projects: A Comparative Study of Developed and Emerging Regions, Reddy, P. and Sigurdson, J. (1997), Strategic location of R&D and emerging patterns of globalisation: the case of Astra Research Centre India, Kumar, N. (2001), Determinants of location of overseas R&D activity of multinational enterprises: the case of US and Japanese corporations

Supply-side objective 1: Attraction of pharmaceutical and agrochemical innovation to the EU (3/3)

The graph to the right depicts the year-on-year change in the spending on pharmaceutical R&D in selected European countries, the United States, Canada, Japan and China.

The rather exorbitant growth rate for the United States in 2004 is probably due to a change in the way the statistics are assessed.

In recent years China has outpaced all other countries when it comes to spending on pharmaceutical R&D. This coincides with China generally exhibiting high rates of growth in GDP as well[1].

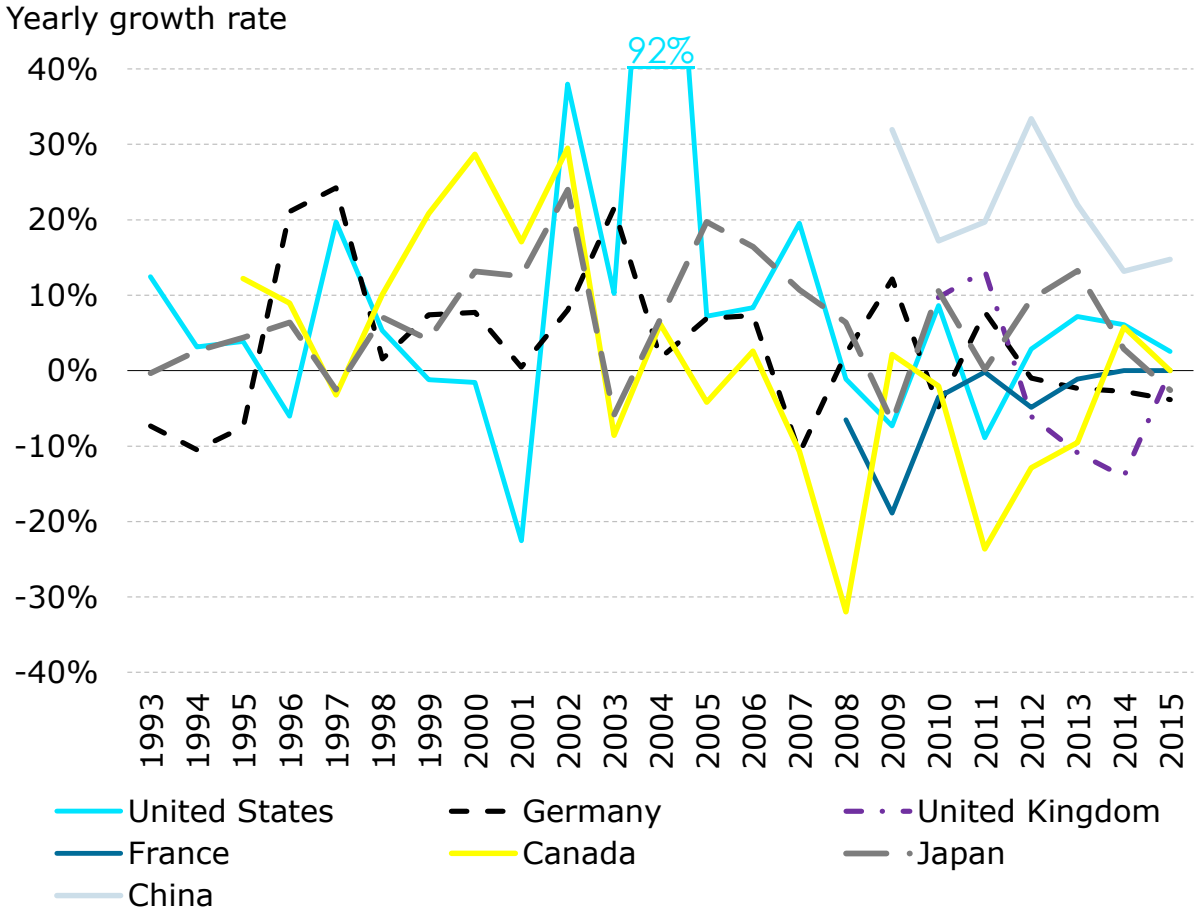
As the number of years that data is available across the countries is variable, the measure of 'Compound Annual Growth Rate' (CAGR) can be used as a common comparison tool. The CAGR describes the average annual growth rate.

For each country during the available years, the CAGR's have been as follows:

United States	7.0%
Germany	3.0%
United Kingdom	-2.2%
France	-6.1%
Canada	0.6%
Japan	6.4%
China	21.5%

According to EFPIA the CAGR for spending on pharmaceutical R&D within the EU has been 4.6% from 2000 to 2015[2]. As such, it can be seen that the United States, Japan and China outpace the European countries on average.

Change in spending on pharmaceutical R&D for selected European countries and the United States, 1993-2015



Note: Graph showing the year-on-year change in spending on pharmaceutical R&D in the selected countries. The European countries have been selected based on data availability and size.
Source: OECD, Business enterprise R&D broken down by industry, ANBERD dataset.

Copenhagen Economics

1 World Bank national accounts data and OECD National Accounts data files, GDP growth (annual %)
2 Calculated based on EFPIA (2017), The Pharmaceutical Industry in Figures, p. 3.

Supply-side objective 2: Prevention of delocalisation of pharmaceutical and agrochemical innovation and manufacturing (1/4)

THE OBJECTIVE IN THE REGULATION

Objective no. 2: Prevention of delocalisation of pharmaceutical and agrochemical innovation and manufacturing

"[A] passive attitude (…) will entail two types of risk (…): on the one hand, a decrease in research due to insufficient resources and, on the other hand, the relocation of research centres away to non-member countries that offer better protection and an environment more conductive to innovation."

- COM(90) 101 final, Recital 7

ECONOMIC RATIONALE

Supply-side objective 2 is, in particular, focused on avoiding the adverse consequences that the European Commission believed (at the time) would impact the market had no measures been taken to remedy the loss of effective protection terms caused by a rise in development times.

The presence of innovation activities within the European Union not only serves to ensure the timely launch and availability of necessary medicines and agrochemical products within the community but, as argued in the European Commission's memorandum, can also have considerable socioeconomic impact.

The invention and development of medicinal products to the stage where they can be submitted for regulatory approval involves an integrated value chain that spans from laboratorial institutions and clinical testing facilities all the way to product safety and quality assurance. The economic footprint of pharmaceutical companies and research centres is consequentially substantial and includes local investment, skilled labour demand and sizable benefits to their respective locations[1].

While pharmaceutical innovators incur substantial up-front investment costs and uncertainty regarding their R&D initiatives, the manufacturing cost of producing a medicinal product once it is developed and approved for marketing can often be rather negligible[2]. Low-value-added activities of pharmaceutical innovators, such as manufacturing, might be more susceptible to being transferred to a low-cost location than skill-intensive high-value-adding activities such as research and development.

In addition, innovator companies could decide to focus on the skilled-labour intensive R&D activities alone and decide to license the manufacturing or even the complete commercial exploitation of a developed and authorised medicinal product to a third party. If the benefits of domestic intellectual property protection only apply to the R&D-intense part of a medicinal product's product life cycle, companies might decide to either contract other players to carry out their less R&D-intense and low-value-adding activities or relocate more cost-sensitive parts of their production value chain in other ways.

Finally, innovation and product development activities carried out within a Member State or within the European Union as a whole could facilitate the monitoring and assurance of product safety and efficacy[3].

EVIDENCE

A decrease in expected profitability from a local market would, in particular, incentivise firms to relocate less skilled-labour-intensive manufacturing or other low-value-adding activities to low-cost countries inside and outside the European Union.

At the same time, it is unclear what effect effective protection period in a country has on the presence of generic manufacturers. If these, as a counterweight to originators, flock to countries with lower average effective protection times, their location of manufacturing or product development facilities might outweigh the effect of innovator relocation[4].

In general, introducing SPCs in the European market has worked to increase pharmaceutical R&D spending as SPCs extend the average effective protection period. This assertion is built upon the econometric results in section 2.1, signifying that the protection period provided in the other EU countries with which a given country trades the most has a significant impact on the domestic spending on pharmaceutical R&D.

Furthermore, the enactment of the Bolar exemption has allowed generic manufacturers to better maintain their activities within the European Union as it has allowed research of generics before expiry of protection[5].

1 WifOR (2015), The Economic Footprint of the Pharmaceutical Industry, Research Report.
2 This might not be the case for all medicinal products and particularly not for biologic products where the manufacturing process can be intricate and expensive.
3 This might be the case if monitoring of the sites by the authorities is easier when the sites are placed within the EU than when they are not. However, sites seeking to export pharmaceuticals to the EU must live up to the Good Manufacturing Practice guidelines and as such this might not be a large driver.
4 Regarding this issue see e.g. DG GROW public consultation including discussion about manufacturing waiver available at https://ec.europa.eu/info/consultations/public-consultation-supplementary-protection-certificates-spcs-and-patent-research-exemptions_en
5 Directive 2001/83/EC, Article 10(6)

Supply-side objective 2: Prevention of delocalisation of pharmaceutical and agrochemical innovation and manufacturing (2/4)

THE OBJECTIVE IN THE REGULATION

Objective no. 2: Prevention of delocalisation of pharmaceutical and agrochemical innovation and manufacturing
"[A] passive attitude (…) will entail two types of risk (…): on the one hand, a decrease in research due to insufficient resources and, on the other hand, the relocation of research centres away to non-member countries that offer better protection and an environment more conductive to innovation."
- COM(90) 101 final, Recital 7

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What is more, as could be seen in section 1.3, the protection provided in the EU is more generous than that in many other countries. As such, this works to dismantle the argument for delocalising pharmaceutical and agrochemical innovation and manufacturing.

However, it is likewise pertinent to point out that several studies from the literature regarding location of R&D activities identifies a range of important factors other than patent protection. These are e.g. education, infrastructure, political stability, taxation regulation and access to the right talent[1]. Furthermore, many of these studies do not identify domestic protection as a decisive factor for the placement of R&D.

This is, however, not detrimental to the results of the econometric model in chapter 2, where we look at the protection in the other EU countries with which a given country trades the most.

According to EvaluatePharma, the average annual growth rate ('compound annual growth rate', CAGR) for spending on pharmaceutical R&D in the world has been 2.5% between 2008 and 2016. For the years 2016 to 2022, it is projected to be 2.4%[2].

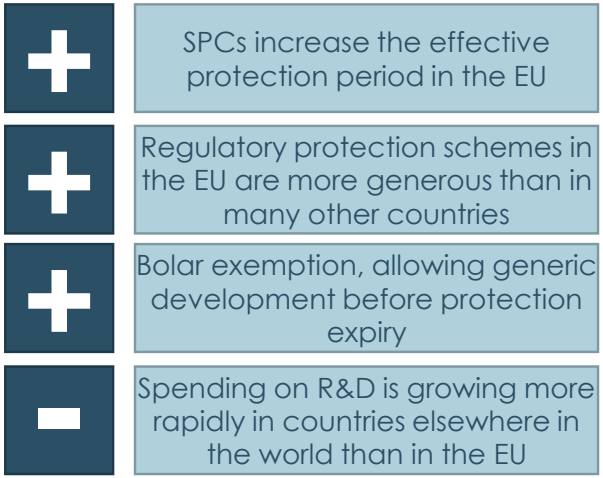
At the same time, it was shown under objective no. 1 that the CAGR for spending on pharmaceutical R&D in China has been 21.5% in the years 2008 to 2015.

In 2012 the spending on pharmaceutical R&D in China equalled the combined spending in Germany, UK, France, Italy and Spain. Since then it has grown much more rapidly than in the aforementioned European countries[3].

Furthermore, a country such as India, which has previously been known mostly for its generics industry, has shown an increase in development within new proprietary compounds in recent years[4].

This could, to some extent, point towards new trends within the placement of pharmaceutical R&D. However, spending on R&D within the EU is still showing an increasing trend and remains high. According to EFPIA, the CAGR for spending on pharmaceutical R&D within the EU has been 4.6% from 2000 to 2015[5].

On the following two pages, empirical evidence regarding the number of employees within the pharmaceutical sector as a whole and the subsector of pharmaceutical R&D is presented. This evidence shows that while employment within pharmaceutical R&D within the European union has increased by 49% between 1990 and 2015, overall employment within the sector has not increased between 2006 and 2014



1 See e.g. Demirbag, M. and Glaister, K. W. (2010) Factors Determining Offshore Location Choice for R&D Projects: A Comparative Study of Developed and Emerging Regions; Reddy, P. and Sigurdson, J. (1997), Strategic location of R&D and emerging patterns of globalisation: the case of Astra Research Centre India; Kumar, N. (2001), Determinants of location of overseas R&D activity of multinational enterprises: the case of US and Japanese corporations
2 EvaluatePharma (2017), World Preview 2017, Outlook to 2022,
3 OECD, Business enterprise R&D broken down by industry, ANBERD dataset.
4 See figure 2 in Differding, E. (2017), The Drug Discovery and Development Industry in India – Two Decades of Proprietary Small-Molecule R&D.
5 Calculation based on EFPIA (2017), The Pharmaceutical Industry in Figures.

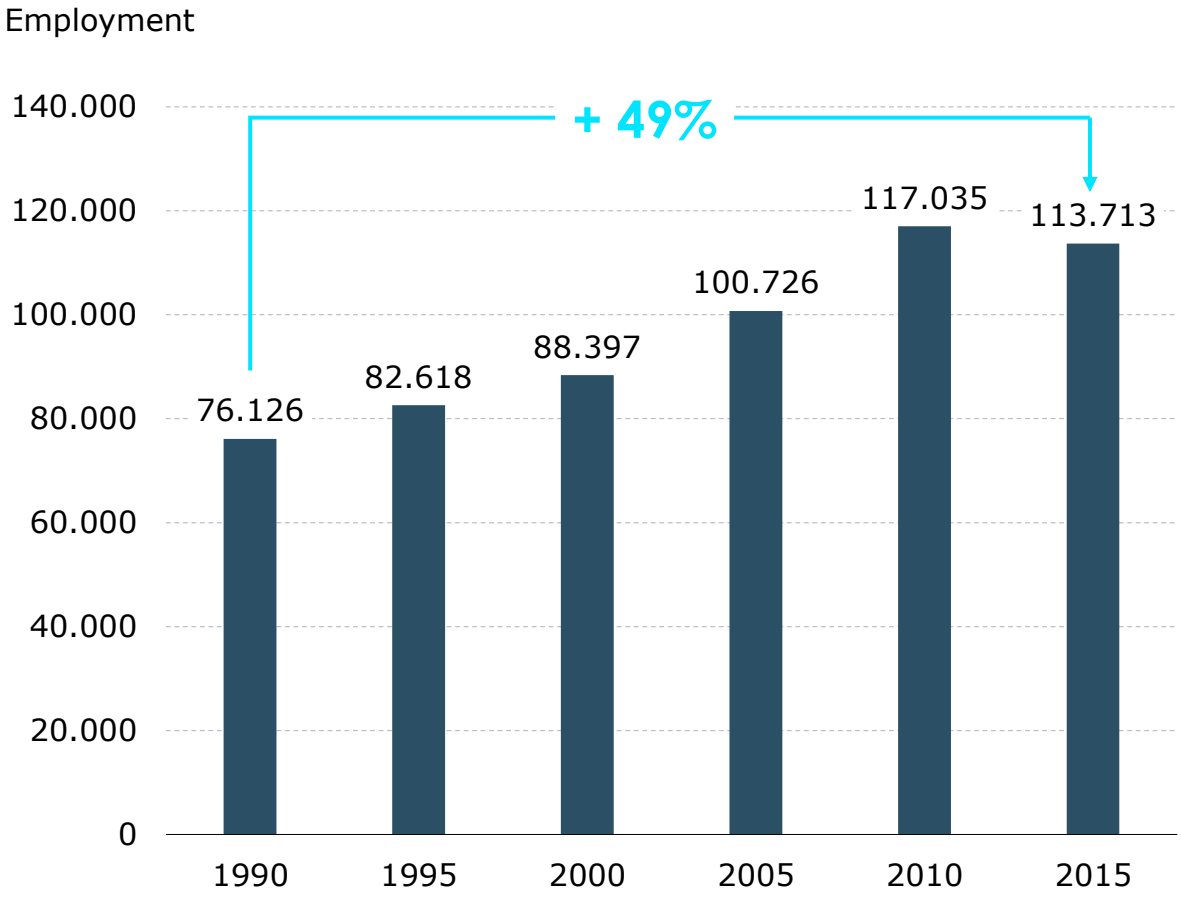
Supply-side objective 2: Prevention of delocalisation of pharmaceutical and agrochemical innovation and manufacturing (3/4)

The graph to the right depicts the number of people employed within pharmaceutical R&D in the European Union, from 1990 to 2015[1].

Overall there has been an increase in employment within pharmaceutical R&D in the European Union of 49% during the period. This does however, cover a steady increase from 1990 to 2010 followed by a small decrease in employment from 2010 to 2015.

What would have happened, had the current regulation governing the SPC[2] not been introduced is unknown.

Employment in Europe within the R&D branch of the pharmaceutical sector, 1990-2015



Note: Data includes Greece & Lithuania (since 2013), Bulgaria and Turkey (since 2012), Poland (since 2010), Czech Republic, Estonia and Hungary (since 2009), Romania (since 2005) and Slovenia (since 2004).
Source: EFPIA based on member associations, available at https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-employment/employment-in-pharmaceutical-rd/

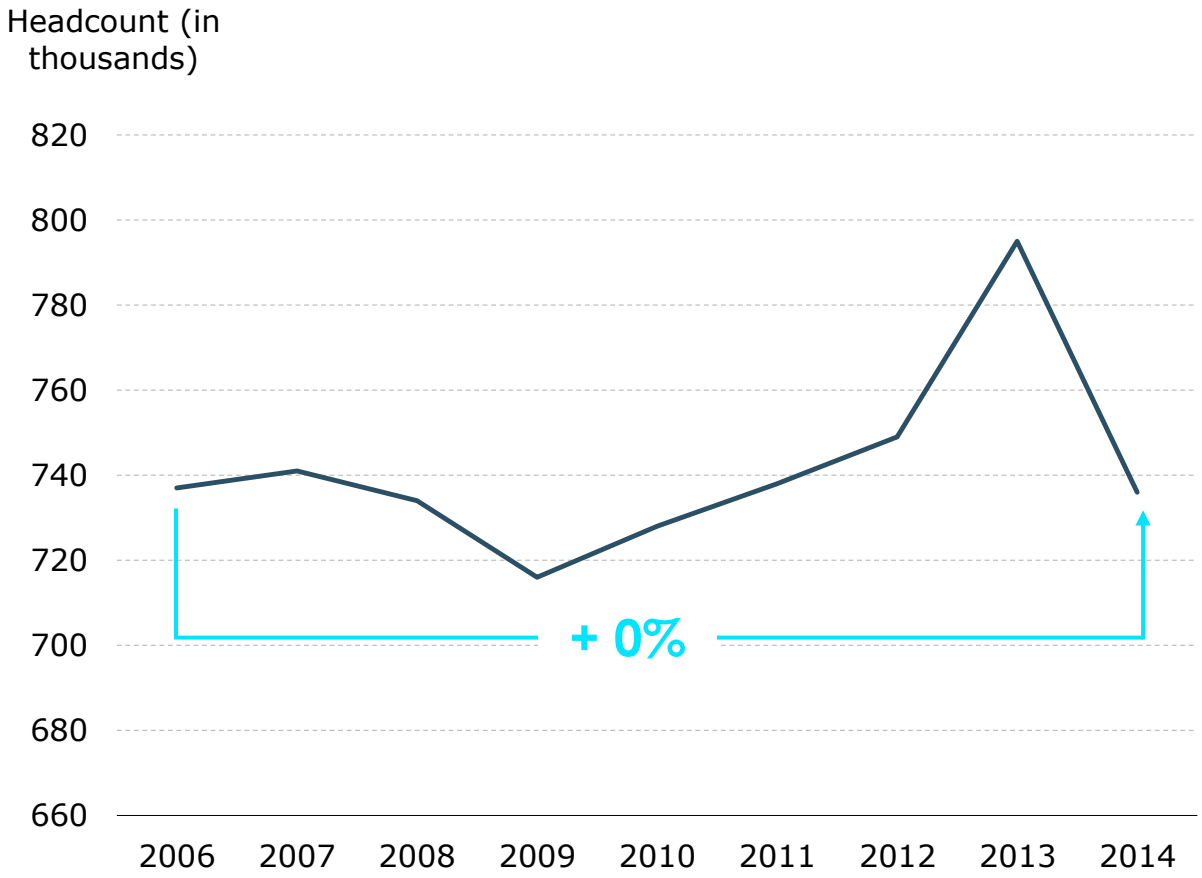
1 Based on EFPIA numbers from member associations, available at https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-employment/employment-in-pharmaceutical-rd/
2 Regulation (EC) No 469/2009.

Supply-side objective 2: Prevention of delocalisation of pharmaceutical and agrochemical innovation and manufacturing (4/4)

The graph to the right depicts the total employment in the European Union within the pharmaceutical industry spanning the years 2006 to 2014.

During the period, there have been certain fluctuations in the number of people employed in the sector. However, when gauging the whole period there has been no change in employment from 2006 to 2014.

Total employment in Europe within the pharmaceutical industry, 2006-2014



Note: Graph depicting the number of employees in the European Union within the pharmaceutical sector, in thousands.
Source: IFPMA (2017), The pharmaceutical industry and global health, table 10, p. 44.

Supply-side objective 3: Ensure that research-based industry has market protection of sufficient period to permit recovery of investments (1/2)

THE OBJECTIVE IN THE REGULATION

Objective no. 3: Ensure that research-based industry has market protection of sufficient length to permit recovery of investments

"[E]ssential to this innovating sector, in that investment in research is financed by means of returns obtained during a period of exclusive exploitation, thereby making it possible to ensure that self-funding continues and to guarantee further research in the future."

- COM(90) 101 final, Recital 5

"The aim of this proposal is specifically to ensure that research based industry has a market exclusivity of sufficient length to permit recovery of their investments."

- COM(90) 101 final, Recital 25

ECONOMIC RATIONALE

From a regulatory perspective, setting the right incentives and exclusivity periods is a question of striking a balance.

On the one hand, the development of medicinal products and the engagement in innovative R&D processes demand extensive amounts of research, significant monetary expenditures and often large up-front investments.[1] Moreover, the development of new medicinal products is a lengthy and time-consuming endeavour that is often paired with considerable amounts of uncertainty relating to the actual success probability of the product being developed, the risk of being refused regulatory approval required for an authorisation to commercialise the invented solution, the risk of being outraced by a competitor developing a substitutable or superior treatment that might capture the targeted market shares, etc.

Innovators will only engage in development projects that eventually lead to the availability of new medicines if they perceive their expected profit to be sufficient compensation for taking on the risks and investment requirements outlined above.[2]

On the other hand, the granting of a commercial exclusivity period to the innovator behind a new medicinal product is contrary to public interest: once an invention has been disclosed, public interest would be to introduce competition as soon as possible in order to reduce the detrimental effects of temporary commercial exclusivity on, for instance, public health budgets and out-of-pocket expenses.

While there is a desire to incentivise firms and to reward firms for engaging in the development of innovative products, there is also fundamental public interest in limiting this remuneration for disclosure to the absolute minimum necessary to achieve the innovation required.

This trade-off is particularly crucial if there is positive correlation between the complexity of product development and public interest in the outcome. That is, if the medicinal products that are most important to society are the medicinal products that are hardest to invent.

EVIDENCE

The main consideration for a firm when deciding whether or not to engage in a product development process ought to be expected profit.

Expected profit is mainly determined by the following factors:

- Development risk of project failure
- Quantity of products that can be sold (i.e. number of patients with the relevant therapeutic need)
- Profit margin (i.e. price minus cost) that can be charged
- Time to (generic) competition from other providers

SPCs provide their rights holder with a prolonged exclusivity period. As such, this additional protection increases the time it takes until competitors – generic or originators circumventing regulatory exclusivity – can enter the market.

Combined with the results obtained in section 2.3, namely the fact that prices tend to decrease upon market entry of generics, this points to that the presence of an SPC should allow an originator company to earn higher profit margins over a longer period of time (i.e. delayed price competition). As such, the uncertainty-weighted expected profit should increase when a company is granted an SPC.

1 The literature shows estimated costs of bringing a medicinal product from the lab to the market between USD 648m and USD 2.6bn. See Prasad, V. and Mailankody, S. (2017), Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval and Di Masi, J. A., Grabowskib, H. G. and Hansen, R. W. (2016), Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs.

2 A pertinent issue relating to this argument relates to the choice that pharmaceutical innovators might have between development projects. As innovators are assumed to display profit maximising behaviour, their profitability calculation will likely focus on which quantity they will be able to sell at which prices over the expected time period between launch and generic entry. As such, they will not necessarily consider the therapeutic value of a treatment in determining which project to pursue and develop. This behaviour might have adverse consequences for public health if pharmaceutical companies choose to develop commercially 'safer' products over projects that might have lower expected profits but higher value for society. A thorough discussion of this choice between project alternatives is however beyond the scope of this study. However, one way of remedying this is to closer connect the achievable prices with the therapeutic value.

Supply-side objective 3: Ensure that research-based industry has market protection of sufficient length to permit recovery of investments (2/2)

Contrary to some US studies[1], the evidence compiled in section 2.2 does not show a positive effect of effective protection periods on EU medicinal product launches. SPC-related extensions do not seem to be decisive drivers in the launch strategy of pharmaceutical companies.

From the graph to the right it can be seen that the average effective protection period for medicinal products has been decreasing over time. The general decrease in average effective protection is depicted by the blue line.

The red line depicts what the average effective protection period would have been, had market protection and data protection not existed. The green line, furthermore, depicts what the average effective protection period would have been if neither market protection, nor data protection, nor SPCs had existed.

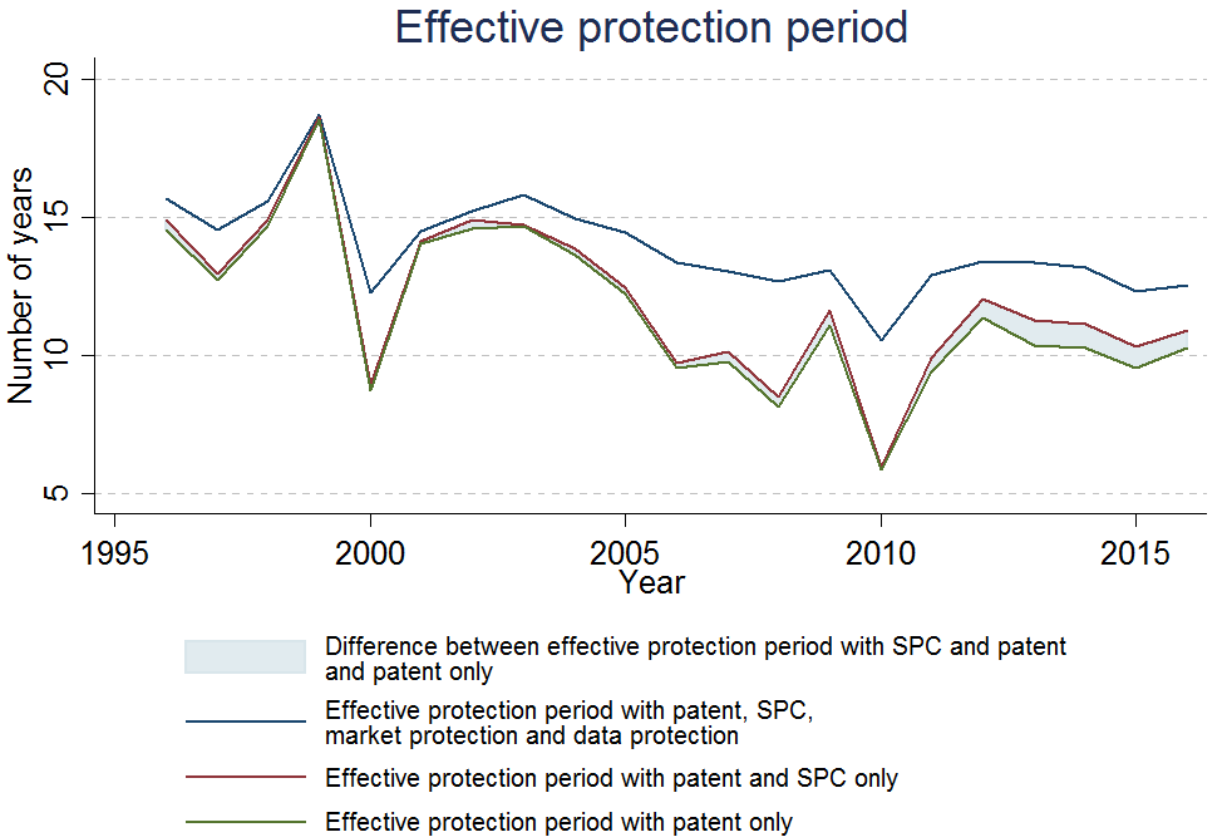
As such, the gap between the red and green line depicts the effect on the average effective protection period of medicinal products of SPCs. From 2010 to 2016 this average effect is 0.6 years across all products.

It is evident from the graph that the effect of the SPC has increased in size in more recent years. As such, the importance of the SPC for the average effective protection period for medicinal products has increased over time.

SPCs delay time until generic competition

SPCs have become increasingly important for the effective protection period

Effective protection period based on different protection schemes, 1996-2015



Notes: Calculation based on unique product-country observations. This means that each product is used in the calculation of the average effective protection period as many times as the number of countries in which it has marketing authorisation. Prior to 1995, data is only available for 12 respectively 13 countries. The last year of complete observation is 2016. The above graph depicts the average effective protection for all observations, irrespective of whether they have been subject to an SPC application or not. For about ten per cent of the sample, supplementary protection certificates are the last intellectual property right to expire. As such, the above graph does not depict the marginal effect of SPCs on the effective protection period.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI

1 See e.g. Goldman et al. (2011) where the authors conclude that an increased effective protection period leads to additional launches.

Supply-side objective 4: Fall in prices of medicines and agrochemicals following SPC expiry, or whether the setting of those prices have reflected the longer exclusivity period for recuperation of investments

THE OBJECTIVE IN THE REGULATION

Objective no. 4: Fall in prices of medicines and agrochemicals following SPC expiry, or whether the setting of those prices has reflected the longer exclusivity period for recuperation of investments provided for by the rules

"[T]he present proposal, moreover, favours a possible fall in the prices of medicinal products covered by this proposal in light of the extension of the period for recuperation of investments."

- COM(90) 101 final, Recital 24

ECONOMIC RATIONALE

The economic rationale behind objective no. 4 can be argued along different lines. The first part of the objective formulation points to price dynamics following SPC expiry, i.e. either loss or weakening of exclusivity following the lapse of a specific IP right.

In essence, once exclusivity lapses or can be legally bypassed in other ways, the market should be accessible for entrants resulting in increased competition and downward price pressure.

The second part of the objective seems to point towards the idea of pharmaceutical companies being focused on recovering and distributing their cost over the time frame of their exclusivity protection. Principally, this reasoning seems to fall short in not accounting for the profit-maximising behaviour of a private company. While firms consider the impact of investment cost and resulting present value considerations in determining whether to engage in a project, pricing upon completion of R&D activities should largely be independent of this.

Instead, from a theoretical economic viewpoint firms would, while protected by IP rights, behave similarly to monopolists, which includes pricing at marginal revenues[1]. Sunk cost would not factor into the price setting process.

At the same time, pharmaceutical companies do not always find themselves in the position of a true monopoly. Rather, competitors can 'compete through innovation' and develop products targeting the same or closely-related therapeutic indications. If a competitive product fulfils criteria for a certain degree of substitutability, firms might deviate from purely monopolistic pricing. In this context, time to expiry can play a role if it correlates with the likelihood of competition arising.

Both prior to and following exclusivity expiry, customers' willingness or ability to switch treatment plays a role in the pricing opportunities available to companies in the market. Economically, these customer reactions can be gauged using elasticities, i.e. the likely demand response in reply to a change to prices (or similar characteristics).

In the literature, prices have at times been observed to actually rise following the expiry of exclusivity. For firms, this can be profitable when a group of patients for certain reasons is unable to change to a substitute product (i.e. when demand is inelastic).[2]

EVIDENCE

The results obtained in section 2.3 point to substantial price decreases in medicinal product prices upon generic entry. Generic entry can occur once all meaningful protection schemes have expired. As such, this result also points to a decrease in price following the expiry of a supplementary protection certificate.

While a slight anticipatory effect of decreasing prices can be observed, this should not be interpreted as a decrease due to prolonged effective protection period but rather a leading effect of imminent competition entering the product market or originator competition.

We are unable to find either economic arguments or empirical evidence supporting the assertion that SPCs should help to decrease prices during protection.

No direct link between price setting while under protection and the length of the protection period

No direct link between protection period and price fall after expiration of protection

1 While firms in a competitive environment will set prices equal to marginal cost, monopolists will set prices at marginal revenue instead, which will generally be higher than marginal cost. A monopolist will price at marginal revenue rather than marginal cost due to the fact that reducing price will reduce the profit made on all other units sold and not just the additional – marginal – unit.

2 See e.g. Frank & Salkever (1992/1997).

Supply-side objective 5: Promotion of competition through innovation (1/2)

THE OBJECTIVE IN THE REGULATION

Objective no. 5: Promotion of competition through innovation
"It is true that the longer exclusivity period, the longer the delay before generics enter the market. (…) However, this will not mean any reduction in competition. The well known effect of the patents system is to promote competition through innovation. (…) Generic products exist only if new medicinal products are developed and disclosed."
- COM(90) 101 final, Recital 25

ECONOMIC RATIONALE

Patents as IP rights grant an inventor temporary exclusivity for the exploitation of their invention. In return, the inventor has to hand a description of the invention to the competent authorities.

That way, patents provide two types of benefits to an economy:

- Increased rewards to successful innovation
- Public disclosure of innovations made by private actors.

On the one hand, the availability of patents encourages companies to engage in innovative behaviour. The opportunity to exclusively exploit an invention sets incentives for firms to pursue innovative novelty and new solutions over merely improving and refining existing ways of addressing a known problem.[1]

While this excludes others from using the same invention during the original inventor's exclusivity period (usually 20 years), this does not necessarily mean that there cannot be competition in a product market. Companies can, conditional on not infringing the originator's patented invention, develop similar, comparable, or different medicines that target the same therapeutic indication as the original product. That way, companies can compete for the same patient group irrespective of patent protection.

EVIDENCE

Through providing a longer period of exclusive rights for an invention, the SPC scheme might encourage more competition through innovation.

Competition through innovation means that both (or more) companies with originator products on the market have incurred a development cost for R&D, including clinical trials. As such, the price pressure between originator companies might be of a lesser nature than when generics enter. As the SPC scheme delays the time at which generics can enter the market, SPCs make competition by innovation more profitable than if SPCs had not existed.

However, SPCs could likewise have a negative impact on innovation activities. This can be the case if entities are allowed to engage in so called 'SPC squatting'. In this practice, a patentee could potentially obtain an SPC on a product based on a patent that someone else - a third party - has developed to marketing authorisation.[2]

This 'third-party issue' could potentially discourage innovators from developing products, e.g. in biotechnology where different antibodies could infringe on broader functional patents. As argued in Carver (2015), such a situation could leave pharmaceutical innovators with a range of unfavourable options.[3] In this way, the current SPC set-up in the EU could reduce innovation incentives in specific cases.

However, at the same time, by extending the protection period provided to originator companies, SPCs increase the expected profit from developing new innovative products. As such, if two companies are simultaneously developing two originator medicinal products for treating the same indication, the possibility of obtaining an SPC increases the profit prospect for both companies, despite the competition they will face. This might bring some products to be developed that would otherwise not have been profitable, in the light of facing generic competition at an earlier stage. Through this mechanism, SPCs might increase the amount of competition through innovation.

On the following page empirical evidence regarding the percentage of first-in-class New Chemical Entities which are discovered in the EU compared to other parts of the world is presented. From this, it can be seen that the EU has maintained its share of first-in-class NCEs at 44% of all, when comparing the period 1982-1992 to the period 1993-2003.

SPCs delay the time at which generics can enter, making originator competition more profitable

The possibility of so-called 'SPC squatting' might discourage originator competition

1 In economic literature, this is often referred to as the difference between static efficiency (cost reduction and product refinement) and dynamic efficiency (establishing novel practices). See e.g. OECD (2006), 'Competition, Patents and Innovation'.
2 See e.g. Schovsbo, Klinge & Minssen (2017) for an overview of related issues.
3 Carver (2015) 'Eli Lilly v. Human Genome Sciences: A case of what is implicitly, but necessarily and specifically in point!', at https://gowlingwlg.com/en/global/insights-resources/eli-lilly-v-human-genome-sciences-a-case-of-what-is-implicitly-but-necessarily-and-specifically-in [last accessed 2017-09-04]

Supply-side objective 5: Promotion of competition through innovation (2/2)

In the United States, the U.S. Food & Drug Administration (FDA) has a 'first-in-class' designation. First-in-class medicinal products, for example "*use a new and unique mechanism of action for treating a medical condition*"[1].

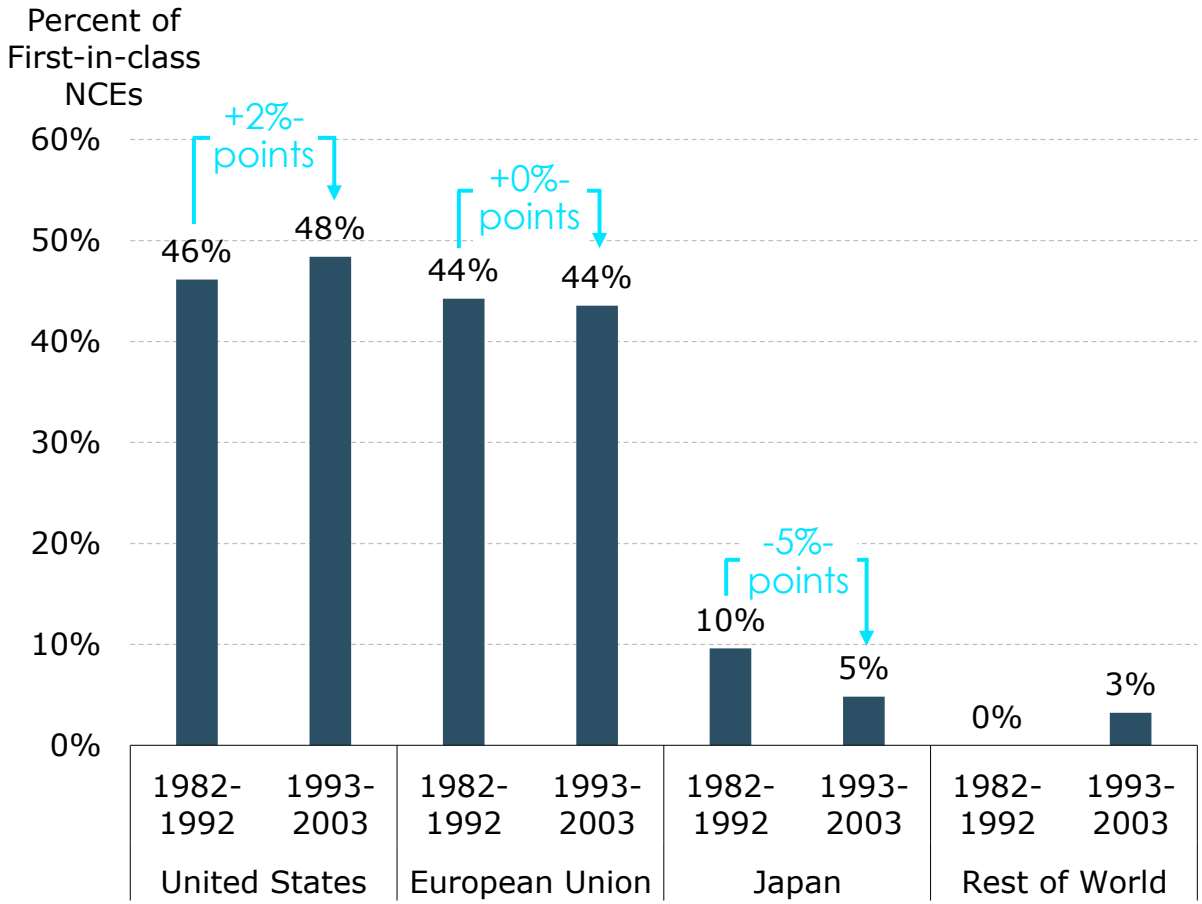
Using this definition, Grabowski and Wang (2006)[2], have looked at the distribution of New Chemical Entities (NCEs) designated as first-in-class, across the United States, the European Union, Japan and the Rest of World. The results of the analysis is depicted in the graph to the right.

According to the authors, the first-in-class designation can be used to identify particularly novel, and to a certain extent, the most therapeutically important products[2].

Between the period 1982-1992 and 1993-2003, the share of first-in-class NCEs developed in the United States and in the European Union have been almost unchanged, as a share of the total number of first-in-class NCEs in the world.

Using the first-in-class definition from the FDA has a few shortcomings. First of all, the authors have had to exclude NCEs not yet launched in the United States, even if these were launched elsewhere. This is done, as the first-in-class classification is unavailable for other parts of the world than the United States. This could work to understate the number of first-in-class NCEs developed in the European Union, as all NCEs not launched in the United States are excluded.

First-in-class New Chemical Entities (NCEs) discovered in the United States, Europe, Japan and the Rest of World, comparing the time period 1982-1992 to 1993-2003



Note: First-in-class NCEs are distributed by headquarter of the company. NCEs not yet launched in the United States are excluded from the analysis.

Source: Grabowski, H. G. and Wang, Y. R. (2006), The Quantity and Quality of Worldwide New Drug Introduction, 1982-2003, Exhibit 4, p. 457.

1 See FDA website (FDA.gov).

2 Grabowski, H. G. and Wang, Y. R. (2006), The Quantity and Quality of Worldwide New Drug Introduction

Supply-side objective 6: Encourage innovation demanded and needed by customers, patients and stakeholders (1/2)

THE OBJECTIVE IN THE REGULATION

Objective no. 6: Encourage innovation demanded and needed by customers, patients and stakeholders

"The aim of this proposal (…) is to improve the protection of innovation in the pharmaceutical sector (…) to permit the European pharmaceutical industry (…) to guarantee therapeutic, scientific, economic and social progress which is indissolubly linked with the discovery and use of new medicinal products."

- COM(90) 101 final, Recital 1

ECONOMIC RATIONALE

For a new medicinal product to display the 'progress' characteristics described above in a given market, two things generally have to be true:

- The product needs to be invented and developed to approval.
- Upon approval, the product needs to be launched – made available to patients – in the given market.

As previously discussed, pharmaceutical companies' development and launch decisions are mainly driven by the profits that a company can expect to receive from engaging in a research project, net of the up-front investments that are necessary to develop the product up to receiving the authorisation to launch it on a market.

When looking at a company's decision whether to develop a product at all, likely the entirety of all markets that could qualify for launch will be considered in gauging the profitability of the initiative.

When looking at whether to launch a product in a specific market, conditional on the product having been developed prior to that, the most likely determinant is the expected profitability in that market alone. However, for certain markets additional strategic concerns, such as reference price regimes, can also be of importance when deciding whether and when to enter the market.

As discussed earlier and abstracting from development risk, there should be three key drivers of development and launching decisions:

- The quantity of products that can likely be sold.
- The profit margin (price minus cost) at which the quantity can be sold.
- The time period where this profit margin can be expected to be high (effective protection period).

EVIDENCE

An SPC is likely to increase the effective time of protection provided to a medicinal product. This is supported by the fact that in the present data material SPCs are the last protection to expire in 10% of cases. On average, the SPCs extend the effective protection by 2.6 years for these 10% of products. As such, if an SPC has been granted, it should be more profitable to launch a product in a specific market. In addition, if SPCs have been granted in numerous markets or in particularly important markets, this effect might also increase the overall incentive to develop a product in the first place. That way, SPCs could have a positive effect on the provision of innovative products that meet the needs of patients and stakeholders on the market.

On the other hand, the results obtained in section 2.2 show that there is no measurable effect from an increased effective protection period on product launch. As elaborated in section 2.2, this might be due to the fact that market attractiveness correlates with effective protection period. Drivers for early launch are found to be wealth and size of population. These can be seen as proxies for achievable price and expected quantity sold. Furthermore, evidence from the literature points to external reference pricing as an important driver of launch.

As will be shown in section 3.4, there is considerable fragmentation in the usage of SPCs across the European Union. Companies are more likely to apply for SPC protection in larger markets, which are however already more attractive *per se*.

One could argue that an SPC might thus have a stronger effect on launch probabilities in markets that are less attractive (e.g. in terms of GDP per capita). However, given the uncertainty and heterogeneity of outcomes attributed to a non-unitary SPC title, it appears that companies decide not to file for the additional protection in some of these less attractive markets. This in turn could reduce companies' incentives to launch a product in such a market at all as it would imply a reduction in expected profits.[1]

1 Please refer to section 3.4 for analysis and discussion of the impact of SPC fragmentation.

Supply-side objective 6: Encourage innovation demanded and needed by customers, patients and stakeholders (2/2)

THE OBJECTIVE IN THE REGULATION

Objective no. 6: Encourage innovation demanded and needed by customers, patients and stakeholders
"The aim of this proposal (…) is to improve the protection of innovation in the pharmaceutical sector (…) to permit the European pharmaceutical industry (…) to guarantee therapeutic, scientific, economic and social progress which is indissolubly linked with the discovery and use of new medicinal products."

- COM(90) 101 final, Recital 1

… continued from previous page.

Regarding the objective of the SPC encouraging innovation demanded and needed by customers, patients and stakeholders, this can be difficult to find a rational argument for.

The SPC extension of protection is dependent upon the development time spent, not the therapeutic value derived from the final medicinal product. As such, the SPC extends protection in general for all medicinal products with a patent and a development time longer than 5 years, regardless of whether these are demanded by customers, patients and stakeholders.

As was shown in section 2.1, an increase in effective protection period in the other EU countries with which a given country trades the most had a positive effect on domestic spending on pharmaceutical R&D. As likewise previously mentioned, this likely entails that the enactment of the SPC has contributed to increasing pharmaceutical spending on R&D within the EU (and the rest of the world).

Seeing companies as profit maximising entities, as economic theory suggests, the increase in pharmaceutical innovation will be directed towards the areas where the highest expected profit can be identified.

As SPCs generally increase expected profits across the board for medicinal products, it is difficult to see how this regulation could help encourage innovation in a specific direction.

Expected profits are tied closely to expected prices. As such, tying reimbursement and pricing more closely to the demand and need for innovation would directly encourage more innovation within this area.

There is one condition, however, for which it is conceivable that the SPC regulation would help to encourage innovation demanded and needed by customers, patients and stakeholders, this condition being that demanded and needed innovation projects take longer than 5 years to develop more often than non-demanded and non-needed projects. If this is truly the case, most of the products eligible for the SPC extension will be those mentioned in the objective. As such, the profitability of these products will increase, encouraging more investment in these projects as opposed to projects developing non-demanded and non-needed products. This means that if the products demanded and needed by customers coincide with the products being eligible for an SPC, the SPC legislation will have helped encourage innovation demanded and needed by customers, patients and stakeholders.

SPCs are not granted based on therapeutic value or the fulfilment of unmet medical needs

SPCs increase profitability of medicinal products and thus encourage innovation in general

Demand-side objectives

Shortened effective patent protection reduces innovation incentives for developers of medicinal, veterinary and agrochemical products. In particular, reduced incentives could lead to insufficient innovation in product categories where requirements for research and development efforts are particularly high, diseases are particularly complex, or the affected stakeholders have limited advocacy.

By granting product developers an extended effective patent protection term, the regulator aspires to remedy these market failures. As such, the grant of an SPC seeks to provide substantial benefits to consumers by leading product developers to provide innovative products where they are needed most.

As a consequence, strengthening supply-side innovation incentives should in the medium- to long-term lead to increased product amenability on the market.

Demand-side objectives

SPC objectives: Product amenability	
	1 Accessibility and diffusion of innovative products across the internal market
	2 Preventing supply shortages and missed or deferred market launches
	3 Availability of generic medicinal products
	4 Preventing limits to innovative product amenability through industry pricing strategies

Demand-side objective 1: Accessibility and diffusion of innovative products across the internal market

ECONOMIC RATIONALE

In order to produce the largest attainable consumer and patient benefit, new and innovative medicines would have to be launched and be available in not only the most attractive markets within the European Union but throughout the Community as a whole.

The European Medicines Agency provides originators and generic manufacturers the opportunity to file for a Community-wide authorisation to market their products. If such an authorisation is granted, the respective company is allowed to launch and commercialise its medicinal product(s) in all concerned markets. As such, this scheme should considerably reduce obstacles to entering even smaller or niche markets as long as they are covered by the centralised authorisation scheme.

Simultaneously, the availability of such community-wide, or unitary, marketing authorisations highlights the lack of similar centralised provisions for important components of companies' calculations of expected profits and launch choices. In particular, patents and patent-extending SPCs are subject to national application and/or validation proceedings[1].

The fragmentation of exclusivity mechanisms provides companies with two arguments for not launching their product(s) in the entirety of the Community: increased cost of filing and maintaining protection (e.g. through patent and SPC maintenance fees) as well as increased uncertainty, mainly through the presence of heterogeneity in patent or SPC grant decisions for the same patent-product pair across countries (Mejer 2017).

If, based on this, companies decided not to launch a product in a certain market, consumers and patients would be subject to adverse effects ranging from having to pay higher prices for medicines (if there is less competition in a market) to losing access to a certain medicinal product completely if it is not launched at all.

EVIDENCE

Being granted an SPC for a medicinal product in a specific pharmaceutical market would increase effective protection in this market and thus most likely make it more worthwhile for a company to launch their product in the respective market.

However, the results obtained so far indicate that effective protection is particularly high in markets that are already more attractive for product launch to begin with. It appears that companies seek to protect their products especially in those countries where the products make them the most money.

A particularly important driver in this context seems to be reference pricing regimes between countries in which an innovator might be interested in launching a product. As discussed in section 2.2, the presence of price regulation and price referencing can have a considerable impact on both price levels and product launch sequence.

Another important outcome from section 2.2 is that the effective protection period does not seem to drive the launch of medicinal products. Perhaps because this has already been factored into the launch decision. What does seem to have a positive influence on launch, however, is the wealth and potential patient base of a given country. This means that small non-wealthy countries will be detrimentally affected and experience longer launch lags than large affluent countries.

Given that there is uncertainty and cost associated with filing for an SPC or patent in a less attractive market, companies might elect not to do so and then, facing a shorter period of effective protection, might decide not to launch a product at all.

In this sense, SPCs most likely do not contribute to the diffusion and accessibility of medicinal products across the internal market.

On the other hand, a unitary SPC title could likely produce such incentives to a higher degree: even if a company were to file for an SPC only in an otherwise attractive market, such a title would have validity for other markets as well. This would in turn increase effective protection in those markets as well and might bring the increase in expected profits that actually makes a company launch its product there – either earlier or at all.

No immediate connection between effective protection period and diffusion of new medicinal products

1 Effort is being put into establishing a unitary European patent. However, the process has been halted several times and as of this writing the implementation date is still unknown. The possibility of a unitary SPC title is not part of the current implementation plans.

Demand-side objective 2: Preventing supply shortages and missed or deferred market launches (1/2)

ECONOMIC RATIONALE FOR THE PREVENTION OF SUPPLY SHORTAGES

A supply shortage represents a situation in which the manufacturer(s) of a medicinal product is (are) unable to produce an adequate supply of the product to meet either the current or projected demands of the buyers, i.e. healthcare systems and patients.[1]

Supply shortages can occur at local, national or international levels, and may of course vary both in terms of severity and duration.

Supply shortages impose costs on both healthcare systems and the individual patients:[2,3,4,5]

- Individual patients are harmed since their treatment may have to be either delayed or foregone, or substituted for a treatment with less efficacy or safety.
- Healthcare systems face significant costs from supply shortages as healthcare professionals have to spend time managing the supply shortage, e.g. finding alternative treatments.

These severe human and financial costs of supply shortages represent the economic rationale of this objective.

Supply shortages may have a variety of different *immediate* causes:

- Supply shocks: the ability of one or more manufacturers to supply the medicine abruptly decreases, e.g. because of market exit or a plant being shut down.
- Demand shocks: e.g. changes in medical recommendations or the indications for which a medicinal product is approved.

A prominent explanation of supply shortages in the academic literature is low profit-margins[6]. With regard to biologic products, a possible further explanation might be that some biologics and biosimilars are produced on demand and hence are more sensitive to unforeseen changes in demand.

There are several mechanisms by which low profit margins may increase the likelihood of a supply shortage:

- Low profit margins incentivise suppliers to keep relatively small inventories which reduces costs for the individual supplier. However, it may also cause the supplier to be unable to meet demand should production be ceased or temporarily suspended, e.g. due to quality or safety concerns. If profit margins were higher, companies would be willing to keep a larger inventory because the potential cost of not being able to supply the market would be larger, therefore making up for the cost of the inventory.
- Essentially, the same logic applies to the maintenance of the production facility. Suppliers are more likely to accept a risk of production being suspended if the opportunity cost of this is low. Because of this, suppliers may choose to postpone investments in the maintenance of the production facility, which increases the risk of a suspension of production, which again may be an immediate cause of a supply shortage.

In short, low profit margins make markets more vulnerable to supply shortages because they decrease the incentive of companies to ensure that demand can be met.

Empirical evidence for the relationship between low profit margins and the risk of supply shortages can be found in Yurukoglu et al. (2016).[2] See section 4.3. for more detail.

Low profit margins may have different causes, either regulatory in the form of price ceilings or market-based due to competition. The latter of these is typically associated with markets for medicinal products that have experienced generic entry.

EVIDENCE

As described above, generic competition may have the adverse effect of driving prices down to a point where low profit margins increase the risk of a supply shortage.

Given that an SPC will extend the protection period of the originator product, it ultimately works to delay generic entry. Because generic entry might be associated with an increased risk of supply shortages, SPCs might thus be said to alleviate the risk of supply shortages to some extent.

However, it is important to keep in mind that SPCs only delay the problem – they do not cause a structural change that reduces the risk of supply shortages. Furthermore, although SPCs have a beneficial impact on the risk of supply shortages, they do so at the expense of a longer protection period, which will likely come at a cost for the buyers of the medicines.

SPCs delay the point in time when generics can enter

1 http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/01/WC500200301.pdf
2 Yurukoglu et al. (2016), The Role of Government Reimbursement in Drug Shortages.
3 Kim, Sang Hyun and Morton, Fiona Scott (2015), A Model of Generic Drug Shortages: Supply distributions, Demand Substitution and Demand Control.
4 Economist Intelligence Unit (2017), Cancer medicines shortages in Europe: Policy recommendations to prevent and manage shortages.
5 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60667-5/fulltext?rss%3Dyes
6 See e.g. M.E. Markowski (April 2012), "Drug Shortages: The Problem of Inadequate Profits".

Demand-side objective 2: Preventing supply shortages and missed or deferred market launches (2/2)

ECONOMIC RATIONALE FOR THE PREVENTION OF MISSED OR DEFERRED MARKET LAUNCHES

The provision and supply of adequate medicinal products is a key component of regulators' interest in pharmaceutical and agrochemical markets. The main objective of supplementary protection certificates as an intellectual property right is to help remedy the market failures that lead originator companies to supply too little of the required innovative products to the customers – or to supply them only with a considerable lag to the first international launch of the same product.

Reiterating the earlier argument, increasing the effective protection period can induce companies to launch a product, or to launch it earlier, by increasing the profits to be expected from launch.

EVIDENCE

As documented above, the results obtained in section 2.2 point to no distinguishable effect of effective protection on product launch. This is likely due to a correlation with overall market attractiveness – the most important driver of a company's decision on when and where to launch a product.

A further impact factor is the presence of reference pricing between potential launch countries. As discussed in section 2.2, launch decision and sequence cannot be seen as independent in the presence of price referencing.

As a consequence, pharmaceutical companies might decide to launch a product with a delay or not at all in certain markets to avoid missing out on additional profits in other markets.

There is considerable heterogeneity in the number and speed of new medicinal product launches throughout the internal market, with larger countries receiving earlier access to new medicines[1].

It seems unlikely that the SPC in its current fragmented form can contribute to increasing the launch attractiveness of otherwise neglected markets.

However, it should be noted that a unitary SPC might be better fit to achieve such an objective. Under a fragmented system, an SPC has to be applied for in each country separately, so in some less attractive markets the effort associated with obtaining an SPC might not be worthwhile. However, were the SPC unitary, a company seeking to obtain an SPC in one country would automatically obtain one for all countries. This would obviously bring more homogeneity to the system and might encourage launch in more markets. At the same time, it is worth keeping in mind that overall launch lag periods between international and EU launch seem to be decreasing over time, as described by Kyle (2017)[2].

No immediate connection between protection period and market launch

1 See results in section 2.2. This is likewise supported by findings in Cockburn et al. (2016), where it is found that market attractiveness, in the form of GDP per capita, is an important driver of new product launch.

2 Kyle, M. (2017), "Economic Analysis of Supplementary Protection Certificates in Europe".

Demand-side objective 3: Availability of generic medicinal products (1/3)

ECONOMIC RATIONALE

Generic medicinal products can enter a market once the exclusivity for a respective originator product has lapsed. Generic manufacturers can start to develop their products earlier and from the expiry of data exclusivities by cross-referencing the testing and trial data submitted by the originator to the competent authorisation authority.

As stated, referring to supply-side objective 5 above, "*Generic products exist only if new medicinal products are developed and disclosed*".

The initial development of originator medicinal products is essential for the development of subsequent generic substitutes. Only when an originator medicinal product is patented and disclosed can someone else use the knowledge protected in the patent filing.

In general therefore, there should be a positive correlation between the number of originator medicinal products developed initially and the number of generics developed subsequently: without the original product there cannot be a generic.

At the same time, it may be that technological advancements have made reverse-engineering[1] easier. If this is the case, it may be that disclosure of knowledge is less important today – at least as far as small molecule medicinal products are concerned. On the other hand, generic manufacturers are heavily reliant on the originator's disclosure of pre-clinical and clinical testing data to the European Medicines Agency or other such competent authority.

EVIDENCE

While data protection might have a more tangible impact on the generic development process, one ought to keep in mind that patents are still important in protecting pharmaceutical innovation. In the majority of cases in the current data material, a patent is the last protection scheme to expire. As such, the patent is still important for the very existence of a generic – even though its impact on the availability of a generic conditional on an originator product being developed is likely negligible.

Similarly, the effect of SPCs on the availability of generic products will likely not relate to the speed or location at which they enter. Instead, if the very existence of an SPC increases the expected profitability of a project in such a way that an R&D initiative is carried out rather than abandoned, the SPC will contribute to the existence of the generic product as such. The presence of an SPC will defer generic entry by the SPC term (i.e. up to five and a half years if also granted a paediatric extension) but should not impact the length of the generic launch lag (or the speed of generic entry) from the point in time where exclusivity of any form eventually expires, provided that the SPC is the last exclusivity scheme to do so.

The impact of an SPC on the timing of generic entry for a product conditional on this product being developed with or without the SPC is negative as an SPC extends the period of meaningful effective protection. Supplementary protection schemes do delay generic entry.

The presence of a correlation between SPC filing and product market attractiveness on the one hand and generic entry and product market attractiveness on the other hand could obscure any effect that might be observed from SPCs on generic entry.

As noted by Kyle (2017), originator firms will seek to extend the effective protection period of the most profitable products and file SPCs especially for these. At the same time, generic manufacturers will also try to enter these most profitable markets first. Consequently, observed correlation between SPC coverage and generic entry could in part be due to joint sorting on market attractiveness. As such, the degree to which SPCs should be allowed to postpone generic entry remains the question of a trade-off between innovation and product accessibility. On the one hand, extended effective protection might lead to more but delayed generics (due to more innovator medicinal products reaching the market[2]). On the other hand, delaying generic entry for too long can lead to a situation where the generics are so far outdated that demand has shifted towards new innovator medicinal products.

The following two pages provide empirical evidence of the share of total volume on the pharmaceutical market, which generics make up. In general it can be seen that share of generics has been increasing over time, in most countries where data is available. However, whether this is directly tied to the enactment of the SPC or other generic policies cannot be inferred.

SPCs encourage new innovative products for which generic versions can be made

SPCs delay the time at which the generic products can enter the market

1 Reverse-engineering is a process by which a company figures out the composition of a product by thoroughly examining the product, instead of relying on a detailed description e.g. in a publicly available patent file.

2 Or, potentially, more innovative but risky product developments being completed instead of less innovative alternatives that firms might choose in case of lower expected profits that can be earned due to a shorter exclusivity timeframe.

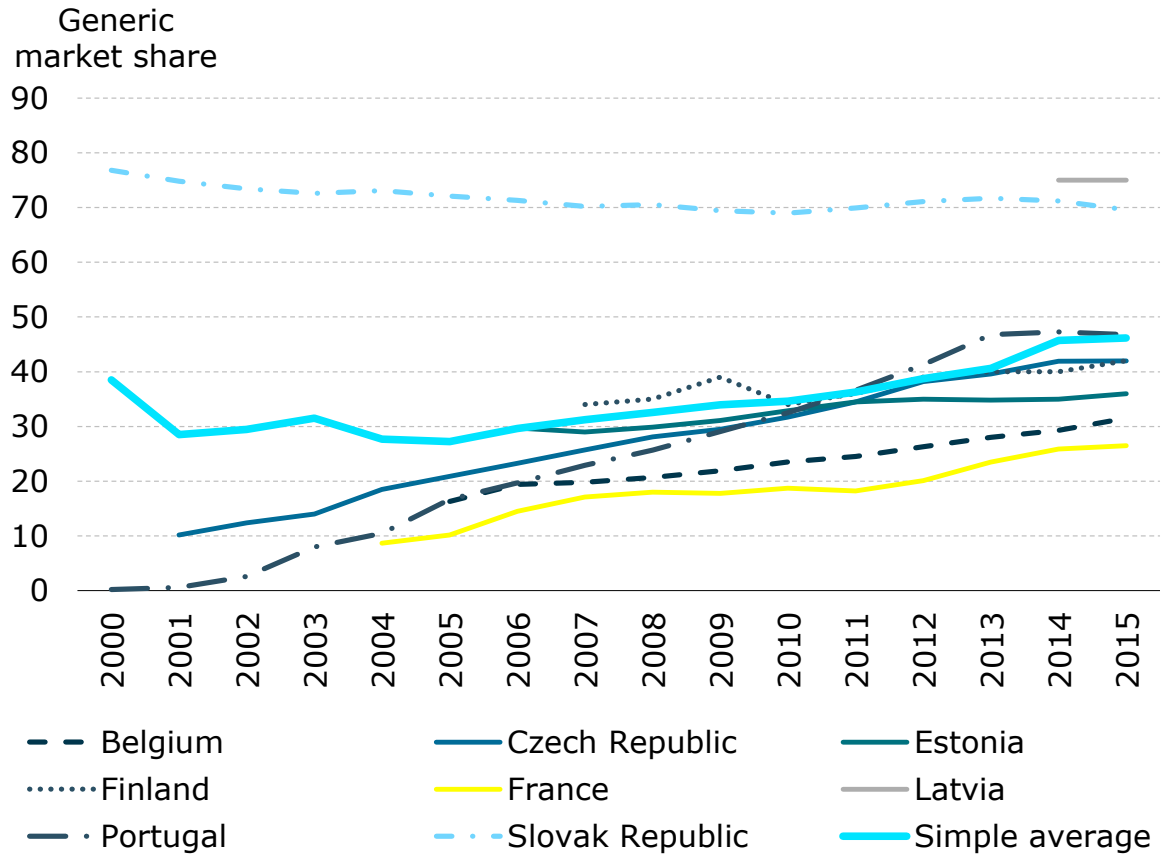
Demand-side objective 3: Availability of generic medicinal products (2/3)

The graph to the right depicts how large a share of the total volume on the pharmaceutical market, is made up by generics in the given countries as recorded in the OECD dataset on the pharmaceutical market[1].

Data availability is highly differentiated across countries. However, from 2000 to 2015 a general tendency for generics to make up an increasing share of the total volume on the pharmaceutical market seems to be discernible.

To what degree this is influenced by the SPC regulation[2] is not immediately possible to deduct. However, the general tendency does seem to suggest that the SPC regulation, granting a longer protection period to originator products, has not been detrimental to having a development where generics have gotten to make up a larger share of the market for medicinal products, measured by volume.

Generic share of pharmaceutical market by volume, total pharmaceutical market, 2000-2015



Note: Comparing directly with the generic market share in 2007 for the different countries, given by figure 11 in the Sector Inquiry, the numbers reported by the OECD are generally lower. This could e.g. be due to differences in the definition of which products are generics, as well as whether data is for the whole market, or e.g. only the re-imbursed part.
Source: OECD "Pharmaceutical Market" dataset, available at https://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_PHMC

1 OECD "Pharmaceutical Market" dataset, available at https://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_PHMC
2 Regulation (EC) No 469/2009.

Demand-side objective 3: Availability of generic medicinal products (3/3)

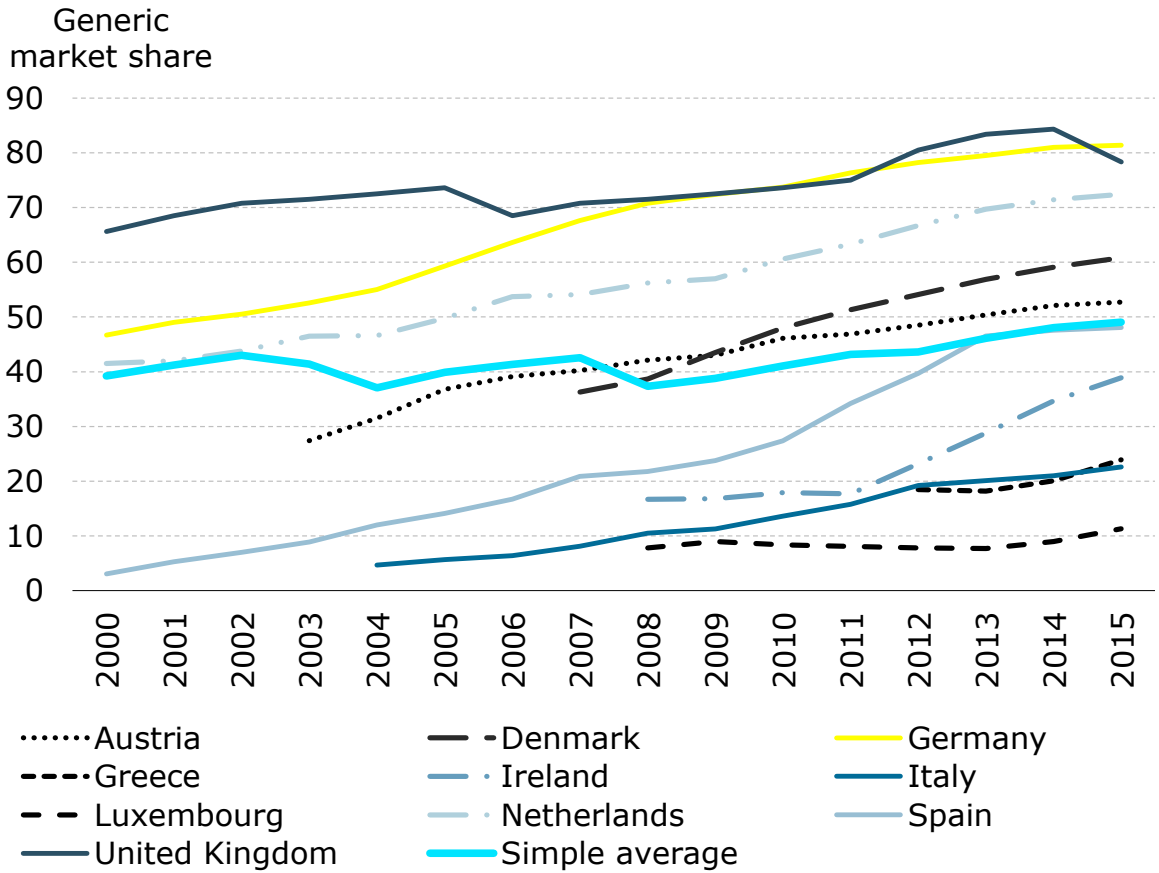
For some countries, data for the total pharmaceutical market is not available in the OECD database. For some of these countries data on the re-imbursed part of the pharmaceutical market is available instead.

The graph to the right depicts the generic market share of volume of pharmaceuticals sold on the re-imbursed part of the markets in the given countries.

Generally the tendency is the same as could be seen in the graph on the previous page; from 2000 to 2015 generics have increased their market share, measured by volume.

As was the case on the previous page, it is not directly possible to discern how much the regulation on SPCs[1] have influenced the depicted development. However, the general increase in generic market share does seem to suggest that the SPC regulation has not been detrimental to an increasing use of generics.

Generic share of pharmaceutical market by volume, re-imbursed pharmaceutical market, 2000-2015



Note: Comparing directly with the generic market share in 2007 for the different countries, given by figure 11 in the Sector Inquiry, the numbers reported by the OECD are generally lower. This could e.g. be due to differences in the definition of which products are generics, as well as whether data is for the whole market, or e.g. only the re-imbursed part.
Source: OECD "Pharmaceutical Market" dataset, available at https://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_PHMC

1 Regulation (EC) No 469/2009.

Demand-side objective 4: Preventing limits to innovative product amenability through industry pricing strategies

ECONOMIC RATIONALE

Section 2.4 of this report identified pricing drivers within the pharmaceutical company along two dimensions: market structure, as well as tender impact and future perspectives.

Said driver dimensions included the following factors[1]:

- Number of competitors (or breadth of medicinal category).
- Market share and switching behaviour.
- Size of the contestable market share.
- The length of the average patient's treatment period.
- The length of tender periods.
- The regularity (or frequency) of tendering procedures.
- The corporate structure of competing companies.
- Tendering guidelines and conformity.
- The length of patent protection and the competing companies' pipelines.

EVIDENCE

As discussed earlier, providing companies with a longer protection period should not have the effect of lowering prices. Aside from the above factors, firms will likely only consider a binary judgement on exclusivity in their pricing considerations: whether there is competition or whether the firm still maintains exclusivity.

If the company is not challenged by competitors on the market, the granting of a longer protection period ought not to influence its pricing decision. Economic theory would suggest that the company will charge the price the competitive situation allows, so as to maximise profit. A longer protection period would, as such, allow the company to charge a premium price for a longer period by delaying generic entry.

If it is only the existence of exclusivity (as an indicator of time periods when higher prices can be charged on the market) that matters for pharmaceutical companies' price setting considerations, the type of intellectual property right providing said exclusivity should not be of importance. As such, the presence or absence of an SPC for a specific medicinal product should not directly impact price setting, but only indirectly by virtue of extending the exclusivity time period (where higher prices can be charged). The way exclusivity comes about is not decisive for price setting, the categorical existence or non-existence of exclusivity in a given time period is.

Prices for pharmaceuticals decrease substantially once exclusivity lapses and generic competitors enter the market even though, at least for the US, in parts of the market this can even lead to price increases, see for instance Frank & Salkever (1992/1997). This has, however, not been observed within the EU and hence might be due to special constructs of the US market.

It is not possible to identify an economic theoretical founded argument as to why the effective protection period in itself directly should influence the pricing strategy of the firm. However, SPCs do extend the period in which a company can employ a certain pricing strategy before generic competition can enter. Moreover, the protection period might influence the pricing strategy indirectly by influencing the competitive situation on the market.

The only scenario where SPCs can surpass limits to product amenability would likely be when they push a company's expected profit calculation across the launch decision threshold. However, this would be unrelated to industry pricing strategies.

Economic theory would suggest companies set profit-maximising prices

1 See section 2.4.

Market impact objectives

Extending the effective patent term should increase innovation incentives for product developers – but at the same time it also grants additional market power. Supplementary protection certificates therefore represent a trade-off to the regulator.

On the one hand, patent term extension ought to benefit both producers and consumers by leading to an improved supply of innovative products, by allowing the European pharmaceutical, animal health and plant protection industry to catch up to its international global competitors, and by strengthening research-based industries.

On the other hand, the regulatory scheme ought not to grant excessive market power to product developers and producers. The extended patent protection ought not to result in excessive pricing or otherwise excessive profits and revenues in the affected industries that go beyond the intended innovation incentives.

Moreover, the implementation of the SPC scheme as such ought to mitigate potential adverse consequences such as barriers to the movement of goods or distortions to competition that might have arisen in alternative scenarios of national level regulatory initiatives.

Finally, the SPC scheme ought to leave the regulated industries with the flexibility to adapt to global advances and developments in research, trade and innovation models.

Market impact objectives

SPC objectives: Impact evaluation	
	1 Fall in prices of SPC-protected products relative to products without SPCs
	2 Extended protection that is justified by revenues and profits for the different categories of eligible medicinal and plant protection products
	3 Close the gap between the European pharmaceutical industry and major competitors in the international market (e.g. Japan, USA) COM(90) 101 final Rec. 6, Rec. 15

Market impact objective 1: Fall in prices of SPC-protected products relative to products without SPCs

ECONOMIC RATIONALE

The main mechanism in which the introduction of supplementary protection certificates aims to promote and stimulate innovation is by extending the time period of exclusive commercial exploitation. That way, a profit-maximising firm can increase its expected profit for an R&D project. If the incremental increase in expected profit is sufficient to turn a net present value calculation from negative to positive, SPCs might incentivise pharmaceutical companies to develop medicinal products that would not otherwise have been brought to the market.

The reason why a pharmaceutical company might decide not to engage in a development project without an SPC (or even with an SPC) is usually threefold:

- Development risk of complex products.
- Commercialisation risk of products with uncertain or difficult-to-forecast product markets.
- Substantial up-front investment requirements or early stage development costs.

Essentially, all of these factors impact a company's expected profit calculation boiling down to the expected number of units that can be sold in the product market at the expected profit margin (i.e. price minus cost). A firm will typically try to maximise both of these dimensions within the confines set by regulations, tenders, or governmental negotiations.

EVIDENCE

Within their exclusive commercial exploitation period, firms have a strong economic incentive to maximise profits irrespective of the research and development costs in the product development process leading up to product launch.

As such, SPCs can incentivise firms to participate in otherwise insufficiently profitable development initiatives: SPCs raise the overall attainable profit which a pharmaceutical company factors into its *ex ante* estimation of expected profits. In this context, expected profits can be understood as the discounted and risk-weighted forecast of cash flows conditional on development success.

We have not identified any economic arguments that suggest that the SPC should cause a fall in prices of pharmaceuticals for profit-maximising companies. This assertion can only be supported by assuming that pharmaceutical companies seek to earn back a certain return on each medicinal product developed. This assumption runs contrary to standard economic theory and there is no empirical evidence to support this.

SPCs could, however, influence price setting if the increased R&D causes the likelihood of a competitor ("me-too"-product or new product treating the same indication) entering the market during the protection period to rise. In this case there would be two effects working in opposite directions. The presence of an SPC would increase prices by delaying the entry of generics, while it would decrease prices through increased competition through innovation.

We have not found evidence that suggests that the typically smaller price decrease from more competition by innovation should generally dominate the typically larger price increase from delayed entry of generics.

Profit-maximising behaviour, as economic theory suggests, does not support a fall in prices related to SPCs

Market impact objective 2: Extended protection that is justified by revenues and profits for the different categories of eligible medicinal and plant protection products

ECONOMIC RATIONALE

Supplementary protection certificates provide innovation stimulus by influencing firms' *ex ante* perspective on the decision to carry out or cancel investments in product development.

The patent term restoration effect of an SPC factors into a company's estimation of expected profits and whether these will be of a volume sufficient to account for potential up-front investments into the research and development process.

In this sense, the analysis of *ex post* outcomes can prove difficult or even misleading. Firms will use the protection available to them to protect all types of products, including blockbusters and medicines for rare diseases.

Looking at *ex post* profitability in isolation is likely going to understate the effect of development or commercialisation risk from the *ex ante* perspective.

While this risk might not materialise in the end, it will have factored in the initial calculation of expected profits carried out at project start.

Thus, when evaluating the justification of the protection extended to different categories of medicinal and plant protection products, this should be done from an *ex ante* perspective.

EVIDENCE

SPCs are not dependent on the revenue or profit a pharmaceutical company obtains from a given product. The SPC extension is exclusively awarded based on development time.

The SPC extension mitigates some of the inherent risk when developing medicinal products. By providing restoration of lost effective patent term, SPCs increase the expected profit, even for risky projects. This should hopefully help to bring more therapeutically valuable products to the market than would otherwise have been the case. The mechanism through which this works, is by increasing the expected profit in the *ex ante* business case calculations on the profitability of undertaking a given pharmaceutical R&D project.

As can be seen from the case studies in section 5.2, the SPC regularly ensures that these medicinal products have 15 years of protection. Bearing in mind that this selection of medicinal products is non-random, it still indicates the risk mitigating effect of the regulation.

The discussion of whether the extended protection is justified by revenues and profits contains a wide range of competing arguments. The sheer complexity of the innovation system in the pharmaceutical sector makes it a multifaceted issue[1].

Looking at the *ex post* revenue earned from certain medicinal products, these might in some cases seem to be unfathomable and unjustifiable. One such case could be e.g. Humira which has been granted an SPC[2]. During 2016 alone Humira generated sales of more than USD 16bn[3].

However, this is in the case of a blockbuster medicinal product. For less profitable products, an SPC will have correspondingly lower impact on the total revenue. At the same time, studies point to the fact that only 1 out of 10 products entering phase 1 of clinical trials makes it all the way to approval[4]. This means that successful products have to bear the cost of all unsuccessful and failed development attempts as well.

As such, a thorough review of whether a longer protection period is justified by revenues and profits demands intimate access to the financial accounts of the individual pharmaceutical companies. For the purpose of this study, no such access is available.

SPC extension is not based on revenue or profit, but exclusively on development time

SPCs increase the overall profitability of medicinal products

1 The literature shows estimated costs of bringing a medicinal product from the lab to the market being between USD 648m and USD 2.6bn. See Prasad, V. and Mailankody, S. (2017), Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval and Di Masi, J. A., Grabowskib, H. G. and Hansen, R. W. (2016), Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs.

2 See chapter 5 for a case study on Humira.

3 http://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868 (Accessed 07.09.2017)

4 BIO, Biomedtracker and Amplion (2016), Clinical Development Success Rates 2006-2015.

Market impact objective 3: Close the gap between the European pharmaceutical industry and major competitors in the international market (i.e. Japan, USA) (1/4)

THE OBJECTIVE IN THE REGULATION

Objective 3: Close the gap between the European pharmaceutical industry and major competitors in the international market (e.g. Japan, USA)

"Over about the last 10 years there has been a fall in the number of molecules of European origin that have reached the research and development stage (40% as against 65% 10 years ago) and a slow erosion of European market shares as compared with those of the USA and Japan.

With regard to the latter, it should be noted that, apart from a general context which is more favourable than that of the Community, notably as regards social security systems, price levels and the relative size of the national markets, US and Japanese companies have since 1984 and 1988 respectively, benefitted from patent term restoration for medicinal products on their national markets."

- COM(90) 101 final, Recital 6

"[I]t is to be hoped that the European pharmaceutical industry will be able to close some of the gap which has arisen between itself and its major competitors in the international market. In the USA, the Waxman-Hatch Act entered into force in September 1984. In Japan, the revision of the Patents Law took effect on 1 January 1988."

- COM(90) 101 final, Recital 15

ECONOMIC RATIONALE

The European Commission's 1990 memorandum observes a decrease in molecules developed by European manufacturers, as well as an erosion in their respective market shares.

These developments are more than likely correlated: as products mature, their exclusivity protection is bound to expire at some point. Once generic competition is possible and occurs, competitors will enter the market and contest for the market share of the incumbent.

If incumbents are not able to bring a comparable number of new products to the market that could substitute for the effects of competition on products where exclusivity lapses, companies will probably not be able to regain all of the market share lost and thus face the aforementioned decline.

While this development has been observed for European manufacturers leading up to the SPC regulation, it is not necessarily intuitive that it would be related to the landscape of intellectual property rights in their home market. After all, pharmaceutical companies nowadays compete on a global scale. European manufacturers compete in the same European markets and are subject to the same European regulations as their counterparts from Japan and the US. In turn, European manufacturers have equal opportunities to benefit from the existence of innovation incentives created under e.g. the Hatch-Waxman act in the United States[1].

EVIDENCE

Through the results in section 2.1 on the relationship between effective protection period and innovation it can be seen that protection in the other EU countries with which a given country trades the most has a positive effect on pharmaceutical R&D spending. Moreover, as there is much intra-EU trade, a scheme like the SPC covering all EU member states should work to increase spending on pharmaceutical R&D within Europe.

Furthermore, as can be seen from the table in section 1.3, the regulatory protection schemes of Europe are generally more favourable than in any of the other countries surveyed.

As such, these results suggest that the regulation should help to close the gap between the EU and other regions.

However, as is also pointed out in section 2.1, the literature indicates that there are many country-specific factors which play an important role in influencing the placement of R&D[2]. This is likewise supported by the results in section 2.1. In this regard it is important to remember that increasing the profit prospects of medicinal products in Europe favours both companies with R&D in Europe and those with R&D outside Europe. The other aspects mentioned in the literature of e.g. a well-educated workforce and infrastructure help to incentivise R&D in the specific countries.

SPCs encourage spending on pharmaceutical R&D

1 The Hatch-Waxman act is the informal name for the Drug Price Competition and Patent Term Restoration Act (Public Law 98-417) in the United States.

2 See e.g. Demirbag, M. and Glaister, K. W. (2010), Factors Determining Offshore Location Choice for R&D Projects: A Comparative Study of Developed and Emerging Regions.

Market impact objective 3: Close the gap between the European pharmaceutical industry and major competitors in the international market (i.e. Japan, USA) (2/4)

THE OBJECTIVE IN THE REGULATION

Objective 3: Close the gap between the European pharmaceutical industry and major competitors in the international market (e.g. Japan, USA)

"Over about the last 10 years there has been a fall in the number of molecules of European origin that have reached the research and development stage (40% as against 65% 10 years ago) and a slow erosion of European market shares as compared with those of the USA and Japan.

With regard to the latter, it should be noted that, apart from a general context which is more favourable than that of the Community, notably as regards social security systems, price levels and the relative size of the national markets, US and Japanese companies have since 1984 and 1988 respectively, benefitted from patent term restoration for medicinal products on their national markets."

- COM(90) 101 final, Recital 6

"[I]t is to be hoped that the European pharmaceutical industry will be able to close some of the gap which has arisen between itself and its major competitors in the international market. In the USA, the Waxman-Hatch Act entered into force in September 1984. In Japan, the revision of the Patents Law took effect on 1 January 1988."

- COM(90) 101 final, Recital 15

... continued from previous page.

On the following two pages, we provide evidence regarding the distribution of New Chemical Entities (NCEs) between the US, EU, Japan and the Rest of the World. The evidence compares the period 1982-1992 to the period 1993-2003.

It can be seen that when it comes to the number of NCEs, the EU is the region with largest share of world total in both periods. However, the share has decreased by 6%-points in the EU between the two periods, while it has increased by 10%-points in the US. As such, this seems to suggest that the US is catching up, when looking at the sheer number of NCEs.

A measure of 'research productivity' is likewise presented on the following pages. As defined in Light (2009)[1] 'research productivity' is obtained by dividing the percentage of New Chemical Entities each region develops, with the share of pharmaceutical R&D spending a region constitutes.

Using this measured, it can be seen that the 'research productivity' has increased in the EU while decreasing in both the US and Japan. At face value, this seems to suggest that the European pharmaceutical companies have become more efficient in the R&D effort over time.

1 Light, D. W. (2009), Global Drug Discovery: Europe is Ahead

Market impact objective 3: Close the gap between the European pharmaceutical industry and major competitors in the international market (i.e. Japan, USA) (3/4)

A 2006 paper by Grabowski and Wang[1] studied the number of New Chemical Entities (NCEs) developed in the two periods 1982-1992 and 1993-2003. The authors assigned a nationality to all NCEs, based on the headquarter placement of the developing company. This makes it possible to compare the number of NCEs in the United States, European Union, Japan and the Rest of World.

The graph to the right depicts the percentage of total developed NCEs in each time period, attributable to the given region[2].

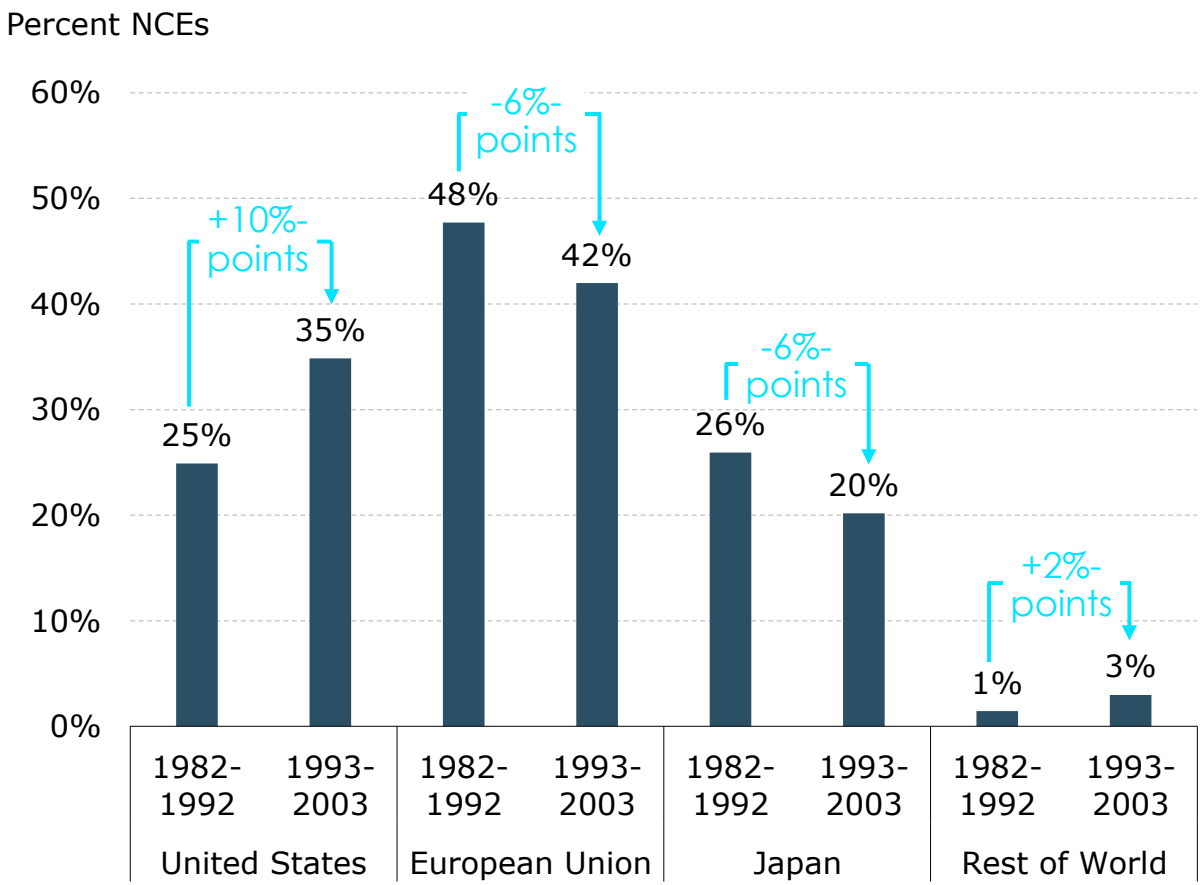
Based on this analysis, the share of NCEs developed in the European Union has fallen 6 percentage-points from 48% to 42% between the two time period.

During the same period, the share of NCEs developed in the Unites States has increased by 10 percentage-points, from 25% to 35% of world total.

As such, more NCEs are discovered in the European Union than in the Unites States, albeit the US seems to be catching up between the two time periods analysed here. It can thus be discussed to what degree the EU is experiencing a gap to other regions of the world.

However, the next page reveals an interesting relationship between the spending on pharmaceutical R&D and the number of new NCEs in the United States and the European Union.

New Chemical Entities (NCEs) discovered in the United States, Europe, Japan and the Rest of World, comparing the time period 1982-1992 to 1993-2003



Note: NCEs are distributed by headquarter of the company.
Source: Grabowski, H. G. and Wang, Y. R. (2006), The Quantity and Quality of Worldwide New Drug Introduction, 1982-2003, Exhibit 4, p. 457.

1 Grabowski, H. G. and Wang, Y. R. (2006), The Quantity and Quality of Worldwide New Drug Introduction.
2 This page examines the United States, Europe, Japan and the Rest of World. As this constitutes both countries and regions, using the wording region has been chosen for the sake of simplicity.

Market impact objective 3: Close the gap between the European pharmaceutical industry and major competitors in the international market (i.e. Japan, USA) (4/4)

According to Light (2009)[1] a measure of 'research productivity' can be obtained by dividing the percentage of New Chemical Entities said region develops, out of the total for the three regions with the share of pharmaceutical R&D spending a region constitutes.

E.g., in 1990 spending on pharmaceutical R&D in the United States was EUR 5.3bn[1]. Out of the total spending on pharmaceutical R&D in the United States, Europe and Japan collectively, this constitutes 33.3%[1].

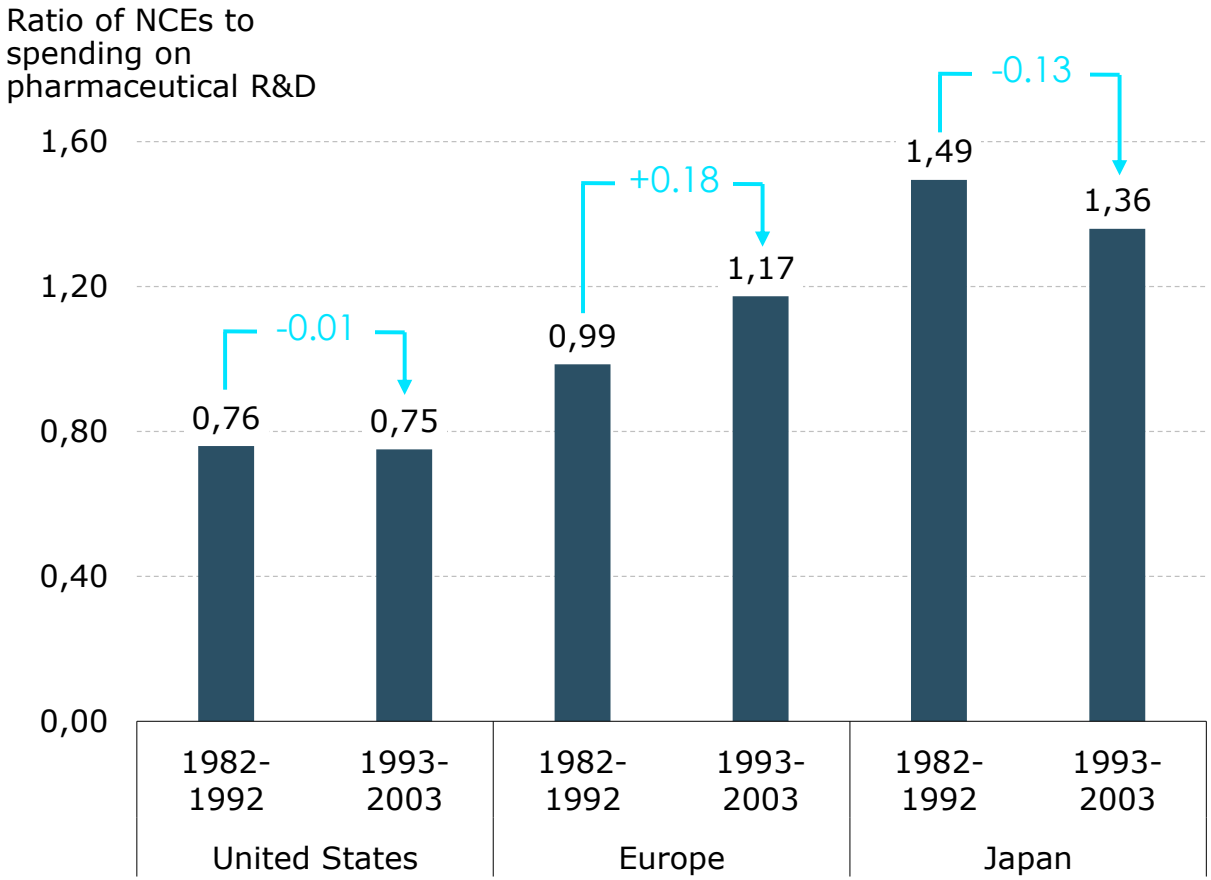
To obtain a ratio between spending on pharmaceutical R&D and development of NCEs of 1, the United States would likewise have to have developed 33.3% of all NCEs in the three regions in the period 1982-1992.

However, the United States developed 25.3% of NCEs in the three regions in said period[1]. As such, the ratio of investment in pharmaceutical R&D to NCEs developed was 0.76 for the United States in the period 1982-1992.

Between the two periods analysed in the graph to the right, 'research productivity' fell in the Unites States and Japan, while increasing in Europe.

This measure has several limitations. It is e.g. comparing spending on pharmaceutical R&D in one year, with the number of NCEs developed over several years. Furthermore, as it can be seen from the previous graph of development times, there is a considerable lag between spending on R&D and introduction of a new product. However, the measure can serve to give some sense of the 'research productivity' across regions.

Ratio of percentage of New Chemical Entities (NCEs) to percentage of spending on pharmaceutical R&D in United States, Europe and Japan, comparing the period 1982-1992 to 1993-2003



Note: Graph showing the ratio of the percentage of NCEs to the percentage of spending on pharmaceutical R&D in the United States, Europe and Japan. A ratio of 1 means that the region constitutes the same percentage of new NCEs across the three regions, as it does of spending on pharmaceutical R&D across the three regions. NCEs are distributed by headquarter of the company. Numbers for the Rest of World not available.
Source: Light, D. W. (2009), Global Drug Discovery: Europe is Ahead

1 Light, D. W. (2009), Global Drug Discovery: Europe is Ahead

3.2 SPC SCOPE

SPCs try to remedy protection lost due to required regulatory obligations

The fundamental issue that SPCs try to remedy is the time lag that occurs between invention and commercialisation in certain industries. This sub-chapter sets out to identify and analyse additional industries and sectors that could fall into this scope.

THE ROLE OF SPCs IN PHARMACEUTICALS

The development of medicinal products is subject to considerable regulatory monitoring and approval procedures.

Following the thalidomide-scandal in the late 1950s and early 1960s, a strict authorisation scheme has to be followed before a pharmaceutical company is allowed to place a medicinal product on the market[1]. This was done to ensure that medicinal products allowed to be marketed were safe and efficacious.

In combination with the general length of development times for medicinal and agrochemical products, more than 10 years can pass between invention and commercialisation[2].

The development and approval process has considerable bearing on the effectiveness of patents as innovation incentives within the pharmaceutical industry. As patents are usually filed close to the time of invention, their effective duration is shortened significantly by a multi-year development and approval period.

The legislation governing SPCs seeks to balance the need for data to ensure safe, efficacious medicinal products of high quality against maintaining the commercial business case to provide the amount of innovation demanded by society[3].

OTHER INDUSTRIES WITH SIMILAR SCOPE OF CHALLENGES

The introduction of SPC-like intellectual property rights, *sui generis* rights or incentive schemes that remedy this issue by restoring the effective patent term (at least to an extent)[4] could also be relevant for other industries.

In particular, these industries should fulfil the following criteria:

- Patents and/or other intellectual property rights are of crucial importance in the industry.
- Innovation is a key factor for firms to compete and knowledge plays a key role in production processes.
- The industry is heavily regulated, products are subject to regulatory approval before they can be marketed, and/or there are other factors that prohibit firms from exploiting inventions commercially.

Products covered under current regulation

- Medicinal products: for human use, for animals
- Plant protection products (agrochemicals): pesticides, insecticides, herbicides, fungicides, nematicides, fertilizers, growth agents & concentrations

Sectors which might face similar challenges to the pharmaceutical sector and might be candidates for SPC-type incentive schemes and areas within SPC-protected sectors that could need specific attention

- Medicinal devices & diagnostics
- Food sector
- Seeds
- Substances w/o therapeutic effect of their own (catalysers)
- Personalised medication
- Intelligent pills
- Chemicals
- Biopharmaceuticals
- New uses of patented products

1 Thalidomide was a medicinal product originally used against morning sickness in pregnant women. After authorisation however, it turned out that the product caused children to be born without limbs. See e.g. https://www.theguardian.com/society/2012/sep/01/thalidomide-scandal-timeline

2 See e.g. Prasad, V. and Mailankody, S. (2017), who find development times in the range from 5.8-15.2 years, Keyhani, S., Diener-West, M. and Powe, N. (2006), who find development times in the range 2-17.3 years and graph p. 66.

3 See e.g. Regulation (EC) No 469/2009, (3) and (4).

4 Most kinds of inventions will require development and testing before they can be commercialised. The benchmark for patent restoration should not be to reduce effective development times to zero.

SPC candidate industry: medical devices & diagnostics

The medical devices sector provides products and solutions relating to **diagnosis** as well as the **prevention**, **monitoring and treatment of diseases**.

The sector covers a wide range of products, from patient products such as thermometers to hospital equipment such as X-ray machines.

INDUSTRY SPECIFICS

- 95% of firms are SMEs[1].
- In some regards, the market is less transparent than in other industries, e.g. the pharmaceutical industry, as the database for medical devices in the EU (EUDAMED) is not publicly accessible[1].

INNOVATION IN THE SECTOR

New developments in other sectors are an important source of innovation for the medical device sector. A study performed by the European Commission also points out that developing clusters relating to technology and/or diseases is a way of boosting innovation in the sector.[2]

REGULATORY REQUIREMENTS

In April 2017, two new regulations regarding medical devices were enacted. These were Regulation (EU) 2017/745 and Regulation (EU) 2017/746. Regulation 2017/745 will enter into force in 2020, while Regulation 2017/746 will enter into force in 2022. Among other things, the two new regulations increase the control of high-risk devices and reinforce the rules on clinical evidence[3].

Before a device can be marketed in the EU, the manufacturer needs to receive a Conformity Certificate for the device. A Certificate of Conformity ensures that the device meets a minimum set of regulatory, technical and safety requirements. As part of this assessment, a clinical evaluation is required. In order to receive approval to perform the clinical evaluation, an application needs to be sent to the Member State where the clinical evaluation is to take place. In the final stage, a Conformity Certificate is issued by so-called notified bodies. Member States are individually responsible for appointing an authority that approves the notified bodies.[4]

The new regulation aims to improve the quality, safety and reliability of medical devices and includes tighter controls, especially on high-risk devices such as implants. For these types of products, experts at the EU level need to be consulted before a product is placed on the market. The new regulation also extends the type of products covered by the regulation and includes stricter controls on clinical trials and on the notified bodies.[5]

If regulatory changes coincide with an increase in development time, this (in isolation) might be an argument for introducing protection of SPC-type scope.

RELEVANCE OF PATENTS

Patents within the medical devices sector are common and in 2015 patents related to medical technology accounted for the highest volume of applications at the European Patent Office.[1]

At the same time, there is evidence that bringing a medical device to the market is faster[6] and significantly less costly than it is for medicinal products for instance, and also that the threat of competition from perfect substitutes is lower.[1] This indicates that the need for SPCs might be of lower importance in the medical device industry if average development times do not exceed 5 years.

FACT BOX

The medical devices sector…

…covers products used for **diagnosis**, **prevention**, **monitoring and treatment** of **diseases.**

…is effectively **regulated** at the **EU level.**

… was the subject of a **market study** by the European Commission in 2010.[2]

…products require a **Conformity Certificate** to be placed on the market.

…commonly makes use of **patents**.

…products are brought to the market **faster** and at a **lower cost** than products in the **pharmaceutical industry.**

1 https://ec.europa.eu/growth/sectors/medical-devices_en [last accessed: 2017-09-07]
2 European Commission (2010), Exploratory Process on the Future of the Medical Devices.
3 https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en [last accessed: 2017-12-11]
4 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (1).
5 http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=9119&lang=en [last accessed: 2017-09-07]
6 See e.g. Roin, B.N. (2014), The Case for Tailoring Patent Awards Based on Time-to-Market.

SPC candidate industry: food sector

Covers both **food** and **beverages and** is the **largest manufacturing sector** in the EU.

INDUSTRY SPECIFICS

- Highly harmonised industry benefitting significantly from the single market.

INNOVATION IN THE SECTOR

In order to promote innovation, the European Commission introduced the policy "Food 2030"[1] in 2016. The policy aims to boost innovation and investment in the sector, in particular by promoting nutritious, environmentally sustainable and resource-efficient food.

According to the European Commission, there are many opportunities for European companies to receive funding for food-related research, and through such EU programmes several projects relating to food, nutrition and agriculture have been developed. Furthermore, the European Commission stresses the importance of cooperation among various actors in the food sector in order to further develop innovation in the market.[2]

REGULATORY REQUIREMENTS

All companies operating in the food-business have a responsibility to provide only food that can be considered safe with respect to the food-safety requirements in the EU.

In brief, this can be said to include products that are not harmful to human health.[3]

In addition, many food-related products require a scientific assessment to evaluate their safety before risk managers can authorise them for the EU market. In this case, the company producing/providing the product is required to provide evidence that these substances are safe or, in the case of health claims, that these are backed by sound science.

The products covered by this specific regulation include additives, enzymes, flavourings, food contact materials (used for instance for packaging), pesticides, genetically modified organisms, food-related processes and processing aids. Furthermore, products with nutrition or health claims also require specific evaluation before they can be placed on the market. This scientific assessment is conducted by the European Food Safety Authority (EFSA).[4]

RELEVANCE OF PATENTS

Based on the European Commission agenda, it appears that emphasis is placed on establishing partnerships, networks, and creating availability of research funds rather than promoting innovation through intellectual property protection such as patents.

The exception to this might be the field of genetically modified organisms where patents frequently occur.[5] Another field, partly related, is the seed sector which is described separately on the next page.

SPCs or similar scope extensions to intellectual property rights seem to be less optimally fit to the food sector as much of the innovation in the industry does not seem to depend on incentives in the form of intellectual property rights.

FACT BOX

The food sector…

…covers both **food** and **beverages.**

…is **regulated** at the **EU level.**

…faces requirements for a **scientific assessment** ensuring **food-safety** for many of its products.

… is the subject of the European Commission's 2016 "**Food 2030**" policy aiming to **promote innovation** in the sector.

1 https://ec.europa.eu/research/bioeconomy/index.cfm?pg=policy&lib=food2030 [last accessed: 2017-09-07]
2 https://ec.europa.eu/research/bioeconomy/pdf/european_research-innovation_for_food_and_nutrition_security.pdf#view=fit&pagemode=none [last accessed: 2017-09-07]
3 Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.
4 http://www.efsa.europa.eu/en/applications/regulatedproducts [last accessed: 2017-09-07]
5 Moschini, G. (2010). Competition issues in the seed industry and the role of intellectual property. Choices, 25 (2).

SPC candidate industry: seeds[1]

The seed sector includes crops such as **corn**, **cotton and soybeans.**

INDUSTRY SPECIFICS

- Dependent on private investments.
- Highly affected by biotechnological evolution.

INNOVATION IN THE SECTOR

Innovation is crucial in the seed sector, and at the same time it is highly dependent on sizeable research and development investments.

In line with the biotechnology revolution and the introduction of genetically modified organisms, there has been an innovation culture in the market. Annual spending on R&D is approx. 15% of turnover on average within the sector[1].

REGULATORY REQUIREMENTS

The European seed market has a total value of EUR 7bn. There are currently 7,200 companies employing approx. 52,000 people. Out of these 12,500 people are employed within R&D[1]. The European market for seeds is the largest market worldwide. Furthermore, Europe is the largest exporter of seeds in the world[2].

The regulation in the seed sector is closely linked with the food industry, and is particularly relevant for genetically modified seeds.

Genetically modified seeds fall under the category of products which are covered by the regulation that require scientific assessment in order to evaluate their safety before they can be authorised to enter the EU market. Hence, companies which have genetically modified products need to apply for such a scientific assessment at the EFSA before their product can be launched.

RELEVANCE OF PATENTS

There is an increased relevance of patents in particular for corn and soybeans. These days, however, patents are also available for many other varieties of seeds, both for genetically modified species as well as for germplasms (i.e. the DNA of a non-genetically modified variety)[3].

Considering the need for innovation and the substantial underlying investments required, the prevalence of patents seems vital.

FACT BOX

The seed sector…

…covers both **genetically** and **non-genetically modified crops.**

…is **regulated** at the **EU level.**

…requires a **scientific assessment** ensuring **food-safety** for genetically modified seeds that are to be used within the food-industry.

… is an industry crucially **dependent on innovation.**

… often sees that **significant investments** are required for innovation.

… places high importance on patents.

1 The European Seed Association (2016), Representing the seed industry, available at https://www.euroseeds.eu/system/files/publications/files/esa_16.0300.2.pdf (last accessed 12/12-2017).
2 The European Seed Association, Breeding and seed production in the 21st century – challenges and expectations of the EU seed industry, available at https://ec.europa.eu/food/sites/food/files/plant/docs/ppm_legis_review_breeding_and_seed_prod.pdf (last accessed 12/12-2017).
3 G. Moschini (2010), "Competition issues in the seed industry and the role of intellectual property".

It remains debatable whether SPC-like protection should be extended to other industries

MEDICAL DEVICES FULFIL THE LAID OUT CRITERIA

The medical devices and diagnostic sector seems to fulfil the laid out criteria for SPC-type or similarly scoped protection. However, development times for many of the products in the sector do not seem to exceed the threshold of 5 years[1]. As such, while companies would benefit from the introduction of SPCs, the overall economic need to do so seems to be considerably less pronounced than in the pharmaceutical or agrochemical sector.

FOOD AND SEEDS PROBABLY DO NOT MERIT COMPARABLE PROTECTION

Both the food and closely-related seed industries display some of the laid out characteristics. However, neither seem to fulfil all of the criteria emphasising the need for SPC protection in other industries.

The food sector is less reliant on intellectual property rights and patents, rendering extensions to these less impactful as innovation stimulus.

The seed sector seems to generally fulfil the criteria laid out, yet strict regulatory control is limited to genetically modified seeds and does not extend to the entire industry.

	Crucial importance of IPRs (patents)	Key role of innovation in the industry	Regulatory approval requirements (that might cause delayed product launches)
Medical Devices & Diagnostics	✓	✓	✓
Food		✓	✓
Seeds	✓	✓	

1 Roin, B. N. (2014), The Case for Tailoring Patent Awards Based on Time-to-Market, table 1, p. 719.

3.3 TERM OF SPC PROTECTION

Impact of the SPC protection term in the literature

EFFECT OF DECREASING LAUNCH LAGS

As illustrated in the graph earlier, the development time for medicinal products seems to have increased during the last 20 years. Not accounting for potential alternative explanations, this development should – *ceteris paribus* – have a negative impact on the profitability of pharmaceutical development projects compared to other projects with shorter development times, as it reflects a shorter time period of commercial exclusivity before a medicinal product is subject to generic competition.

At the same time, however, pharmaceutical companies seem to benefit from a decrease in EU launch lags for their products. As noted by Kyle (2017), the lag between the initial global and the first European launch of the average observed medicinal product has decreased since 1990. A decrease in time to launch, for instance driven by increasingly efficient administrative proceedings[1], is likely to increase the profitability of pharmaceutical companies (even though the decrease in launch time is smaller than the increase in average development time).

SORTING & GENERIC ENTRY

Sorting poses an inherent obstacle to the determination of the impact that the introduction of supplementary protection certificates might have had on generic entry. Sorting (or selection) occurs when data is not randomly sampled but rather follow an observed or unobserved rule. In the case of SPCs, sorting might be present if there is a correlation between the profitability and amount of generic competition and the propensity to seek an SPC. The sorting effect makes it difficult to get a meaningful interpretation of observed correlations. What might look like a proper treatment effect, e.g. of a policy change, might actually just be the effect of the sorting rule that determines which observations respond to the policy change. If this is the case, general conclusions cannot be drawn from the observed effect or they would be subject to bias.

While Kyle (2017) finds that SPC-protected medicinal products usually experience earlier generic entry than medicinal products that are not protected by a corresponding certificate, this finding is subject to substantial caveats. In particular, sorting could occur along two dimensions:

- Sorting on profitability: Most likely, incumbent or originator companies will seek SPC (and other) protection for the medicinal products that are most profitable to them. At the same time, these are the very medicinal products that, due to their flourishing markets, are likely to be most attractive to the generic manufacturers planning to enter the market as soon as exclusivity protection lapses. This issue can, for instance, be illustrated in pharmaceutical companies' attempts at 'stacking protection'.[2]

- Sorting on expected competition: There might be reasons for which certain medicinal products are easier to reverse-engineer into a generic product than others or why they might be more attractive for generic manufacturers to target. If originator companies are aware of these facts, they could be more likely to apply for supplementary protection for those very products where they perceive the highest threat of expected generic competition.

Kyle (2017) observes similar outcomes in a hazard model specification where SPC-protected medicinal products experience faster generic entry but where the observed relationship is likely not causal. The author notes that expected profit seems to be the most important driver for generic entry and protection, concluding that "*protection is sought where it is needed: where additional protection is not pursued, generic entry is less attractive for other reasons*."

While the presence of SPCs might be found to correlate with higher or earlier generic entry, this might just be an expression of rent seeking by pharmaceutical companies on already more profitable products.

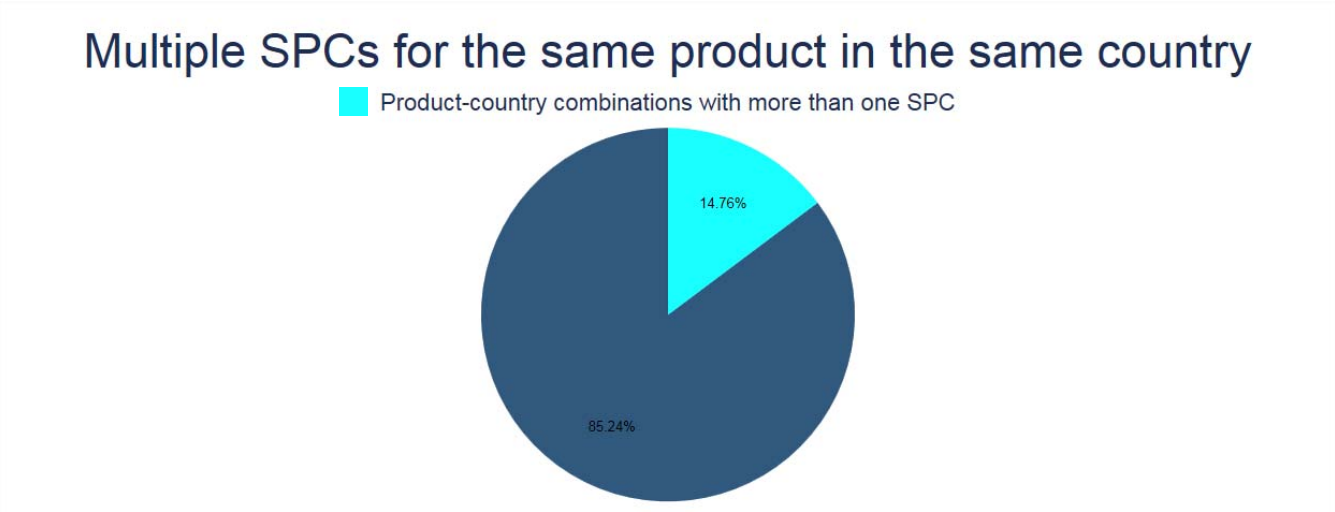
FILINGS AND UNCERTAINTY

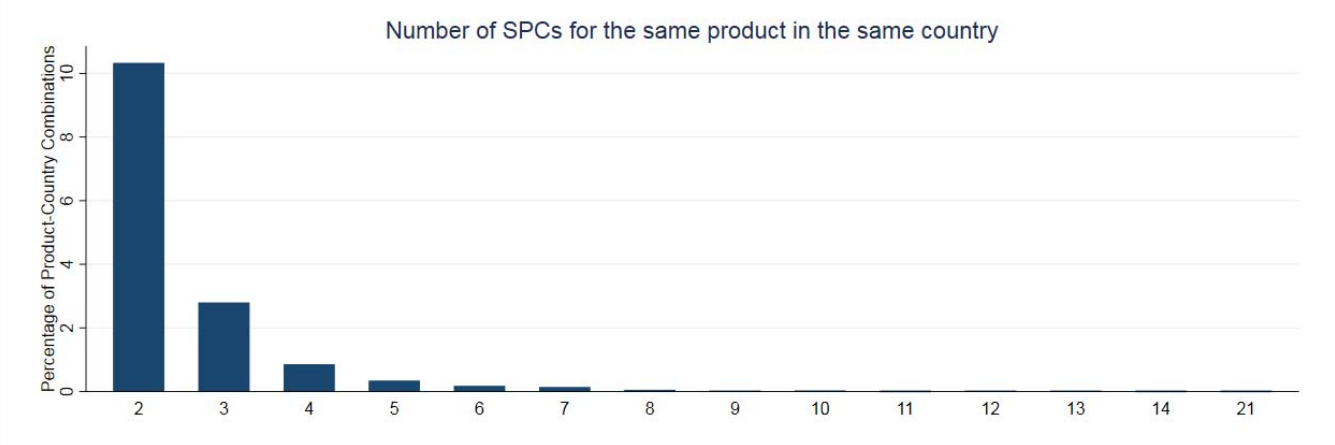
Over time, medicinal products, development and respective filing opportunities have become more and more complex[3]. As noted by Mejer (2017)[4], the potential uncertainty related to the scope and expiry of exclusivity protection has increased accordingly.

Exacerbated, among other things, by the possible existence of multiple SPCs held by multiple companies on a single medicinal product, the increasingly opaque exclusivity picture poses additional challenges especially to generic manufacturers.[5] While originator companies could potentially stand to benefit from the arising confusion, generic competitors will likely not. In fact, it does not appear far fetched to imagine a scenario where an increased likelihood of 'accidental' infringement increases delays to generic entry or at least raises the cost to generic manufacturers of investigation into marketing opportunities.

1This is supported by the fact that on p. 182 we report that approval times have decreased for EMA. This would work to decrease the time it takes to bring a product to the market. At the same time, we report on p. 182 that the number of procedures per clinical trial have gone up, potentially prolonging the time clinical trials take.
2 See for instance Kyle (2017), where the linear probability of obtaining an SPC for a medicinal product significantly increases the number of patents filed.
3 See e.g. p. 66 and p. 182.
4 Mejer, M. (2017) "25 Years of SPC Protection for medical products in Europe: Insights and challenges".
5 As depicted on the next page, 15% of product-country combinations are connected to multiple SPCs.

15% of product-country combinations have been granted more than one SPC





Note: Upper pie chart showing share of products that, in the same country, were granted multiple SPCs vs. share of products that, in the same country, were granted exactly one SPC. Lower bar chart showing the distribution of products that received multiple SPCs in the same country as percentage of the overall population of granted SPCs (N = 13,352).
Source: Alice de Pastors SPC database

The compensation of lost effective patent protection time creates certain incentives regarding launch timing (1/2)

COMPENSATION OF EFFECTIVE PATENT PROTECTION

The SPC compensates pharmaceutical companies for effective patent protection time lost, due to development. If a medicinal product takes more than 5 years to develop, the SPC compensates one-to-one for each year lost up until 10 years of development time. Development time is calculated from time of the first patent protecting the product, until first marketing authorisation within the EU.

A direct consequence of this is that if a medicinal product takes anywhere between 5 and 10 years to develop, the effective patent protection period will be 15 years, if an SPC is applied for and granted[1].

In some cases this compensation of development time might in theory create incentives to delay launch of new innovative medicinal products. This will be explored on this and the following page.

Unfortunately the current data material does not lend itself to an analysis of whether deliberate delay of launch takes place as an effect of the one-to-one compensation granted by the SPC. In the following, we explore economic theoretical considerations and arguments for and against deliberate delay of launch of new medicinal products. As such, any moral and/or ethical considerations are not taken into account.

REASONS FOR LAUNCHING AS SOON AS POSSIBLE

If a pharmaceutical company has developed a new medicinal product and the development time has been e.g. 5 years, deliberately delaying launch would not decrease the effective patent protection period, as an SPC can be applied for.

However, if a company delays launch of a new medicinal product, they should take the time discounting of future profit into account. Time discounting means that a euro today is worth more than a euro next year and as such it is better to earn a given amount today than to earn the same amount in a year[2]. Consequently, even though delaying launch would not decrease the effective patent protection period, it would delay the time at which profit is earned. This would hence decrease the present value of said profit stream.

Another factor to take into account when delaying launch is that another firm might enter the market with a new and better innovative medicinal product in the future.

Say that a new competitor will do this exactly 15 years from the date at which a company is deciding whether or not to delay launch of a product which had a development time of 5 years. If the company launches now, they will have effective patent protection for 15 years and competition by innovation will not happen until after the effective protection period has fully elapsed and generics can enter the market as well.

If the company instead delays launch by a year, they will still have 15 years of effective patent protection, but the last year will now be worth much less, as another company will enter the market with a better product. This will conceivably decrease profit significantly. As such, launching as soon as possible might be the best strategy in this hypothetical case.

Whether or not a competitor will enter the market with a new innovative product and when this could potentially happen is, of course, subject to speculation and hence is probably unknown at the time of launch decision. However, the company might have some idea of the probability that this will happen and hence attribute some level of risk to this event.

The above theoretical discussion has shown that if a company decides to delay launch voluntarily, they face the risk of new innovations outperforming their product before loss of patent protection. Furthermore, time discounting means that their future profit is worth less than present profit and hence, all other things being equal, would mean that launch as soon as possible is the best option.

Likewise however, there might be certain reasons for deliberately delaying launch of a new product, further described below.

POSSIBLE REASONS FOR WAITING TO LAUNCH

If a company already has a product on the market to treat a certain indication and it has developed a new, possibly better product, there may be an incentive to delay launch.

If the product the company currently has on the market is still protected by patent protection so that no generics yet exist, introducing the new product would effectively make the company compete against itself. Of course this is only the case if there are no other originator products on the market, in which case, launching the new, possibly better product might mean that the company could obtain a larger share of the market.

1 See p. 70 for the distribution of development times.
2 E.g. because a euro today can be invested to earn return or interest.

The compensation of lost effective patent protection time creates certain incentives regarding launch timing (2/2)

If the development time of the new medicinal product has been e.g. 5 years and there are currently no competing products on the market, entering the market to compete with its own product might not be the most profitable option. If the company delays launch for up to 5 years, the protection period of the new product will still be 15 years if it is granted an SPC. However, this depends on the new product being protected by a patent other than the old product for which an SPC can be applied for. As such, if the two products contain the same molecule this might not be possible.

Seen in isolation, the best profit-maximising strategy in the above example might be for the company to delay launch of the new product to avoid competing with its own product.

Another reason to delay might be if a company has a reason to suspect that a new medicinal product might be used to treat more than one indication.

If the development time for the indication for which the company originally planned to seek authorisation took e.g. 5 years, waiting to launch for up to 5 years would not have an effect on the patent protection period of the product. It would still be 15 years.

However, if the product is approved for the original indication at the end of the 5-year development period and is after e.g. 2 years on the market approved for a second indication, the effective protection period left is 13 years. This means that after 13 years generics can enter the market for the second indication as well.

However, if the company delays launch of the first indication for 2 years and obtains simultaneous approvals for the two indications, the product will have an effective patent protection period of 15 years. This means that both markets will be protected against generic entry for 15 years[1].

WHETHER OR NOT TO DELAY LAUNCH

From an economic theoretical point of view, the decision of when to launch essentially comes down to an assessment of an economic business case encompassing the expected profit if the new product is launched right away, compared to expected profit if launch is delayed.

In this business case the previously described considerations regarding risk of competition by innovation and time discounting of future profit play an important role. These considerations have to be viewed in the light of the amount of compensation granted for delaying launch. In the case of the SPC this is one-to-one.

However, it is important to note that all direct compensation for lost development time might create the above-mentioned incentives. The degree of compensation will then serve to determine the power of the incentive. For example, if compensation was only six months for every additional year spent during development, the strength of the above-mentioned incentives to delay launch would be weaker. All other things being equal, this would decrease the expected profit of the business case of waiting to launch.

In the above sections, economic theoretical considerations and arguments for either delaying launch or bringing a product to the market as soon as possible have been explored. It is important to note that the considerations are merely made from an economic theoretical point of view. As such, neither ethical nor moral considerations have been taken into account.

1 There might still be other originator products on the market and generics of these or other medicinal products no longer protected by IP rights.

The allocation criteria for the SPC are decoupled from the ability of a product to earn a return on investment

THE ALLOCATION CRITERIA FOR SPCs

SPCs are allocated on the basis of development time, i.e. time from first patent until marketing authorisation is obtained for the product.

Essentially, the possibility of obtaining an SPC if the development period extends beyond 5 years increases the total amount of R&D projects which ex ante constitute a positive business case.

As the SPC is allocated based on development time, the value of the SPC varies greatly across products. The higher volume and/or price the product has on the market, the higher the value of the SPC. Some products reach blockbuster status even before expiry of the patent and commencement of the SPC[1].

In the above sections, several objectives of the SPC regulation were reviewed. Among these were the following potentially conflicting objectives:

- Supply-side objective 3: Ensure that research-based industry has market protection of sufficient length to permit recovery of investments.
- Demand-side objective 3: Availability of generic medicinal products.
- Market impact objective 2: Extended protection that is justified by revenues and profits for the different categories of eligible medicinal and plant protection products.

On the one hand, the regulation seeks to provide the pharmaceutical companies with an expected profit sufficient to undertake R&D of new innovative medicine. On the other hand, the regulation seeks to make new medicine accessible to patients through e.g. generic competition.

When reviewing the incentives for medicinal products, it is imperative to have in mind how any possible changes would affect the ex ante business case of developing new medicinal products.

Unconditionally changing the protection period of the SPC would e.g. have an effect on the ex ante business case of all products eligible to obtain an SPC. This might have unintended consequences for products which are barely profitable and would not be developed without the current incentives provided by an SPC.

If, instead, a provision was made whereby the maintenance of an SPC was conditional upon some sort of revenue cap, this would only partly affect the business case for pharmaceuticals where there is a remote possibility that they will attain said level of revenue. This means that it might be possible to make changes to the existing incentives that would not have detrimental effects on the ex ante business case, but which would better adhere to the objectives of the regulation.

There might, however, be some judicial and practical problems in implementing such a provision. The above is not to be seen as a recommendation, but as an example of how different changes have different effects on the ex ante business case.

PAEDIATRIC EXTENSION OF THE SPC

If a non-orphan medicinal product with an SPC fulfils the obligations agreed upon in a paediatric investigation plan (PIP), a six-month extension of the SPC can be granted. For an orphan medicinal product a 2-year extension of the market exclusivity period can be granted instead.

To obtain a positive compliance check it is not necessary that the medicinal product is found to provide any benefit for the paediatric population. As long as the PIP is fulfilled, the reward can be awarded. This contributes to making sure that there are no adverse incentives at play when conducting a PIP.

The allocation criteria for the extension based on paediatric studies means that the main reward, the extension of the SPC, is usually valuable because it extends the time before generic companies can enter the market for the indication in adults as well.

As such, the size of the reward is dependent on the volume of sales within the adult population. In that sense there is, so to speak, a decoupling of obligation and reward. The paediatric reward becomes worth more to the pharmaceutical companies, the larger the adult patient group is (and the higher the price is)[1].

1 See e.g. the case study on Humira in section 5.2.

Regulatory exclusivity is increasingly important

To manufacture a generic product, generic pharmaceutical companies use the knowledge developed and disclosed by originators, namely the testing and trial data, as well as the composition of the medicinal product launched by the originator on the market.

As such, a 'true' generic entry is conditional on the expiry of market and data protection as the potential competitor would not be able to refer to the originator data otherwise.

However, firms can enter the market for a specific medicinal product earlier if they invest in the creation of their own testing and trial data. That is, competitors can circumvent the data protection barriers and create a so called "me-too"-product. In such a setting, the entrant faces considerably less market risk than the incumbent:

- The entrant can profit form the actual invention behind the project through reverse-engineering, incurring substantially less R&D cost.
- The entrant can be relatively sure that clinical trials and authorisation proceedings will be successful, leading to a reduction in development risk.

While an entrant would still face commercial and competition risk, the up-front financial hurdles for entry are significantly reduced, as the first part of an R&D process has already been undertaken by the other company. Entry could potentially occur once IP protection in the form of patents and SPCs has expired.

As such, the market and data protection provisions can be interpreted as 'easier to circumvent' than exclusivity protection for pharmaceuticals, leading to earlier possibilities for competition to enter the market.

The line chart on the following page illustrates this point and emphasises the increasing relevance of these considerations. Over time, a larger share of the average protection period seems to be time where companies are only protected by regulatory exclusivities. The gap between average protection including regulatory exclusivities and average protection encompassing only patent and SPC protection is increasing throughout the sample studied.

While the average marginal protection effect of regulatory exclusivities only amounts to a few months in the beginning of the sample, this difference extends to a few years in the later parts of the sample and certainly from 2005 onward. On the one hand, this illustrates the increasing commercial relevance of regulatory exclusivities. On the other hand, this points to an increased opportunity for "me-too"-product competition that utilises other actors' inventions with new clinical data.

The average extension of regulatory exclusivities beyond the protection provided by patents and SPCs further highlights an interesting argument: while it might only be for 10% of observed medicinal product-country combinations that the SPC actually extends the period of effective protection, the certificate also impacts the market when not extending the exclusivity time frame[1]. This can furthermore be seen in the context that 45% of the unique products in the dataset have obtained an SPC in at least one country[2].

The existence of patent protection or SPC-extended patent protection grants patentees and SPC holders a stronger defence against competition than the regulatory exclusivities. While competition through innovation is possible when a patent is in place, competitors cannot circumvent protection by compiling their own data without infringing the patented or SPC-protected invention.

In this sense, the introduction of SPCs has probably had its largest impact in changing the way that pharmaceutical companies evaluate their research and development projects *ex ante*, i.e. before deciding whether or not to commit to investment. The prospect of additional protection against competition is likely to impact such an assessment.

The line chart on the following page further illustrates the increase in average development times. While regulatory exclusivities extend from the grant of marketing authorisation forward, patent protection expires independently of the timing of a marketing authorisation. In the graph, this is evidenced by the steeper decline in the protection granted by patent and SPC vis-à-vis the change in protection including regulatory exclusivities.

1 See pp. 215-216 for a further description of this.
2 See p. 84.

The average effective protection provided by relevant intellectual property rights is developing at an uneven pace

From the graph to the right it can be seen that the average effective protection period for medicinal products has been decreasing over time[1]. The general decrease in average effective protection is depicted by the blue line.

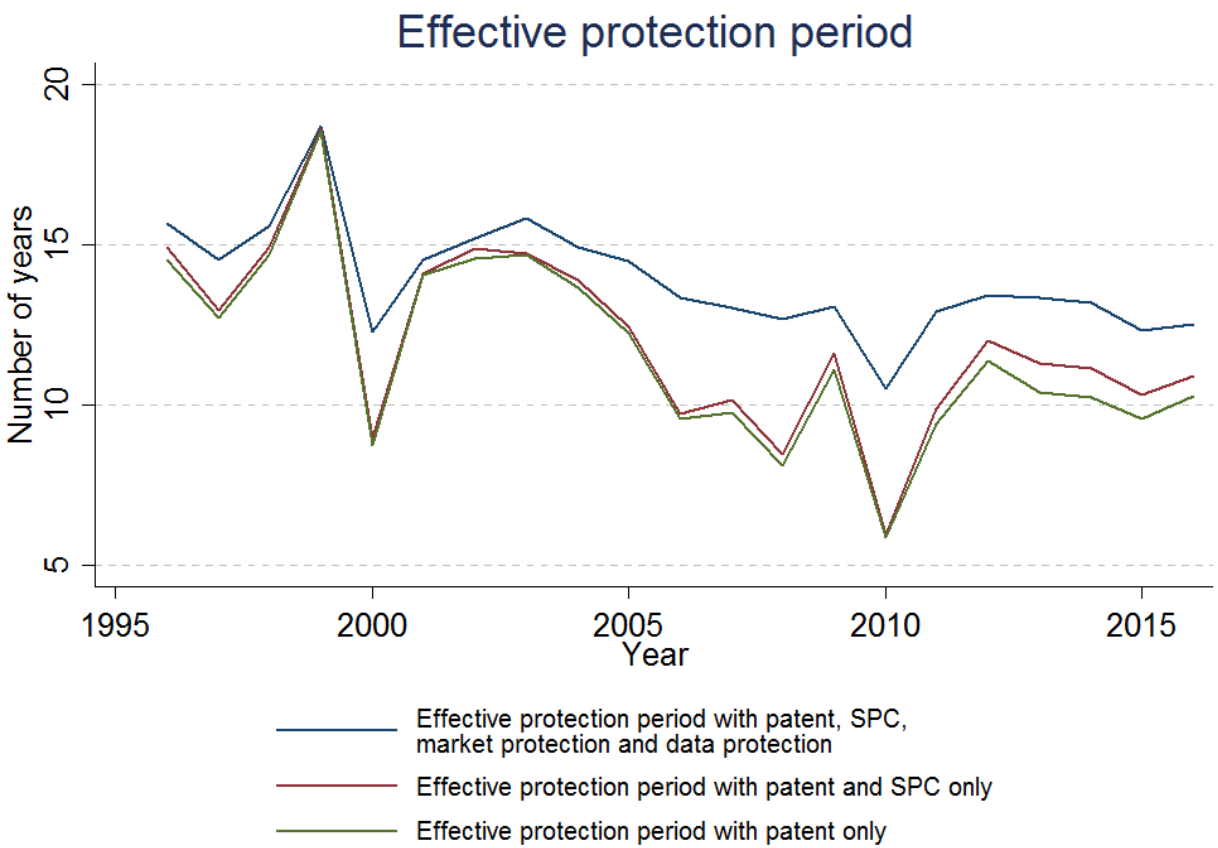
The red line depicts what the average effective protection period would have been, had market protection and data protection not existed. The green line, furthermore, depicts what the average effective protection period would have been if neither market protection, nor data protection, nor SPCs had existed.

It can be seen from the graph that the gap between what the average effective protection period is when all protection schemes are taken into account, and what it would have been if only patent had existed, has increased over time.

This points to more medicinal products being dependent on the regulatory protection periods to provide them with effective on-market protection.

Furthermore, the increasing gap between the green and red lines suggests that SPCs have likewise increased in importance for the effective protection period of medicinal products.

Effective protection period based on different protection schemes, 1996-2015



Notes: Calculation based on unique product-country observations. This means that each product is used in the calculation of the average effective protection period as many times as the number of countries in which it has marketing authorisation. Prior to 1995 data is only available for 12 respectively 13 countries. The last year of complete observation is 2016. The above graph depicts the average effective protection for all observations, irrespective of whether they have been subject to an SPC application or not. For about ten percent of the sample, supplementary protection certificates are the last intellectual property right to expire. As such, the above graph does not depict the marginal effect of SPCs on the effective protection period.
Source: Copenhagen Economics based on unique dataset created from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 This graph has likewise been shown on p. 200, while a related graph is depicted on p. 73.

Impact of innovation and changes in marketing authorisation and product testing methods

Personalised (or stratified) medicine[1]
"[P]ersonalised medicine refers to a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. Personalised medicine relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs."

- EU Health Ministers Council conclusions on personalised medicine for patients (2015/C 421/03)

PERSONALISED MEDICINE: THE ROLE OF PATENTS IN DATA AGGREGATION

Personalised, or stratified, medicine focuses on the development of customised treatments either for individuals or small groups of individuals[1].

Burk (2015) points out that the, generally uncertain, incentivising effect that patents might have in the context of pharmaceutical innovation might not function properly in the context of personalised medicine. If solutions, diagnostics and treatments are customised to small groups of individuals, the resulting market fragments might be too small for patents to allow innovators to earn profits sufficient to cover their initial outlays. Burk (2015) warns that 'single sale pricing' mechanisms might make personalised treatment inaccessible to large consumer groups.

While patents might not promote innovation in personalised medicine in the way they might in other sectors of the industry, Burk (2015) uses a recent US Supreme Court ruling[2] to illustrate how patents are used by firms to gather data critical to further product development. In the case at hand, the patentee enforced their IPR while it was valid and excluded anyone from using their product without licensing it.

Consequently, the patentee was able to collect an extensive and, given the exclusive usage of the product, unique dataset on the treatment and therapeutic indication it was used for. As described in Burk (2015), this patent-levered data aggregation can be said to be "*having some good news and having some bad news*".

On the one hand, the patent and its enforcement allowed the patentee to aggregate otherwise unachievable data. The compiled data could be used to shed light on otherwise difficult-to-observe diseases or to develop and test better medicines.

On the other hand, the enforced patent put the patentee in a position where they had exclusive access to the aggregated dataset and where they could preclude others from using it or gaining access. In particular, this becomes an issue if the patentee is able to use the data as proprietary know-how that grants them a favourable market position beyond the expiry of the patent originally used to collect the information.

Another related issue is how to apply the definitions of the prevalence criteria for orphan medicinal products if medicinal products become customised to a degree where the relevant patient group is essentially only one individual.

For further discussions on personalised medicine, please refer to chapter 4 of this report.

PATENTABILITY

In the case in point, the developed treatment was based on the isolation of DNA sequences. The patent was invalidated by the court on the grounds that it covered ineligible subject matter.

As such, patents might not function as a proper mechanism for fostering innovation if:

- They do not provide the right incentives (e.g. fragmented markets in personalised medicine).
- The substance of the invention is not patentable to begin with (DNA, for instance).
- The grant of patent puts the patentee in a strong market position even beyond expiry (e.g. where collected and aggregated data is turned into proprietary knowledge).

Consequently, if patents are not a suitable innovation incentive, SPCs would not be either.

1 Please refer to https://ec.europa.eu/research/health/index.cfm?pg=policy&policyname=personalised&cookies=disabled and http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ%3AC%3A2015%3A421%3AFULL for additional information [last accessed 29/01-2018].
2 Association for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

The nature of R&D and innovation models in relevant markets

R&D AND INNOVATION MODELS

Pharmaceutical research is constantly evolving, lately from small molecule to increasingly biologic medicinal products. Presently a paradigm shift might be observed in the innovation system within the pharmaceutical industry[1].

The industry is making increased use of digitalisation and big data technology, as well as artificial intelligence. Particularly in the context of biological data processing, computational power and algorithms are becoming increasingly important.

While these technologies and developments are themselves protected by intellectual property rights, different rights – other than product patents – become more relevant in providing protection to the innovations behind them[2].

MARKET DEVELOPMENTS IN THE PHARMACEUTICAL SECTOR

The development and continued involvement of advanced data methods and digitalisation described above culminates in different challenges to the pharmaceutical sector and the respective regulators in the European Union and its member states, as summarised by e.g. Minssen & Pierce (2017 – *forthcoming*)[3] and Minssen (2017)[4].

1. Increasing usage of 'big data' technology in life sciences and, as a result, sizable IPR-protected data collections could pose as barriers to entry that potential competitors would have to overcome by exerting considerable effort to provide similar data accumulation.

2. The development and support of large research infrastructures. On the one hand, large infrastructures can help tackle complex research endeavours. On the other hand, the organisation of such infrastructures requires a vast degree of co-ordination and collaboration and might create an asymmetric distribution of product development capabilities across market participants.

3. There is continued conflict between public involvement and interest and the exclusivity granted to innovators in the form of intellectual property rights.

4. The role of intellectual property rights in the context of managing the trade-off between sharing initiatives and data transparency. As argued in Price & Minssen (2015), there is a trade-off between cost and benefit in introducing additional regulatory disclosure requirements. Data sharing promotes independent verification, precompetitive collaboration and potentially the development of treatments for rare diseases. At the same time, data sharing reduces patient data privacy and may increase litigation risk for innovators, lead to data misuse, or reduce the incentives for developing new indications for already marketed medicinal products.

5. The role of innovation and R&D incentives in regulating and incentivising the development of precision medicine and personalised treatments.

6. The emergence of e.g. artificial intelligence and machine learning might create challenges for some of the legal formulations regarding patentability, e.g. the nature of when a certain innovation is "obvious" might be challenged by new technological advances[1].

1 Abbott, R. (2017), Everything is Obvious.
2 These could e.g. be regulatory protection schemes.
3 Minssen, T. and Pierce, J (2017), "Big Data & Intellectual Property Rights in the Health and Life Sciences".
4 Minssen, T. (2017), "Big Data, IPRs & Competition Law in the Pharma & Life Sciences – emerging issues in a rapidly evolving field".

Overall effects of incentives and rewards: what are the implications for supplementary protection certificates?

THE RESULTS OBTAINED IN CHAPTER 2 DO NO PAINT A CLEAR PICTURE

The econometric and quantitative analysis in chapter 2 produced a range of interesting results regarding the relationship between effective protection, innovation, availability and accessibility.

Firstly, section 2.1 indicated that an increase in effective protection among the other EU countries with which a given country trades the most would lead to an increase in domestic spending on pharmaceutical R&D. As SPCs on average increase effective protection periods, this should in turn lead to an increase in innovation spend in the countries that trade with a given country. As the SPC is EU-wide and EU countries trade with each other, the SPC should have led to more pharmaceutical innovation within the EU.

Secondly, section 2.2 indicated that little evidence could be found relating effective protection period and product availability (as measured by international launch lags). As SPCs mainly work by extending effective protection, it does not appear that the presence of supplementary protection would influence product availability. This might be due to the fact that the effective protection period has already been factored into the launch decision.

Thirdly, section 2.3 indicated that accessibility (as measured by medicinal product prices) is mainly driven by the timing of exclusivity expiry. Following the lapse of exclusivity, generic competition is possible and prices for both originator products and generic substitutes tend to fall, while price developments during the period of exclusivity protection tend to show less clear developments. As such, it is unlikely that SPCs have an effect on pricing and pricing developments during the protection period. SPCs do however postpone the timing of protection expiry and consequently also postpone the point in time from which potential price reductions materialise until protection has lapsed.

GENERAL DEVELOPMENTS IN EFFECTIVE PROTECTION PERIOD CAN HAVE VARIOUS REASONS

Effective protection period seems to have been declining since the introduction of SPCs in the European Union. While this at first sight might suggest that SPC-protection is merited and that there might be a case to even extend it, this interpretation is likely to be too simple.

The relationship between the need for protection and increasing development times is probably not easy to interpret or even meaningful. There are different reasons for why development time might be increasing and firms should not necessarily be compensated for all of these.

The main driver for product launch and development decisions seems to be the profit that can be expected from pursuing the respective project. While the time period of exclusive commercial exploitation (which is prolonged by an SPC) is important for this calculation, profits are also impacted by the price of a product and the number of units sold.

THE EFFECT OF SPCs AS AN INCENTIVE POSES A TRADE-OFF

SPCs lead to delayed generic entry and hence delay the downward price pressure associated with it. The usage of SPCs allows pharmaceutical companies to obtain greater profits.

However, SPCs also seem to increase innovation and thereby foster the supply of innovative products. It seems likely that SPCs increase expected profits for R&D projects in such a way that more projects reach the development stage. Put plainly, SPCs can be seen as a trade-off from the regulator's perspective. On the one hand, as described above, SPCs postpone generic entry and hence the inherent downward price pressure. On the other hand, SPCs seem to increase innovation.

THE QUESTION BEHIND THIS TRADE-OFF IS OF POLITICAL RATHER THAN ECONOMIC NATURE

As elaborated upon above, it seems that the SPC regime poses a regulatory trade-off: the incentive scheme can increase innovation and the supply of novel products to the market, but does so at the expense of later generic entry, higher prices and increased profits for pharmaceutical companies.

Solving this trade-off will have a substantial economic impact on the entire market. In the end, however, the way in which this trade-off is to be resolved remains a political rather than economic question.

Insights from elsewhere: evidence on US patent restoration

IMPACT OF A PAEDIATRIC EXTENSION

Regulation (EC) No 1901/2006 (2) states that "*Such* [clinical] *studies may not have been undertaken for use in the paediatric population and many of the medicinal products currently used to treat the paediatric population have not been studied or authorised for such use. Market forces alone have proven insufficient to stimulate adequate research into and the development and authorisation of, medicinal products for the paediatric population*".

Consequently, it was found that legal instruments were needed to encourage clinical trials to be undertaken within the paediatric population to ensure more information on the workings of pharmaceuticals pertaining specifically to children.

Since 2006, an SPC-additional patent extension has been available for paediatric medicines in Europe. If an originator company can prove that it has carried out tests in compliance with a paediatric investigation plan (PIP), an additional six months of exclusivity can be granted for the paediatric and adult population.

In a study of the effect of a similar legal instrument in the United States, Baker-Smith et al. (2008) show that the presence of a dedicated six-month extension substantially increased the number of products brought to the market.[1]

The additional revenues realised by innovators of paediatric medicines proved to exceed the costs of additional testing, making it profitable for originators to develop products for previously ill-supplied markets.

At the same time, such additional extension further increases the time to generic competition.

For a further discussion of the role of the paediatric extension in Europe, please refer to sections 4.1.3, 4.2 and 4.3 of this report.

IMPACT OF HYPOTHETICAL EXCLUSIVITY EXTENSIONS

Goldman et al. (2011) estimate the impact of a hypothetical increase of the data exclusivity period available to small molecule medicinal products in the US. At the time of the study, small molecule medicinal products were, upon successful filing, granted a data exclusivity period of 5 years, extendable to 8 years for additional indications (paediatric extensions of six months were available as well).

On the contrary, biologic medicinal products in the US are granted 12 years of data exclusivity, i.e. regularly 5 to 7 years of additional protection. The authors devise a dynamic modelling approach designed to estimate the impact of a hypothetical harmonisation of exclusivity terms, namely, a scenario where small molecule medicinal products receive the same 12-year exclusivity that is granted to biologics.

While their model specifications are subject to numerous assumptions and simplifications, they find that an increase in protection period would primarily increase medicinal product revenues and lead to an increase in the number of medicinal product approvals. The authors further note that, while the projected increase in innovation would generate welfare gains due to increased life expectancy, it would also increase per capita spending on medicines.

1 The authors observe a general increase in 'labelling changes' due to compliant paediatric studies from 11 between 1990 and 1997 to more than 130 between 1997 and 2007. Their study on the additional returns to innovators focuses on clinical trial data for nine orally administered antihypertensive medicinal products that were submitted to the US FDA with a request for paediatric evaluation.

3.4 IMPACT OF SPC FRAGMENTATION

Unitary Patents and Unitary Supplementary Protection Certificates

REQUIREMENTS FOR GRANT OF AN EXTENSION CERTIFICATE

The legal requirements for obtaining SPCs are determined by Regulation (EC) No 469/2009 (which replaced Regulation (EC) No 1768/1992). Article 3 of the regulation states the following requirements for grant of an SPC for a medicinal product:

" *...at the date of [the] application:*

- *(a) the product is protected by a basic patent in force;*
- *(b) a valid authorisation to place the product on the market [...] has been granted [...];*
- *(c) the product has not already been subject of a certificate;*
- *(d) the authorisation [...] is the first authorisation to place the product on the market.* "

Currently, the requirements (a) through (d) above are to be fulfilled in the member state of application, not throughout the Community as a whole.

THE UNITARY PATENT PACKAGE

The European Union introduced the first components of its unitary patent package (UPP) through regulations 1257/2012 and 1260/2012. In essence, the regulatory package amends European patents by allowing the patentee to request unitary effect of patent protection in the participating member states. The responsibility to grant unitary patents will reside with the European Patent Office (EPO). The unitary patent package further includes a unified patent litigation system centred around a unified patent court (UPC). The UPC will enter into force once certain ratification criteria are met by the participating member states. Following the UPC's entry into force, the UPP regulations will become applicable as well.

However, the process of introducing a unitary patent has, as of this writing, been halted by court proceedings in Germany[1].

THE EFFECT OF A UNITARY PATENT ON THE GRANT OF AN SPC

The introduction of the unitary patent intuitively raises two questions regarding the role of SPC patent extension certificates:

- Will a unitary patent fulfil the 'basic patent' requirements of Article 3 (a), Regulation (EC) No 469/2009?
- Should the introduction of unitary patents lead to the introduction of unitary SPCs?

To incentivise companies to actually use the new UPP system, the answer to the first question is likely to be positive. Answering the second question requires a more nuanced analysis of the incentives, costs and benefits of a unitary certificate, including:

- Administrative cost of obtaining a valid market authorisation (MA) in all member states.
- Cost of delayed or revoked MAs in single states.
- Cost related to fragmented UPP implementation (Spain and Croatia do – as of now – not participate).
- Benefits of a harmonised exclusivity landscape.
- Benefits of a centralised patent validation procedure for holders of medicinal and agrochemical patents.
- Etc.

Status quo: relevant IPRs

	Coverage	Application
Patent	National (NPO) or subject to national validation (EPO)	NPO or EPO
MA	National or community-wide (EEA)	Centralised (EMA) or through mutual recognition procedure
SPC	National	NPO

Note: National Patent Office (NPO) and European Patent Office (EPO)

The road to UPP

2010:
Agreement on enhanced patent co-operation

2011:
Presentation of proposed regulations

2012:
Regulations approved and signed

2013:
Regulations enter into force

???
UPC enters into force
Regulations become applicable

Source: European Patent Office – Unitary Patent FAQ

1 http://www.theregister.co.uk/2017/08/22/reason_for_europewide_patent_system_freeze [last accessed: 29/01-2018]. However, several countries have not yet ratified the agreement, see http://www.consilium.europa.eu/en/documents-publications/treaties-agreements/agreement/?id=2013001

NPO = National Patent Office, EEA = European Economic Area, IPR = Intellectual Property Right, the EMA = European Medicines Agency.

SPC fragmentation increases uncertainty

Cross-country differences can be observed both for the number of pending SPC applications (at times referred to as 'backlog') and for the number of applications either granted or not, as depicted in the maps to the right.

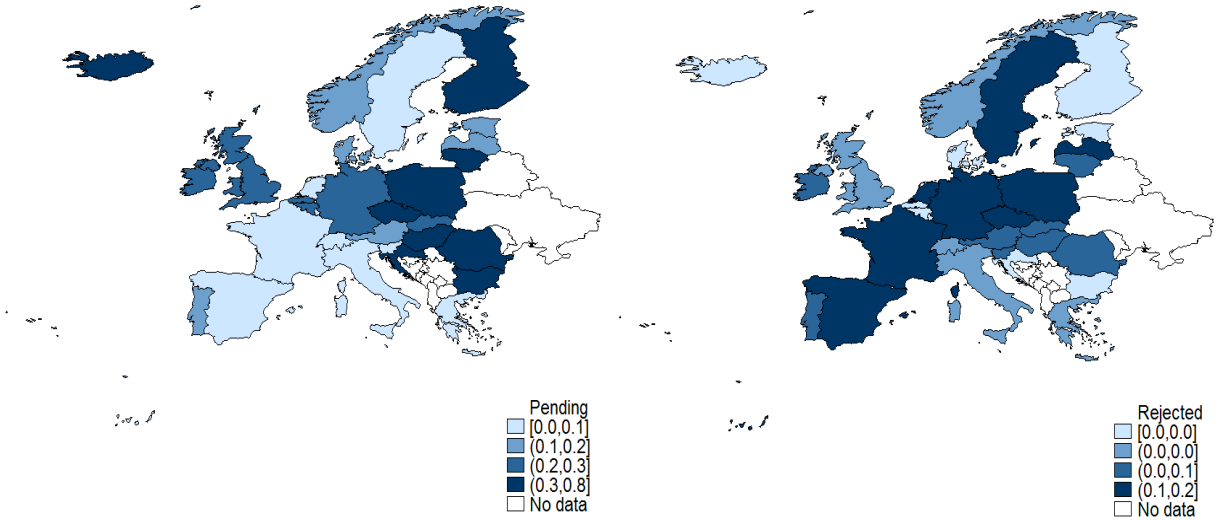
Mejer (2017)[1] finds a slightly higher proportion of pending applications in countries that joined the scheme in 2004 or later and substantial variation in general across all countries, which might be evidence of "*differences across national offices in examiner capacity, examination proceedings and differences in the interpretation of substantive patent law by the national offices*". Looking at grants, the author concludes that smaller Member States seem to have a higher proportion of granted applications and that a higher volume of applications seem to coincide with a lower grant rate in the respective country.

Additionally, her data seems to suggest that identical product-patent pairs can frequently expect different outcomes in different Member States. Taken together, this picture suggests that the fragmentation of SPCs most likely increases uncertainty for both originators trying to protect their products and potential generic entrants trying to figure out whether they have freedom to operate.

POTENTIAL FOR A UNITARY SPC

Kyle (2017)[2] notes that a unitary SPC would lead to an increase in the number of SPCs, particularly where these would not be pursued otherwise, e.g. due to low expected generic competition. Most importantly, a unitary SPC might eliminate the potentially adverse variation identified above and further increase the returns to successful SPC invalidation proceedings, incentivising potential generic entrants to pursue those at a greater rate.

Share of pending (left-hand side) and rejected (right-hand side) SPC applications in EEA countries



Note: Maps showing the fraction of pending and rejected SPC applications across countries. The map to the left shows the fraction of pending applications, while the map to the right shows the fraction of rejected applications. The darker the colour, the larger the proportion of SPC applications pending (left figure) or rejected (right figure).
Source: Alice de Pastors SPC database.

1 Mejer, M. (2017), "25 Years of SPC Protection for medical products in Europe: Insights and challenges".
2 Kyle, M. (2017), "Economic Analysis of Supplementary Protection Certificates in Europe".

Usage of SPCs increasing over time but lack of a unitary title reduces the effectiveness of the IPR

INCREASED USAGE OVER TIME

The number of SPC applications has been increasing over time, when measured by the first year of EU marketing authorisation. Looking at SPCs by filing year is likely to overstate the number of applications made in the early 1990s. This is mainly due to the fact that several cohorts of medicinal products became eligible at the same time. As to be expected and as can be seen from the graph to the right, the application filing year is slightly lagging the year of marketing authorisation.

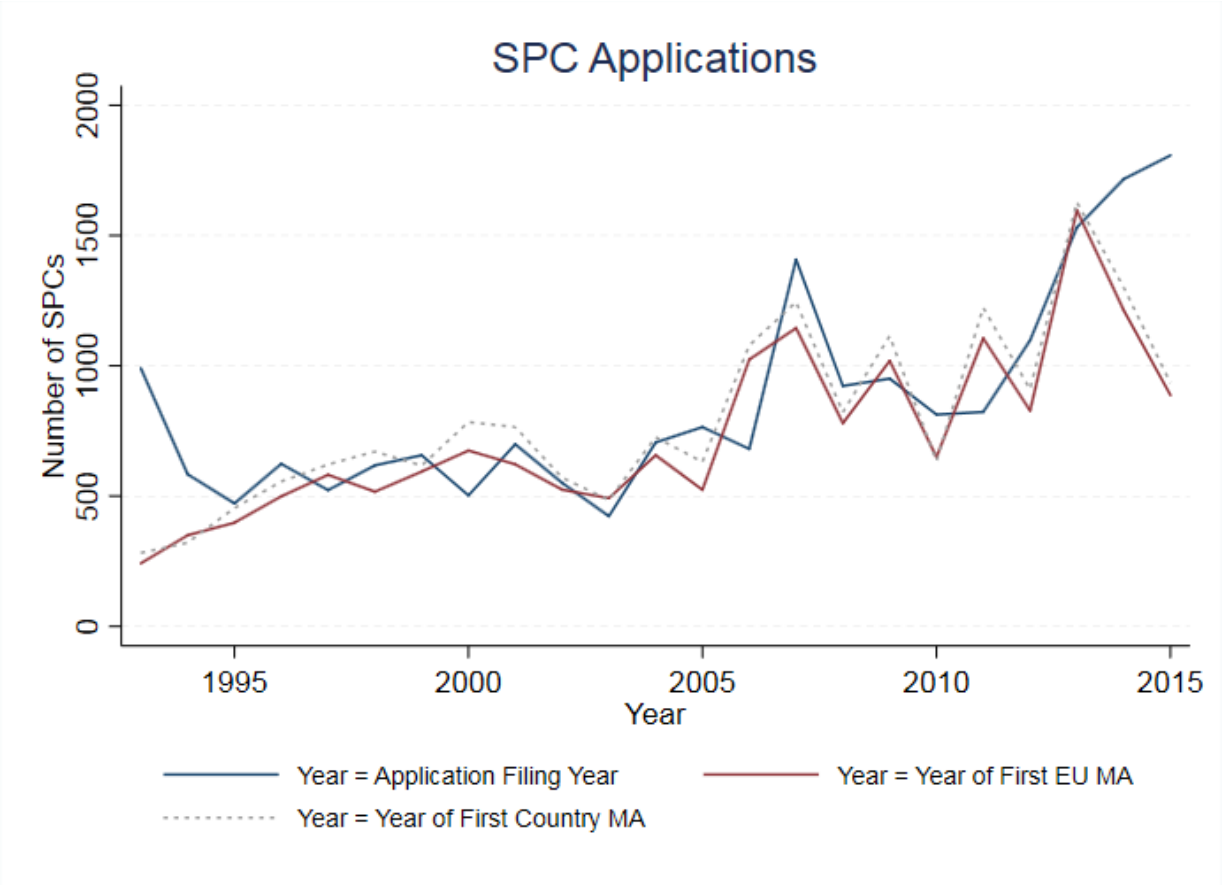
Many applications were received at the initiation of the SPC scheme but most of these actually referred to products launched on the market a few years earlier.

NEGATIVE IMPACT OF FRAGMENTATION

The fragmentation of the SPC scheme creates considerable uncertainty for and costs to applicants. On the one hand, firms seem to face heterogeneous grant outcomes across countries for the same product-patent pair (Mejer 2017). Potential generic entrants, on the other hand, have little reliable information on the full scope of product protection, and potential invalidation proceedings would have to be started in every country where an SPC is filed.

Consequently, originators face increased maintenance fees, generic entrants face increased research cost, and both most likely face higher legal costs when it comes to disputes or invalidation proceedings. Moreover, companies have to respect an increasing amount of national case law[1] when interpreting the SPC regulations. The combination of these effects probably reduces innovation-promoting effects that a properly functioning SPC might have on the market.

Number of SPC applications over time, 1993-2015



Source: Alice de Pastors SPC database

1 And European Court of Justice case law.

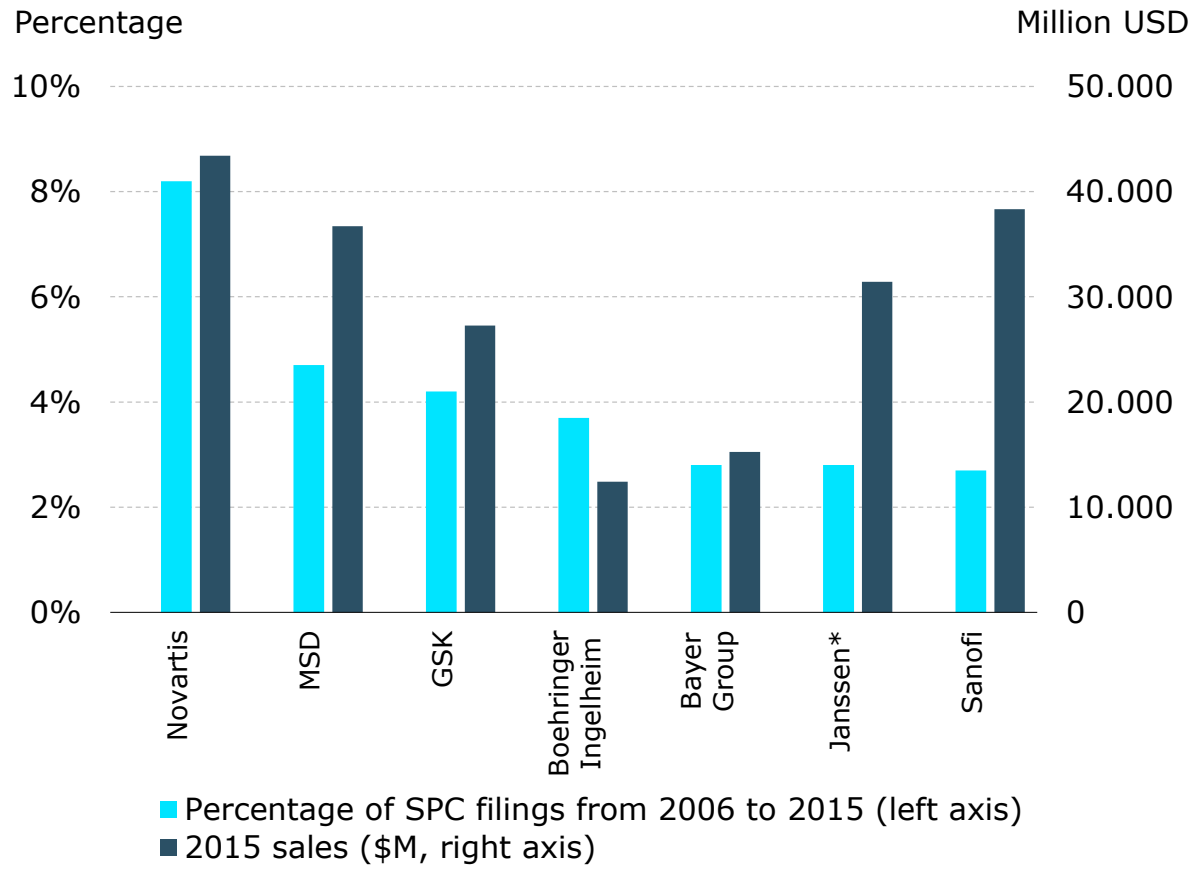
SPCs filed by pharmaceutical companies

From 2006 to 2015, the 7 pharmaceutical companies depicted in the graph to the right combined filed 29% of all SPC applications within the EU[1].

When comparing how large a percentage of all SPC filings each company makes up to their 2015 sales, there seems to be a correlation between the size of the company, measured by 2015 sales and their relative share of all SPC filings, when looking at Novartis, MSD, GSK, Boerhinger Ingelheim and Bayer Group. However, when likewise looking at Janssen and Sanofi, this relationship seems to disappear. As such, it cannot be concluded that there is a clear relationship between company size and the share of all SPC filings.

As whether or not an SPC can be applied for is dependent on the development time, the fact that there is no clear relationship between sales and share of SPC filings, could suggest that companies have different development profiles of their pharmaceutical portfolio. This might stem from companies concentrating on different therapeutic areas and that the development time for medicine in general differ across therapeutic areas.

Companies filing the most SPCs between 2006 and 2015 and their 2015 sales



*Note: The left axis depicts how a large a percentage of all SPC filings between 2006 and 2015 the filings for each company constitutes. The right axis depicts total sales for each firm in 2015 in million USD. * Sales for Janssen is taken from the below source as Johnson & Johnson, as Janssen is the pharmaceutical part of the company.*
Source: Percentage of SPC filings from Alice de Pastors, SPC-news 30 (2016 issue) available from http://thespcblog.blogspot.dk/2016/11/the-spc-blog-once-again-thanks-alice-de.html and 2015 sales from https://scrip.pharmaintelligence.informa.com/-/media/marketing/scrip-100/pdf/Scrip100_LeagueTables.pdf?la=en

1 Alice de Pastors SPC-News 30, 2016 issue

Fragmentation can distort innovation and incentives (1/3)

ABSENCE OF A UNITARY SPC

SPCs increase the effective protection period for medicinal products in the markets where an SPC is granted. As such, SPCs also increase the expected profits for originator companies – the main driver behind launch and development decisions.

Filing and applying for an SPC, as well as maintaining it, is associated with cost and effort for originators. In addition, the presence of heterogeneity in the application outcomes for the same product-patent pair across countries (as documented in Mejer 2017) creates uncertainty as to whether an SPC that is filed for will actually be granted. If this heterogeneity is an expression of differences in the interpretation of SPC regulations by different regulators, it might also imply that originators face variation in invalidation probabilities.

In the current fragmented SPC set-up therefore, originators might decide not to file SPC applications in every country where they would have the opportunity to do so. In fact, the evidence collected by Kyle (2017) indicates that firms mainly file in the markets that *per se* are more attractive for product launch.

While a successful filing in any such market would grant supplementary protection in all participating countries were a unitary SPC title to exist, this is not true in the current case of fragmentation throughout the Community. Instead, a filing company will – in the extreme case – only be granted supplementary protection in the market where there would have been a higher likelihood of product launch even without presence of an SPC, due to the market being more attractive.

The above effect can distort innovation if the grant of an SPC changes the expected profitability of launching a product in a market to the extent that a firm changes its decision to do so in the market in question. If the product launch is expected to be profitable when an SPC is granted but not otherwise, the uncertainty introduced by the heterogeneity in application outcomes could deter a firm from entering the market (e.g. if the 'uncertainty discount' – probability of application refusal due to outcome heterogeneity – is large enough). Instead, the firm might decide to enter only those markets where entry is profitable to begin with.

In this situation, if a company were granted an SPC in this already profitable market, the effect of the certificate would be to merely shift additional rents from other stakeholders to the originator. In cases where the entry-deterrence effect of application uncertainty can be observed in numerous markets, the cumulative effect on expected profits might even propel firms not to develop a product at all. This could be true in particular if uncertainty causes firms to see a sufficient number of markets as non viable for entry so that the overall expected profit from the product development falls below the relevant threshold for *ex ante* investment decisions.

IF THERE WAS A UNITARY TITLE

While a unitary SPC could potentially remedy some of this, the one-off nature of granting decisions might pose a different challenge to companies. If an SPC application is rejected in a single country, the effect will impact all markets party to the unitary scheme. In the same way that a unitary SPC might increase expected profits, it also increases the expected loss conditional on an application being rejected.

Fragmentation can distort innovation and incentives (2/3)

The blue line in the graph to the right depicts the number of countries in which an SPC is applied for in the year that the first application for an SPC for the product is handed in.

The red line depicts the total number of countries in which an SPC is applied for, in total for each product, by first year of filing.

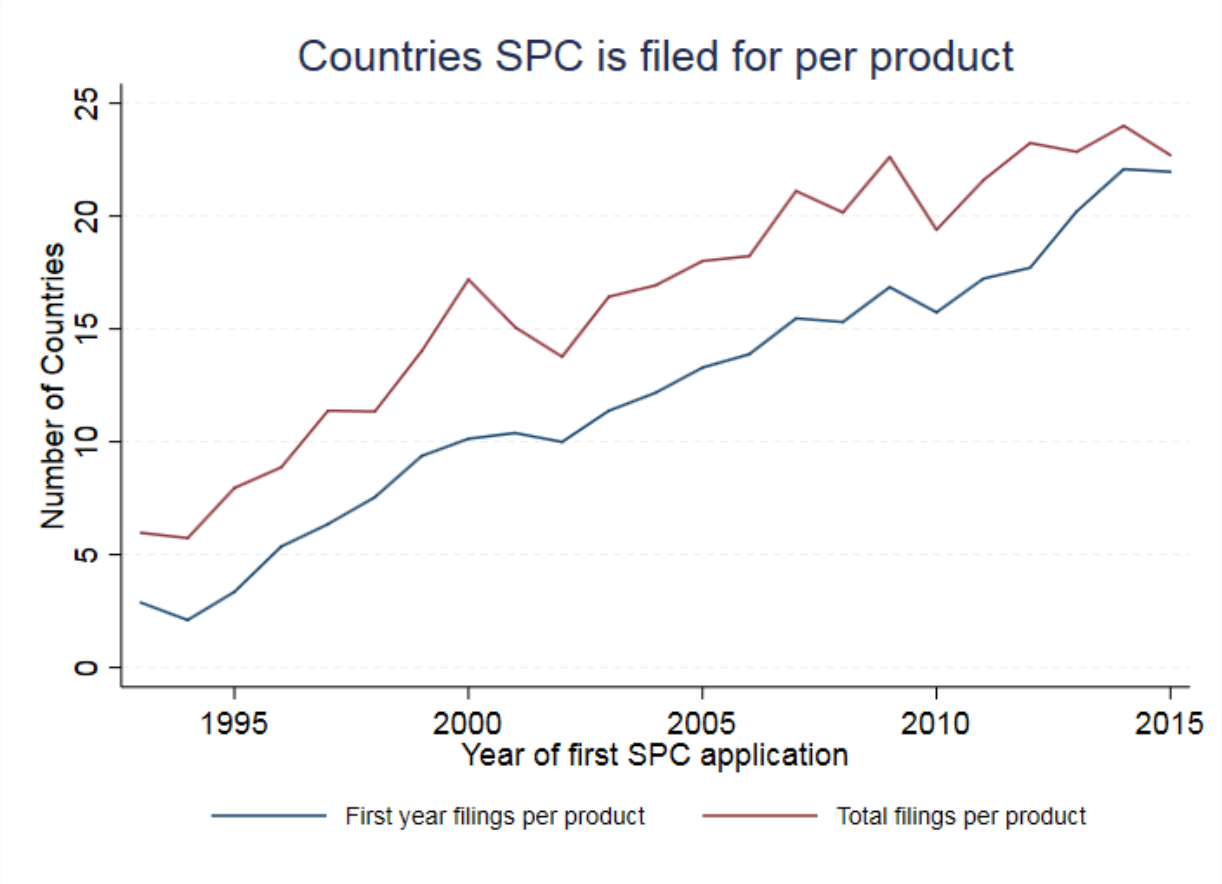
As such, the difference between the two lines depicts the number of SPCs applied for in years subsequent to the first SPC application being filed. This is interesting as SPC applications have to be filed within six months of marketing authorisation being granted. As such, the difference between the lines suggests that it is quite common not to apply for an SPC in all countries at the same time.

Both the red and blue lines can be seen to be increasing over time, which means that SPCs have been applied for in more countries in recent years compared to the beginning of the period. However, this might be due to the fact that more countries have enacted the regulation providing SPCs.

There seems to be a convergence of the two lines taking place towards the end of the period. However, this could be because we are unable to observe applications in the future and, as such, the number depicted by the red line may be revised upward in the fullness of time.

If SPCs where applied for in all countries at the same time for all products, the two lines would coincide. The difference thus depicts that seeking SPCs across Europe is not done simultaneously.

Number of countries where applications for SPCs are filed and the degree to which this is done in the same year or subsequently, 1993-2015



Note: Graph showing the number of countries SPCs are applied for and to what degree the applications are submitted in the same year or subsequently.
Source: Alice de Pastors database on SPCs collected from published data from National Patent Offices.

Fragmentation can distort innovation and incentives (3/3)

The graph to the right depicts the degree to which products, for which SPC applications have been filed in multiple countries, have experienced differences in the final outcome.

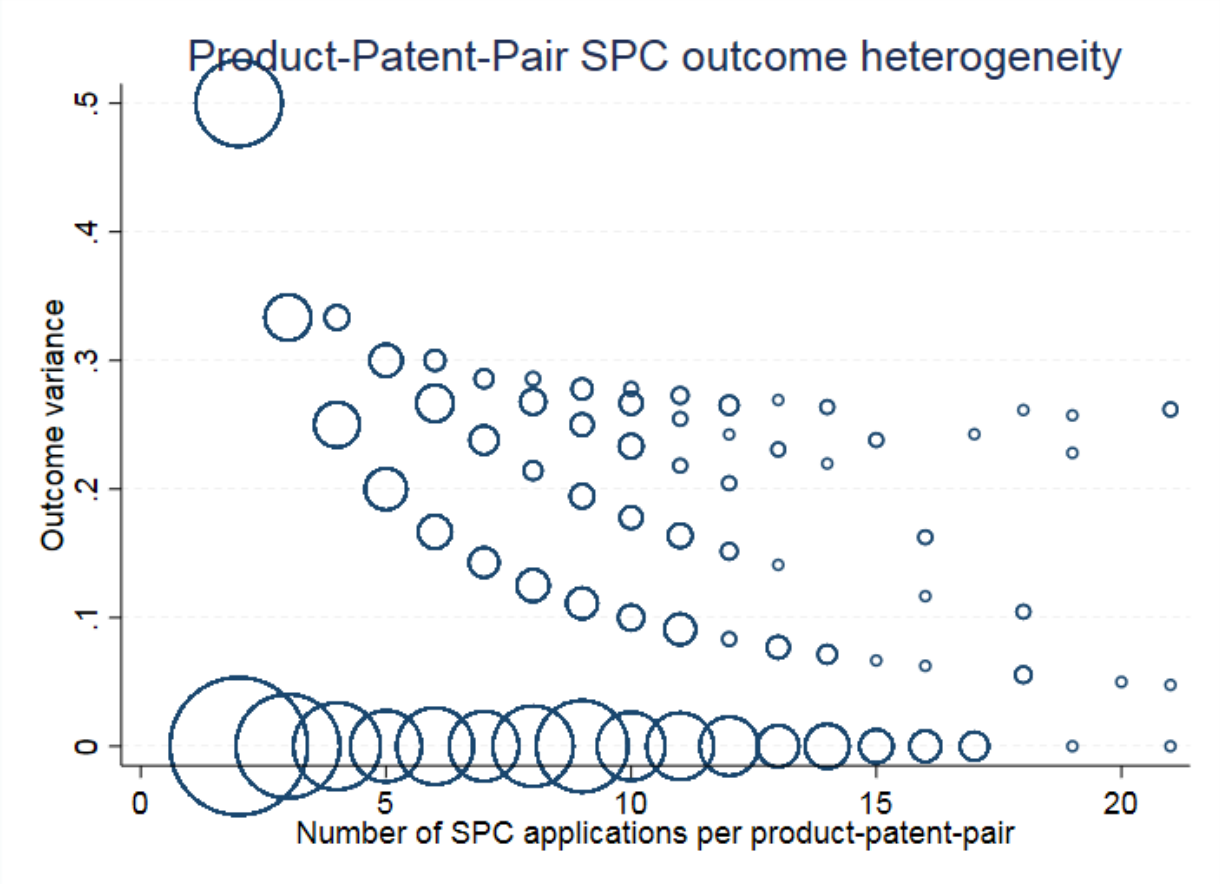
Consequently, the graph provides information as to whether a product having obtained an SPC in one country has had an application for an SPC in another country rejected.

The x-axis depicts the number of SPC applications handed in per product. The y-axis depicts the degree to which outcomes differ across all the applications.

The size of the circles depicts the number of products for which the number of applications (shown on the x-axis) have been handed in and the given outcome variance (shown on the y-axis) has been experienced, i.e. the larger the circles, the more products with this combination of applications and outcome variance. The higher up the y-axis a circle is located, the more applications for the same product with different outcomes. From the graph it can be seen that many products with a differing number of SPC applications do not experience any variance in application outcome.

However, there are also quite a large number of products which experience difference between outcomes across countries for SPC applications for the same product, i.e. in some countries an SPC is granted while in other countries the application is rejected (for the same product). This shows that the fragmentation of the SPC system results in uncertainty for companies as to how many countries an SPC can be obtained in.

Difference in SPC application outcome across countries, 1992-2015



Note: Pending applications excluded, pairs with only one SPC application excluded (81% of distinct pairs), one outlier (37 applications) excluded. Size of circle represents the number of distinct product-patent-pairs at the outcome variance-application number data point. Outcome variance measures the degree to which a pair has been subject to different outcomes in different countries for SPC applications relating to the same patent-product combination.
Source: Alice de Pastors SPC database

3.5 SPCs FOR PLANT PROTECTION PRODUCTS

SPCs for plant protection products are often overlooked (1/3)

THE PLANT PROTECTION REGULATION

The 1996 regulation also introduced supplementary protection for agrochemical products (Regulation No 1610/96 "concerning the creation of a supplementary protection certificate for plant protection products"). The European Commission commonly defines plant protection products as containing "*at least one active substance and hav*[ing] *one of the following functions:*

- *Protect plants or plant products against pests/diseases, before or after harvest*
- *Influence the life processes of plants (such as substances influencing their growth, excluding nutrients)*
- *Preserve plant products*
- *Destroy or prevent growth of undesired plants or parts of plants*

They may also contain other components including safeners and synergists".[1]

Arunasalam & De Corte (2016)[3] provide a legal perspective on the development of the agrochemical SPC since its inception in 1996. In particular, they highlight the differences and commonalities between the different 'SPC-sectors', emphasising the uniqueness of plant protection products (PPP) compared to pharmaceuticals and the resulting regulatory requirements.

As noted by Kyle (2017), there are considerable differences that need to be taken into account when comparing the pharmaceutical sector to the agrochemical sector or just the agrochemical sector in Europe to the agrochemical sector in the US.

These difficulties are further exacerbated by a lack of readily available and accessible data, on both a national and supranational level.

Most court litigation with reference to SPC regulations refers to medicinal products. The resulting rulings have little, if any, bearing on the agrochemical market.

THE PLANT PROTECTION INDUSTRY

The plant protection industry in general is substantially different from the pharmaceutical sector. Most importantly, there is a noticeably higher degree of company concentration in agrochemicals and in corresponding patent ownership[2], i.e. the number of players in the industry is low. Furthermore, the use of combination products in the PPP sector is more prevalent than for the pharmaceutical sector[3].

Interviews conducted with companies active in the development of plant protection products point towards a lower commercial risk rate (or at least a perceived one) for agrochemical products compared with pharmaceuticals. However, the interviews also point towards a risk-portfolio approach to new R&D. In this sense, the risk-mitigating effect of the SPC allows the industry to venture into more risky R&D projects than would otherwise have been the case.

The regulation for plant protection contains no such thing as market protection as is the case for pharmaceuticals. Furthermore, no incentives similar to e.g. those for orphan medicinal products or investigations within the paediatric population exist. Data protection is, however, provided within the agrochemical sector.

PLACEMENT OF R&D

When it comes to the placement of R&D within the agrochemical sector there are certain important factors to be aware of. The research part can be undertaken in a laboratory setting and can, as such, be placed anywhere in the world. The decision of placement will probably be greatly influenced by some of the same factors influencing the placement of R&D in general. These include a well-educated workforce and good infrastructure[4].

For the development part, where testing of the agrochemicals' effects on real crops is undertaken, there are certain restrictions on geographical placement. These restrictions pertain to the geographical region where crops grow and the different climate zones. As such, trials for agrochemicals are restricted to certain geographical areas of the world, depending on the scope of the product.

The above division of R&D means that, within the agrochemical sector, research is probably more flexible in its geographical placement than development is.

1 See the European Commission's webpage on pesticides, https://ec.europa.eu/food/plant/pesticides_en [accessed 2017-08-30].
2 Kyle, M. (2017), Economic Analysis of Supplementary Protection Certificates in Europe.
3 Arunasalam, V-C. & de Corte, F. (2016), Supplementary protection certificates for plant protection products: the story of 'The Ugly Duckling'.
4 See e.g. Demirbag, M. and Glaister, K. W. (2010), Factors Determining Offshore Location Choice for R&D Projects: A Comparative Study of Developed and Emerging Regions.

SPCs for plant protection products are often overlooked (2/3)

DECREASE IN INNOVATION

Since the 1980s, the number of active ingredients introduced into or in development within the agrochemical sector has decreased by a rather significant amount.

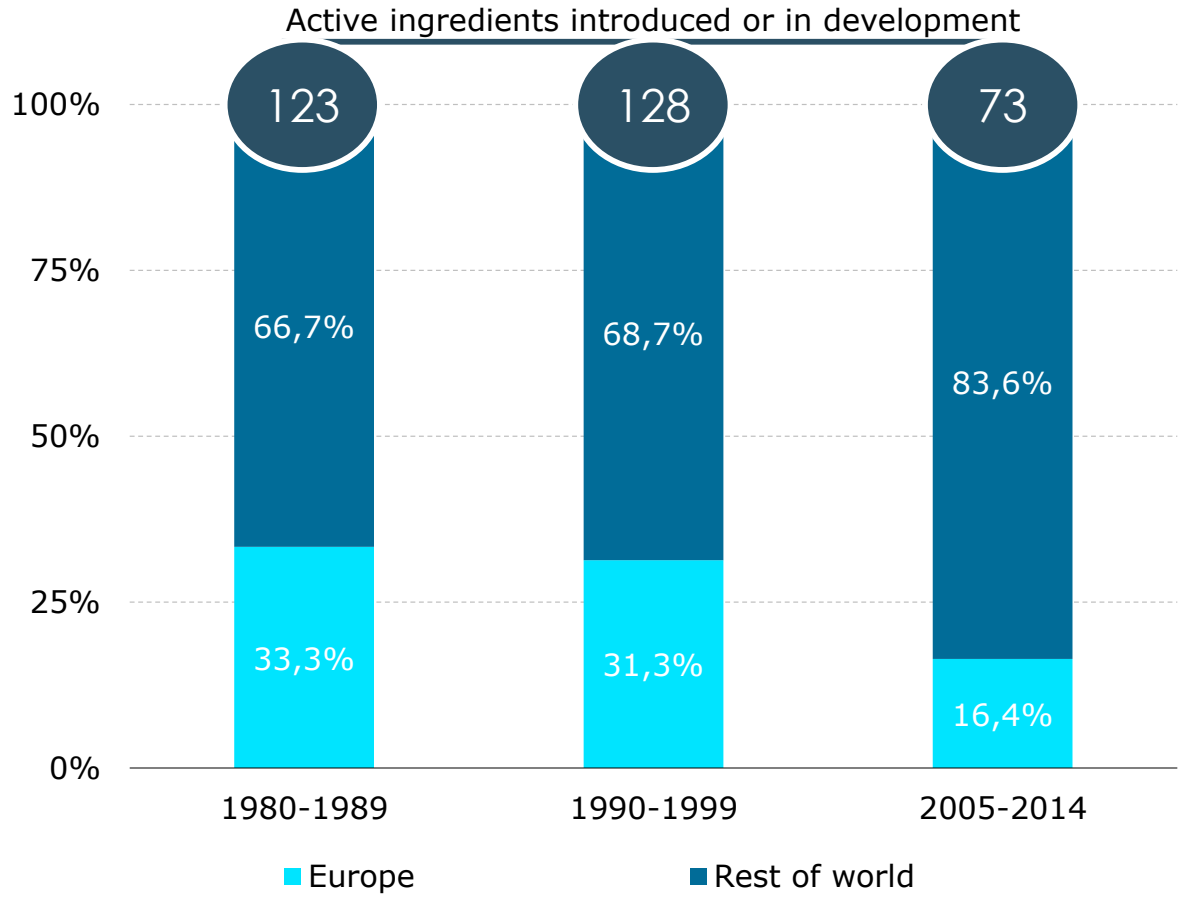
Furthermore, the percentage of new ingredients focused on Europe has likewise fallen. As such, the number of available products for plant protection within Europe seems to have experienced a decreasing rate of innovation.

INCREASE IN R&D COST

The decrease in new innovation could be due in part to the increasing costs of bringing a new active ingredient to the market. In 1995 the average cost was estimated to be USD 152m. In the years 2005-2008, this estimate had increased to USD 256m[1].

The majority of the increase was due to increases in the cost of development. Development mainly covers the trials undertaken to obtain registration. From 1995 to 2005, the research cost of bringing a new active ingredient to the market increased from USD 72m to USD 85m At the same time, development costs rose from USD 67m to USD 146m per active ingredient[2].

Number of active ingredients introduced or in development and distribution between Europe and the rest of the world, 1980-2014



Notes: The number of active ingredients introduced or in development within the agrochemical sector is depicted in the top three circles. The percentage distribution depicts the share of products which are focused on either the European market or the rest of the world.

Source: Arunasalam, V-C. & de Corte, F. (2016), Supplementary protection certificates for plant protection products: the story of 'The Ugly Duckling' and McDougall, P. (2013), R&D trends for chemical crop protection products and the position of the European Market.

1 McDougall, P. (2013), R&D trends for chemical crop protection products and the position of the European Market.
2 The reported numbers are taken from a report commissioned by the European Crop Protection association which is an industry organisation representing the originator industry within agrochemicals. As such, the reader should be aware of the industry affiliation. However, numbers and statistics are hard to come by within the sector and hence all sources must be utilised to obtain a better picture.

SPCs for plant protection products are often overlooked (3/3)

NO BOLAR EXEMPTION

No direct Bolar exemption (or research exemption) exists within the agrochemical sector. This means that it is legally uncertain to what extent generic companies can undertake R&D on originator chemicals in order to develop generic versions prior to patent expiry.

This is as interesting an issue within the agrochemical sector as it was in the pharmaceutical one. If generic companies are unable to undertake development before the expiry of all relevant patents, originator products are in effect protected against generic competition for a longer period than the relevant patents last.

DATA SHARING

The conducted interviews indicated that generic companies within the agrochemical sector cannot refer to originator data created during trials to the same extent as is possible within the pharmaceutical sector.

This means that generic companies have to run trials themselves, to a greater extent than is necessary within the pharmaceutical sector. The direct effect is that generic companies experience higher costs.

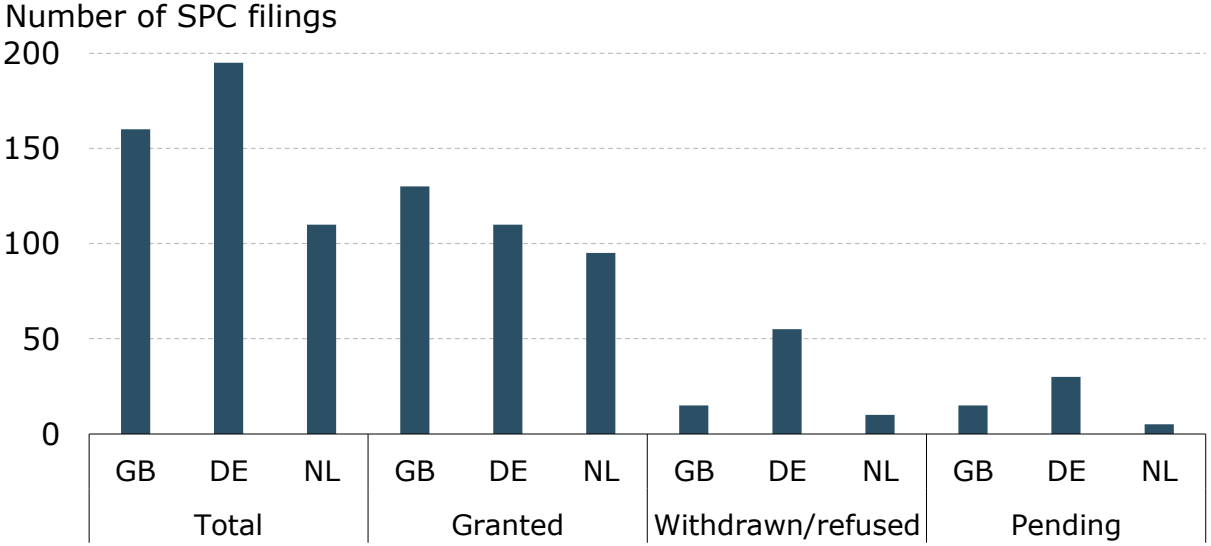
As such, when generic entry takes place in the agrochemicals market, there is a limit to the amount of price pressure generic companies can place on originator products. The higher costs associated with undertaking trials themselves curb the competitive pressure they can bring to the market.

SPC DATA

Data illustrating the usage and impact of SPCs in the plant protection industry is hard to come by. Generally speaking, there is no centralised register and no database comparable to e.g. the Alice de Pastors database for SPCs awarded to pharmaceuticals.

The information below comes from Arunasalam & de Corte (2016)[1] and mainly illustrates that even 20 years on from the introduction of SPCs for plant protection products little information is available, and there seems to be fewer filings generally in the PPP sector than in the pharmaceutical one.

Number of SPC filings within plant protection products for three patent offices between 1997 and 2015



Note: Graph showing the number of SPCs granted, withdrawn/refused and pending for plant protection products in the United Kingdom (GB), Germany (DE) and the Netherlands (NL).
Source: Reproduced from figure 1 in Arunasalam, V-C. & de Corte, F. (2016), Supplementary protection certificates for plant protection products: the story of 'The Ugly Duckling'.

1 Given the authors' industry affiliation, this information is to be evaluated carefully.

CHAPTER 3 APPENDIX

Average effective protection period added by the SPC, when it is the last IPR to expire, excluding secondary patents

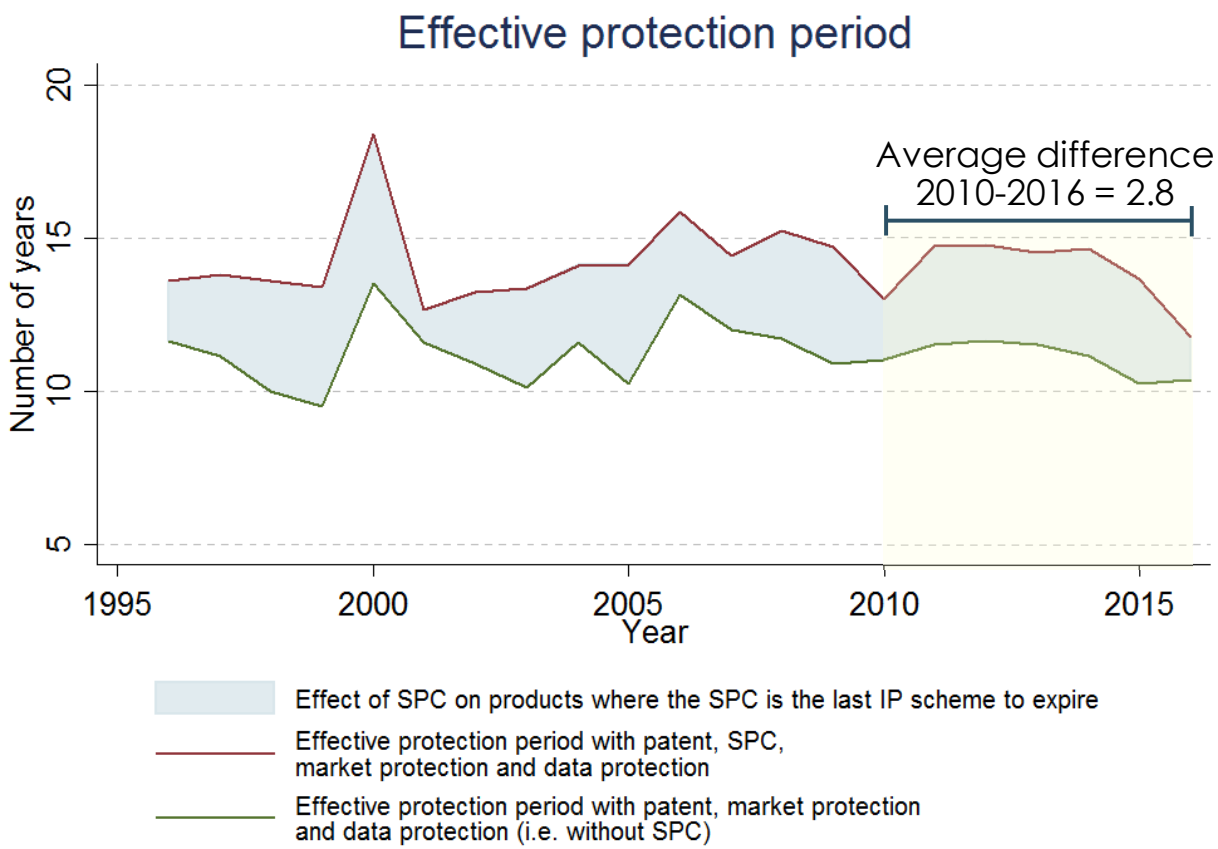
The graph to the right depicts the effect of SPCs on the average effective protection period for products where an SPC is the last IP right to expire, when excluding secondary patents.

The red line depicts the effective protection period if patent, SPC, data protection and market protection are taken into account. The green line depicts what the effective protection period would have been, had there been no SPC for these products where the SPC is last to expire.

In that sense, the difference between the two lines can be understood as the average marginal protection extension conditional on an SPC being the last protection scheme to expire.

In the period 2010-2016 the SPC added on average 2.8 years of protection, to products where the SPC is the last protection to expire, when excluding secondary patents. As seen earlier, this period is 2.6 when secondary patents are included.

Effective protection period for products where an SPC is the last IP scheme to expire, without secondary patents, 1996-2016



Notes: Graph showing the effective protection period based on which protection instruments are used in the calculation. The graph only includes medicinal product-country combinations where an SPC is the last IP scheme to expire. As such, the difference between the lines depicted signifies the average increase in protection for products where SPCs actually extend the protection period. Given that the observation-level is unique medicinal product-country combinations means that a specific medicinal product is used in the calculation of the average as many times as it has an SPC in a member state. Secondary patents are excluded.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

Last protection scheme to expire, when excluding secondary patents

The table to the right reports the last IPR to expire, when secondary patents are excluded from the analysis.

When comparing to the table on p. 185, where secondary patents are included, it is clear that patents less often are the last IPR to expire, when secondary patents are excluded. This is as expected.

When excluding secondary patents, the SPC is the last protection scheme to expire for 78% of the observations, where an SPC has been granted.

When looking at all observations, this number is 13%. This might seem low, but is likely due to the fact that a given product does not necessarily have an SPC in all countries, where it is launched. If e.g. a product is launched in 20 countries, but only has an SPC in 5 of these this means that only 25% of the observations for this product has an SPC. If the SPC is only the last IPR to expire in 3 of the countries where it was granted, this would mean that for this given product, the SPC would be the last IPR to expire in 15% of the observations.

Last protection scheme to expire, when excluding secondary patents, 1996-2016

	Full sample		Observations with granted SPC	
Last IP scheme to expire	N	(%)	N	(%)
Patent	2,691	38	0	0
Supplementary Protection Certificate	920	13	930	78
Market protection*	2,875	40	238	20
Data protection**	644	9	22	2
Total	**7,130**	**100**	**1,190**	**100**

Note: Table showing the last protection scheme to expire for the unique dataset created for the analysis, when secondary patents are excluded from the analysis. The cases where data protection is the last protection scheme to expire are all before enactment of the 8+2(+1) system in 2005, as market protection under this regime is always longer than data protection.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

* Market exclusivity for orphan medicinal products are counted in this category.
** For certain observations before the 2005 changes to the 8+2+1-scheme, data protection is the last IPR to expire.

Copenhagen Economics CE

CHAPTER 4

Effective protection period and individual contributions

Outline of chapter 4

4.1 Impact on effective protection period

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Chapter 4 – Main conclusions

EFFECT OF REGULATORY INCENTIVES ON EFFECTIVE PROTECTION

The effective protection period is calculated as the time elapsed from the date of marketing authorisation until the last protection scheme expires.

Effective protection period
= date of last protection to expire
– date of marketing authorisation

In the period from 2010 to 2016, market protection prolonged the average effective protection period by 2.4 years[1]. For products where market protection is the last protection to expire the average extra period provided by market protection was 4.8 years in the period from 2010 to 2016.

For products where market protection is the last scheme to expire, the one-year extension based on approval for a second indication provides an average increase in the effective protection period close to zero (3.7 days) in the years between 2010 and 2016.

Market exclusivity for orphan medicinal products has on average provided 1.6 extra years of protection to the orphan medicinal products where market exclusivity was the last protection scheme to expire.

The paediatric extension has on average provided close to zero (2.9 days) extra effective protection. This small average difference is mainly due to the fact that only 10% of products have an SPC as the last protection to expire.

INNOVATION

The number of orphan designations granted has increased from 14 in 2000 to 209 in 2016. As the number of orphan medicinal products obtaining marketing authorisation has also increased, this suggests that there has been an increase in innovation within the area.

In the period from 2008 to 2015, 859 paediatric investigation plans (PIP) have been agreed upon and 99 positive PIP compliance checks have been done. This entails quite a large increase in the body of information on medicinal products for paediatric use.

AVAILABILITY

In section 2.2 we did not identify a statistically significant effect of the domestic effective protection period on the probability of product launch. This likewise pertains to the effect of the regulatory incentives, as these essentially in the same manner work to prolong the average effective protection period for medicinal products.

However, it can be seen from the analysis that orphan medicinal products are launched earlier and in more countries than non-orphan medicinal products. Whether this is due to the orphan incentives or e.g. the fact that orphan medicinal products have a smaller patient base and usually higher price in each individual country cannot be determined based on the available data.

An important consideration regarding availability is that in many EU countries central authorities decide whether or not to reimburse new innovative medicinal products. These decisions are often based on a Health Technology Assessment (HTA), where price effectiveness is assessed. As such, there are two formal barriers to entering the markets for medicinal products in European countries. One is obtaining marketing authorisation, e.g. through the centralised procedure and the other is to obtain a positive opinion regarding reimbursement from the national authorities (or insurance agencies).

ACCESSIBILITY

Insofar as the legislative instruments work to postpone the point in time when generic products can enter, the ensuing fall in prices is likewise deferred. As such, at face value the incentives work to contribute to higher prices for medicinal products.

However, in section 2.1 we found that that there was a positive relationship between longer effective protection period in all of the EU and the spending on pharmaceutical R&D. As such, this encourages more originator innovation. As there can be no generics without originator products, in some way the legislative instruments work to make more generics accessible in the future. Furthermore, more innovation increases innovator-on-innovator competition, which is one of the factors driving down prices before generic entry.

1 Calculated as the difference between the average effective protection period with all protection schemes and what the average effective protection period would have been, had market protection not existed.

4.1 IMPACT ON EFFECTIVE PROTECTION PERIOD

4.1.1 DATA PROTECTION AND MARKET PROTECTION

Summary of protection from market protection and data protection

INTERPLAY BETWEEN INCENTIVES

Market protection and data protection are regulatory protection periods, running from the granting of marketing authorisation[1].

Data protection protects the data that a pharmaceutical company has produced in preclinical and clinical trials from use by other pharmaceutical companies in submitting an application for marketing authorisation[1]. Submitting the data to the authorities is a prerequisite for obtaining marketing authorisation.

Market protection ensures that during this period a generic product cannot be placed on the market[1].

Data protection runs for 8 years. After this period, generic companies can submit an application for marketing authorisation, referring to the data submitted by the originator company. However, market protection runs for 10 years, meaning that the generic medicinal product cannot be placed on the market for another two years. The gap of two years from expiry of data protection until expiry of market protection allows generic companies to obtain marketing authorisation before market entry is possible, potentially allowing them to enter the market from the day market protection expires.

If a new innovative product is approved for a new indication within the 8 years of data protection, an additional year of market protection is added to its total protection. This means that in total a product can obtain regulatory protection for 8 years of data protection, two additional years market protection with the possibility of extending this by another year. This yields what is often called the 8+2+1 system.

The regulatory protection conveyed by market protection and data protection is overseen by the appropriate authorities. In the case of centrally approved products in the EU, this is the European Medicines Agency and the European Commission.

Market protection and data protection run in parallel to any patent and SPC protection. As market protection and data protection are regulatory protection periods granted by the authorities, they cannot, like a patent or an SPC, be invalidated by a court of law[2]. However, a court of law may declare data and/or market protection initially granted to a medicinal product, as a result of a marketing authorisation decision, to be inapplicable or unenforceable depending on the specific circumstances of the case.

COMPETITION

Should no patent or SPC be protecting the active ingredient of a product, another company can enter the market with a product containing the same active ingredient, even though the product of the first company enjoys data protection and/or market protection.

This can happen if the second company is willing to undertake their own clinical trials, building their own proprietary dossier for regulatory approval, instead of referring to the data produced by the originator company.

As such, this shows one of the key differences between IP rights and regulatory protection.

MINIMUM PROTECTION PERIOD

Patents, SPCs, market protection and data protection have different durations and run from different points in time. As such, depending on when a marketing authorisation for a medicinal product is obtained, any one of these protection schemes might be the last scheme to expire.

A standard patent is valid for 20 years. An SPC can extend the protection period by a maximum of five years. Before 2005, data protection lasted for 6 years in some EU countries and 10 in others for nationally authorised products[3]. After 20 November 2005 the 8+2+1 scheme came into effect[4].

Even though patents and SPCs have expired, a new innovative medicinal product will always enjoy at least 8 years of data protection followed by two additional years of market protection, possibly extended by one year. This means that there is effectively a 'floor' of 10 years of effective protection period for new innovative pharmaceuticals being granted market authorisation in the EU.

1 Directive 2001/83/EC, Article 10(1).
2 Regulation (EC) No 726/2004.
3 For centrally approved products the protection period was 10 years before 2005 as well.
4 Regulation (EC) No 726/2004, Article 90.

Effect of data protection and market protection across all medicinal products (1/2)

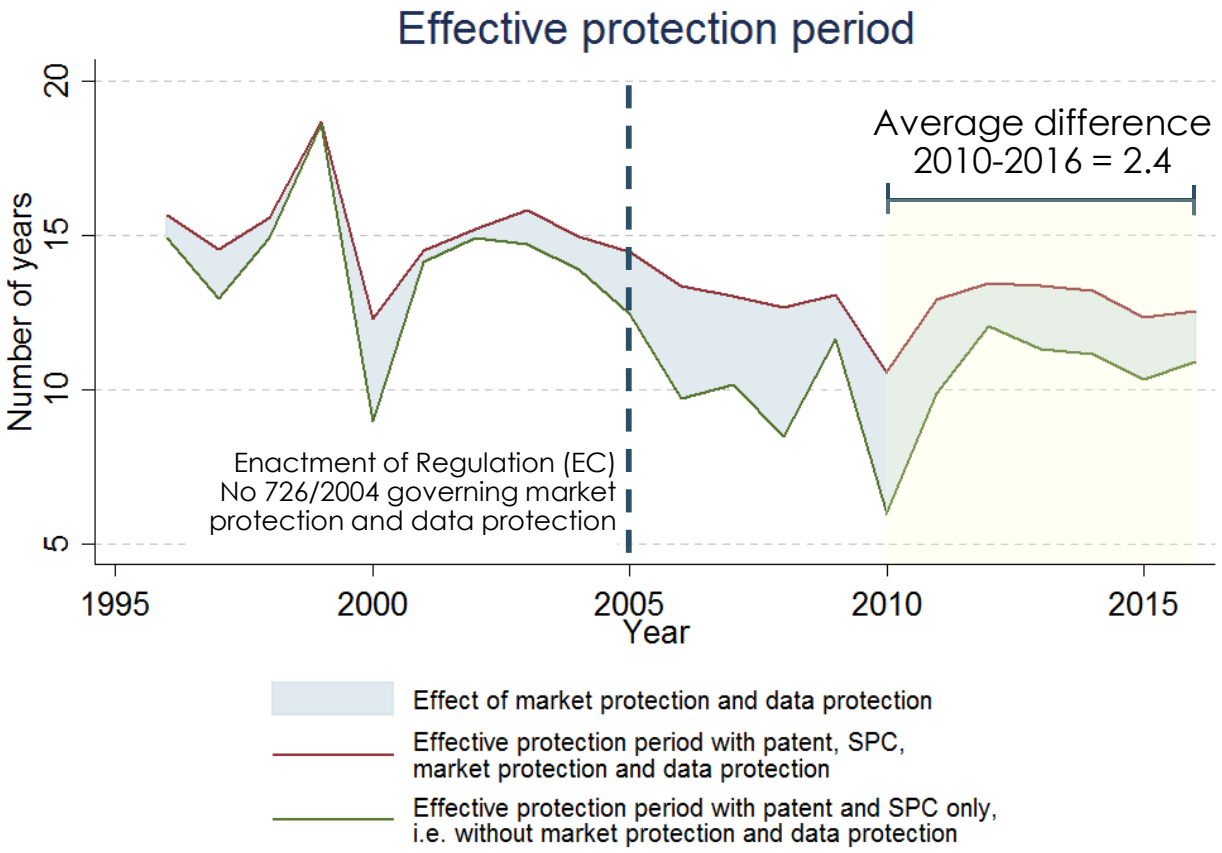
The graph to the right shows the difference between the effective protection period with and without market protection and data protection, for all products in this study[1]. As such, the graph compares the current legislative situation with a counterfactual one, where regulatory market protection and data protection did not exist[2].

In the unique dataset created for this study, a product is identified based on trade name. Each product has an observation for each country in which it has obtained a marketing authorisation. This means that if a product is centrally approved, it will have one observation for each EU member state. The reason for this is that the number of patents and hence the protection periods granted by these might differ from one country to the next. Furthermore, SPCs are also granted at the national level, and as such the existence of these might differ from country to country.

In recent years, the regulatory market protection and data protection have added an average of approximately 2.4 years of effective protection period to the pharmaceuticals in the sample.

Since 2005, market protection sets a floor of at least 10 years of effective protection period for new innovative pharmaceuticals in the European member states, regardless of authorisation procedure[3]. Before 2005, the minimum protection period of 10 years was already provided for centrally approved products[4].

Effective protection period with and without market protection and data protection for all products, 1996-2016



Notes: Graph showing the effective protection period based on two scenarios. The graph includes all medicinal products observed in the sample. The difference between the lines signifies the average effect on the effective protection period for all products as an effect of market protection and data protection. In the sample, a medicinal product is observed as many times at it has a marketing authorisation in a member state. Medicinal products with a negative development time are excluded from the graph.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI

1 For an in-depth review of how the unique dataset is constructed, please refer to the appendix for chapter 1.
2 Behavioural changes by the agents as an effect of the change in the counterfactual scenario have not been taken into account.
3 Regulation (EC) 746/2004, Article 14(11).
4 Regulation (EEC) No 2309/1993, Article 13(4).

Effect of data protection and market protection across all medicinal products (2/2)

Comparing the period before 2005 with the period after, it can be seen from the graph on the previous page that the extra protection period provided by data protection and market protection has had an increasing importance.

From 1996 to 2005, the average extra protection gained from data protection and market protection was 1.6 years. This increased to 2.6 years in the period 2006-2016.

A comparison with the development time graph depicted in section 1.4.2 shows that the development time seems to increase from one level before 2005 to another higher level after 2005.

As such, it seems that the minimum protection period of 10 years granted by market protection after 2005 has made this type of protection more important to pharmaceutical companies, since it ensures a certain level of protection.

Furthermore, the fact that market protection ensures a certain 'protection floor' through a minimum protection period, means that the regulation governing this scheme contributes to curtail some of the uncertainty and risk pharmaceutical companies face when developing new medicinal products. The minimum of 10 years of market protection ensures that no matter how many problems and issues a company encounters in the R&D process, potentially delaying market entry, the product can never have less than 10 years of market protection.

Effective protection from data protection and market protection when one of these is the last protection to expire

While the graph on p. 256 looked at the effect of data protection and market protection on the effective protection period for all products, the graph to the right shows the isolated marginal effect for medicinal products where data protection or market protection is the last to expire.

In recent years, having regulatory market protection has provided 4.8 years of extra protection for the sub sample of medicinal products where this scheme is the last to expire. As such, for these products this protection incentive increases the effective protection period substantially.

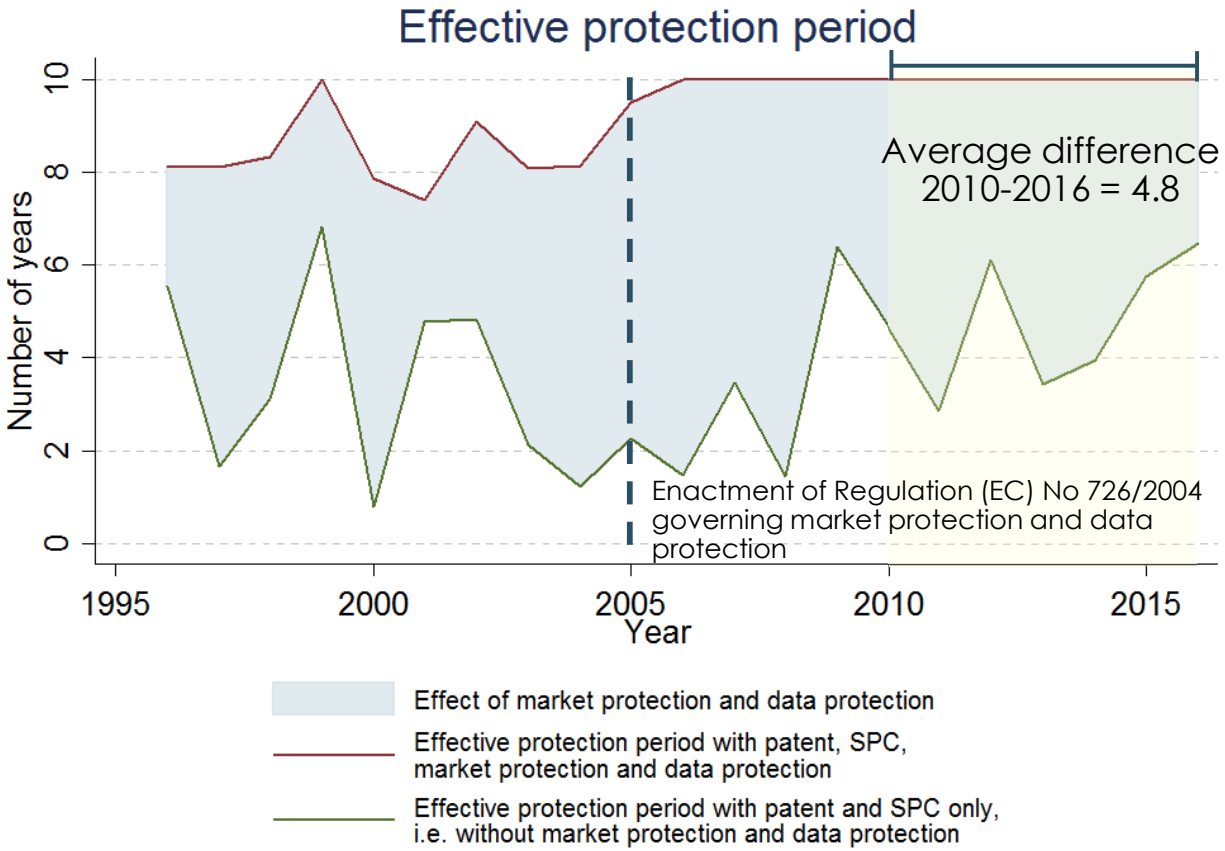
In the graph, the 'floor' of minimum 10 years of effective protection period provided by market protection after 2005 is readily apparent.

Before 2005, some member states provided 6 years of data protection, while others provided 10 years.

Data protection is the last protection to expire in 7% of all cases[1], while market protection is the last to expire in 32% of all cases. This means that in 39% of all cases in the sample either data protection or market protection is the last protection to expire.

The fact that data protection and market protection are the last protection schemes to expire in 39% of all cases, while extending the effective protection period by on average 4.8 years for these products, signifies that these protection schemes are rather important for pharmaceutical companies[2]. Furthermore, the 'floor' of at least 10 years of protection helps mitigate some of the ex ante risk regarding the duration of the protection period pharmaceutical companies face when making their development decisions.

Effective protection period with and without market protection and data protection for products where market protection or data protection is the last IP protection to expire, 1996-2016



Notes: Graph showing the effective protection period based on two scenarios. The graph only includes medicinal products where market protection or data protection is the last protection scheme to expire. The difference between the lines signifies the average effect on the effective protection period for products where market protection or data protection is the last to expire. In the sample a medicinal product is observed as many times at it has a marketing authorisation in a member state. Medicinal products with a negative development time are excluded from the graph.

Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 Data protection can only be the last protection to expire before Regulation (EC) No 726/2004 was enacted in November of 2005.

2 In the case studies included in chapter 5, SPC or patent is the last form of protection to expire for most products. However, the products included in the case studies are not randomly chosen, and there might be some selection as to which products have e.g. secondary patents. It is e.g. conceivable that companies are more willing to spend time and resources applying for secondary patents and SPCs the more profitable a given product is. As chapter 5 contains e.g. blockbusters, this might at least partly explain the fact that all cases have a patent or SPC as the last protection to expire.

The one-year extension of market protection based on approval for a second indication only extends the effective protection period for a few products

If a product which has obtained marketing authorisation is authorised for a second indication within the 8-year period of data protection and provides significant clinical benefit to the patients suffering from this condition, the parallel 10-year market protection period can be extended by one additional year.

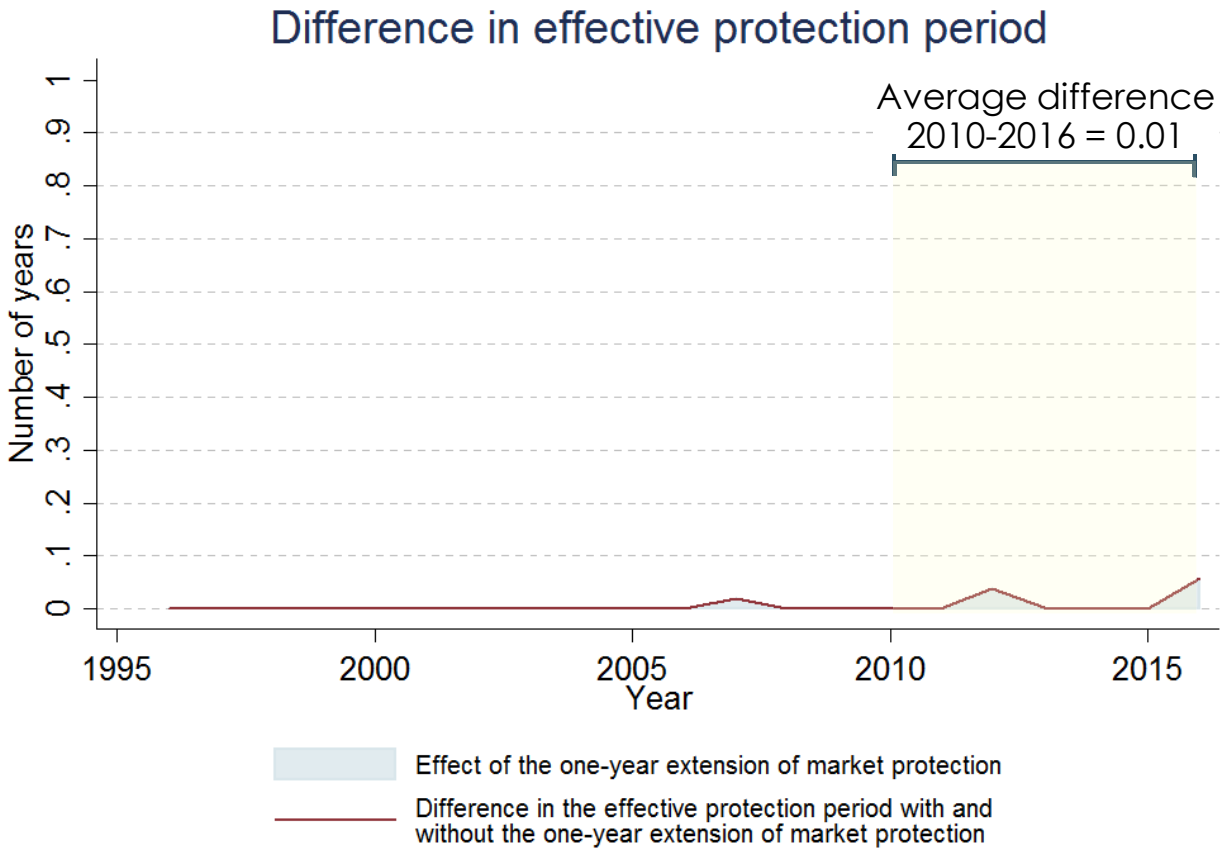
The graph to the right shows the effect of the one-year extension of market protection for products where market protection is the last protection scheme to expire.

The one-year extension only extends the effective protection period in 12% of the instances in which it is granted. For the remaining 88% of products having obtained the extension, an SPC or patent expires at a later point in time. As such, the average effect of the one-year extension for products where data protection or market protection is the last to expire is limited.

The average of 0.01 year by which the incentive extends the effective protection period for products where market protection is the last to expire corresponds to 3.7 days.

Overall, 31 products have obtained the one-year extension.

Average increase in effective protection period through the one-year extension of market protection for products where market protection is the last to expire, 1996-2016



Notes: Graph showing the difference in effective protection period with and without the one-year extension of market protection for all medicinal products where market protection is the last protection scheme to expire. In the sample, a medicinal product is observed as many times at it has a marketing authorisation in a member state. Medicinal products with a negative development time are excluded from the graph.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

4.1.2 ORPHAN INCENTIVES

Summary of protection and other benefits from the orphan designation

ORPHAN DESIGNATION

At any time during the development process when pharmaceutical companies believe that a product under development can be used to treat a rare disease and they can present enough data to support this, they can apply for an orphan designation with the EMA.

If a medicinal product obtains an orphan designation and retains it through the marketing authorisation procedure, the product can be placed on the market as an orphan medicinal product.

Both before and after a marketing authorisation has been granted, a medicinal product having obtained an orphan designation enjoys a range of incentives.

ORPHAN INCENTIVES

Before marketing authorisation, a range of incentives have been put in place to encourage the development of medicinal products for treating rare diseases.

Obtaining an orphan designation is free of charge. Furthermore, protocol assistance can be obtained from the agency during the development process. Such protocol assistance involves scientific advice on how to conduct the tests and trials required to demonstrate quality, safety and efficacy in a satisfactory way[1].

There is a 40% fee reduction on the marketing authorisation application, and for SMEs it is free of charge. For paediatric products it is also free[2].

For SMEs, there is a 90% fee reduction for post-authorisation inspections, while pre-authorisation inspections are free of charge. Annual fees during the first year after marketing authorisation are also free for SMEs[2].

Besides these incentives, special research grants are available from the European Commission directly aimed at orphan medicinal products[3]. In many member states, various national incentives are also present[4].

Hence, the orphan regulation contains more incentives than just the obtained protection period which also influences the attractiveness of developing orphan medicinal products.

After marketing authorisation, an orphan medicinal product enjoys 10 years of market exclusivity, with the possibility of a 2-year extension of this if a paediatric investigation plan is completed.

MARKET EXCLUSIVITY

During the period of market exclusivity "*...the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.*"[5] This effectively means that during this period no other similar product can be placed on the market treating the same indication.

However, the regulation also states that "*a marketing authorisation may be granted for the same therapeutic indication, to a similar medicinal product if: (a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or (b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or (c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.*"[3] This effectively means that if another company can show that their product for treating the same rare condition is clinically superior and brings significant benefit to patients, it can be placed on the market even during the period of market exclusivity[6].

As such, market exclusivity protects against competition from generic companies and other originator companies with similar medicinal products that do not provide additional value to patients. It does, however, not protect against competition by innovation.

From an economic viewpoint, the protection granted by market exclusivity might spur further innovation as this is effectively the only way to enter the market during the 10 years where another orphan medicinal product has market exclusivity. As such, spending time developing a similar medicinal product will yield no return, while developing a new and innovative and better medicine will.

1 European Commission (2015), Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products. For SMEs the protocol assistance is free of charge.
2 See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp [last accessed: 30/01-2018]
3 See European Commission website on rare diseases: http://ec.europa.eu/research/health/index.cfm?pg=area&areaname=rare [last accessed 30/01-2018]
4 Giannuzzi, V., Conte, R., Landi, A., Ottomano, S. A., Bonifazi, D., Baiardi, P., Bonifazi, F. and Ceci, A. (2017), Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: and increased common effort is to be foreseen.
5 Regulation (EC) No 141/2000, Article 8(1)
6 See e.g. the case study on Tobi Podhaler in chapter 5 for examples of this.

The Committee on Orphan Medicinal Products evaluates all applications for orphan designation in the EU (1/2)

A frequently discussed issue when it comes to orphan medicinal products is the so-called *salami-slicing* of indications.

HOW SALAMI-SLICING OF INDICATIONS WORKS

Over time, research into diseases has helped the medical community to obtain a more thorough understanding of these. Sometimes research has revealed that what was commonly understood as one disease actually consisted of several subgroups at a more granular level. These subgroups might be very similar and the differences between them almost indiscernible. However, the subgroups may also be very different[1].

The issue of salami-slicing of indications arises in cases where the original disease is a non-orphan indication. However, when looking at the subgroups, some (or all) of these would by themselves qualify as orphan indications through the prevalence criteria. If it is possible for a company to obtain an orphan designation based on a new medicinal product being able to treat one of these subgroups, it can obtain all the benefits associated with having an orphan designation. If, at a later point the company seeks marketing authorisation for the whole indication, it will have undertaken what is known as salami-slicing. The issue is that through slicing the indication into subgroups, the company could obtain an orphan designation for a medicinal product which was actually not an orphan medicinal product.

DESIGNATION IS UNDERTAKEN BY THE AUTHORITIES

In the EU, all applications for designation as an orphan medicinal product are submitted to the Committee for Orphan Medicinal Products (COMP), which is a part of the European Medicines Agency.

Upon having reviewed the application, the COMP issues an opinion to the European Commission, which is responsible for granting the orphan designations.

As such, the COMP is responsible for assessing whether a submitted application for orphan designation lives up to the criteria set forth by the orphan regulation[2]. If an application for an orphan designation based on a subset of a non-orphan indication is submitted, the COMP must evaluate whether the available evidence makes it plausible that the product can only treat this subset of the indication and not be used for the overall disease and whether this enables it to obtain an orphan designation.

In this sense, the COMP acts as a safeguard against salami-slicing of indications in the EU.

MITIGATING RISK

Not to be confused with salami-slicing of indications is the fact that an orphan medicinal product may be approved for treating several distinct rare diseases. This can e.g. happen if an orphan medicinal product was first developed for treating one condition but at a later time can be shown to be effective in treating another condition as well.

The fact that an orphan medicinal product can be used to treat several orphan designations is good for the patients concerned, who may not otherwise have been able to seek treatment. It also increases the profitability prospect of the product from the company's viewpoint.

However, as the R&D processes of medicinal products are long and risky[3], knowing whether a given medicinal product developed for treating one disease can also be used to treat other diseases might not become evident until after the development phase.

This means that a company might develop a medicinal product on the assumption that it can only be used for treating one orphan indication. This might mean that without the orphan incentives the ex ante business case for developing the medicinal product is negative. However, after having developed the medicinal product and after discovering that it can be used for more than one indication, the ex post business case might be positive, even without the orphan incentives. The point is that at least in this theoretical case the company cannot know this until after development.

As a result, the orphan regulation helps mitigate some of the risk faced by companies when developing medicines with the prospect of having a narrow patient base.

1 https://www.christenseninstitute.org/blog/salami-slicing-precision-medicine-orphan-drug-act/
2 Regulation (EC) No 141/2000.
3 See section 1.4.2.

The Committee on Orphan Medicinal Products evaluates all applications for orphan designation in the EU (2/2)

It might, however, also be the case that the orphan regulation 'overcompensates' the pharmaceutical companies for developing orphan medicinal products for more indications after first approval[1].

After the first approval, many of the R&D costs have been defrayed, and hence development for further indications is likely to be less expensive than for the first indication.

Further approval will, however, often imply more clinical trials, which can constitute a large expense. As such, if the business case for undertaking clinical trials and documenting the product's safety and efficacy in treating another indication constitutes a positive business case, even without the orphan incentives, the incentives can be said to 'overcompensate' companies.

The orphan regulation includes a provision whereby the member states can have the EMA initiate a review into whether an orphan medicinal product still lives up the requirements on which its status was granted[2].

This means that if the designation was granted based on the prevalence criteria, changes in the number of patients affected by the disease might warrant a review. In cases where the designation is granted on the criteria of the company not being able to obtain a sufficient return on investment without designation, an unforeseen high profit from the product can warrant a review.

However, in the case where a designation is granted based on the prevalence criteria, which all orphan designations currently are, there is no possibility of initiating a review based on whether the product has turned out to provide the company with a profit amounting to evidence of 'overcompensation'[3].

As such, if a product can be used to treat several rare diseases and hence possibly provide the company with a return on investment much larger than expected, this is not taken into consideration if designations for more orphan indications for said product are processed by the EMA and these are based on the prevalence criteria.

However, without further insights into the R&D costs of the companies, determining whether 'overcompensation' takes place in certain cases is rather difficult.

1 Here, 'overcompensation' means that the development of the medicinal product for more indications constitutes a positive business case even without the orphan incentives.
2 Regulation (EC) No 141/2000, Article 8(2).
3 Input provided by the European Medicines Agency.

Market exclusivity increases the average effective protection period for orphan medicinal products by 1.6 years at the margin

The graph to the right shows the marginal effect of market exclusivity on the effective protection period of orphan medicinal products where market exclusivity is the last protection to expire[1].

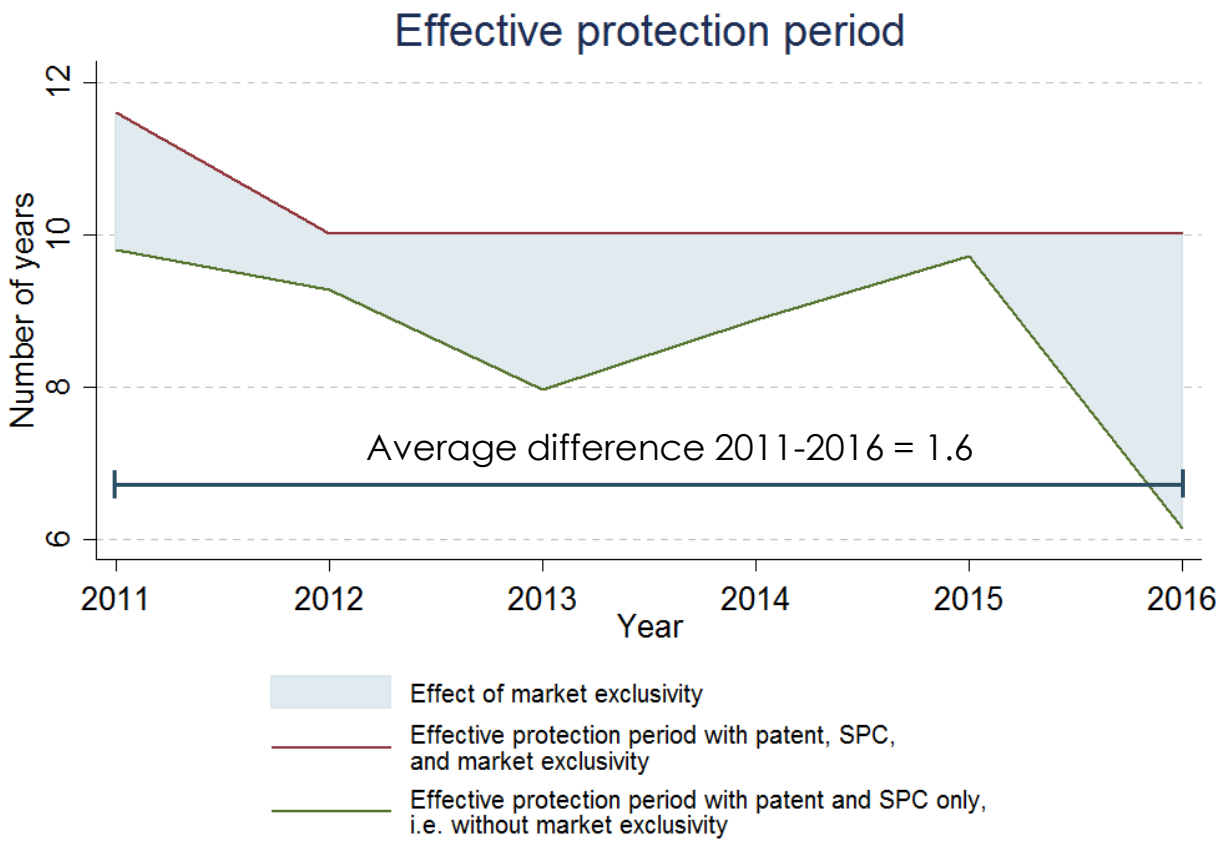
From the graph it can be seen that some of the products depicted in 2011 have obtained the paediatric reward of two additional years of market exclusivity. In the other years none of the products have obtained the paediatric reward.

As the number of observations is limited, the fluctuations in the effective protection period are more pronounced.

Out of all the orphan medicinal product-country observations present in the sample, 12.9% have market exclusivity as the last protection period to expire, i.e. after patent and data protection. As such, it seems that for orphan medicinal products, patent and SPC are on average the most important instruments for granting the effective protection period they currently have. As can also be seen from the graph to the right, for orphan medicinal products, the possibility of having an average minimum protection period of 10 years means an average increase in the effective protection period of 1.6 years compared to a situation without market exclusivity.

For orphan medicinal products it is, however, also important to remember that the designation and marketing authorisation bring more benefits than the effective protection period conveyed by regular data protection and market protection.

Effective protection period for orphan medicinal products where market exclusivity is the last form of protection to expire, 2011-2016



Notes: Graph showing the effective protection period based on two scenarios. The graph only includes orphan medicinal products where market protection or data protection is the last protection scheme to expire. The difference between the lines signifies the average effect on the effective protection period for orphan medicinal products where market protection or data protection is the last to expire. In the sample, a medicinal product is observed as many times at it has a marketing authorisation in a member state. Medicinal products with a negative development time are excluded from the graph.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI

1 As there is a limited number of orphan medicinal products in Europe, an effect of this is that the number of observations on average is 6 per year, and the graph only includes the years 2011-2016.

4.1.3 PAEDIATRIC INCENTIVES

Summary of paediatric obligations and rewards

PAEDIATRIC REGULATION

The regulation governing the current obligations and rewards for medicinal products for paediatric use was implemented in 2007[1].

The regulation "*aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations.*"[2]

To achieve the above, several so-called rewards for undertaking paediatric studies exist.

OBLIGATION AND REWARD

The incentives for undertaking paediatric studies are based on an obligation and a reward for meeting said obligation. The obligation is to comply with a paediatric investigation plan (PIP), agreed upon by the EMA on the basis of the European Medicines Agency's Paediatric Committee (PDCO) opinion. The reward is an extension of a protection scheme, once the PIP has been completed in compliance with the latest decision and further requirements are fulfilled (e.g. results reflected in the Summary of Product Characteristics (SmPC), product authorised in all member states). All applications for marketing authorisation for new medicinal products must include results from a PIP unless a deferral or waiver has been granted. The same is true when a holder of a marketing authorisation wants to apply for adding a new indication, pharmaceutical form or route of administration for an already authorised medicine which is protected by IP rights[3]. Decisions on PIPs are made by the EMA.

If a medicinal product has an SPC and compliance with a PIP is approved, a 6-month extension of the SPC enters into effect[4]. Because of this extension, which can only be obtained if the product has an SPC, it can make sense for the company to apply for an SPC even though the formal duration period calculated is negative.

In a court ruling, it has been established that the award of an SPC with a negative duration is possible[5]. This will be attractive to companies when a paediatric extension of the SPC will make the total SPC period positive. If the calculated duration of an SPC e.g. is negative by 2 months, but a paediatric extension is awarded, the total duration of the SPC will be a positive 4 months.

If the product in question is an orphan medicinal product and it complies with a PIP, a 2-year extension of market exclusivity is granted, instead of the 6-month extension of the SPC[6]. The extension of market exclusivity is granted even though the product has an SPC which expires at a later date than market exclusivity including the extension. In this case, an extension of the SPC would provide more of an incentive for the company as this would increase the effective protection period[7]. The fact that it is not possible to choose to extend the SPC rather than the market exclusivity for a pharmaceutical with an orphan designation might create an unintended motivation for companies to waive their orphan designation to obtain the extension of the SPC instead[8]. It should also be noted that the regulation is designed in such a way that these two incentives cannot be cumulated[6].

Besides the two incentives for medicinal products with an SPC and orphan medicinal products, there is a third paediatric incentive for developing well-known substances for the paediatric population. This is known as the so-called paediatric use marketing authorisation (PUMA).

For a product to fulfil the PUMA requirements, it must be 1) already authorised, 2) no longer covered by an SPC or a patent 3) to be developed exclusively for use in children. As such, this incentive is aimed at already known treatments which need developing further for use in children. If a PUMA is granted, the product enjoys 8 years of data protection and a parallel period of 10 years of market protection[9].

Besides the above extensions of protection periods, applicants can request scientific advice from the EMA on a PIP, which is free of charge for questions relating to the development of paediatric medicines.

1 Regulation (EC) No 1901/2006 became effective in January 2007.
2 Regulation (EC) No 1901/2006 (4).
3 Regulation 1901/2006, Article 8.
4 Regulation (EC) No 1901/2006, Article 36(1).
5 See e.g. Merck - Case C 125/10.
6 Regulation (EC) No 1901/2006, Article 37.
7 Technopolis group, Ecorys and Empirica for DG SANTE (2016), Study on the Economic Impact of the Paediatric Regulation, Including its Rewards and Incentives.
8 See e.g. case studies on Glivec and Tracleer in chapter 5.
9 Regulation 1901/2006, Articles 30, 31 and 38. Only three products have been authorised using this procedure. See e.g. case study on Bucculam in chapter 5.

Marginal effective protection gained from the paediatric reward of 6-month extension of the SPC for products where an SPC is the last form of protection to expire

The graph to the right depicts the effect of the 6-month paediatric extension of the effective protection period for products where an SPC is the last protection scheme to expire.

In the graph, the red line depicts the difference in the average effective protection period for products where an SPC is the last protection to expire, between including and excluding the 6-month paediatric extension.

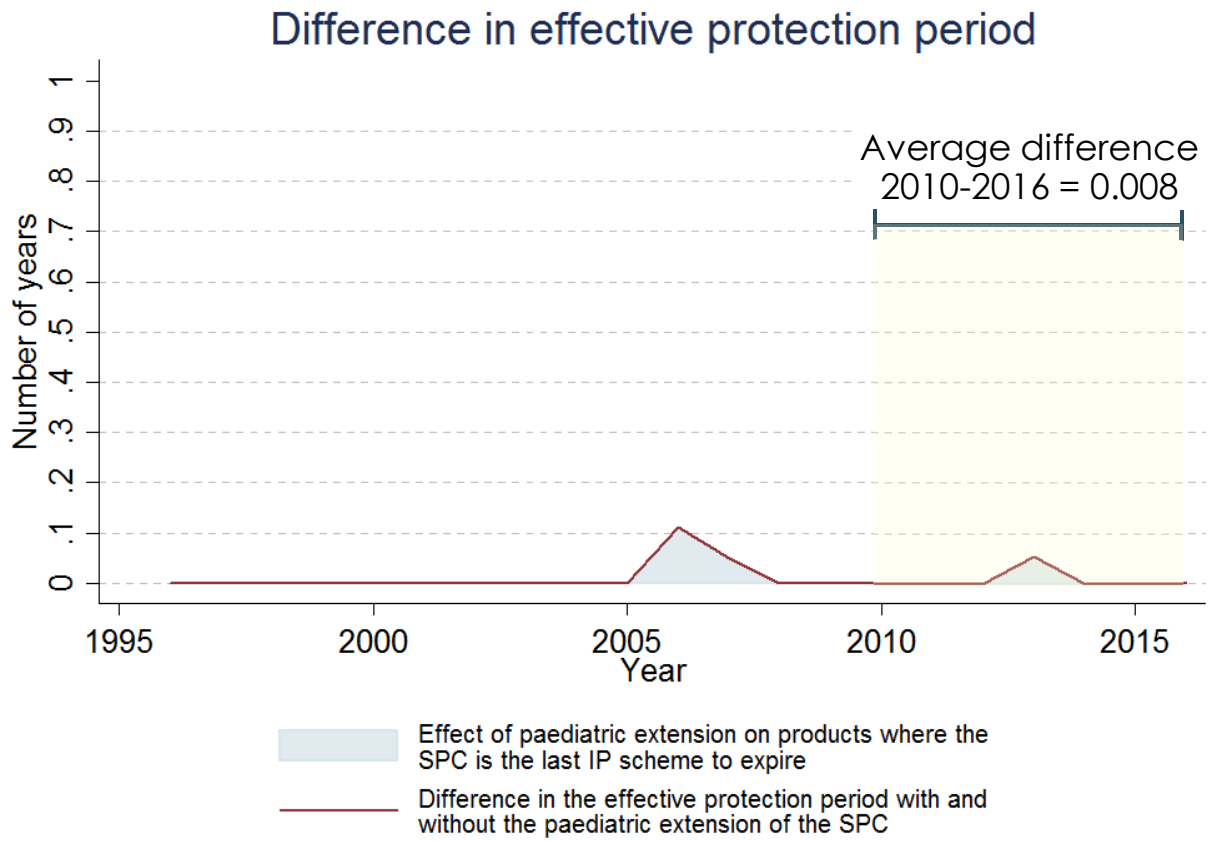
For some products having obtained the 6-month extension, another protection scheme expires at a later point in time. This is the reason for the effect depicted in the graph being less than half a year.

The paediatric extension of the SPC has a limited effect on the average effective protection period for all products where an SPC is the last protection scheme to expire.

Out of all the products where an SPC is the last protection to expire, 5.1% have a positive PIP compliance check. However, in many cases the positive PIP compliance check fell later than 2 years before expiry of the SPC. For these products, an application for a paediatric extension of the SPC is void[1].

The timing issue described above means that out of all products for which the SPC is the last protection scheme to expire, only 4.1% have had the possibility of applying for the paediatric extension[2] even though 5.1% have a positive PIP compliance check. As such, when studying the average effect of the paediatric extension on all products where an SPC is the last protection scheme to expire, the difference depicted in the graph to the right will naturally be small.

Effective protection period with and without the 6-month paediatric extension of the SPC for products where the SPC is the last form of protection to expire, 1996-2016



Notes: Graph showing the difference in effective protection period based on two scenarios. The graph only includes medicinal products where the SPC is the last protection to expire , excluding orphan medicinal products as these cannot obtain the 6-month extension of the SPC. The difference between the lines signifies the average effect of the 6-month extension of the SPC due to paediatric studies on the effective protection period for products where an SPC is the last protection to expire. In the sample, a medicinal product is observed as many times at it has a marketing authorisation in a member state. The calculation of the protection period without the paediatric reward is based on the assumption that all products with an SPC and a positive PIP compliance check dated at least 2 years prior to expiry of the SPC have received the 6-month extension. This is expected to be a good assumption as obtaining the extension is in the interest of the companies, which only need to file the application in due time. Medicinal products with a negative development time and orphan medicinal products are excluded from the graph.

Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 Regulation 1901/2006, Article 52 (2) 4.

2 This is excluding orphan medicinal products as the paediatric reward for these is a two year extension of the market exclusivity period.

The effective protection period could have been increased for some products if a positive PIP compliance check had been obtained earlier

Out of all products in the full dataset, 5.5% have a positive PIP compliance check. This means that for 5.5% of all products, a company has undertaken a paediatric investigation plan, and compliance with the plan has been approved by the competent authorities[1]. When looking only at products where an SPC is the last protection to expire, 5.1% of these have a positive PIP compliance check.

However, for a company to be able to obtain the reward of a 6-month extension of the SPC as a reward for undertaking paediatric studies, the application must be submitted more than two years prior to the expiry of the SPC. Companies obtaining a positive PIP compliance check later than two years before expiry of the SPC cannot apply for an extension.

For all products where the SPC is the last protection scheme to expire, 4.1% have a positive PIP compliance check earlier than two years prior to the expiry of the SPC[2]. However, 1% of the products for which an SPC is the last scheme to expire have obtained a positive PIP compliance check later than two years before expiry of the SPC. The effective protection period for these products would have been increased by an extension of the SPC. They have also lived up to their obligation to undertake studies in the paediatric population. However, the compliance check of the study was obtained too late to apply for the reward.

In many cases, PIPs are modified one or more times. In 43% of all modifications, the agreed timeline is changed[3]. Hence it seems that unanticipated delay is not unusual.

In the dataset it is not possible to identify why a given PIP compliance check is obtained later than two years before the expiry of the SPC.

The distribution of positive paediatric investigation plan checks

	Full dataset	Products where an SPC is the last protection to expire
Positive PIP compliance check	5.5%	5.1%
– Positive PIP compliance check earlier than two years before expiry of SPC	n/a	4.1%
– Positive PIP compliance check later than two years before expiry of SPC	n/a	1.0%

Note: Table showing the distribution of positive paediatric investigation plan checks. Figures shown pertain to the full unique dataset and the sub-sample of products where an SPC is the last protection to expire.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 EMA and/or the Paediatric Committee (PDCO) for centrally approved products, otherwise the competent national authorities.
2 It should be noted that a PDCO compliance check is not sufficient to obtain reward, and the EMA compliance statement following the completion of the respective procedure is needed to claim the reward.
3 Technopolis group, Ecorys and Empirica for DG SANTE (2016), Study on the Economic Impact of the Paediatric Regulation, Including its Rewards and Incentives.

Marginal effective protection from the paediatric reward of 6-month extension of the SPC for products with a positive paediatric investigation plan compliance check

The graph to the right depicts the effect of the 6-month paediatric extension on the effective protection period for products with a positive PIP compliance check, excluding orphan medicinal products. The difference compared to the graph on p. 271 is that it depicted the marginal effect for products where the SPC was the last form of protection to expire.

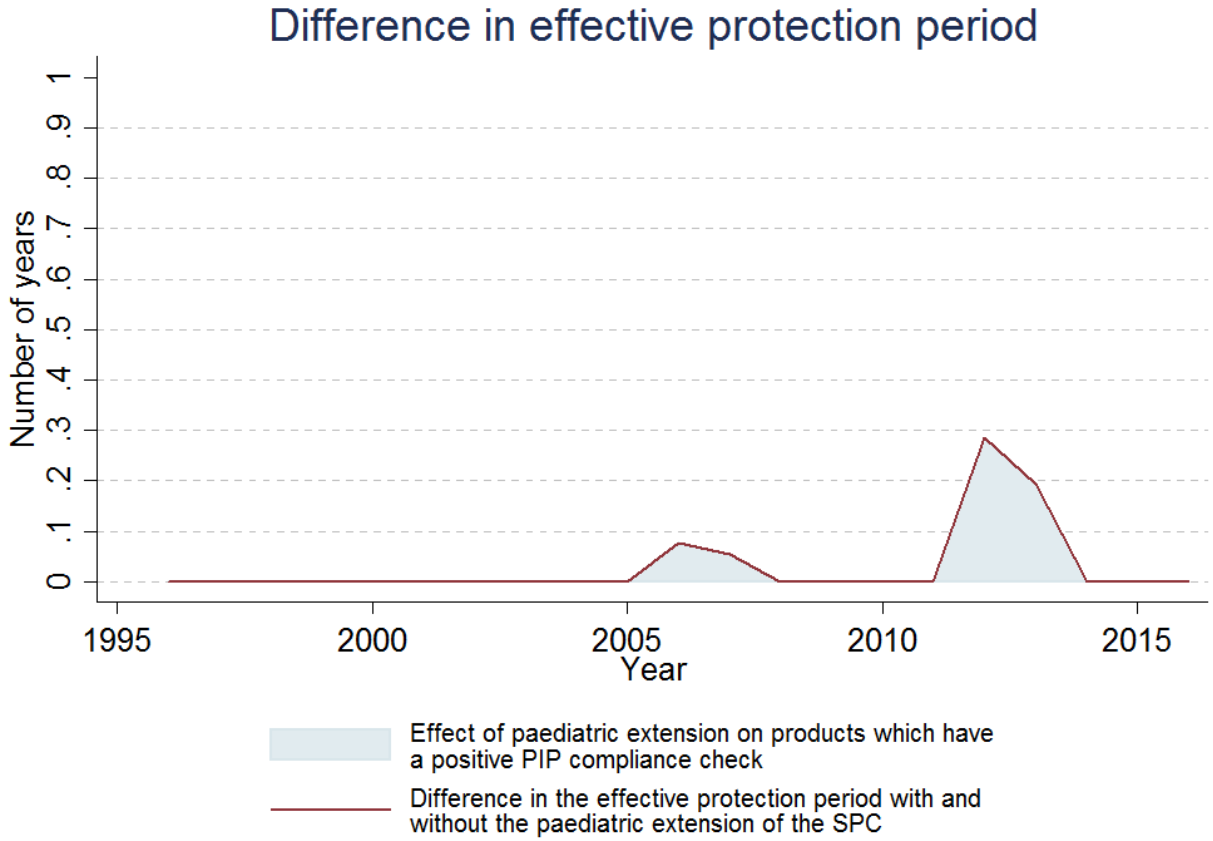
The average effect on the effective protection period of the paediatric reward of extending the SPC by 6 months seems to be modest.

This is driven by the fact that only 8.7% of the observations with a positive PIP compliance check have the SPC as the last protection to expire, while for 87.8% a patent is the last protection to expire. This is e.g. due to secondary patents.

Out of the 8.7% of the observations with a positive PIP compliance check where an SPC is the last protection to expire, 24.2% obtained the positive PIP compliance check later than two years before the expiry of the SPC, and hence were unable to apply for the extension.

For the orphan medicinal products in the current data material, it was possible to identify two products with positive PIP compliance checks[1]. For one of the products, a patent protects the product for a longer period of time than market exclusivity including the 2-year paediatric reward extension. As such, the effective protection period is not extended by the paediatric reward. For the other product, an SPC is the last protection to expire. This means that for the paediatric reward to extend the effective protection period for this product, the company should have been able to choose the 6-month extension of the SPC rather than the 2-year extension of the market exclusivity period.

Effective protection period with and without the 6-month paediatric extension of the SPC for products with a positive paediatric investigation plan compliance check, 1996-2016



Notes: Graph showing the effective protection period based on the protection instruments used in the calculation. The graph only includes medicinal product-country combinations with a positive PIP compliance check, excluding orphan medicinal products as these cannot obtain the 6-month extension of the SPC. As such, the difference between the lines depicted signifies the average increase in protection for products which have lived up to their obligation of undertaking a PIP. The observation level is unique medicinal product-country combinations, which means that a specific medicinal product is included in the calculation of the average as many times as it has a marketing authorisation. The calculation of the protection period without the paediatric reward is based on the assumption that all products with an SPC and a positive PIP compliance check dated at least 2 years prior to the expiry of the SPC have received the 6-month extension. This is expected to be a good assumption as obtaining the extension is in the interest of the companies, which only need to file the application in due time. Medicinal products with a negative development time and orphan medicinal products are excluded from the graph.

Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI

1 According to data from the EMA 8 orphan medicinal products had completed a PIP by 2016. Five of them obtained the 2-year extension of the market exclusivity period. The remaining three products no longer have orphan status.

4.1.4 SUMMARY

Different regulatory protection schemes have different effects on the average and marginal effective protection periods of medicinal products

Looking both at the average (across all products) and marginal effects (only products where the investigated protection scheme is the last to expire) of the various regulatory protection schemes on the effective protection periods of medicinal products, data protection and market protection grant the longest extra protection period. These two protection schemes are universal for all products (except orphan medicinal products, which obtain market exclusivity). Furthermore, they are the last protection schemes to expire in 39% of cases.

The orphan incentives granting market exclusivity for 10 years (+2 years for a paediatric extension) have quite a considerable effect on the margin for these products.

The fact that the one-year extension of market protection for approval of a second condition and the 6-month extension of the SPC due to a positive PIP compliance check do not have substantial marginal effects[1] does not necessarily mean that they are not important for incentivising pharmaceutical companies in specific development initiation decisions.

For the individual medicinal product being granted one of these extra protection schemes they might mean the difference between a good and a bad business case. Furthermore, in the ex ante R&D decision made by pharmaceutical companies, these schemes might contribute to decreasing the uncertainty about future revenue sufficiently to incentivise the company to undertake the research.

However, it might also be that these incentives are not currently working in the way intended or to the degree intended[2]. A further analysis of why the marginal effect of these two extensions of the protection period is rather small would be informative.

Effects of the various regulatory protection schemes on the effective protection period of medicinal products, 2010-2016

Protection	Average effect	Marginal effect
Data protection and market protection	2.4 years	4.8 years
1-year extension (as an effect of approval for second indication)		0.01 years (3.7 days)
Orphan incentives (market exclusivity)		1.6 years
Paediatric incentive (6-month extension of SPC)		0.008 years (2.9 days)

Note: Table depicting the average and marginal effects of the various regulatory protection schemes. Average and marginal effects are calculated for the period 2010-2016, except for market exclusivity where data is only available for 2011-2016. Market exclusivity for orphan medicinal products includes the possible two year extension due to paediatric studies.
Source: Copenhagen Economics based on unique dataset collected from Drug Patent Watch, PATSTAT, the EMA and MRI.

1 The marginal effects describe the *actual* extension of the effective protection period provided by the given protection scheme.
2 See p. 299 for further information on the paediatric regulation and for an overview of other reports studying this.

4.2 EFFECT ON INNOVATION

Data protection and market protection seem to have contributed to incentivising increased pharmaceutical R&D

RELATIONSHIP BETWEEN PROTECTION AND R&D

Generally speaking, the literature on the relationship between protection schemes and the amount of R&D undertaken is ambiguous.

One key observation is that if e.g. the protection period for medicinal products increases in the European Union, this affects all products placed on the EU market. These products might be researched and developed within the EU, but the crucial R&D might as well be placed outside the EU. Enhancing the protection period in the EU will as such benefit companies selling their products in the member states, no matter where their R&D is placed.

The question then is whether a positive relationship can be found between the two variables in spite of this fact.

Based on the econometric results presented in chapter 2, we find that there is indeed a positive relationship between the effective protection period for medicinal products and the amount of R&D undertaken within the pharmaceutical sector. More specifically, a positive relationship can be found to exist between protection in the markets where medicinal products are sold and the amount of R&D invested in by companies.

There might be a range of different reasons for this. During interviews for this study, some interviewees pointed out e.g. that the protection framework might signal to companies how "innovation-friendly" a country or region is. In an industry where R&D projects have a long time horizon and risk is an integral part of the business model, having a higher degree of certainty as to how the framework for protection will be in the future can prove to be rather important[1].

Furthermore, a rather simple profitability argument might likewise explain this finding. If protection is increased, so might profitability, all else being equal, as generic competition is delayed. When the products become more profitable, it makes financial sense to invest more in the R&D of new products.

PROTECTION SCHEMES AND INNOVATION

Data protection and market protection could be seen on the previous pages to extend the average effective protection periods for all medicinal products by 2.4 years. For the 39% of products where one of these schemes were the last to expire, the marginal extra effective protection period gained was 4.8 years.

It could also be seen that the other regulatory protection schemes have contributed to increasing the effective protection period for medicinal products, however, to a lesser degree than data protection and market protection.

In so far as the regulatory protection schemes have increased the effective protection time for medicinal products, it is conceivable that they have increased the amount of pharmaceutical R&D undertaken in the EU member states.

As per the argument put forward in the previous section, it is also quite conceivable that these schemes have also contributed to increasing pharmaceutical R&D in other locations around the world where the companies selling their medicinal products in the EU carry out their R&D.

1 Pointed out by several interviewees during structured interviews with key stakeholders. This is not necessarily to do only with the legislative framework, which is fairly standardised for medicinal products across the EU, but may also have to do with the implementation and the actual workings of the regulation. E.g. the legislation on SPCs is the same across all EU member states, but there is still a fair amount of variation in the decisions made in the various member states (see section 3.4).

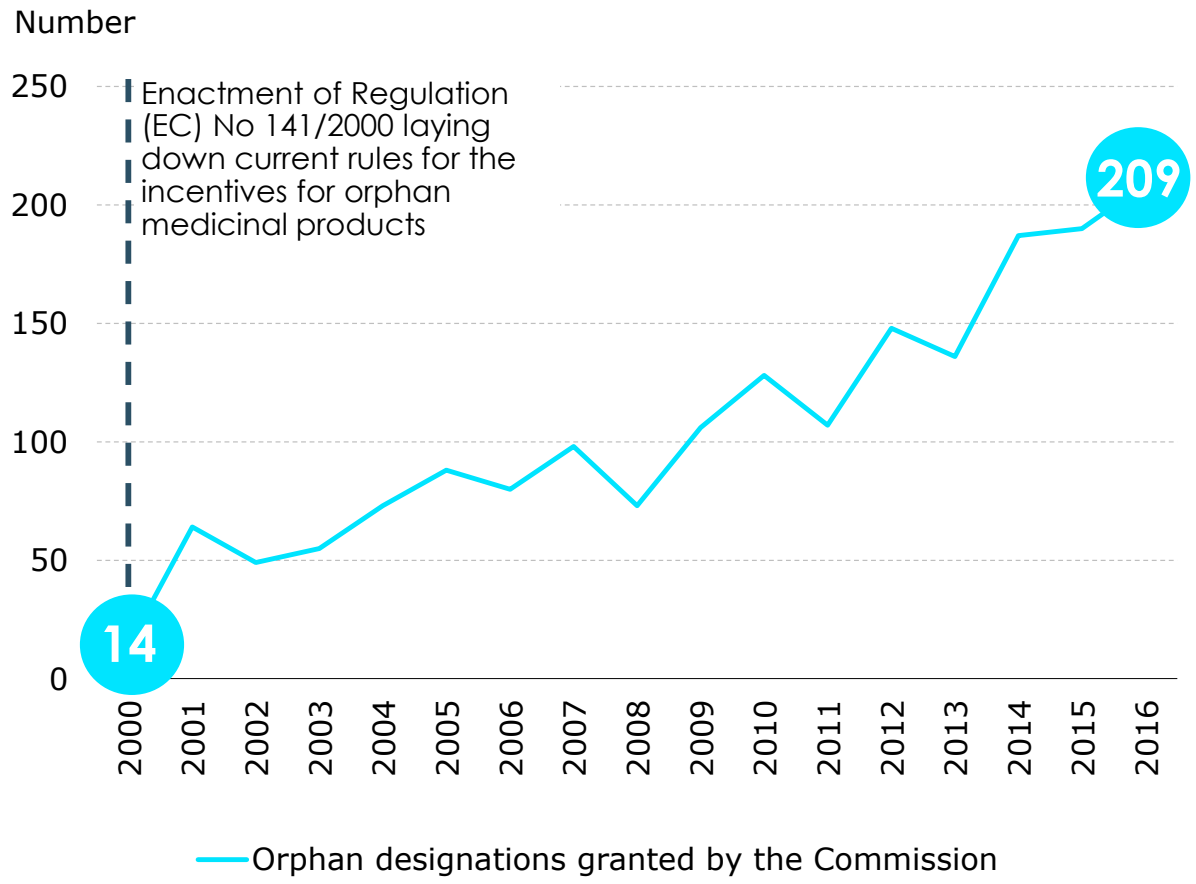
The number of orphan designations has been increasing steadily since the introduction of incentives through the enactment of the current regulation on orphan medicinal products

Since the enactment of the current regulation governing the incentives for orphan medicinal products, the number of orphan designations granted by the Commission per year has increased almost 15-fold, from 14 in 2000 to 209 in 2016.

The number of marketing authorisations granted per year also increased from 0 in 2000 to 14 in 2016. However, a lag of several years is expected from the designation of an orphan medicinal product until an application for marketing authorisation can be submitted and either granted or refused by the authorities. As such, the increase in the number of orphan designations granted by the European Commission might entail a granting of more marketing authorisations for orphan medicinal products in the future[1].

Data on orphan designations does not exist further back than 2000, when Regulation (EC) No 141/2000 was enacted. As such, there is no "before" measure with which to compare. However, looking at the graph to the right there seems to be a clear positive trend in the form of an increasing number of orphan designations being granted each year. If the number of orphan designations can be seen as an expression of the amount of innovation within the field, it thus seems like the incentives embedded within the orphan regulation have helped spur more innovation within this field[2].

Number of orphan designations granted by the European Commission, 2000-2016



Note: Graph showing the yearly number of orphan designations granted by the European Commission.
Source: Sante (2015), State of orphan designation.

1 Assuming that the failure rate for orphan medicinal products does not increase in an equivalent manner, offsetting the increase in designations.
2 In ECORYS (2015), "How well does regulation work? The cases of paediatric medicines, orphan medicinal products and advanced therapies", it is furthermore concluded that the "…*regulations have been successful in addressing diseases with unmet medical needs*".

Considerable lag between agreement of paediatric investigation plan and positive compliance check

The number of paediatric investigation plans obtaining a positive compliance check has increased over time[1].

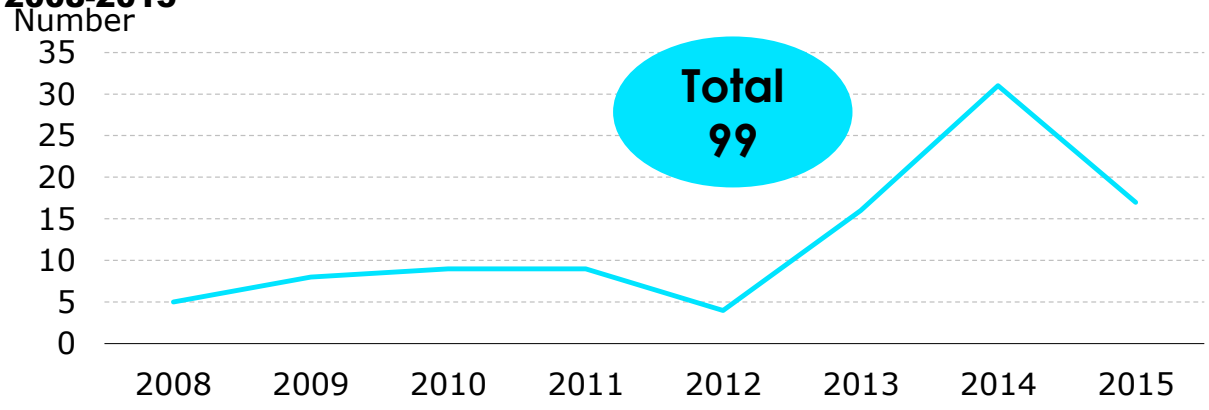
From the lower graph to the right, it can be seen that a total of 859 PIPs were agreed between 2007 and 2015. However, as most PIPs have a duration of 5 to 10 years[2], 99 PIPs obtained a positive compliance check between 2008 and 2015. This suggests a considerable lag between agreements on PIPs and positive compliance checks.

This observation explains the rather small number of products with a positive PIP compliance check, compared to the number of agreed PIPs. Furthermore, as most PIPs have a duration of 5 to 10 years, the peak in agreed PIPs in 2010 will probably not be reflected in the number of positive PIP compliance checks until the 2015-2020 period. As such, an increase in the number of positive PIP compliance checks may be expected in the future.

Whether these will lead to more extensions of SPCs depends on the ability of companies and authorities to ensure that the final compliance check is undertaken more than two years prior to the expiry of an SPC.

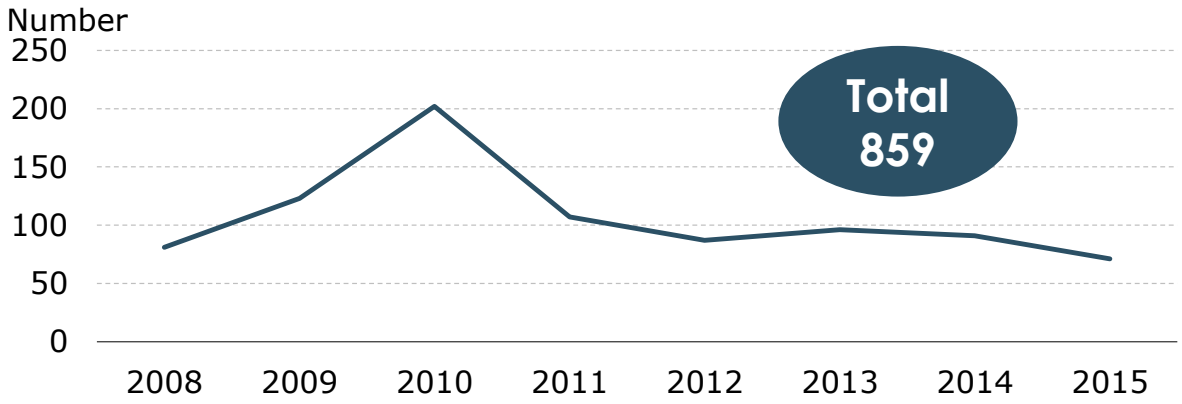
To the extent that more paediatric investigation plans will bring about more innovation within medicines for the paediatric population, it seems that the regulation has helped to increase innovation within this area.

Number of positive paediatric investigation plan compliance checks, 2008-2015



Source: European Medicines Agency (2016), 10-year report on experience with the paediatric regulation.

Number of agreed paediatric investigation plans, 2008-2015



Source: European Medicines Agency (2016), 10-year report on experience with the paediatric regulation.

1 A compliance check is recorded as positive if the PDCO has adopted an opinion on final/full compliance with the agreed PIP.
2 European Medicines Agency (2016), 10-year report on experience with the paediatric regulation.

Many new medicines with a paediatric indication and new paediatric indications have been approved since the implementation of the paediatric regulation

The graph to the right shows the number of new medicines with a paediatric indication and the number of new paediatric indications.

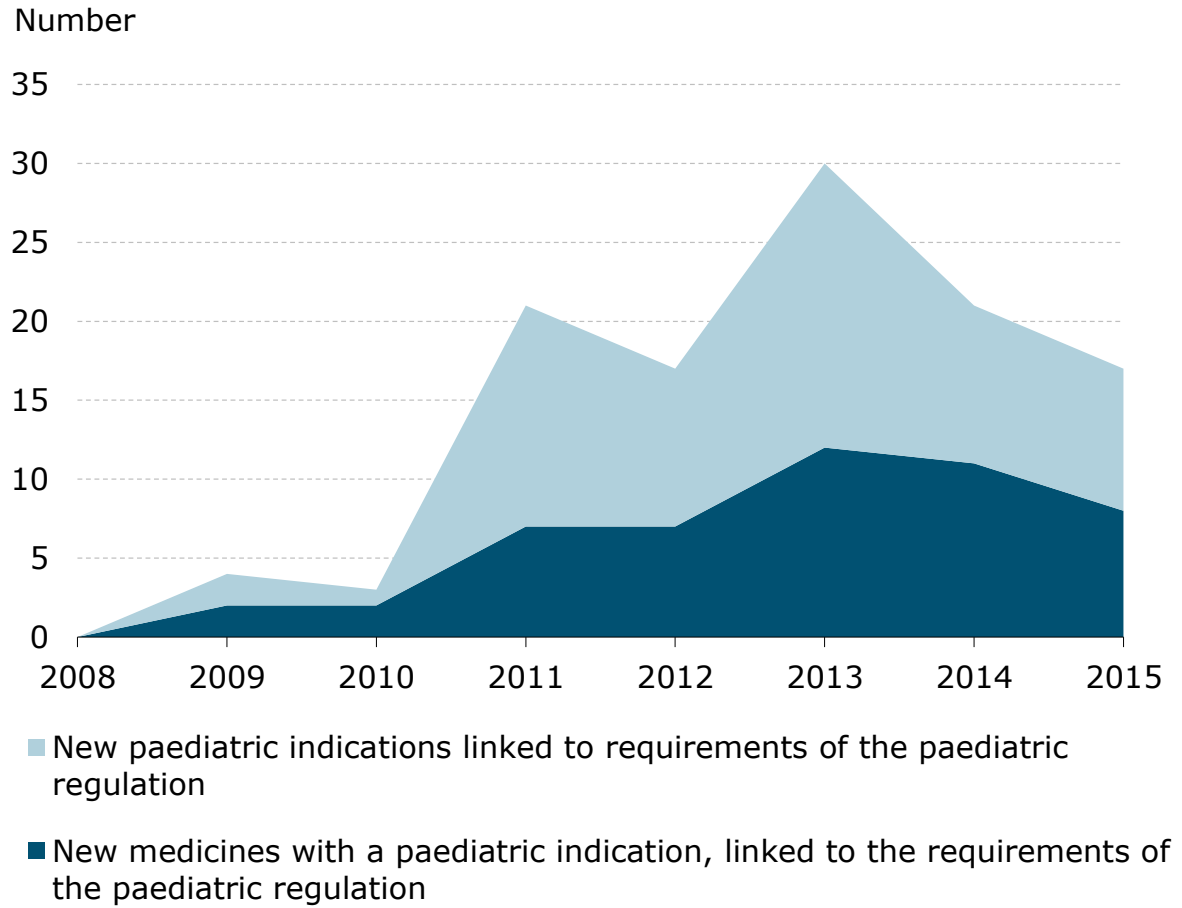
The number of new medicines is the number of new medicinal products approved for use in the paediatric population.

The number of new paediatric indications is the number of already authorised medicinal products which obtain an approval to treat an indication in the paediatric population.

As such, both these measures depict increases in the number of products available for the treatment of children.

As can be seen from the graph, especially the number of "New paediatric indications" seems to have experienced a significant increase over time.

Number of new medicines and new paediatric indications approved per year, 2008-2015



Note: Information unavailable for 2008.
Source: European Medicines Agency (2016), 10-year report on experience with the paediatric regulation.

Paediatric investigations have helped increase the information available regarding the effect of medicinal products in the paediatric population

Part of the objective of the paediatric regulation was to incentivise pharmaceutical companies to undertake more studies within the paediatric population to provide more information as to how pharmaceuticals work within this part of the population[1].

As such, the volume of new paediatric information added to the summary of product characteristics (SmPC) for medicinal products is of great interest.

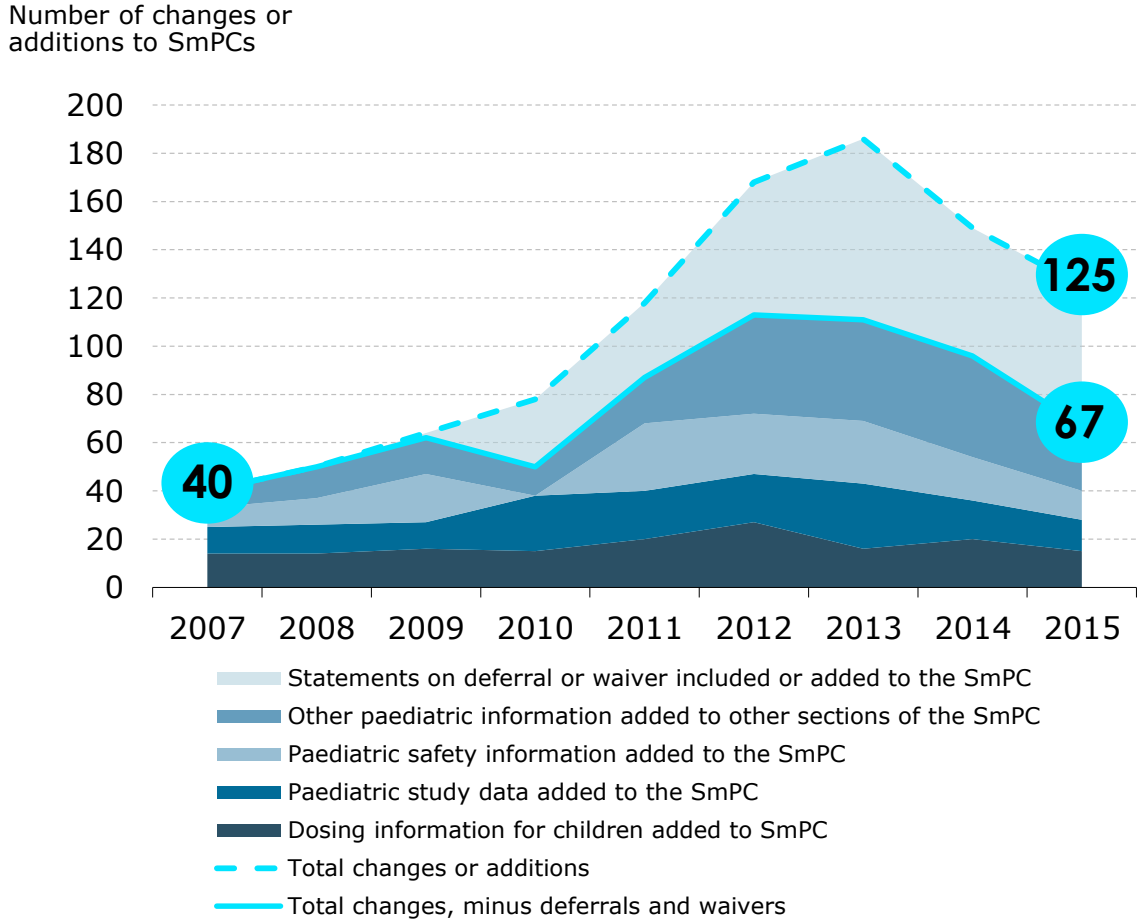
The graph to the right depicts the number of additions or changes made to SmPCs concerning paediatric information.

From 2007, the number of changes or additions made to SmPCs increased, until peaking in 2013. In 2014 and 2015, there was a slight decrease. However, this is mainly due to a fall in the number of changes stemming from "statements on deferral or waiver included or added to the SmPC".

In 2007, the total number of changes or additions made to SmPCs was 40. In 2015, the figure had increased to 125. This signifies a more than threefold increase in the volume of information added to SmPCs regarding the paediatric population.

However, excluding "Statements on deferral or waiver", the total increase in information was from 40 in 2007 to 67 in 2015. A "Statement on deferral or waiver" means that it is included in the SmPC, whether the company has obtained a waiver not to conduct paediatric studies or has obtained a deferral, to do so at a later time. As such, this information is not directly linked to an increase in paediatric clinical knowledge.

Changes or additions made to the summary of product characteristics regarding paediatric information, 2007-2015



Note: SmPC is an abbreviation of summary of product characteristics. Observation for "Paediatric safety information added to the SmPC" is missing for 2010.
Source: European Medicines Agency (2016), 10-year report on experience with the paediatric regulation.

1 Regulation (EC) No 1901/2006 (4) 281

Trade secrets as an alternative to the patent system (1/2)

TRADE-OFF

An important point to consider, when evaluating the effect on innovation of various legal schemes, is the full disclosure of inventions when a patent is taken out versus non-disclosure if the invention is protected as a trade secret.

When an invention is disclosed in a patent application, the technical details become public knowledge. As such, the invention and its inherent knowledge are shared with the world and can be used by all entities in future R&D.

In exchange for such disclosure, the holder of the patent is granted the right to exclude others from using the knowledge commercially for a certain period. This period is of a finite nature. For a trade secret, the period of protection might, in principle, be indefinite. Hence, trade secrets might be detrimental to new innovation, whereas patents disclosing new knowledge might help spur further R&D.

As such, the more companies use patents instead of trade secrets to protect their new inventions, the larger the amount of public knowledge new innovation can build upon.

LEGAL BASIS

The legal basis for trade secrets in the European Union is defined in Directive 2016/943*.[1]
Article 2 of the directive defines trade secrets as information meeting the following requirements:

- It is a secret in the sense that it is not generally known or readily accessible to people within the circles that normally deal with the kind of information in question.
- It has commercial value because of its secrecy.
- The person in control of the secret has taken reasonable steps to keep it secret.

As such, trade secrets are an alternative to other intellectual property protection schemes.

However, there is a key point to note in Article 3(b) of the same directive, which states that the acquisition of a trade secret is considered lawful if it is obtained by observation, study or disassembly of a product or object that has been made available to the public or is in the lawful possession of the acquirer of the information who is free from any legally valid duty to limit the acquisition of the trade secret.

This means that reverse-engineering a medicine is a lawful way for potential competitors to obtain information of its composition.

TRADE SECRETS IN THE PHARMACEUTICAL INDUSTRY

Because of the legality of acquiring information through reverse-engineering, the option of using trade secrets to protect a product might be of limited applicability for pharmaceutical companies.[1,3,4] Of course, this relates especially to the final composition of the medicine when this is easily reverse-engineered.

However, the process with which a medicinal product is produced may not be obvious or possible to reverse-engineer from the final product, and it might therefore be more likely to be protected as a trade secret.

So, if the innovation is not in some way embedded in the final product or detectable from the final product, trade secrets are an option for pharmaceutical companies seeking to protect their market.

COSTS AND BENEFITS FOR THE COMPANY COMPARED TO PATENTS

The key benefit of trade secrets as opposed to patents is that they offer potentially indefinite market protection. If competitors do not discover the information necessary to manufacture the medicine, they cannot enter the market.

A perhaps lesser benefit is that some costs related to the process of patenting the product are avoided.

The main drawback of trade secrets as opposed to patents is that they do not prevent independent discovery by other companies. This means that if a competing company can discover the information necessary to manufacture the medicine, it can then proceed to bring it to market.

While a patent only lasts a set number of years, it ensures that competitors cannot enter the market with the same product during this period.

1 Full name: DIRECTIVE (EU) 2016/943 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure, http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016L0943&from=EN
2 http://www.pharmaworldmagazine.com/european-policy-trade-secrets-directive/
3 http://www.ipprolifesciences.com/specialistfeatures/specialistfeature.php?specialist_id=12#.WhV7ZVXiaUk
4 https://hbr.org/2013/11/filing-for-a-patent-versus-keeping-your-invention-a-trade-secret
5 http://press.pfizer.com/press-release/pfizer-completes-acquisition-wyeth

Trade secrets as an alternative to the patent system (2/2)

THE CASE OF PREMARIN BY PFIZER

Premarin, a hormone replacement therapy product used to treat the negative symptoms of menopause, was first marketed in 1942 by Wyeth.

A series of patents were filed in the years surrounding the initial marketing of the product. However, long after the expiry of these patents, Wyeth (acquired by Pfizer in 2009[1]) continued to be the only supplier of the medicine.

This was due to the fact that competitors had been unable to discover the extraction process, which Wyeth had kept as a trade secret rather than patent it.[2,3]

This is one example of how trade secrets can be an effective alternative to patenting in certain cases, also in the pharmaceutical sector.

EFFECTS OF TRADE SECRETS ON SOCIETY

A key feature of the patent system is that other companies can make use of the information covered by the patent to produce generic products or to build new research. As such, while patents may make the use of certain information strictly exclusive, it does so for a finite period of time. As the information becomes public, other agents may build on this information to create new innovations.

This facilitates a continual accumulation of knowledge, while ensuring the necessary incentives for private innovation.

With trade secrets, this is not the case. Information can stay private for an indefinite period, which potentially hampers the process of innovation in society.

1 http://press.pfizer.com/press-release/pfizer-completes-acquisition-wyeth
2 http://www.ipprolifesciences.com/specialistfeatures/specialistfeature.php?specialist_id=12#.WhV7ZVXiaUk
3 https://hbr.org/2013/11/filing-for-a-patent-versus-keeping-your-invention-a-trade-secret

4.3 EFFECT ON AVAILABILITY

The relationship between IP protection and launch of new medicinal products is ambiguous

The econometric analysis in chapter 2 did not identify a statistically significant effect of the effective protection period within a country on the probability of launch of new medicinal products.

VARIATION IN IP PROTECTION

However, as we are looking only at products launched within the EU member states, the lack of statistical significance might to a large extent be due to the fact that most European countries have the same protection schemes for IP in general and medicinal products specifically.

This is e.g. supported by the findings in Cockburn et al. (2016), where the authors analyse the effect of among other things patent regimes across countries and regions with large variation in IP rights. When including both countries with no IP protection and countries with a high level of IP protection, the authors are able to identify a rather pronounced effect of the IP regime on the availability of medicinal products. Changing IP protection in a country from nothing to more than 18 years of patent protection entails a decrease in launch delay of 55%[1]. Taken at face value, this effectively means that looking in isolation at this parameter, enacting 20 years of patent protection for a basic patent as inherent in e.g. the TRIPS agreement in a country with no IP protection will lead to medicinal products being launched about twice as fast after the change compared to before.

CENTRALISED PROCEDURE

It is possible to obtain a centralised marketing authorisation within the EU. The centralised procedure approves a medicinal product in all EU member states at the same time through a single application. For some products the centralised procedure is mandatory[2].

From an economic point of view, when a company has obtained a centralised marketing authorisation, the barriers to launching a product in more countries are lower than if an application for authorisation had to be submitted in each individual country. This might provide an incentive to launch in more EU countries than would otherwise have been the case. As such, having more products centrally approved might contribute to decreasing the difference between EU member states regarding launch of new medicinal products.

PRICE REFERENCING

Another reason for the lack of statistical significance of the effective protection period on availability in chapter 2 might be that other mechanisms are dominant for companies in their launch decisions. One such mechanism might be the use and extent of price referencing.

Price referencing between countries within the EU is a highly debated issue. Many EU countries use some form of price referencing, but the calculation methods employed and the country basket referenced vary greatly between countries[3].

One potential issue concerning price referencing is that it might help lower prices, but that this might happen at the expense of availability of medicinal products, especially in lower-income countries. This can e.g. be the case if a high-income country references the prices of a low-income country. In this case, the pharmaceutical companies will have an incentive to delay launch in the low-income country to be able to negotiate a higher price in the high-income country[3]. As such, the effect of price referencing might be highly tied to the income of a country and hence the attractiveness of the market. Hence, price referencing might have the positive effect that lower prices can be negotiated in high-income countries, but the negative consequence that companies delay launch of new products in low-income countries.

As our econometric models takes account of both population size and GDP, we are to some extent implicitly taking account of the use of external price referencing.

DATA MATERIAL ON ORPHAN MEDICINAL PRODUCTS

In the available data material, it is possible to identify orphan medicinal products and their launch across the EU member states. The following pages show the results of this analysis.

1 More than 18 years of patent protection is categorised in the study as having a "long patent protection". In the TRIPS agreement,a minimum of 20 years of protection provided by a basic patent is mandatory. All EU member states are members of the WTO and hence must live up to the provisions of the TRIPS agreement.

2 According to the EMA website on the centralised procedure, "the great majority of new, innovative medicines" are approved through the centralised procedure. See the EMA website on the centralised procedure for a list of medicines with mandatory centralised procedure.

3 Creativ-Ceutical for European Commission (2014), External Reference Pricing of Medicinal Products: Simulation-based Considerations for Cross-Country Coordination.

Orphan molecules are launched faster and in more countries than non-orphan molecules

From the graph to the right it can be seen that molecules which are present in orphan medicinal products are launched faster and in more countries than molecules which are not present in orphan medicinal products[1].

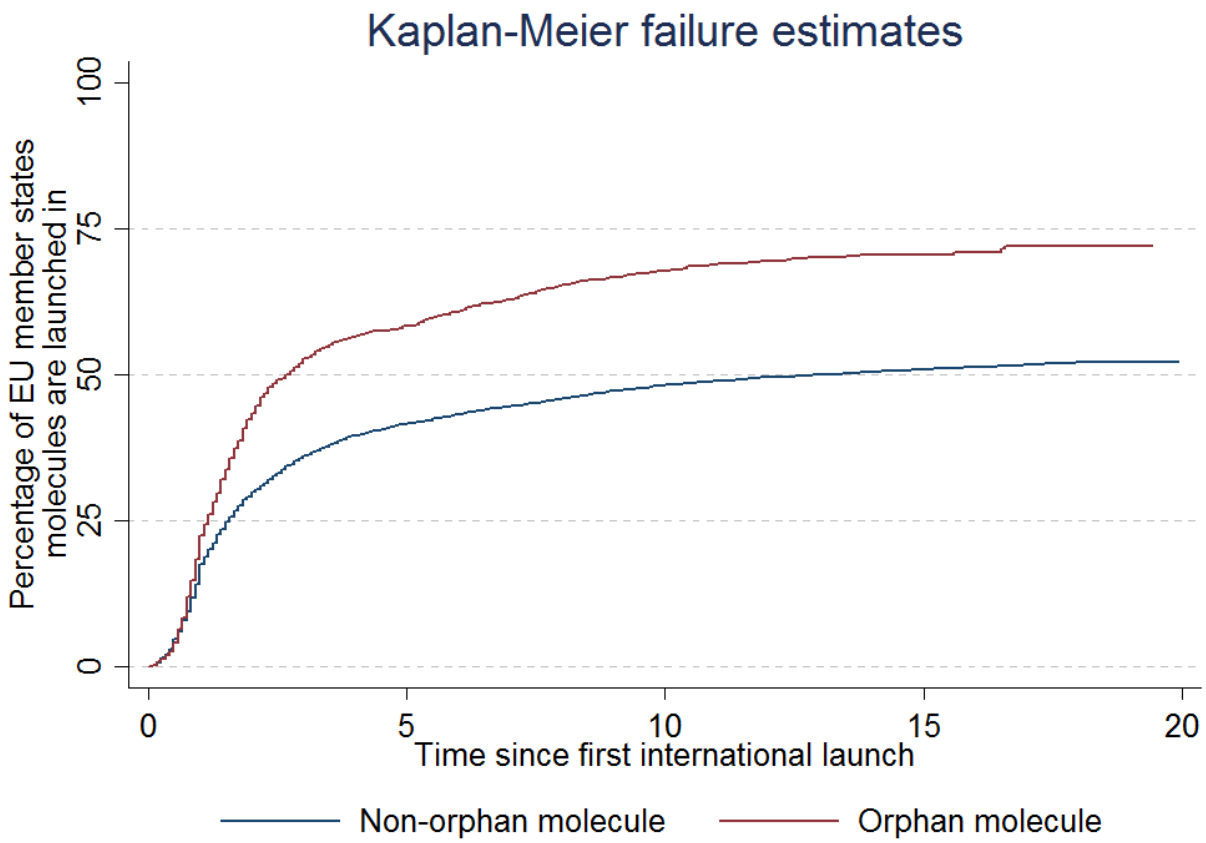
There can be several reasons for this difference in launch probability.

All orphan medicinal products have to be centrally approved by the EMA. When an orphan medicinal product obtains approval, it is as such always an approval pertaining to all EU countries. All else being equal, it is possible that having to obtain central approval by default for these products makes launching in more countries more likely for these products as a group.

For many rare diseases, no treatment is currently available. This means that there are no competitors in the market, and hence no need to think about size of possible market share etc. when launching a product. This might contribute to faster and more extensive launches. Furthermore, pressure may be exerted by patient advocacy groups and the general public for a given product to be launched in a given country.

Additionally, orphan medicinal products have a much smaller patient base than non-orphan medicinal products[2]. This might make it more important to launch in many countries to obtain a satisfactory return on investment[3].

Fraction of EU member states in which orphan and non-orphan molecules are launched, 1996 and 2015



Note: Graph showing the fraction of EU member states in which molecules present in orphan medicinal products are launched, based on time since first international launch. Separated into orphan and non-orphan molecules. A molecule is identified as being an orphan molecule if it is used in an orphan medicinal product.
Source: Copenhagen Economics based on IMS data provided by the European Commission and data on orphan medicinal products from the European Medicines Agency.

1 However, whether the treatment is available to patients also depends on pricing and reimbursement decisions.
2 It is one of the criteria for being granted an orphan designation and maintaining it through the approval process that no more than 5 in 10,000 citizens within the EU is affected.
3 This, of course, depends on the distribution of patients across countries and the prices obtained.

Looking at orphan medicinal products instead of molecules still shows that orphan medicinal products are launched in many countries

The graph to the right analyses the launch of orphan medicinal products identified via trade names. The difference compared to the previous page is that the unit analysed in the current graph is product, compared to molecule on the previous page.

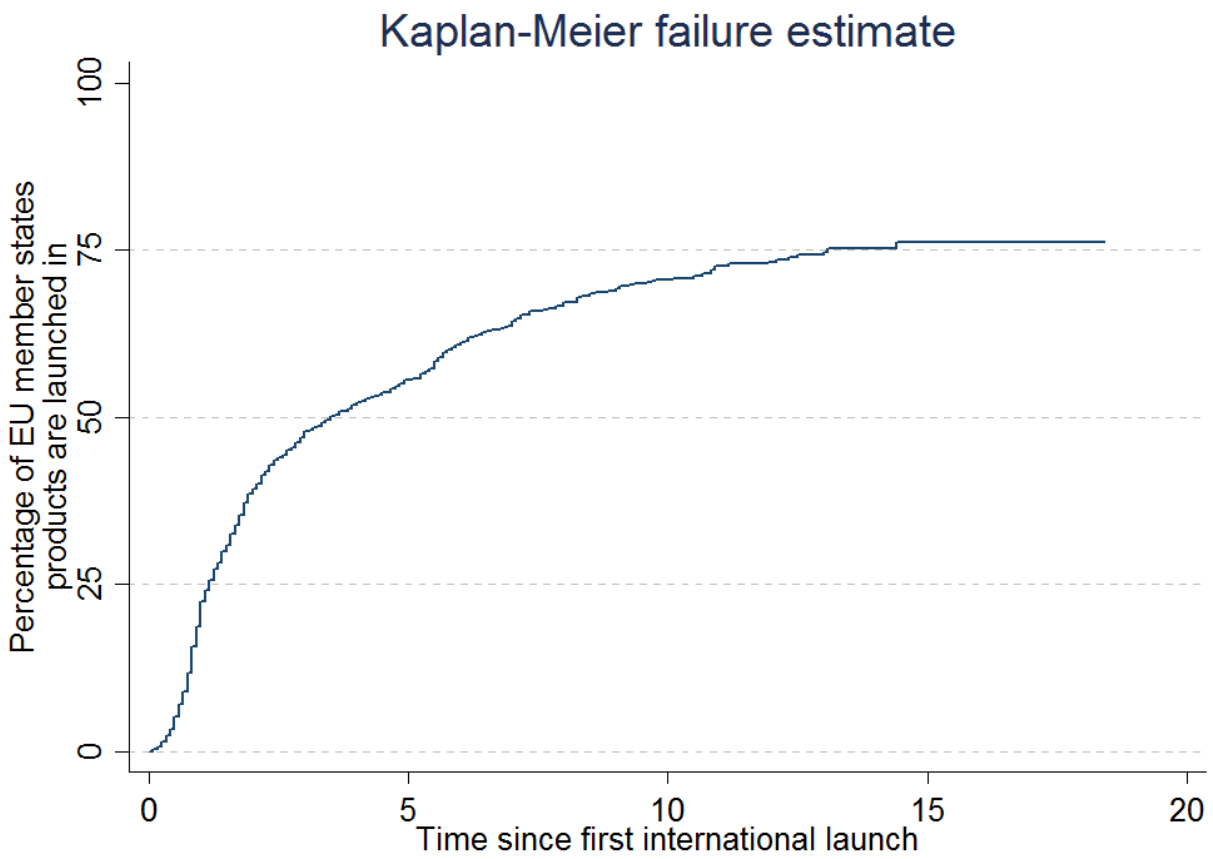
A given molecule, as identified by name, can be present in several different products. Some of these products might be designated as orphan medicinal products, while some are not. This means that a molecule can be used in an orphan medicinal product and a non-orphan medicinal product at the same time[1].

When using molecule as the unit of measurement, it is irrelevant whether the molecule is launched in a country in an orphan medicinal product or a non-orphan medicinal product. What matters is that the molecule is available in the country.

In the graph to the right, it matters whether or not a given molecule is available in an orphan medicinal product in a given country. As such, the blue line depicts only launches of orphan medicinal products in EU member states.

However, even when changing the unit of measurement from molecule to product, the tendency remains the same. Orphan medicinal products are launched in an estimated 75% of countries, 20 years after first international launch.

Fraction of EU member states in which orphan medicinal products are launched, 1996 to 2015



Note: Graph showing the fraction of EU member states in which orphan medicinal products are launched, based on time since first international launch.
Source: Copenhagen Economics based on IMS data provided by the European Commission and data on orphan medicinal products from the European Medicines Agency.

1 See e.g. case study on Cometriq and Cabometyx in chapter 5.

Certain considerations regarding the paediatric regulation may be important

ADDRESSING THE NEEDS OF CHILDREN

In section 4.2, it was shown how the number of medicines approved for children as well as the volume of information regarding the paediatric population contained in the summary of product characteristics have increased since the enactment of the paediatric regulation.

However, one thing is the volume of knowledge within the area, another is whether this meets the actual needs of children.

It is worth considering whether the new approved medicines and added information about existing products actually cover medicines used by children or perhaps more closely mimic the medicines important for the adult population.

In the US it has e.g. been shown that the paediatric incentives have led to many new studies in the paediatric population. However, the distribution of new products approved for children did not resemble the prescription pattern in children. This means that the new approved products did not seem to fall within the areas which are most important for the paediatric population[1].

Furthermore, a majority of the medicinal products which were granted paediatric exclusivity were rarely used in children. Correspondingly, medicinal products often used in children were underrepresented in the paediatric studies[1].

These same points have been made about the workings of the paediatric regulation in the European Union[2].

A 2017 report from the European Commission likewise concludes that "*Those positive results* [more research and new products] *do however not evenly spread among all therapeutic areas, but concentrate in some, often linked to research priorities in adults rather than children*"[3].

This could seem to suggest that the paediatric regulation is adding information about the use of medicine in children. However, not in all cases does the added information necessarily seem to align to a high degree with the unmet medical needs of the paediatric population. Nevertheless, the results presented in section 4.2 and in recent reports[2,3] on the paediatric area show encouraging positive effects on the increase in the body of knowledge regarding the paediatric population, as well as the number of medicines approved for children.

1 Boots et al. (2007), Stimulation programs for pediatric drug research – do children really benefit?
2 Ecorys, Technopolis group and Empirica for the European Commission (2016), Study on the economic impact of the Paediatric Regulation, including its incentives and rewards.
3 European Commission (2017), State of paediatric medicines in the EU.

Low prices might entail low profit margins, which might have the adverse effect of increasing the risk of supply shortages

A factor which severely influences the availability of medicinal products is the risk of supply shortages.

SUPPLY SHORTAGES

A supply shortage is a situation where the manufacturers of a medicinal product are unable to produce a supply of the medicine that is adequate to meet either current or projected demand. A supply shortage may be local, national or international.[1]

In the European Union, medicine supply shortages are generally dealt with at the national level. However, where a supply shortage affects several member states or is related to safety concerns, the European Medicines Agency may be involved.[2]

CONSEQUENCES OF A SUPPLY SHORTAGE

A shortage of supply of a given medicine may cause doctors and patients to seek out alternative medication that may not be as effective or well-tolerated by the patients.

If such alternative treatment options are unavailable, doctors and patients are forced to delay or forego treatment.[3] Where these medicines are 'medically necessary', a shortage can cause serious or even life-threatening situations for patients.[4]

Furthermore, the management of supply shortages induces time costs on the health care systems.[5] This is due to the fact that time spent managing a supply shortage could have been spent treating patients. Finally, use of alternative medication or dosages increases the risk of errors or adverse effects.[6]

In summary, supply shortages are detrimental to society in that they:

- Impose significant costs on the health care systems, specifically time spent managing the shortages.
- Harm patients who have to either forego or delay treatment, or be treated with an alternative medicine that is less effective or less well-tolerated.

LOW PROFITS AS THE ROOT CAUSE OF SUPPLY SHORTAGES

In Markowski (2012)[7], the author states that the underlying cause of supply shortages is likely to be inadequate profits.

A low profit margin may cause manufacturers to optimise operations by reducing inventories, thereby avoiding costs associated with stockpiling of products.

By having low inventories, companies run the risk of not being able to supply the market for a period of time if something happens to negatively impact production capacity. From the company's economic viewpoint this risk has to be weighed against the cost of keeping large inventories.

If profit margins are low, the loss associated with not supplying the market for a period of time is lower, and thus less likely to incentivise the company to incur the costs of keeping large inventories.

However, low inventory levels leave the market vulnerable to supply shortages if market conditions change suddenly.[8]

Examples of such sudden changes include:

- Increases in demand, e.g. following new recommendations from the authorities.
- Decreases in supply, e.g. as a result of plants being closed due to quality or safety concerns. Another cause could be market exit by another manufacturer, which can dramatically reduce supply.

Low profit margins may have different causes, either market-based competition that drives down prices (such as when an originator drug goes off patent and generic companies enter),[8] or regulation such as price ceilings or cost floors.

REIMBURSEMENT POLICIES

In a 2016 paper,[3] Yurukoglu et al. showed that a change in the reimbursement policies in the US affected the frequency of shortages. The authors provide statistical evidence that the shortages are linked to the decreases in reimbursement. Naturally, this result is compatible with the argument presented in Markowski (2012)[7] that inadequate profits can be a root cause of supply shortages.

Given this relationship between supply shortages and reimbursements, one straightforward way of combating supply shortages is to increase reimbursements. However, this obviously comes at a cost for the payers. As such, a trade-off exists between low medicine costs and the risk of supply shortages.

1 http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/01/WC500200301.pdf
2 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000588.jsp&mid=WC0b01ac05807477a5
3 Yurukoglu et al. (2016), The Role of Government Reimbursement in Drug Shortages.
4 Kim, Sang Hyun and Morton, Fiona Scott (2015) A Model of Generic Drug Shortages: Supply distributions, Demand Substitution and Demand Control.
5 Economist Intelligence Unit (2017) Cancer medicines shortages in Europe Policy recommendations to prevent and manage shortages.
6 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60667-5/fulltext?rss%3Dyes
7 M.E. Markowski, "Drug Shortages: The Problem of Inadequate Profits" (April 2012).
8 Ventola (2011), The Drug Shortage Crisis in the United States.

Conditional marketing authorisations and the Health Technology Assessment (1/2)

Conditional marketing authorisations (CMAs) might help to make new medicinal products available earlier than would otherwise have been the case.

However, after having obtained a CMA, in many countries a new medicinal product has to be approved for reimbursement. As there is less empirical evidence of the efficacy of products with a CMA compared to products with a 'regular' marketing authorisation, being approved for reimbursement can prove challenging. This might affect the availability of medicinal products with a CMA.

CONDITIONAL MARKETING AUTHORISATIONS

Conditional marketing authorisations were established in 2006 in Commission Regulation No 507/2006.[1] It allows for the granting of a marketing authorisation even in the absence of the comprehensive evidence that is usually required, provided that the medicine fulfils certain conditions.

CMAs may be granted to medicines that are either intended to treat or prevent life-threatening or seriously debilitating diseases, intended to be used in an emergency, or designated as orphan medicinal products (see Article 3 of the aforementioned regulation).

As laid out in Article 4 of the regulation, a CMA requires that the following conditions are met:

- The product has a positive risk-benefit balance.
- It is likely that the applicant will be able to provide the comprehensive clinical data.
- Unmet medical needs will be fulfilled.
- The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data is still required.

Simply put, conditional marketing authorisations allow medicines to be marketed sooner than would otherwise be possible if the expected gain from their use outweighs the risk posed by introducing a medicine supported by less evidence for its safety and efficacy than otherwise required.

After having received a conditional marketing authorisation, the company is obligated to complete ongoing studies or new studies in order to show that the benefit-risk balance is indeed positive for the medicine. After the obligations have been met, the medicine can be granted a full marketing authorisation.

KEY FIGURES ON THE USE OF CMA IN THE EU

In 2017, the European Medicines Agency published a report detailing the use of conditional marketing authorisations in the 10 years following their introduction.[2]

In total, 30 conditional marketing authorisations were granted between 2006 and June 2016. Of these, 11 have been converted into full marketing authorisations, and 2 have been withdrawn for commercial reasons.[2]

All of these CMAs were given within four therapeutic areas (number of CMAs in parenthesis): oncology (17), infectious diseases (9), neurology (3) and ophthalmology (1).[2]

The median time from granting of a CMA to conversion to a 'full' marketing authorisation was 4.21 years.[2]

FROM MARKETING AUTHORISATION TO TREATMENT ACCESS

A centralised marketing authorisation allows the medicine to be marketed throughout the EU. However, this does not necessarily mean that the medicine will be made available for the treatment of patients in the individual member states. This is due to the fact that the individual member states have agencies that conduct Health Technology Assessments (HTA) before recommending public funding/reimbursement of a particular medicine.[3] These assessments are based on therapeutic benefit, relative effectiveness, cost-effectiveness and even budget impact.[3]

In order to qualify for reimbursement/public funding in the respective member states, the medicine has to obtain a positive recommendation by the relevant HTA agencies. Such recommendations are, of course, crucial for the company because of their effect on sales.

Furthermore, since the final reimbursement decision is country-specific, a medicine may be recommended for public reimbursement in some countries, but not in others.

This adds another layer of uncertainty regarding the profitability of a medicinal product.

1 https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf
2 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf
3 Lipska et al. (2015) Does Conditional Approval for New Oncology Drugs in Europe Lead to Differences in Health Technology Assessment Decisions?

Conditional marketing authorisations and the Health Technology Assessment (2/2)

This is pertinent to the case of conditional marketing authorisations because some sources indicate that there seems to be a perception in the industry that a *conditional* marketing authorisation translates into a lower probability of the medicine being recommended for public funding.[1,2]

HTA ASSESSMENTS

In Lipska et al. (2015)[3], the authors examine HTA recommendations in 6 different member states for 25 oncology medicinal products that were granted marketing authorisations between 2007 and 2012. Of these, 8 were given a CMA, with the remaining 17 given 'standard' marketing authorisations.

The main finding of the study is that there were *"little to no differences between recommendations of HTA bodies by pathway"*. This seems to contradict the perception that having a conditional marketing authorisation reduces the probability of a recommendation from the HTA bodies.

The authors also discuss two possible effects of a CMA on the probability of HTA recommendation. CMAs are disproportionally often given to medicines with a high unmet medical need, which would tend to increase the probability of an HTA recommendation. However, CMAs are based on less comprehensive data, and therefore there is less certainty about the efficacy, which may make payers reluctant to pay. This would tend to lower the probability of an HTA recommendation.

However, two caveats are appropriate. Firstly, the study examines only a subset of the CMAs that belong to a particular therapeutic area, and whose marketing authorisations fall within a specific time period. It is difficult to determine whether the observed results would hold in a wider setting.

Secondly, companies may internalise the HTA process into their decision-making. Specifically, companies who apply for a conditional marketing authorisation are likely do so based on an assessment that the HTA bodies will recommend public reimbursement based on the available evidence.

If companies thought otherwise, it could make sense for them to produce the necessary evidence to obtain a full marketing authorisation if this increased their chance of gaining HTA recommendations.

This would imply that there might be medicines that meet the requirements for obtaining a conditional marketing authorisation, but where the company behind chooses not to apply for one because it deems the probability of HTA recommendations to be greater (by a sufficient amount to justify the additional costs) if a full marketing authorisation is obtained.

Whether or not this is the case is very difficult to observe.

USE OF CONDITIONAL MARKETING AUTHORISATIONS

In Hoekman et al. (2015), the authors compared oncology medicines that were given a conditional marketing authorisation with oncology medicines given a standard marketing authorisation.

The two groups were compared in terms of the evidence providing the basis for the MA, timelines from first-in-human testing to marketing authorisation and finally in terms of procedural characteristics of the marketing authorisation process.

Based on this analysis and interviews with companies and regulators, the authors concluded that rather than being used as a "'prospectively planned pathway" to early access, CMAs are used as a "rescue option" when a full marketing authorisation cannot be obtained on the basis of the submitted data.

THE ECONOMICS OF THE DECISION TO APPLY FOR CMA

If CMAs reduce the probability of HTA recommendations compared to MAs *all else being equal,* then the decision to go for a CMA has to be made by weighing the benefits of early access against the risk of lower sales due to fewer HTA recommendations.

1 Hoekman et al. (2015) Use of conditional marketing authorization pathway for oncology medicines in Europe.
2 https://ec.europa.eu/health//sites/health/files/files/committee/stamp/2015-05_stamp2/3a-com.pdf
3 Lipska et al. (2015) Does Conditional Approval for New Oncology Drugs in Europe Lead to Differences in Health Technology Assessment Decisions?

4.4 EFFECT ON ACCESSIBILITY

As generics are priced lower than originator products, delaying their entrance entails higher spending on medicinal products

LITERATURE ON GENERIC PRICES

In general, it has been shown in the literature that generics are priced lower than originator products at entry. However, analyses on the effect on originator prices have shown ambiguous results[1].

Some studies find that after generics enter the market, originator prices tend to fall. This is the most intuitive reaction and can be attributed to competitive pressure from the generics, forcing originators to decrease prices to maintain a certain market share.

Furthermore, it has been shown that when more generics enter the same market, prices tend to fall even more both for originator and generic products.

However, some studies have likewise found that some originators increase prices after generic entry. This finding seems counter-intuitive in light of the above arguments. However, this behaviour might be the most economically profitable in some cases.

As shown in section 2.4, depending on e.g. the propensity of patients to switch to a new cheaper generic medicine, the most profitable action of an incumbent originator company might be to increase prices after generic entry.

However, pricing decisions may also be impacted by ethical and moral considerations, and the above observations are merely offering a theoretical explanation for the empirical findings.

ECONOMETRIC FINDINGS

In line with the literature, our analysis in chapter 2 shows that generics are priced lower than originator products at entry. Generics enter at a price approximately 40% lower than the originator price. In the course of the first five quarters, this price differential increases to around 50% of the originator price at entry.

Furthermore, our results show that originator prices fall after generic entry. During the first 5 quarters, this price fall is around 20%[2].

RELATIONSHIP TO EFFECTIVE PROTECTION PERIOD

As was shown earlier, the various regulatory protection schemes have contributed to increasing the effective protection period for medicinal products, albeit to differing degrees.

The most pronounced effect was produced by market protection, which has contributed to increasing the average protection period for medicinal products by 2.4 years. As such, market protection has delayed the point at which generic companies could enter the market by an average of 2.4 years.

Had the various protection schemes not existed, or had they had a shorter duration, it is conceivable that generics would be able to enter the market at an earlier point in time. This could possibly entail a reduction in pharmaceutical prices at an earlier point in time than what is happening today.

Not having as extensive protection as today would conceivably make it possible to shift some of the spending from originator products to generic products. This would entail a saving, the size of which depends on how much of the spending it would be possible to shift.

However, as new innovative medicinal products are mainly brought to market by the originator pharmaceutical companies, a reduced protection period might hamper the current level of innovation within pharmaceuticals.

The literature on the relationship between IP protection and innovation is ambiguous. However, the results presented in chapter 2 of the present study suggest that a reduced protection period within the EU will entail less spending on pharmaceutical R&D.

If fewer resources are spent on pharmaceutical R&D, the amount of innovation within the sector will decrease unless compensatory productivity gains can be realised. Less innovation would mean fewer products and/or longer intervals between new products coming onto the market. As such, this would be detrimental to patients in need of treatment.

It is therefore conceivable that a reduction in the effective protection period in Europe would entail faster entry of generics and hence lower prices. However, it is quite likely that this will decrease the amount of innovation within the pharmaceutical sector.

1 See literature review in section 2.3.

2 An important caveat is that due to data restrictions the analysis included only medicinal products in tablet form. See section 2.3 for further elaboration on this.

4.5 EFFECT ON PRICING STRATEGIES

The effect on pricing strategies depends largely on the specific form of regulatory incentives provided (1/2)

DATA PROTECTION AND MARKET PROTECTION

Data protection conveys the negative right of preventing other companies from using the data produced by the originator in their application for marketing authorisation. The 2-year period of market protection after data protection has expired ensures that even if a generic product obtains a marketing authorisation, the product cannot be placed on the market before the end of this period.

Even though a product is protected by data protection and market protection, there are, however, still ways for other companies to enter the market with competing products.

One way is if the molecule concerned is not protected by any IP protection. In this case, a second company is free to undertake clinical studies for a product containing said molecule and to develop their own dossier with which to file an application for marketing authorisation.

As described in chapter 1, an example of how this could happen would be the following. Company A has placed product M on the market, containing molecule Z. Molecule Z is not protected by patents or SPCs. However, product M has data and market protection. Company B now creates its own product called N containing molecule Z. Company B undertakes clinical trials and creates its own proprietary data on the efficacy and safety of product N. Company B now applies for marketing authorisation for product N using its own data material. Marketing authorisation is granted. Now there are two products on the market, both containing molecule Z, even though product M by company A is covered by data and market protection.

As such, if another company expects the profit from their potential market share during the 8+2 years of data protection and market protection to exceed the costs of creating the data for a full dossier themselves, there will be a positive business case for doing so. From an economic, theoretical standpoint this puts a ceiling on the bargaining power of the originator company when setting the price; if it sets a price high enough for entry of other companies to be profitable, it might face competition.

However, it also puts a lower bound on the price a company exploiting the above possibility will be able to charge. As it has to do clinical testing to enter the market, there will be a need to recoup this cost. Hence, it will be unprofitable to set the price too low. This might curb the competitive pressure from a company using this way of market entry.

As such, the possibility of the situation described above happening is probably higher, the more profitable the market is.

Another way competitors may enter the market during the period of data protection and market protection is through competition through innovation. If another company develops a new molecule for treating the same indication, it is free to enter the market with its product, even though another originator company is already in the market, with its product.

Both these possible ways for competitors to enter the market during the period of data protection and market protection mean that these incentives do not grant unlimited bargaining power to the pharmaceutical companies.

However, when it comes to generic entry, i.e. companies not undertaking their own clinical testing but relying on the data of the originator, they do grant a certainty that this will not happen before the end of the 10-year market protection period.

ORPHAN MEDICINAL PRODUCTS

Being granted market exclusivity for bringing a new innovative orphan medicinal product to the market prevents similar products with no further benefits for patients from entering the market for a 10-year period. This period can be extended to 12 years if the company complies with the obligations in an agreed-upon paediatric investigation plan.

This means that if two companies are simultaneously developing two similar products for treating the same rare disease, only the first to obtain a marketing authorisation may enter the market. The other will potentially have to wait 12 years before being able to follow, by which time a new and improved product might have entered the market, rendering the old treatments obsolete. In this case, the market exclusivity incentive effectively produces a winner-takes-all situation. However, another product might enter the market in case it is clinically superior[1].

1 Regulation (EC) No 141/2000, Article 8(3, a).

The effect on pricing strategies depends largely on the specific form of regulatory incentives provided (2/2)

From a theoretical point of view, knowing that no competitors can enter the market with either a similar product or a direct generic version of a product puts the company in a more powerful bargaining situation when negotiating prices with payers than if the medicinal product had not had an orphan designation and hence was protected by data protection and market protection.

In the case of orphan medicinal products, there is no risk of competitors entering the market with a similar product if they expect their potential market share to be above some profitability limit. Competition can only happen through innovation which brings improvements to patients.

In cases where a company is the first to bring a product to the market for treating a given disease, there is also no pricing of previous medicines to guide the price setting and provide a frame of reference.

From the company's point of view this might lead to a broader range of prices to choose from, but might also make price setting more difficult. There is no signal about what payers have been willing to pay for medicines of the given kind in the past. Furthermore, no data exists as to what payers have so far been willing to pay for improved treatments.

From the payers' point of view, no reference price exists from which to draw inference. This may lead to discussion of what a payer is willing to pay for the benefits of a given treatment.

In some cases, it might actually provide the payer with increased bargaining power; when a medicine is already available on the market and an improvement comes along, it is difficult to argue for a lower or unchanged price.

However, it might also put the payer in a worse bargaining position; if they choose not to buy the medicine because they find it too expensive, there is no alternative treatment for the patients for which the medicine is intended. This might create a severe pressure from the general public for reimbursement of the product.

PAEDIATRIC EXTENSION

For many new medicinal products obtaining marketing approval, undertaking investigations of the effect of the medicine in the paediatric population is mandatory.

However, obtaining a positive compliance check for a paediatric investigation plan provides a 6-month extension of the SPC if the product has one.

As such, the paediatric obligation is rewarded by extending the protection period.

In a pricing situation, extending the period in which generics cannot enter will put the company in a better bargaining position.

However, as shown previously in the chapter, the paediatric extension does not provide much of an extension of the effective protection period at the margin. As such, this increase in bargaining power is probably confined to a fairly small number of products.

Furthermore, we have not identified any specific information as to why the pricing strategy of companies should change specifically for the paediatric extension, beyond the obvious fact that it extends the protection provided by the SPC and hence extends the period in which the company can employ the pricing strategy applied during SPC protection. See section 3.1 for specific information on the SPC.

4.6 EFFECT ON HEALTHCARE BUDGETS

The interplay between protection and price negotiations in a country

There are generally two sides to the pricing of medicinal products and hence to the effect on healthcare budgets.

One side is governed by the protection schemes granted to new medicinal products. As has been shown and discussed at length earlier, the longer the protection period, the later the time at which generic companies can enter the market. At face value, longer protection thus alleviates some of the competitive pressure on pharmaceutical companies. However, as also discussed earlier, this does not necessarily equate to no competition as competition between originator companies exists as well.

Another element having an effect on the prices obtained by the pharmaceutical companies is the reimbursement side.

After products have been granted marketing approval, in many countries companies must negotiate a price with a central authority responsible for the reimbursement of pharmaceutical expenses in the given country.

The competitive situation in the market is an important factor in determining the bargaining power of the companies and the reimbursement authorities in these price negotiations, and hence there may be a connection between the protection schemes and the negotiable prices[1].

PROTECTION SCHEMES

As elaborated upon above, one side of the pricing strategy for medicinal products is made up of the protection schemes granted to these products. This includes both the IP protection systems such as patents and SPCs, and the regulatory protection schemes such as data protection and market protection.

These protection structures protect originator medicinal products against competition, albeit in different ways and to varying degrees. The competition landscape is one element of chief importance when setting prices in any industry. As such, through their effect on the competitive situation, the protection schemes for medicinal products influence the pricing possibilities of pharmaceutical companies.

REIMBURSEMENT

In most EU countries, the people receiving treatment with medicinal products do not directly pay for their treatment themselves. In most countries, either a private or a public insurance/reimbursement system is in place. From an economic point of view, the fact that the people receiving treatment do not directly pay for it themselves is a so-called market failure. It creates an incentive for patients to always demand the newest medicine, regardless of the price and perhaps more importantly, regardless of the relationship between price and clinical benefit, compared to the second-best medicinal product.

The reimbursement authorities in the Member States are responsible for negotiating prices with the pharmaceutical companies based on an assessment of clinical value and willingness to pay.

As such, the final decision on whether or not to reimburse a new medicinal product (effectively deciding whether it should be available in the given country or not) lies with the reimbursement authorities in the various Member States.

However, as the protection schemes, possibly granted at an EU level, influence the competitive situation surrounding a product, there is an interlink between the protection schemes and the bargaining position of the companies and reimbursement authorities, respectively.

This means that it might be pertinent to see the two systems as interconnected components rather than completely independent of each other. However, there are many other factors determining the bargaining power of the various players, and the degree to which the protection period is important might vary based on the interplay with these other factors as well.

1 There is, of course, a range of other factors which are also very important here. They include e.g. the willingness to pay exhibited in the past and the available patient base.

The cost of the paediatric regulation based on a 2016 study

STUDY ON THE ECONOMIC IMPACT OF THE PAEDIATRIC REGULATION

In 2016, a study estimating the economic impact of the Paediatric Regulation was published[1].

The study estimated that between 2008 and 2015 the total cost to the industry of the obligations inherent in the Paediatric Regulation was EUR 16.8bn, corresponding to EUR 2.1bn annually or EUR 18.9m per PIP.

Using data on eight medicinal products and extrapolating these findings, the study concludes that the combined adjusted economic value to the companies of the eight products studied was EUR 926m.

Appraising the societal value of the regulation is much more difficult than estimating the associated cost. Some of the positive effects of an increase in paediatric studies might be improved quality of life for children, avoided mortalities, hospitalisation costs, outpatient costs, time lost by informal carers and other improvements stemming from better treatment of children.

It is also important to note that some studies show that medicines are not suited for treating children. In these cases, the benefit to society is knowledge on what not to do.

The study compares the estimated positive effects on society from the paediatric studies undertaken to the extra cost stemming from the fact that the paediatric reward of extending the SPC for 6 months delays generic entry and hence competition.

It is important to note that these results are exploratory in nature, as appraising the monetary value to society is inherently difficult.

For two of the eight products, the study finds a positive benefit-cost ratio. For the other six products, the ratio is negative. This means that for two products the value to society outweighed the extra monopoly rent paid to companies. For the other six products, society paid more, so to speak, than the studies were worth.

However, when taking into account the fact that the regulation might entail certain spillover effects from investments in new R&D, contributing to job creation and growth, the study finds that the total societal value outweighs the total extra cost.

As such, for some of the parties involved, the regulation might entail additional expenditure, but from a societal perspective in general, the cost-benefit ratio is positive.

A 2017 report from the European Commission on the "State of paediatric medicines in the EU" reviews the effects of the paediatric regulation[2]. The economic results reviewed in the report are those of the 2016 study.

In general, the report concludes that the paediatric regulation has led to more research and medicinal products being approved for children, as also shown in section 4.2. The report does, however, conclude that "*the Regulation works best in areas where the needs of adult and paediatric patients overlap*"[3], which is based on the observation that paediatric studies are often linked to therapeutic areas which are priorities within the adult population.

As such, it seems that the paediatric regulation is helping to ensure that the development of paediatric medicinal products has become a more integral part of pharmaceutical innovation. However, as the current reward is dependent on sales within the adult population, most knowledge exists in the fields most highly prioritised in the adult population.

1 Ecorys, Technopolis group and Empirica for the European Commission (2016), Study on the economic impact of the Paediatric Regulation, including its incentives and rewards.
2 European Commission (2017), State of paediatric medicines in the EU.
3 European Commission (2017), State of paediatric medicines in the EU p. 24.

The effect on healthcare budgets of changing the protection periods provided to medicinal products is uncertain

SCENARIO ANALYSIS IN SECTION 2.5

In section 2.5, a scenario analysis of the possible savings from changing the mean effective protection period for medicinal products was presented.

The savings from decreasing the protection period provided for medicinal products were seen to materialise through lower prices due to competing generic products being able to enter the market at an earlier point in time.

The possible savings identified were, however, based on the assumption that the agents affected by such a changed effective protection period would not change their behaviour.

Looking at the literature reviewed in section 2.1 and the results presented in the same section, it would seem that a common change in the protection regime in the whole of the EU would, however, entail changes in e.g. the spending on pharmaceutical R&D within the EU.

However, changing any one of the protection schemes which count towards the total protection period for medicinal products might entail changes of varying degrees.

This is so because different protection schemes are the last to expire for different products. This means that a different number of products will be affected by generic competition ex post, depending on which protection scheme is changed. Furthermore, from an ex ante point of view there is much uncertainty as to which products will benefit from which kind of protection, e.g. whether a product will be able to obtain an SPC or not. Therefore, the whole framework regarding protection of medicinal products plays a role in the ex ante business case even though only one scheme will be the last to expire for a given product ex post.

As such, the possible savings from changing the protection period are associated with ex post considerations, while the possible behavioural effect on e.g. pharmaceutical R&D is seen from an ex ante point of view.

DIFFERENT PROTECTION SCHEMES

Market protection (and data protection) is the last IP scheme to expire in 39% of cases in the data material available for the present study[1]. At face value, this means that changing the period of market and data protection will impact the effective protection period of 39% of products.

This means that the savings from changing this will apply for 39% of products, i.e. generic competition will be able to enter the market earlier for only 39% of products.

However, this is an ex post consideration. From an ex ante point of view, the business case for many more products might be affected.

As previously elaborated upon, the market and data protection scheme grants a minimum period of protection for medicinal products of 8+2 years. This ensures a certain 'floor' of minimum protection. In an ex ante view, this is valuable as it is then known with certainty that no matter what happens during the development process (unless the R&D process is discontinued), the protection period can never be less than 8+2 years.

Changing the duration of this protection period will as such have a bearing on all medicinal products where the company ex ante attributes a positive probability that market protection will be the last protection scheme to expire.

In direct continuation of the above, it can be said that changing the protection period for either orphan medicinal products or the paediatric rewards would only entail possible savings for products where these schemes are the last to expire.

The important point here is the pivotal difference between the ex post savings and the ex ante effect on business cases.

As such, from the scenario analysis in section 2.5 it could be seen what the possible savings from an increase in generic competition might be. However, this has to be counterbalanced with the possible impact on the ex ante business case calculations of the pharmaceutical companies.

1 See table at the beginning of chapter 3.

4.7 PROPORTIONALITY OF INCENTIVES TO GOALS

Objectives of the regulation (1/3)

ORPHAN REGULATION

The regulation on orphan medicinal products was introduced due to the low number of patients suffering from rare diseases, which supposedly led to the pharmaceutical industry being reluctant to invest in R&D in this area[1]. In many cases, it would conceivably be unprofitable for pharmaceutical companies to research treatments for such diseases.

However, as is stated in Regulation (EC) No 141/2000 that "*patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry*".

To remedy the situation and hence incentivise R&D into orphan medicinal products, Regulation (EC) No 141/2000 governing the incentives provided to orphan medicinal products was enacted.

Through incentives such as fee reductions and waivers, scientific assistance, special research grants and a distinct protection scheme in the form of 10 years of market exclusivity, the regulation has sought to increase innovation within the treatment of rare diseases.

However, as the regulation on orphan medicinal products states that "*experience in the United States of America and Japan shows that the strongest incentive for the industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered*", the incentives providing 10 years of market exclusivity might be said to be of chief importance.

PAEDIATRIC REGULATION

The regulation governing the obligations and rewards for medicinal products for paediatric use was introduced due to the fact that many medicines used for children were given off-label. Hence, too little information was generally available on the workings of various medicinal products worked in children[2]. The paediatric regulation realises that children cannot simply be treated as small adults, and hence the carrying out of specific studies in the paediatric population is of paramount importance to prescribing medicines for paediatric use.

Regulation (EC) No 1901/2006 states that *"… many of the medicinal products currently used to treat the paediatric population have not been studied or authorised for such use. Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population"*.

More specifically the objectives of the regulation are *"… to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations"*.

As such, the objectives of the paediatric regulation are twofold. One aim is to incentivise the development of medicines for the paediatric population. The other aim is to ensure information on the workings of medicines in the paediatric population.

DATA PROTECTION AND MARKET PROTECTION

To obtain marketing authorisation for medicinal products, extensive data has to be collected and submitted to the authorities. The data is produced through pre-clinical and clinical testing. In the approval process, the data is used to prove the quality, efficacy and safety of medicinal products.

As such, the data includes all relevant knowledge pertaining to the use of medicinal products in patients. To the company having created said data, it is extremely valuable. The data is the proprietary property of the innovative company.

When data protection expires, generic companies can cross-reference to the originator company's data when submitting a marketing authorisation application. However, during the additional 2 years (possibly extended by another year) of market protection, a generic product cannot be placed on the market even if it obtains marketing authorisation.

1 https://ec.europa.eu/health/human-use/orphan-medicines_en.

2 EMA (2016), 10-year Report to the European Commission, General report on the experience acquired as a result of the application of the Paediatric Regulation.

Objectives of the regulation (2/3)

The overarching goal of the regulation on data protection and market protection is thus to provide originator companies with a minimum period of 10 years during which generic companies cannot enter the market with a direct copy of their product. This period should incentivise companies to undertake pharmaceutical research as they are always guaranteed a minimum of 10 years to recoup at least some of their investment.

However, data protection and market protection do not protect against competition by innovation. This means that should another company develop a medicine to treat the same disease, but containing another molecule, it is free to seek marketing authorisation for this. Through this provision, data protection and market protection should as such not deter new innovation, but might rather encourage it.

THE INCENTIVES

In section 4.1.4 it could be seen that data protection and market protection are by far the most important mechanisms for extending the effective protection period of medicinal products. Both the average and marginal effects were quite pronounced.

The market exclusivity inherent in the orphan regulation also had a considerable effect, while both the paediatric incentive and the one-year extension of market protection for approval of a new indication had rather marginal effects.

While for data protection, market protection and the paediatric incentives, the longer effective protection period is the most important incentive for companies, for orphan medicinal products other incentives are also at play, including e.g. fee reductions and scientific advice.

However, all the initiatives are intended to create economic incentives for the companies. The fee reductions inherent in the orphan regulation directly affect the cost of bringing an orphan medicinal product to market. Scientific advice indirectly affects the cost by focusing the research plans so that they comply with the regulation. Both these incentives reduce development costs.

Increasing the effective protection period or conversely guaranteeing a minimum period of protection through data protection, market protection and market exclusivity affects the likelihood of generating a return on the investment after development.

To the extent that regulatory protection mechanisms stave off competition, the initiatives delay the time when companies are exposed to generic competition and hence downward price pressures. When negotiating prices with e.g. reimbursement authorities, this will put companies in a better negotiating position than if no or a shorter protection period existed. As such, this might allow companies to charge a premium price for a longer period.

However, even if generic products cannot enter the market, this does not necessarily mean that there is no competition in the market. Other originator companies might launch their own products based on their proprietary molecules.

In this case, originator companies will face competition even though their products are protected by IP rights or regulatory protection mechanisms.

It should be noted that competition between different originators having developed their own products for treating the same indication might be less fierce than competition from generics. This is the case if originator companies are concerned with recouping their initial R&D investment. If all competing companies have incurred high costs to bring their individual products to market, they may be reluctant to engage in fierce price wars. Generic companies, which often have much lower costs, might be more willing to “dump” prices to win market share.

Summing up, the above makes it clear that some initiatives provide certain cost reductions, while others provide the prospect of charging a premium price. This also means that some initiatives impose certain extra costs on the healthcare budgets of the European countries, while other initiatives increase costs, depending on the competitive situation.

PROPORTIONALITY

Whether the incentives are proportionate to the goals is, in the end, a political assessment. The previous chapter has sought to illuminate the effect of the various specific incentives.

Objectives of the regulation (3/3)

It has e.g. been shown how the amount of information and the number of medicinal products for treating disease in the paediatric population have increased since the enactment of the paediatric regulation.

Furthermore, it has been shown that the number of orphan designations has increased almost 15-fold since the enactment of the regulation. To the extent that this increase in the number of designations will lead to more treatment options for patients suffering from rare and neglected diseases in the future, this can be seen as an increase in innovation within the area and hence contributing to fulfilling the objective of the regulation.

The main instrument for achieving this has been the granting of extra regulatory protection for pharmaceutical companies.

The longer protection period means that the time when generic companies can enter the market is delayed. As also shown in chapter 2, generics are priced lower than originator products. Furthermore, the price of originator products decreases after generic entry. This is supported by some findings in the literature, while others find that originator products increase in price after generic entry. However, across the board, it is found that generic medicinal products are cheaper than originator products. Delaying the time when generics can enter will thus result in a higher cost to healthcare budgets.

However, as shown in this chapter, the granting of regulatory protection periods seems to have increased innovation within the orphan and paediatric area.

Furthermore, the econometric results from section 2.1 seem to reveal that there is a positive relationship between the amount of protection provided in other EU countries with which a country trades the most and the domestic spending on pharmaceutical R&D.

As there is a substantial amount of intra-EU trade, this means that in so far as the results of section 2.1 hold, the overall framework for protection within the EU impacts the spending on pharmaceutical R&D within the EU.

Quantifying the value of the extra innovation which might be due to the incentives described in this chapter is a daunting task. As the counterfactual situation is empirically unobservable, any such calculations would be associated with very considerable uncertainty. As such, providing any such calculation is deemed to be fruitless from a professional theoretical, economic point of view.

In the end, the question of whether the incentives are proportionate to the goals is a political one. This chapter and the other chapters in the report have sought to shed light on the workings of the incentives of the pharmaceutical regulation and any possible outcomes of this.

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CHAPTER 5

Case studies

Outline of chapter 5

5.1 List of medicines

5.2 Blockbusters

5.3 Orphan medicinal products

5.4 Generics

5.5 Antibiotics

5.6 Vaccines

5.7 Conditional marketing authorisations

5.8 Paediatric-use marketing authorisations

5.9 General considerations

Chapter 5 – Main conclusions (1/2)

DEVELOPMENT TIME AND PROTECTION PERIOD

Most of the case studies analysed in this section show development times of less than 10 years, but more than 5 years. We have previously seen how 50% of products in the sample have a development time of between 5 and 15 years. Most of the cases studied fall within this interval, albeit with development times of 10 years or less.

As most products studied in this section have a development time between 5 and 10 years, they qualify for an SPC. Most of the products have obtained this, albeit in a varying number of countries. That most products have obtained an SPC entails that the protection period offered by the combination of first patent and SPC is 15 years in most cases. However, the fact that SPCs have not necessarily been obtained in all countries likewise shows the fragmentation of the SPC system across member states.

Interestingly, all of the blockbuster products studied in this section have obtained an SPC. Furthermore, all except one of the blockbusters have obtained the 6-month paediatric extension of protection (or is expected to). This seems to underline the fact that the value of the reward of completing a PIP depends on the volume and value of sales within the adult population.

FRAGMENTATION

The tables showing in which countries a given product has obtained an SPC, provides valuable insights on the fragmentation of the SPC system. First of all, it is evident that in most cases SPCs are only applied for in a selection of countries. It is likewise evident that for the paediatric extension, differences exist between countries as well. In some countries a paediatric extension has been granted, while in others it is not present for the same product. Moreover, the tables show that it is not uncommon for an application for a SPC to be granted in some countries, while being rejected in others.

When looking across the cases presented in this chapter, Italy and Portugal stand out as the countries with most SPC applications, followed by Denmark, Spain, Greece, Hungary and Luxembourg.

PAEDIATRIC EXTENSION

Regarding orphan medicinal products, an interesting learning from the case studies concerns the extension of protection periods as a result of paediatric studies.

If paediatric studies are completed, an orphan medicinal product can obtain a 2-year extension of the market exclusivity period, regardless of whether it has an SPC or not. A non-orphan medicinal product with an SPC can obtain a 6-month extension of the SPC.

The case studies include examples of products which are withdrawn from the orphan register and subsequently granted the 6-month extension of the SPC. Whether the withdrawal from the register is directly linked to a wish to obtain the extension of the SPC instead of the extension of market exclusivity period is unknown. It is, however, an interesting use of the incentives, which has been deemed legal by a court of law[1]. In doing this, the companies combine the orphan incentives with a subsequent reward of an extended SPC.

SECONDARY PATENTS

In some of the case studies examined in the previous section, the total effective protection period, when counting secondary patents, approaches an average of 30 years across the EU countries. It seems to be the case that the products in this section with the longest total effective protection period are also among some of the most profitable products.

However, it is also evident that the existence of secondary patents not necessarily prevents generic or biosimilar competitors from entering the market. This happens both through patents being challenged but also through inventing "around" the patents, making sure not to infringe any secondary patents when bringing a similar product to the market. As such, the effective protection period depicted for the case studies should not be seen as a period in which entry of competitors is not possible. However, it is interesting that some of the most profitable products seem to have the largest number of secondary patents. This could seem to suggest that more effort is being put into the patenting process, the more profitable the medicinal product is. Whether the number of secondary patents will lead to more court cases in the future, as competitors seek to enter the market, remains to be seen.

1 See Novartis v. Teva described at http://www.limegreenipnews.com/2016/07/italy-teva-vs-novartis-paediatric-extensions-of-spcs-valid-following-removal-of-orphan-designation/ and https://www.lexology.com/library/detail.aspx?g=c45e5f48-de26-46f6-afc8-8c13c2eabb63

Chapter 5 – Main conclusions (2/2)

ORPHAN DESIGNATIONS IN THE US COMPARED TO THE EU

In several of the presented cases, it is evident that the given medicinal product has several orphan designations and perhaps a marketing authorisation as an orphan medicinal product in the United States, but fewer such designations or perhaps none in the European Union. One difference between the US and the EU is the prevalence criteria. In the EU, no more than 0.05% of the population must be affected by the disease for it to be possible for a medicinal product to obtain orphan designation. In the US, this threshold is around 0.06%[1].

However, this does not necessarily mean that the product concerned cannot be used to treat the same diseases in the US and the EU. In many cases, it merely reflects the difference in allocation of orphan designations between the US and the EU. From the sample of non-representative cases in this chapter, it seems that the rules regarding orphan designation in the US allow for more indications to be regarded as rare than is the case in the EU.

MARKET EXCLUSIVITY EXTENDING PROTECTION

The cases include several examples where the 10-year market exclusivity period granted to orphan medicinal products extends the protection period for the given product. This might e.g. be because the orphan disease is not necessarily the first indication the product is approved for, or it might be in cases where a product obtains several orphan approvals.

However, it is likewise evident from the cases that market exclusivity does not grant protection against clinically superior products bringing extra benefit for patients. This implies that it does not look as if this part of the orphan incentives is detrimental to new beneficial innovation.

SECTOR CHARACTERISTIC

As is also apparent from the cases, acquiring molecules from other companies is not uncommon within the pharmaceutical industry. In some cases, start-up companies have developed a medicinal product all the way through phase 2 clinical trials before being acquired by a larger pharmaceutical company.

In 12 of the 21 cases presented in the following, the company currently marketing the product was not involved in the original discovery of the active ingredient. In these 12 cases, the company currently marketing the product has acquired the rights to marketing the product either through acquisitions or licensing agreements.

This indicates the existence of a division of labour through the development value chain where start-ups discover and develop innovations, and when these are to be marketed, the distribution channels and marketing experience of larger pharmaceutical companies are needed. However, keep in mind these are merely case studies; we have not carried out any analysis looking at the scope of this division of labour, its change over time nor of implications.

The cases include products across a wide spectrum of revenues. Several products have a very high revenue, also called blockbusters[2]. These include e.g. Humira, which had revenue of USD 16bn in 2016. At the lower end of the spectrum there are products such as Buccolam with a world wide revenue of USD 47m in 2017.

NON-RANDOM SELECTION

It is important to point out that these case studies have not been randomly chosen from the available pool of medicinal products. As such, the main points and key takeaways are not representative for all medicinal products. Rather they are examined to highlight certain intricacies in the incentives and rewards for medicinal products in Europe.

1 The Orphan Drug Act, available at https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21 defines a threshold pertaining to orphan medicinal products, such that they cannot affect more than 200,000 people in the US or that there is no reasonable expectation of recovering the R&D expenses.

2 Revenue higher than USD 1bn per year.

The following chapter contains 21 case studies of medicinal products

GENERAL OVERVIEW VERSUS INDIVIDUAL PRODUCT VIEW

The analyses carried out in the previous chapters focused on providing a general overview of the workings of the various incentives and rewards for medicinal products in Europe. The general approach allows general conclusions to be drawn and provides an understanding of the effects of the incentives across medicinal products.

However, as has also been pointed out in the general analysis, the lack of an overall effect of an incentive on the average medicinal product does not necessarily mean that it is unimportant for individual products.

Furthermore, the various obligations and rewards contained in the regulations on medicinal products can have different consequences, depending on events affecting the life-times of products[1].

Additionally, the actual use of the various incentives and perhaps especially the interaction between the various incentives in cases from the real market are of interest.

To accommodate these effects and interactions pertaining to individual products in the study, the following chapter contains 21 case studies of a selection of medicinal products.

CASE STUDIES

The cases seek to shed light on a range of different details regarding the workings of both the intellectual property framework and the regulatory structure governing medicinal products – i.e. how do the various incentives combine during the life-cycle of a given product and how do companies behave when choices regarding the various non-cumulative incentives have to be made.

The case studies are not randomly selected from the population of available medicinal products. Rather, the list has been developed in close collaboration with the European Commission.

As such, the medicinal products included in the following have been selected so as to describe certain intricacies, issues, actual uses of incentives and key insights into the framework conditions.

The selected cases can be categorised under the following seven headlines:

- Blockbusters
- Orphan medicinal products
- Generics
- Antibiotics
- Vaccines
- Conditional marketing authorisation
- Paediatric-use marketing authorisation

For the case studies, where possible, we include a calculation of the effective protection period, carried out in the same manner as the calculation used in previous chapters[2].

MAIN INSIGHTS

Many cases provide a range of interesting insights, potentially shedding light on many different aspects of the framework conditions and the actual use of the incentives for medicinal products.

To the extent possible, we describe all these insights for each separate case. However, in the interest of providing clarity and ease the reading of the cases, we conclude each case by stressing one *main insight*. This is our attempt to distil each case, which potentially contains many interesting insights and intricacies, into one key takeaway. This does not mean that all other information given and use of incentives described, besides the one provided in the main insights section, are irrelevant. It is merely an attempt to present the reader with one notable main insight from each case which we find the particular case to be an illustrative example of.

At the end of the chapter a table containing information on the status of SPCs and their applications across countries is presented.

1 By 'life-time of a product' is meant the time spanning from discovery until the product is no longer relevant on the market. The regulations referred to are Regulation (EC) No 726/2004, Regulation (EC) No 469/2009, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006.
2 I.e. including all patents, SPCs and regulatory protection periods to determine how long a given product has protection from generic competition.

5.1 LIST OF MEDICINES

List of medicinal products for case studies

Name	Company	Group	Date of first patent	Date of MA	Date of SPC expiry	Date of PIP compliance check
Humira	AbbVie	Blockbuster	01/08/1997	08/09/2003	April 2018	20/06/2014 01/04/2016 14/10/2016
Sovaldi	Gilead Sciences	Blockbuster	26/03/2008	16/01/2014	January 2029	-
Herceptin	Roche	Blockbuster	15/06/1992	28/08/2000	July 2014/2015	-
Enbrel	Pfizer	Blockbuster	10/09/1990	03/02/2000	February 2015	13/12/2011
Xagrid	Shire	Orphan	-	16/11/2004	-	14/02/2014
Revlimid	Celgene Nordic	Orphan	24/07/1997	14/06/2007	June 2022	-
Imbruvica	Janssen-Cilag and AbbVie	Orphan	28/12/2006	21/10/2014	October 2029	-
Viagra	Pfizer	Orphan (non-orphan)	07/06/1991	14/09/1998	June 2013	-
Revatio	Pfizer	Orphan	07/06/1991	28/10/2005	-	-
Cystadrops	Orphan Europe	Orphan	26/01/2007	19/01/2017	-	-
Tobi Podhaler	Novartis	Orphan	08/05/2001	20/07/2011	2026	-
Glivec	Novartis	Orphan	25/03/1993	07/11/2001	June 2016	09/03/2012
Cometriq Cabometyx	Ipsen	Orphan Non-orphan	24/09/2004	21/03/2014 09/09/2016	March 2029	-
Tracleer	Actelion	Orphan	04/06/1992	15/05/2002	February 2017	21/03/2014
Losec	AstraZeneca	Generic	03/04/1979	1988	November 2002/2003	-
Tygacil	Pfizer	Antibiotic	21/08/1992	24/04/2006	August 2017	12/12/2014
Dificlir	Astellas Pharma	Antibiotic	15/07/2003	05/12/2011	December 2026	-
Cervarix	GSK Pharma	Vaccine	08/10/1999	20/09/2007	September 2022	-
Infanrix Hexa	GSK Pharma	Vaccine	15/05/1993	23/10/2000	October 2015	-
Sutent	Pfizer	Conditional marketing authorisation	15/02/2001	19/07/2006	July 2021	-
Buccolam	Shire	Paediatric-use marketing authorisation	10/09/1975	05/09/2011	-	06/08/2010

Note: Absence of a date for PIP compliance check can reflect the granting of a waiver or deferral as well as the PIP being ongoing, and therefore as yet unfinished. The date of SPC expiry are for the countries in which an SPC has been granted.
Sources: European Medicines Agency website and Alice de Pastors database of SPCs provided by the European Commission.

5.2 BLOCKBUSTERS

Humira by AbbVie (1/2)

INDICATIONS

Humira is a biological medicinal product that acts on the immune system. Humira is approved for treatment of the following indications:
Juvenile idiopathic arthritis, paediatric plaque psoriasis, paediatric Crohn's disease, adolescent hidradenitis suppurativa and Paediatric Uveitis.[3]
In short, these are diseases that cause red scaly patches on the skin (psoriasis), inflammation of the joints (arthritis) or inflammation or ulcers in the gut.

DEVELOPMENT TIME AND PROTECTION

The active ingredient in Humira is Adalimumab. A marketing authorisation for Humira in the EU was granted in September 2003, after the first patent had been filed in August 1997[27]. This implies a development time of 6 years. Humira was developed through a collaboration between the BASF Bioresearch Center in Massachusetts and the Cambridge Antibody Technologies in the UK. In 2000 Abbott bought the BASF center for USD 6.9bn[29]. In 2013 Abbott split into two entities, one being AbbVie, which retained the rights to Humira[29].

In the countries where an SPC has been granted, it is due to expire in 2018,[1] including a 6-month paediatric extension. This implies an effective protection period from the first patent and SPC of 15 years.
According to Abbvie, the composition-of-matter patent in the European Union is expected to expire in most countries in October 2018. The equivalent patent in the US expired in December 2016.[2]
When all patents and protection schemes are included, the average effective protection period across countries in the EU is 28.2 years. This is a relatively long protection period that falls within the 99th percentile when comparing to the histogram in section 1.4.2. This is underlined by the fact that during its lifetime Humira has been protected by more than 100 patents[28].

However, as will be described in more detail overleaf, marketing authorisations have been granted for biosimilar products despite the number of patents. Exactly when the biosimilar products can enter the market remains to be seen.

PAEDIATRIC USE

The European Medicines Agency agreed on three paediatric investigation plans for Humira[27].
In 2015, the EMA approved an extension to the indication, to include the treatment of children and adolescents.[6] This implied a 6-month extension to the SPC protection period.

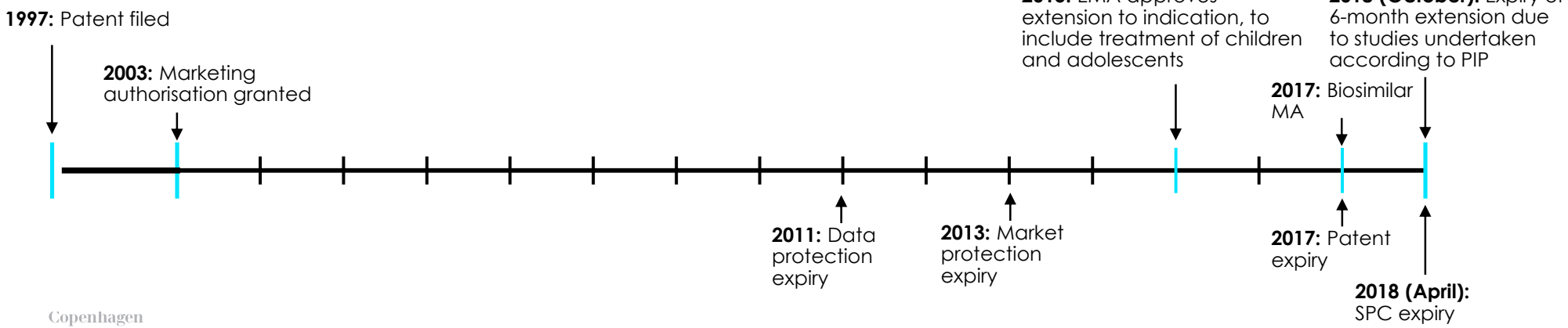
ORPHAN MEDICINAL PRODUCT

While Humira is not designated as an orphan medicinal product in the EU[9], it is designated for six orphan uses in the US and has been approved for four of these. Market exclusivity extends to 2023 for the latest orphan designation in the US.[10]

All the designated indications for which AbbVie has received marketing approval by the FDA are also present in the full indication in the EU marketing authorisation for Humira.

The designations as an orphan medicinal product in the US have been criticised by patient advocacy groups, which claim that Humira is not a 'true' orphan medicinal product as it has later been approved for several other indications and reached blockbuster status.[11]

TIMELINE



Humira by AbbVie (2/2)

PRICE CHANGES AND EXPECTED FUTURE SALES

According to the investor publication Barron's, the price of Humira has increased by more than 13% a year over the past decade, from USD 1,258 to USD 4,441 in the US.[4] Combined with the wide range of indications for which Humira is approved, this has made it the top-selling medicinal product in many of the previous years. In 2016 sales topped USD 16bn.[20]

Following expiry of an SPC in 2018, AbbVie expects international sales of Humira to decrease by 15% a year until 2020. [5]

BIOSIMILARS

In May 2017, the EMA recommended that the biosimilar medicinal product *Imraldi* should be approved[7]. Imraldi was granted a marketing authorisation in August 2017.[17] However, Imraldi cannot be placed on the market until expiry of the last SPC for Humira in October 2018[26].

Additionally, Amgen Europe has obtained duplicate marketing authorisations for the two biosimilars Solymbic and Amgevita (both in March 2017).[15,16,18]

In August 2017, the FDA approved the biosimilar medicinal product Cyltezo, made by Boehringer Ingelheim[8], in the US. In September 2017, CHMP adopted a positive opinion recommending the granting of a marketing authorisation to Cyltezo[24], which was then granted in November 2017.[25] In the press release from Boehringer Ingelheim concerning the marketing authorisation, the company states that the medicinal product is not commercially available, and will only be made available in Europe following the expiry of the SPC for Adalimumab (Humira) in October 2018.[25]
With the entrance of biosimilars into the market, competition can be expected to drive down prices, which will tend to reduce the profit made by AbbVie, as can be seen from their expectation that sales of Humira will decline by 15% a year between 2018 and 2020.[5].

The entry of multiple biosimilars, even in the face of protection from secondary patents, may reflect the attractiveness of the market. Of course, even if secondary patents did not extend the effective protection period, they can still work to broaden protection, e.g. by protecting the manufacturing process.

Biosimilar producers have to conduct a number of studies to demonstrate similarity to the reference medicinal product[21,22], which implies a longer and more costly development period than what is usually the case for chemical generics.[23] This will tend to make price discounts smaller in the case of biological medicinal products than in the case of small molecule medicinal products.

STRATEGY FOR EXTENDED PROTECTION

In the EU, competitors have brought patent cases before UK courts in an attempt to 'clear the way' for biosimilar entry following the expiry of the composition patent.

In 2016, a UK court invalidated two patents relating to Humira, after cases had been brought by Samsung and Fujifilm. Both these companies have announced that they intend to market biosimilars following the expiry of the first patent in 2018 (in Europe).[12,13]

AbbVie has been accused of employing a deliberate strategy of obstructing market entry by dragging out proceedings to cause maximum expense and inconvenience, only to voluntarily offer to invalidate the patents in question before a verdict.[14,15]

It has been argued that by doing so AbbVie effectively increases the barriers to biosimilar entry that are already relatively high as a result of the complexity and costliness of developing biosimilars. In the worst-case scenario, potential competitors come to expect a prolonged legal conflict in connection with the entry of biosimilars. The cost of such conflict could reduce the profitability of attempting entry in the first place, effectively deterring would-be competitors from entering the market.

In the US, AbbVie has protected Humira by a range of secondary patents,[12] covering formulation, manufacturing process, method of treatment etc. AbbVie executives have publicly stated their intent to enforce this patent estate, and their belief that this will be sufficient in delaying biosimilar entry in the US until 2022[2].

MAIN INSIGHT

In the case of Humira, it is striking that one product can be protected by more than 100 patents. However, the existence of secondary patents does not seem to have prevented biosimilar entry following the expiry of the protection relating to the SPC. In fact, multiple competitors have obtained marketing authorisations and are intent on entering the market as soon as the last SPC expires. This level of interest could be due to the inherent size and attractiveness of the market. Even though the product started out as an orphan medicinal product in the US, subsequent authorisations have put it into the blockbuster category.

Sovaldi by Gilead Sciences

INDICATIONS

Sovaldi contains the active ingredient Sofosbuvir and is used to treat hepatitis C.[1] Sovaldi is approved in combination with other medicinal products for the treatment of chronic hepatitis C (CHC).[6] Hepatitis C is an infection in the liver caused by the Hepatitis C virus.[3] In 2016 global sales of Sovaldi amounted to USD 4bn[13] down from USD 10.3bn[14] in 2014, due to growing competition.

DEVELOPMENT TIME AND PROTECTION

The first patent was filed in March 2008.[2] Sovaldi was discovered by Pharmasset, which was acquired by Gilead in 2012 for USD 11bn, after phase 2 trials had been initiated[15]. The medicine was granted a marketing authorisation by the European Commission in January 2014,[3] reflecting a development period of 6 years.

An SPC for Sovaldi has been granted in most EU member states, while applications are still pending in others. The SPC is due to expire in January 2029, thus implying an effective protection period from the first patent and SPC of 15 years.[4]

When all patents and protection schemes are included, the average effective protection period across countries in the EU extends to 18.8 years. This implies an effective protection period that falls in the fourth quartile, i.e. among the 25% of medicinal products with the longest protection when comparing to the histogram in section 1.4.2. This is due to the fact that Sofusbuvir is protected by 14 different patent families[16].

PAEDIATRIC USE

In July 2017, the EMA approved an extension to the indication for Sovaldi, and the indication now includes the use of Sovaldi for adults *and adolescents aged 12 to 18 years.*[7] The EMA has waived the obligation to conduct studies of children aged 3 years and younger, and the PIP is due to be completed by April 2018.[12] Completion of the paediatric investigation plan will imply a 6-month extension of the SPC.

ORPHAN DESIGNATIONS

While Sovaldi is not designated as an orphan medicinal product in the EU, the use of Sovaldi in adolescents was given an orphan designation in the US in 2016, with a marketing authorisation as an orphan medicinal product being granted in 2017.[5]

SIMILAR MEDICINAL PRODUCTS BY GILEAD

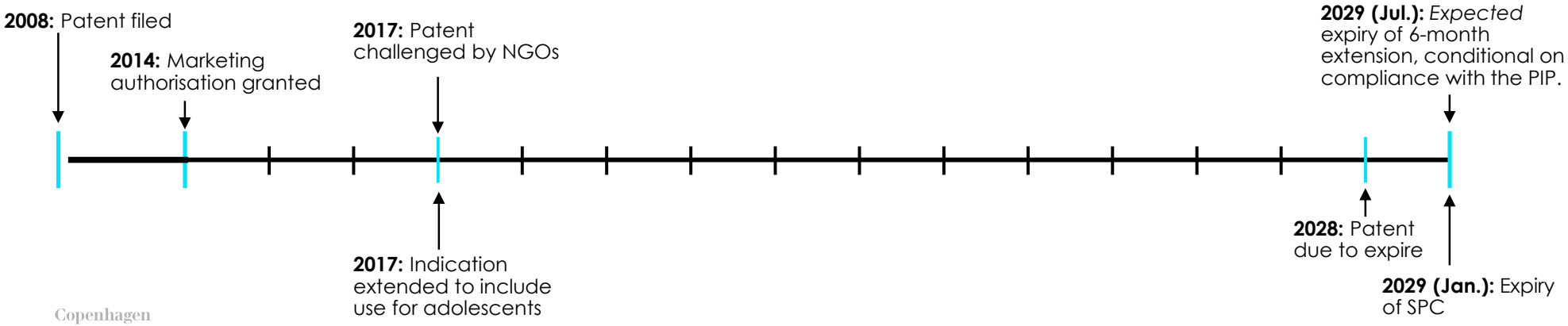
Gilead Sciences also markets Epclusa, Vosevi and Harvoni in the EU. All three medicinal products are used to treat Hepatitis C and contain Sofosbuvir as well as other active ingredients.[9,10,11]

MAIN INSIGHT

The patent for Sovaldi, discovered by Pharmasset and later bought by Gilead, has been challenged repeatedly in Europe, e.g. in March 2017 by Doctors of the World (Médecins du Monde) and Doctors Without Borders. These organisations argue that the science behind the medicinal product is not new, and that the patent is therefore open to challenge.[8]

Patents can thus be challenged by stakeholders that are not potential competitors, but rather view themselves as representing the interests of the patients. Since no rulings have been made yet in this particular case, we cannot, at the time of writing, conclude whether this will impact protection in this particular case.

Timeline



Herceptin by Roche (1/2)

INDICATIONS

Herceptin is a biological medicinal product containing the active ingredient Trastuzumab.[3] Herceptin is the first manufactured Trastuzumab. Herceptin is approved for the treatment of adult patients with metastatic or early breast cancer, as well as the treatment of adult patients suffering from metastatic gastric cancer.[9] Note that Herceptin can only be used for cancers which have been shown to 'overexpress' the protein HER2.[3] Patients are thus grouped according to the specifics of their disease, and in that sense Herceptin represents a personalised medicine.[12] In 2016, global sales of Herceptin was USD 6.88bn.[14]

DEVELOPMENT TIME AND PROTECTION

Genentech, a member of the Roche Group, filed the first patent in 1992.[2]

A marketing authorisation for Herceptin in the EU was granted in August 2000.[3] This implies a development time of 8 years.

An SPC expired in most EU countries in 2014, with expiry in the remainder of the countries in 2015. In the US, the protection is set to run out in 2019.[4] This implies an effective protection period in the EU from the first patent and SPC of around 15 years.

Including all patents and protection schemes, the average effective protection period across countries in the EU is 29 years, which places Herceptin among the medicinal products with the longest effective protection period, more specifically within the 99th percentile when comparing to the histogram in section 1.4.2. This is possible as at least 40 patents protects Herceptin[15].

As will be described thoroughly on the next page, these secondary patents do however not seem to ultimately prevent biosimilar entry, which is possible after a marketing authorisation is granted for e.g. Ontruzant in late 2017.

Whether the secondary patents are the reason for the 2-year delay from SPC expiry in 2015 to biosimilar entry in 2017 could not be verified.

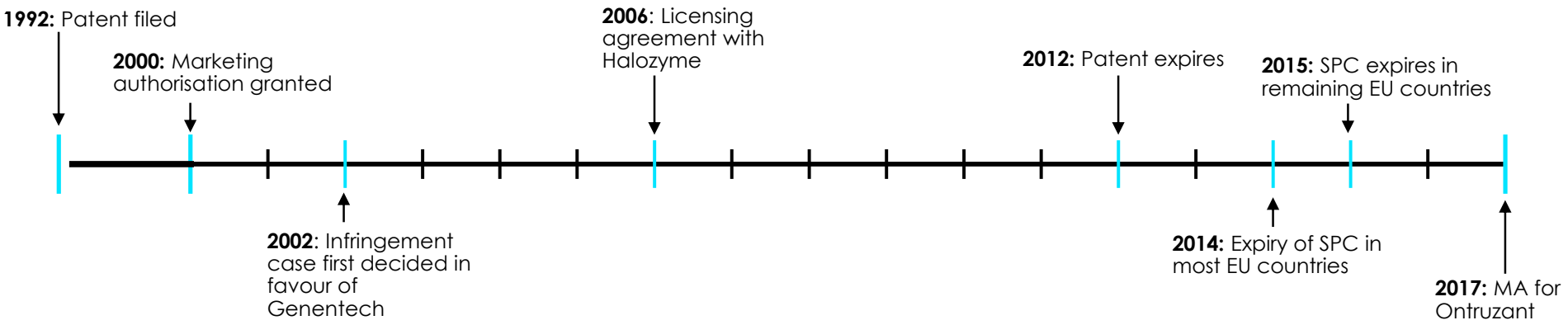
PAEDIATRIC USE

In a *'summary of product characteristics'*, the EMA states that there are no relevant uses of Herceptin in the paediatric population, and that the EMA has waived the obligation to conduct studies on paediatric use.[11]

ORPHAN DESIGNATIONS

While the medicinal product does not have an orphan designation in the EU, its indication for metastatic gastric cancer carried an orphan designation in the US, designated in 2009. Marketing approval was granted in 2010, and market exclusivity ended in October 2017.[10] As written above, Herceptin is also approved for the treatment of metastatic gastric cancer in the EU.

Timeline



Herceptin by Roche (2/2)

PATENT INFRINGEMENT CASE BY CHIRON

During the first half of the 2000s, Chiron repeatedly sued Genentech, claiming that Herceptin infringed patents held by Chiron.

In 2002, a jury ruled against Chiron,[5] a ruling later affirmed by an appeals court in 2004.[6] In 2005, the parties settled remaining patent issues.[7]

LICENSING AGREEMENT

In 2006, Roche entered into an agreement with Halozyme, under which a subcutaneous formulation of Herceptin, Herceptin SC, was developed. This formulation eventually gained a marketing authorisation in 2013.[8]

ENTRY OF BIOSIMILARS

Several companies submitted biosimilar versions of the medicinal product to the EMA in 2017, including Amgen, Mylan and Biocon and Samsung Bioepis.

In November 2017, a marketing authorisation was granted by the European Commission for Ontruzant, a biosimilar produced by Samsung Bioepsis.

However, at the time of writing, biosimilar entry is yet to happen[1].

Trastuzumab biosimilars are expected to be priced at 80% of the price of the original product.[1]

Looking at the results from the literature described in section 2.3, this is a relatively small drop in price in connection with the entry of competitors. This may reflect the inherent costliness of developing biosimilars, e.g. due to the additional studies required before biosimilars can be marketed, in comparison to generics.[13] It might also reflect the fact that the process of manufacturing biological products usually is more resource-intensive than for chemical compounds, and hence the price decrease when generics enter a market might be greater than when biosimilars enter a market.

The period of time from expiry of the SPC in 2015 until (expected) biosimilar entry in 2018 is noteworthy since it represents a period where Roche is not in competition with biosimilar manufacturers, even though the protection granted by the first patent and SPC has expired. Since competition will tend to drive down prices, the absence of competition will tend to benefit Roche.

A possible explanation for this is the existence of the secondary patents described on the previous page.

MAIN INSIGHT

Biosimilars are projected to cause the price of the medicinal product to decrease by 20%. When there is a time lag between expiry of the protection related to the first patent and SPC and biosimilar entry, this represents a benefit for the company that holds the patent and markets the medicinal product. This delay in biosimilar entry, after expiry of all SPCs, might be due to the protection provided by the secondary patents.

Another interesting insight is likewise that at least 40 patents protect Herceptin, granting the product a total effective protection period of 29 years. However, as a biosimilar was able to enter the market in late 2017, this did not completely protect Herceptin from competition, after expiry of the last SPC, albeit there was a lag before biosimilar entry.

Enbrel by Pfizer (1/2)

INDICATIONS

Enbrel is a biological anti-inflammatory medicine containing the active ingredient etanercept.[1] It is administered by injection.

Enbrel is approved for the treatment of the following diseases[2]:

- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Psoriatic arthritis
- Axial spondyloarthritis
- Ankylosing spondylitis
- Non-radiographic axial spondyloarthritis
- Plaque psoriasis
- Paediatric plaque psoriasis

In general, these diseases cause inflammation of the joints (arthritis), the spine (spondylitis), or red, scaly patches on the skin (psoriasis).[1] Notably, Enbrel is approved for some of the same indications as another biological medicinal product, Humira[3] (see case study on Humira). In 2016 global sales of Enbrel was USD 5.72bn.[14]

DEVELOPMENT TIME AND PROTECTION

The active ingredient in Enbrel, etanercept was first developed by Immunex, which filed the first patent in 1990.[4]

Immunex was later acquired by Amgen,[5] which entered into an agreement with Pfizer, under which Pfizer holds the rights to market the medicinal product in Europe.

A marketing authorisation was granted in the EU in February 2000,[1] reflecting a development time of 10 years.

SPCs have been granted in most EU member states[4] and expired in August 2015, following a 6-month extension due to paediatric studies conducted as part of a paediatric investigation plan, completed with a positive compliance check in 2011.[6] This implies a protection period from the first patent and SPC of around 15 years.

In 2011 a patent claimed to extend the protection of Enbrel by 17 years from the date of issuance was issued[15].

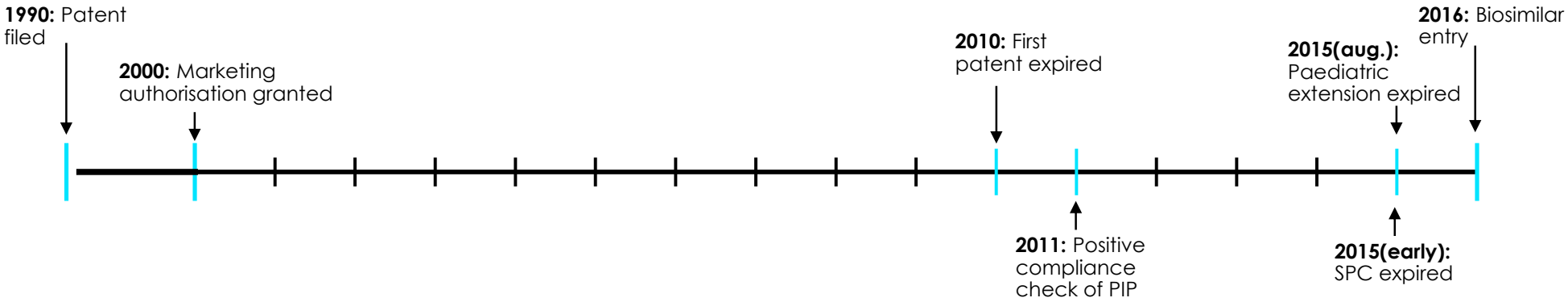
PAEDIATRIC USE

A paediatric investigation plan was concluded with a positive compliance check in 2011.[6]

ORPHAN

Enbrel was not authorised as an orphan medicine, nor has it been designated as such for any indications.

TIMELINE



Enbrel by Pfizer (2/2)

BIOSIMILAR ENTRY

In January 2016, a marketing authorisation was granted to Benepali, with Samsung Bioepis (a collaboration on biosimilars between Samsung and Biogen) as the marketing authorisation holder.[7] This marked the first biosimilar entry on the market. Since then, Erelzi by Sandoz has also been approved[8], and Pfizer has obtained approval for the same medicinal product under the name Lifmior.[9]

In October 2016, several news sources reported that Pfizer had cut prices of Enbrel in Ireland by 30%.[10,11] This was done in compliance with the Irish *Framework on the supply and pricing of medicine,* which states (section 8.1) that a biological medicinal product for which the patent has expired, and where a biosimilar has entered the market, must reduce prices to 80% of the original ex-factory price (the price at which it was first approved for reimbursement by the relevant authority).[12] Additional rebates mean that the price cut amounts to 30%.

According to the news sources, Biogen had priced Benepali at a 30% discount to Enbrel, meaning that after the price cuts by Pfizer, the two medicinal products are selling at identical prices.[10]

The Healthcare Enterprise Alliance, which represents manufacturers of generics and biosimilars in Ireland, stated that the clause amounted to "biosimilar blocking".[10]

Nonetheless, reports suggest that sales of the biosimilar Benepali produced and commercialised by Biogen have surpassed expectations, and the company is quoted as stating that Benepali has been "gaining share at a rate previously unseen for a biosimilar anti-TNF".[13]

MAIN INSIGHT

From a theoretical perspective, the entrance of multiple biosimilars will strengthen competition in the market and contribute to drive down prices.

As such, this is an example of a biological medicinal product that faced biosimilar competition from multiple competitors shortly after the expiry of the protection afforded by the first patent and SPC.

The active ingredient in Enbrel was discovered by Immunex and later, through acquisition and licensing agreements, brought to market by Pfizer.

5.3 ORPHAN MEDICINAL PRODUCTS

Xagrid by Shire

INDICATION

Xagrid contains the active substance Anagrelide[1]. Shire acquired the worldwide rights to Xagrid (or Agrylin, which it is called in some countries), from Bristol-Myers Squibb in 1999[10].

Xagrid is approved for the reduction of elevated platelet counts in at-risk essential thrombocythemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy[2]. ET is a rare chronic disease in which too many blood platelets are produced in the bone marrow.

PAEDIATRIC USE

A paediatric investigation plan has been completed, with a positive compliance check. This implies a 2-year extension of market exclusivity.

ORPHAN DESIGNATION

Xagrid was designated an orphan medicinal product in December 2000[1].

A patent for the active substance in Xagrid (Anagrelide) is not present in the Alice de Pastors database[8] that is used throughout this section. However, from the European Patent Register of the European Patent Office, it is clear that Shire does hold a number of patents related to Anagrelide.[7] It was granted a marketing authorisation in November 2004[1].

The marketing authorisation was granted under *exceptional circumstances,* reflecting the fact that the rarity of the disease meant that it was not possible to obtain complete information about Xagrid[1].

As a result of the exceptional circumstances authorisation, Xagrid is subject to annual review, and the MA holder regularly informs CHMP of all information published regarding the efficacy of the medicine[1].

Xagrid was withdrawn from the orphan register in November 2016 as the 12-year exclusivity period ended[1] (10 years of exclusivity, and an additional 2 years due to PIP studies).

GENERIC ENTRY

In December 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending granting of a marketing authorisation for a generic version of Anagrelide[9].

MAIN INSIGHT

A marketing authorisation under exceptional circumstances can be granted if the indications for which the medicinal product is intended are encountered so rarely that the applicant cannot reasonably be expected to provide the comprehensive data that would normally be required.[5]

This framework thus allows for the introduction of medicinal products that could not be introduced within the regular framework.

Since no safety issues have caused the authorisation to be revoked, this has ultimately been to the benefit of the patients who suffer from the disease.

Timeline

Revlimid by Celgene (1/2)

INDICATIONS

Revlimid is approved for the treatment of multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, subject to certain conditions regarding the patient's previous treatment. These diseases are cancers affecting blood cells and bone marrow.[3] In 2016 global sales of Revlimid amounted to USD 4.42bn.[15]

DEVELOPMENT TIME AND PROTECTION

Revlimid contains the active ingredient Lenalidomide[1] and is developed and marketed by Celgene. The first patent was filed in July 1997[2]. Due to the granting of SPCs, the effective protection from the first patent and SPCs is set to expire in the EU in June 2022.[2]

The marketing authorisation for Revlimid was granted in 2007[3], implying a development time of 10 years.

When the SPC is included, this further implies that the first patent and SPC have afforded an effective protection period of 15 years in the EU.

When all patents and protection schemes are included, the average effective protection period across countries in the EU is 17.9 years, which is in the fourth quartile, i.e. among the 25% of medicinal products with the longest such protection period when comparing to the histogram in section 1.4.2. This is possible, as there are 23 patents protecting Revlimid[16].

A secondary patent was revoked by the European Patent Office (EPO) in 2015,[5] on the grounds that the polymorph patent in question did not meet the requirement of representing an inventive step.[14] Shortly thereafter, Celgene announced its intention to appeal this ruling. The appeal process is expected to last several years, during which the patent remains valid and enforceable, according to Celgene.[5]

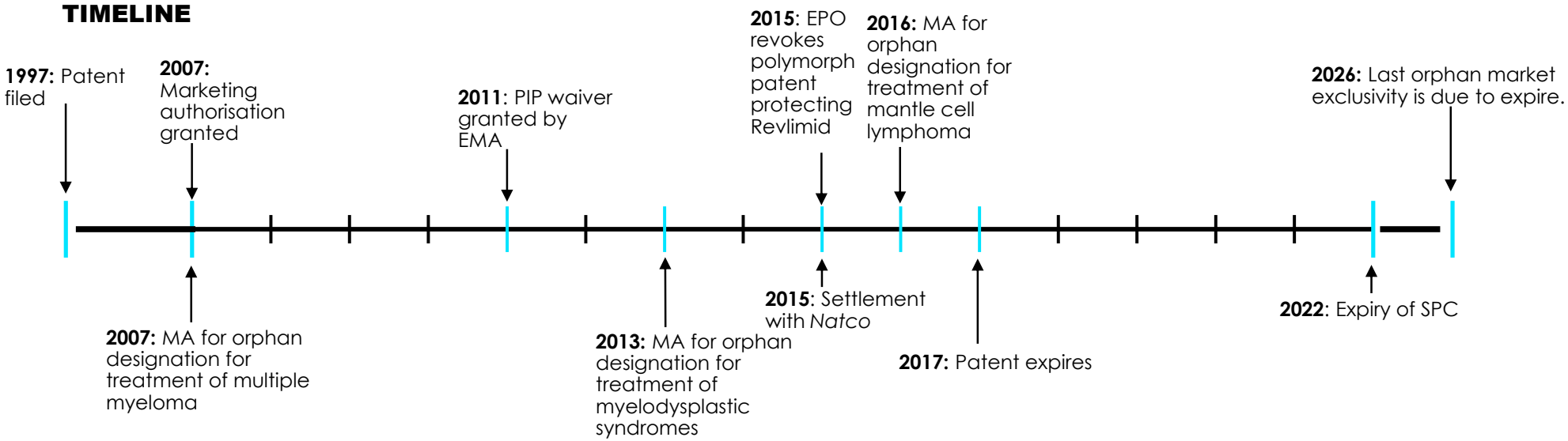
PAEDIATRIC USE

Revlimid was granted a waiver for the paediatric investigation plan by the EMA, on the grounds that the product is likely to be ineffective or unsafe in part or all of the paediatric population.[10]

ORPHAN DESIGNATIONS AND AUTHORISATION

Revlimid has been granted a marketing authorisation and thereby market exclusivity for three orphan designations in the EU, for *treatment of multiple myeloma, treatment of myelodysplastic syndromes,* and *treatment of mantle cell lymphoma*.[7] These are diseases that affect the blood cells and bone marrow.[3]

TIMELINE



Revlimid by Celgene (2/2)

The authorisations were granted in 2007, 2013 and 2016, and each offers 10 years of market exclusivity for that indication. In the US, Celgene has a marketing authorisation for the same three orphan indications, and is the sponsor of an additional six orphan designations for Lenalidomide, however without marketing approvals.[8]

In the US, Revlimid is the number three best-selling orphan medicinal product and is projected to be the number one orphan medicinal product by 2020.[9]

THE BUSINESS CASE FOR DEVELOPMENT

As described on the previous page, Revlimid has been authorised for the treatment of three different orphan indications in the EU. The active ingredient has two additional orphan designations, however without being authorised for use at the time of writing.[13]

The market exclusivity period that can be obtained from the development of an orphan medicinal product is an important incentive for the company that develops the medicinal product. This is particularly pertinent to this case since market exclusivity for two of the orphan indications will extend beyond the expiry of the SPC.

It is important to note that from an economic perspective, each of these indications represent a separate business case. When making the decision to aim for an additional orphan indication for the medicinal product, the company has to weigh the costs, i.e. of new clinical trials, the regulatory process etc., against the potential revenue that can be generated by treating this indication.

Even in the case of a successful medicinal product such as Revlimid, the orphan incentives can therefore be crucial to furthering the treatment of rare diseases. This is the case, in particular, when orphan incentives mean the difference between a positive business case and a negative business case.

However, the orphan incentives may also contribute to making an already positive business case even more profitable. In such cases, it should be considered whether the orphan incentives provide some sort of 'overcompensation'. If the business case is positive without the incentives, according to economic theory the product should be developed even without the orphan incentives. However, this must very much be assessed on a case-by-case basis, encompassing the cost function of the companies as well as the probabilities of all the various possible revenue outcomes. These are difficult to assess for parties other than the individual pharmaceutical companies.

Of course, this is based on purely economic reasoning. Other factors, such as the sense of having an ethical obligation to patients, may also affect the decisions made by the company.

MAIN INSIGHT

What is particularly interesting in this case, is that the fact that the product has obtained several orphan marketing authorisations which entails that the last protection for these extend beyond the granted SPC.

As such, this case illustrate how the orphan framework ensures that companies remain incentivised to demonstrate the use of the medicinal product for new indications even as the expiry of the patent period (and possibly SPC) draws nearer. This is due to the fact that market exclusivity can extend beyond the patent protection (including the SPC).

Imbruvica by Janssen-Cilag and AbbVie (1/2)

INDICATIONS

Imbruvica is a cancer medicine containing the active ingredient Ibrutinib.[2] Imbruvica is approved for the treatment of the following types of blood cancer: *mantle cell lymphoma, chronic lymphocytic leukaemia* and *Waldenström's macroglobulinemia,* subject to certain conditions regarding the prior treatment of the patient.[3] In 2016 global sales of Imbruvica amounted to USD 1.58bn.[7]

PATENTS AND SPC

The first patent for Imbruvica was filed in December 2006,[1] and a first marketing authorisation was granted in October 2014.[2] The active ingredient in Imbruvica, Ibrutinib was discovered by the biotech company Pharmacyclics, which was acquired by AbbVie in 2015 for USD 21bn[8]. This implies a development period of 8 years, which is not unusual, as can be seen from section 1.4.2.

Where an SPC has been granted, it is set to expire in October 2029, leading to an effective protection period from the first patent and SPC of 15 years.[1]

Including all patents and protection schemes, the average effective protection period across the EU member states is 15 years. Thus, at this point, secondary patents do not seem to exist for Imbruvica, or if they do, do not prolong the protection period since they do not extend beyond the expiry of the SPC, employing the average protection period view. However, even if these secondary patents do not extend the protection period, they might broaden the protection, e.g. through protection of the manufacturing process. There are 24 patents protecting Imbruvica[9].

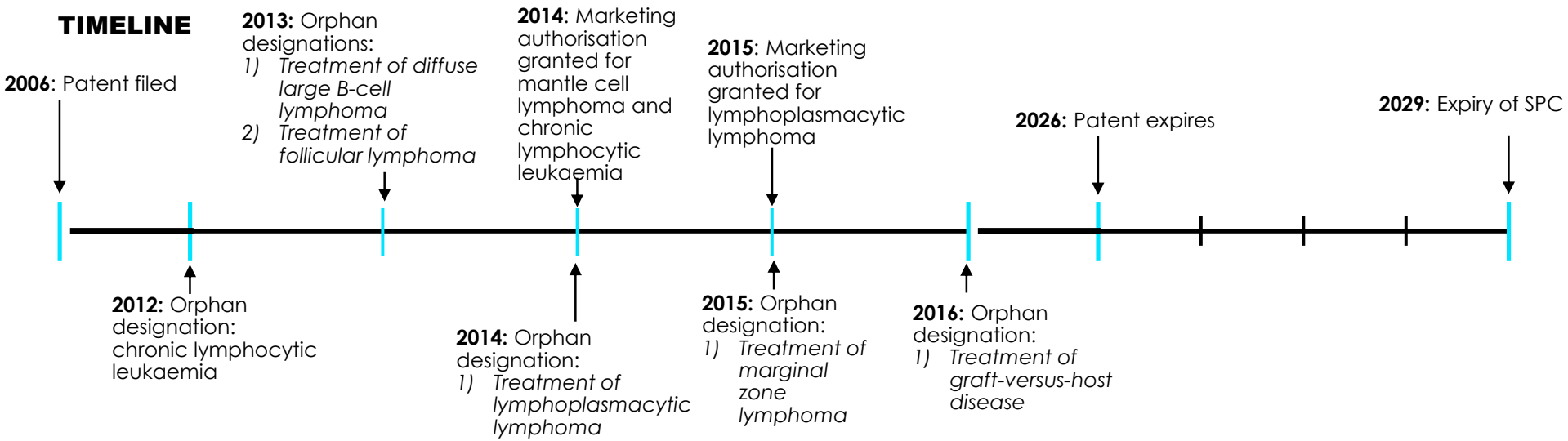
PAEDIATRIC USE

Besides having obtained waivers for particular paediatric conditions[3], a PIP exists for Imbruvica[8].

ORPHAN DESIGNATIONS

In the EU, Imbruvica is designated as an orphan medicine for five indications. Janssen-Cilag has been given a marketing authorisation for three,[2] with the resulting 10-year market exclusivity. Authorisations were granted in 2014 and 2015, while designations are shown in the timeline below.[4,5]

TIMELINE



Imbruvica by Janssen-Cilag and Abbvie (2/2)

MAIN INSIGHT

As described on the previous page, Imbruvica has been authorised for the treatment of three orphan indications, and has orphan designation for two further indications without approval at the time of writing.

When evaluating the need for orphan incentives, it is important to keep in mind that from an economic perspective each of the indications represent a separate business case.

For each indication, the company has to assess whether the costs associated with the process required to eventually gain approval are lower than the potential rewards of the medicinal product being approved for treatment of another indication.

Through fee reductions, protocol assistance and the market exclusivity period, orphan incentives reduce the costs of this investment and increase the potential rewards.

This can potentially make the difference between a negative and a positive business case – thereby making the introduction of a treatment for a rare disease a sound investment economically.

However, the possibility, of course, also exists of the incentives making an already positive business case even more profitable, implying 'overcompensating' incentives.

It should be mentioned that this analysis is based on an exclusively economic reasoning. Other factors may influence decisions by companies on whether to investigate new applications of the medicine or not. One such factor could be the sense of an ethical obligation on the part of the company to ensure the widest possible use of the medicine, ensuring that the largest possible number of patients benefit.

Viagra by Pfizer (1/2)

INDICATION

Viagra contains the active ingredient Sildenafil and is used to treat adult men with erectile dysfunction[1]. The development of Sildenafil was initiated with the aim of finding a way to treat hypertension. Initial tests were disappointing, but some patients reported the unexpected side-effect of penile erections. This led to the development of Sildenafil as a treatment for erectile dysfunction.[9] As understanding of the mechanism behind Sildenafil grew, it was postulated that it could play a role in the treatment of pulmonary hypertension, eventually leading to the development and marketing of Revatio[9] (see case study on Revatio pp. 328-329).

DEVELOPMENT TIME AND PROTECTION

Sildenafil was first patented in 1991,[2] and Viagra was granted a marketing authorisation in the EU in 1998,[1] indicating a development period of 7 years.

SPCs have been granted in various EU member states, most of which expire in 2013.[2]

This implies an effective protection period from the first patent and SPC of 15 years.

Including all patents and protection schemes, the average effective protection period across the EU countries is 16.7 years, which is in the fourth quartile, i.e. among the 25% of medicinal products with the longest such protection period when compared to the histogram in section 1.4.2.

PAEDIATRIC USE

Viagra is not approved for treatment of individuals below 18 years of age. The European Medicines Agency has waived the obligation to submit results of studies with Viagra in all subsets of the paediatric population for the treatment of erectile dysfunction.[4]

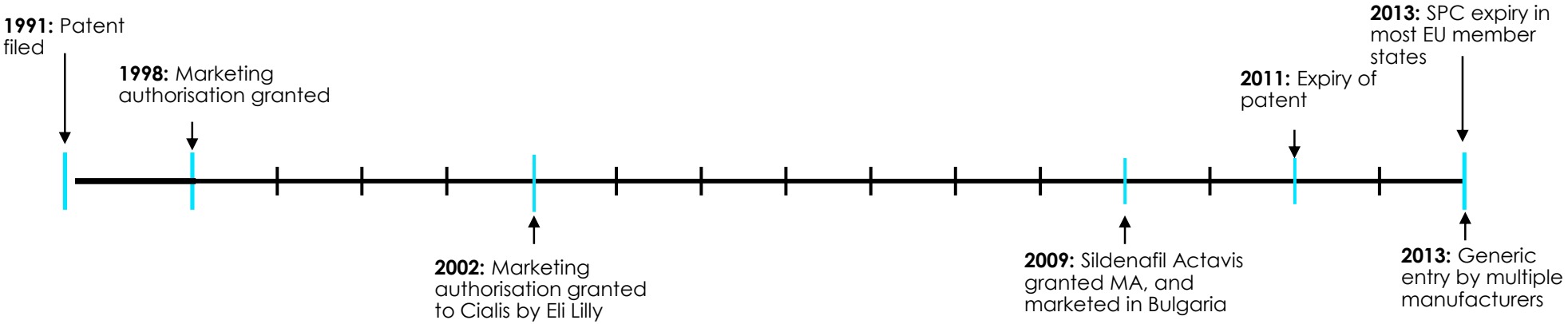
ORPHAN

Viagra is not designated as an orphan medicinal product, however the active ingredient is equivalent to the active ingredient in Revatio, also marketed by Pfizer, which was designated and granted a marketing authorisation as an orphan medicinal product.

OVER-THE-COUNTER APPROVAL

Following a review by the Medicines and Healthcare products Regulatory Agency (MHRA), the UK government agency responsible for regulating medicines, the product Viagra Connect has been approved for sales at pharmacies without a prescription.[11] It was the first Sildenafil version to obtain this approval.[12] The MHRA concluded that the benefits to patients from pharmacy availability of Viagra Connect outweighed the risks entailed.

TIMELINE



Viagra by Pfizer (2/2)

ORIGINATOR COMPETITION

In 2002, another medicinal product was granted a marketing authorisation, approved for the treatment of erectile dysfunction. The marketing authorisation holder is Eli Lilly, which markets the medicine under the name Cialis.[13]

Cialis contains the active ingredient Tadalafil and in 2016 achieved sales of USD 2.47bn.[14] In comparison, Viagra reported sales of USD 1.56bn in 2016.[15]

However, it should be noted that in 2016 Viagra faced generic competition in the EU, while Cialis did not since its SPC is due to expire in 2017.[1]

Nevertheless, this represents a case in which a medicinal product has faced competition from another originator medicinal product. Competition will tend to drive prices down, lowering the revenue generated by the companies selling in the market.

GENERIC ENTRY

In 2009, several generics were granted marketing authorisation; Sildenafil Actavis, Sildenafil ratiopharm, Sildenafil Teva and Vizarsin[10].

In 2013, as the protection period expired in several key countries in the EU, Teva Pharmaceuticals was the first to launch a generic version of Viagra in these markets.[7]

There are currently four generic versions of Viagra with marketing authorisations in the EU.[10]

EFFECT ON PRICES FROM GENERIC ENTRY

The swift entry of several generic versions following the expiry of the protection will tend to reduce prices and decrease profits for the developing company.

In the UK, prices for medicinal products containing Sildenafil have decreased from GBP 10 a pill to around GBP 1 a pill, following generic entry.[8]

MAIN INSIGHT

The case of Viagra highlights the importance of the SPC, which in this case extended the protection by 2 years. Following its expiry, generic entry was rapid and caused prices to fall substantially.

Secondly, the peculiar development story shows the possibility of a medicinal product being repurposed, as was the case when Sildenafil – the active ingredient in Viagra – was found to be effective in treating pulmonary arterial hypertension and marketed as Revatio (see separate case study on Revatio).

Revatio by Pfizer (1/2)

INDICATIONS

Revatio contains the active ingredient Sildenafil and is approved for the treatment of pulmonary arterial hypertension (PAH) for adults and children above the age of 1.[4] PAH is abnormally high blood pressure in the arteries of the lungs.[1]

Notably, the same active ingredient is found in Viagra, another medicinal product marketed by Pfizer.[2] In fact, the only differences between Revatio and Viagra at the time of initial authorisation was the film-coat and shape of the tablets and the debossing (markings on the tablet).[7]

Between 2009 and 2016 the total revenue from Revatio was USD 3.1bn[10].

DEVELOPMENT TIME AND PROTECTION

The patent for Sildenafil is held by Pfizer and was first filed in 1991[3]. Pfizer obtained a marketing authorisation for Viagra in the EU in 1998.[2]

This reflects a relatively short development time of 7 years, cf. section 1.4.2.

The patent for Sildenafil was granted an SPC in various EU member states which expired in 2013.[3]

The marketing authorisation for Revatio was granted in 2005.[1] This reflects a development time as defined in this report of 14 years.

However, Revatio is a repurposed medicinal product in the sense that it represents the use of a known compound (Sildenafil, active ingredient in Viagra) for a new indication (PAH). This will tend to increase the time from patent to marketing authorisation, however, it may not be an accurate representation of the time spent in active development of the medicinal product for the new indication.

PAEDIATRIC USE

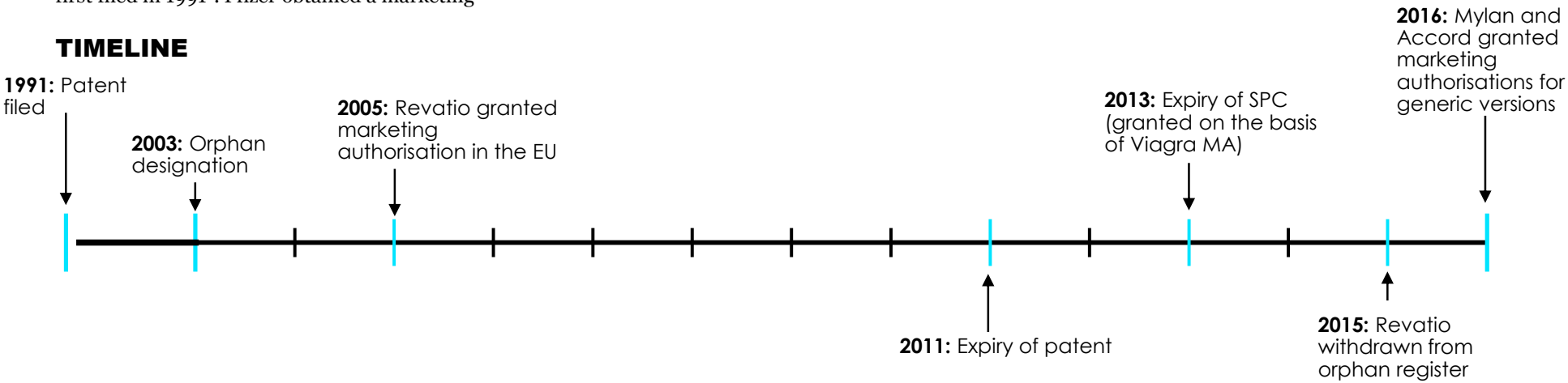
A paediatric investigation plan has been initiated and is due to be completed in 2017.[8] This would ordinarily trigger a 2-year extension of market exclusivity; however, since market exclusivity expired in 2015, Pfizer will not be able to benefit from a paediatric extension.

ORPHAN DESIGNATION

Revatio was designated as an orphan medicine in 2003.[1] It was granted a marketing authorisation in 2005 and withdrawn from the orphan register in 2015, following the end of the 10-year exclusivity period.[1]

The orphan designation and implied market exclusivity are particularly important in this case since the SPC for the active ingredient Sildenafil expired in 2013. Market exclusivity thus gave Pfizer another 2 years of protection for Revatio.

TIMELINE



Revatio by Pfizer (2/2)

GENERIC ENTRY

In 2016, a generic version of Revatio called Mysildecard was granted a marketing authorisation in the EU.[5] The marketing authorisation holder is Mylan S.A.S.

Also in 2016, Accord Healthcare was granted a marketing authorisation for Grandipam, its generic version of Revatio.[6]

THE DEVELOPMENT OF REVATIO

Starting from 1986, Sildenafil was originally developed as a medicinal product to treat hypertension. In the process, the focus turned to treatment of angina, which is chest pain related to coronary heart disease. Trials for the treatment of angina were disappointing, however male participants reported penile erections as an unexpected side effect.

This led to the development of Viagra, targeting erectile dysfunction[9] (See case study on Viagra).

As knowledge of Sildenafil increased, a role in the treatment of PAH was postulated, leading to research in this direction, which culminated with the approval of Revatio.[9]

MAIN INSIGHT

The story of the development of Revatio is interesting since it highlights the implication of market exclusivity. In 2005, as Revatio was granted a marketing authorisation, the SPC for Sildenafil was due to expire in 8 years.

This is due to the fact that Revatio represents a repurposing of an already known molecule. This should tend to make the R&D costs lower than for a completely new molecule. However, clinical trials still have to be undertaken to ensure data proving safety, efficacy and quality in treating the new indication. We have not identified data sources that allow us to quantify the possible differences in costs between development of an 'original' molecule compared with repurposing of said molecule for a new use.

Because of orphan market exclusivity, Revatio had 10 years of protection from competition in the treatment of PAH.

This influences the business case for the development of Revatio since a longer protection period will tend to imply a larger reward. In addition, protocol assistance and fee reductions because of the orphan designation lowered the costs of introducing Revatio on the market.

Whether or not these orphan incentives were decisive in this specific case is, of course, uncertain as it depends on the specific costs of bringing Revatio to the market, as well as the expectations regarding the profitability of treating the disease in the particular case.

Cystadrops by Orphan Europe (Recordati Group) (1/2)

INDICATIONS

Cystadrops is an eye-drop solution containing the active substance Mercaptamine, also known as Cysteamine.[1]
Cystadrops is approved for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.[6] Cystinosis is an inherited disease, where cystine builds up in the body, forming dangerous crystals particularly in the kidneys and eyes.[1] Cystadrops reduces the build-up of these crystals in the eyes.

Cysteamine was first developed and patented by researchers at University of California San Diego (UCSD), who have since licensed out the rights to develop and market medicinal products based on this patent to the pharmaceutical company Raptor in exchange for royalties.[2]

PAEDIATRIC USE

Through clinical trials, the safety and efficacy of the use of Cystadrops in the paediatric population above the age of 2 have been established.[1] Conditional on a final positive compliance check, the studies undertaken as part of a paediatric investigation plan can entitle the medicinal product to a 2-year extension of orphan market exclusivity.

ORPHAN DESIGNATIONS AND MARKETING AUTHORISATION

Cystadrops was granted an orphan designation in 2008 for the treatment of corneal cystiniosis.[5] Nine years later, in 2017, the medicinal product was given a marketing authorisation in the EU.[1]

Because of the MA as an orphan medicinal product, Orphan Europe has market exclusivity for 10 years following the marketing authorisation.

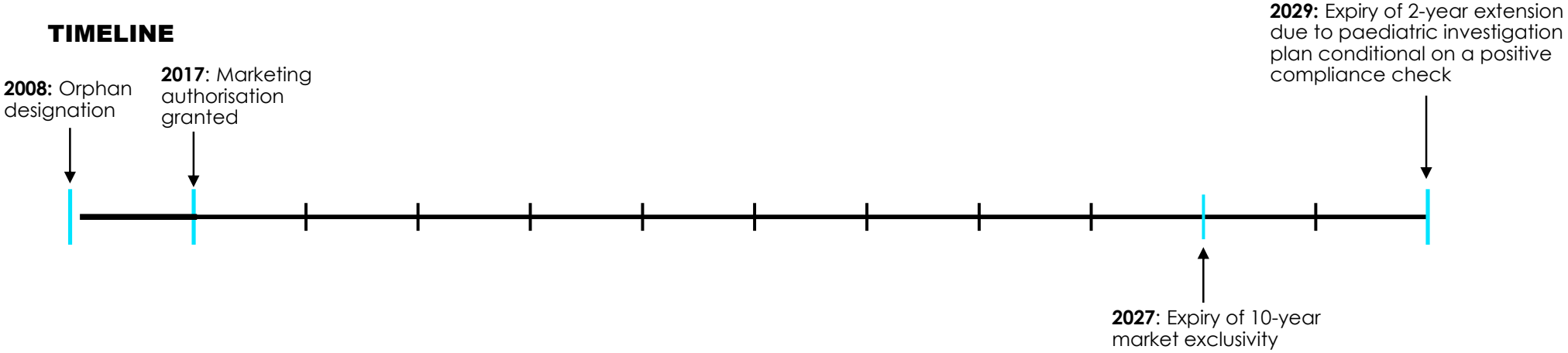
OTHER MEDICINAL PRODUCTS TREATING CYSTINOSIS

Cysteamine is the active ingredient in a number of medicinal products, including Cystagon, which was granted a marketing authorisation in 1997, for which Orphan Europe is also the marketing authorisation holder.[4]

In 2013, a marketing authorisation was granted to Procysbi[3], which was deemed an improvement over Cystagon since patients only had to take it every 12 hours, compared to every 6 hours with Cystagon, which improves compliance with the treatment as well as the quality of life of patients.

Procysbi is marketed in Europe by Chiesi, which bought the right to market the medicinal product in Europe from Horizon Pharma in 2017 for an upfront payment of USD 72.2m, with potential additional payments based on sales.[10]

TIMELINE



Cystadrops by Orphan Europe (Recordati Group) (2/2)

REJECTION OF MARKETING APPLICATION

Notably, an orphan designation for a medicinal product with the same indication was also granted to Lucane Pharma in 2014.[5] Lucane Pharma applied for a marketing authorisation in 2015, which was rejected by the CHMP.[7]

The grounds for refusal were a lack of data on efficacy of the concentration of mercaptamine in the Dropcys solution as well as concerns about other ingredients in the medicine.[7]

MAIN INSIGHT

As part of the assessment of Cystadrops, the CHMP found that Cystadrops represented a significant benefit to patients, and that it was not similar to Procysbi in the sense of Article 3(3, b) of Regulation (EC) No 847/200.[8,9] Concerning the similarity of the medicinal products, the article reads as follows: *'similar medicinal product' means a medicinal product containing a similar active substance of substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication;*

Procysbi is administered orally and reduces intracellular cystine accumulation in non-corneal tissues. Procysbi does not reach the cornea and has no effect there.[8] Cystadrops, on the other hand, is specifically approved for the treatment of *corneal* cystine crystal deposits.[8]

Hence, although both medicines are used for the treatment of the same disease (cystinosis), each medicine targets different parts of the body which are affected by the disease.

This meant that Cystadrops was able to obtain an orphan designation and a marketing authorisation, and benefit from the orphan incentives, including 10-year market exclusivity.

At a glance, this might seem surprising, given that prior medicinal products also treated cystinosis, but since they treated markedly different symptoms, the introduction of Cystadrops was deemed to constitute a significant benefit to patients. As such, this shows how competition within the area of orphan medicinal products is possible, even within the 10-year period of market exclusivity.

Tobi Podhaler by Novartis (1/2)

INDICATIONS

Tobi Podhaler contains the active ingredient tobramycin.[1] The medicinal product is approved for the suppressive therapy of chronic pulmonary infection due to *pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis.[2] The disease is an infection of the lungs, caused by the bacteria *P. aeruginosa*.

DEVELOPMENT TIME AND PROTECTION

The first patent for tobramycin was filed in 2001 by Chiron Corporation[3]. Novartis bought Chiron Corporation for USD 5.4bn in 2006[8].
Novartis was granted a marketing authorisation for Tobi Podhaler in 2011,[1] implying a development period of 10 years. This is a relatively common development time, as can be seen by referring to section 1.4.2

An SPC has been granted in some member states, with applications pending in others. They are due to expire in 2026, which means that the effective protection period from the first patent and SPC will be 15 years.[3]

Including all patents and protection schemes, the average effective protection period across countries is 14.2 years. It is initially surprising that protection from secondary patents do not extend beyond the expiry of the SPC in countries where it has been granted. However, here it is important to keep in mind that the calculation of the effective protection period from secondary patents is done as an average across countries. If secondary patents are not filed in some countries, and an SPC has not been given in certain countries, this lowers the average. There are 7 patents protecting Tobi Podhaler[9].

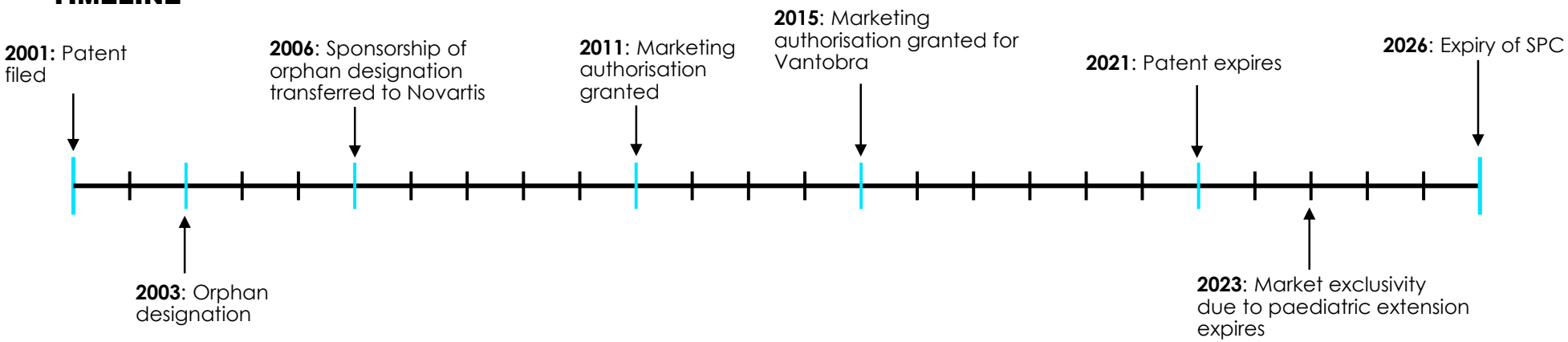
ORPHAN DESIGNATION

In 2003, an orphan designation was granted for tobramycin for the treatment of *pseudomonas aeruginosa*, due to the rarity of the disease. Initially, it was granted to Chiron Corporation, but sponsorship was transferred to Novartis in 2006.[4]

PAEDIATRIC USE

A PIP has been completed, and as a result a 2-year extension of market exclusivity has been granted[6].

TIMELINE



† The authorisation of a hybrid medicine depends partly on results of tests on the reference medicine (here Tobi), and partly on new data from clinical trials.
* The nebuliser changes liquid medicine into a mist that is then inhaled by the patient.

Tobi Podhaler by Novartis (2/2)

HYBRID MEDICINE ENTRY

In 2015, German-based pharmaceutical company Pari received a marketing authorisation for Vantobra. Vantobra is a hybrid medicine[†], containing the same active ingredient as Tobi Podhaler. However, Vantobra contains a higher concentration of the active ingredient and is inhaled using a different kind of nebuliser.[5]

According to the EMA, Vantobra was approved because the CHMP concluded that Vantobra was *clinically superior* to Tobi Podhaler, due to greater safety in a substantial part of the population[7]. Additionally, Vantobra is useful as an alternative to patients who cannot tolerate the dry powder form of tobramycin (i.e. Tobi Podhaler). Finally, the time it takes to inhale Vantobra is shorter than for other tobramycin nebulisers, which increases the likelihood that patients keep to their treatment.[5]

MAIN INSIGHT

For a competitor to enter the market for the treatment of an orphan indication for which an approved medicinal product already exists, the competitor needs to meet higher requirements than the original developer as it can only obtain a marketing authorisation if "*...the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior*"*.

In the case of tobramycin for the treatment of *Pseudomonas aeruginos,* Pari succeeded in obtaining a marketing authorisation by demonstrating to the CHMP that Vantobra was *clinically superior* to the existing medicine, i.e. Tobi Podhaler by Novartis.

This highlights the notions that when deciding whether or not to begin development of a potential orphan medicinal product, companies must take into account the possibility that another company will introduce a superior medicinal product, thus gaining access to the market before the expiry of the market exclusivity period.

This creates uncertainty about the revenue that a company can expect from its investment, even if the investment is initially successful in the sense that the medicine obtains a marketing authorisation.

However, it is obviously for the benefit of patients that they always have access to the best possible treatment.

* Regulation (EC) No 141/2000, Article 8(3c). The second applicant can likewise obtain a marketing authorisation if the current marketing holder gives consent or if the current marketing authorisation holder is unable to supply sufficient quantities of the medicinal product.

Glivec by Novartis (1/2)

INDICATION

Glivec is an anti-cancer medicine, containing the active ingredient imatinib.[1] Glivec has been authorised for a range of indications. Specifically, Glivec treats various types of blood cancer and cancers affecting the stomach and bowels. The specific indications for which Glivec has been approved can be seen under orphan designations. From 2001 to 2017 total revenue for Glivec amounted to USD 50.42bn.[12]

DEVELOPMENT TIME AND EFFECTIVE PROTECTION PERIOD

Imatinib was first patented by Novartis in 1993[2].A marketing authorisation for Glivec was granted in 2001[3], indicating a development time of 8 years. The first patent is set to expire in 2013, however SPCs have been granted in several Member States, extending the protection until 2016.[2]

PAEDIATRIC USE

A PIP has been conducted, leading to a 6-month extension, such that the effective protection period from the first patent and SPC is 15 years. [2,4]

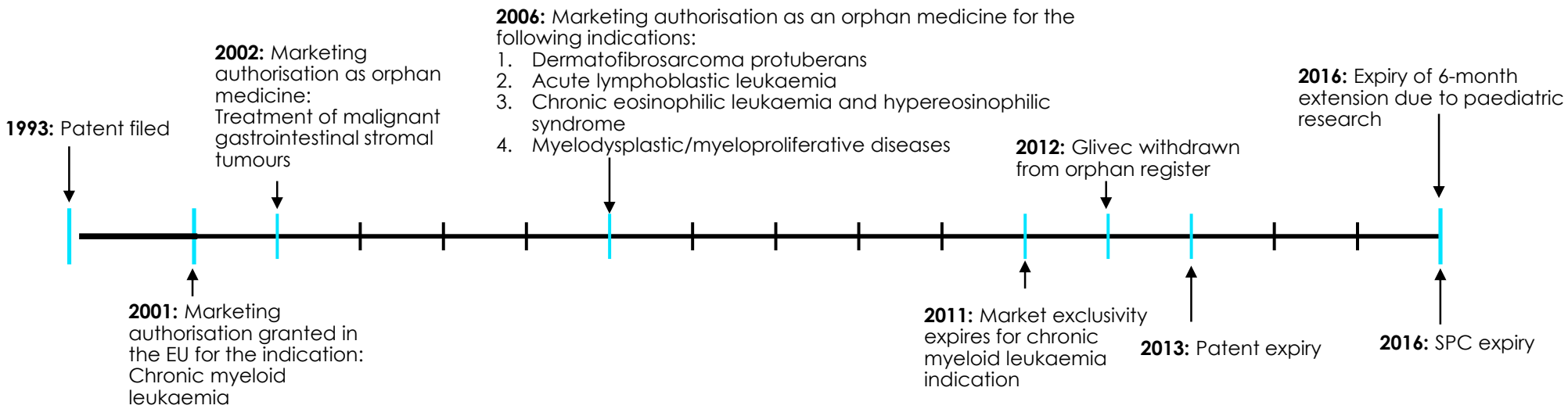
ORPHAN DESIGNATIONS

Glivec is no longer an orphan medicine, however, it has previously been designated and granted a marketing authorisation as an orphan medicine for five different indications (year of authorisation in brackets):

- Treatment of chronic myeloid leukaemia (*2001*)
- Treatment of malignant gastrointestinal stromal tumours (*2002*)
- Treatment of dermatofibrosarcoma protuberans (*2006*)
- Treatment of acute lymphoblastic leukaemia (*2006*)
- Treatment of chronic eosinophilic leukaemia and hypereosinophilic syndrome (*2006*)
- Treatment of myelodysplastic/myeloproliferative diseases (*2006*).

Glivec for the first indication above was removed from the orphan register in 2011, at the end of the 10-year exclusivity period. Glivec for all other indications was removed from the orphan register in 2012 at the request of Novartis.[1]

TIMELINE



Glivec by Novartis (2/2)

WITHDRAWAL FROM ORPHAN REGISTER AND APPLICATION FOR 6-MONTH EXTENSION

In 2013, Novartis applied for a 6-month extension of its SPC, which was eventually granted in several member states.[2] This application was possible because Glivec had already been removed from the orphan register. The withdrawal of the medicinal product from the orphan register made it possible for Novartis to apply for the 6-month extension for all indications. However, it also meant that it forfeited the possibility of a 2-year extension of market exclusivity. In the end, Glivec, for the treatment of all indications for which it had been approved, enjoyed protection for another 6 months, but the indications for which Glivec received marketing authorisation in 2006 did not obtain the 2-year extension that would have potentially extended market exclusivity until 2018.

NOVARTIS VS TEVA

At the beginning of 2016, as the expiry of the SPCs drew close, Teva challenged the validity of the 6-month extension from the PIP, arguing that this extension was invalid because Glivec had previously been an orphan medicinal product.

However, courts in both the Netherlands and Italy ruled in favour of Novartis, noting that firstly Novartis had not already benefitted from the 2-year extension available to orphan medicines, and that secondly the paediatric extension was granted after Glivec had been withdrawn from the orphan register [5,6].

This creates judicial precedence for the practice of withdrawing pharmaceuticals from the orphan register and later obtaining the 6-month extension of the SPC as a reward for undertaking paediatric studies.

GENERIC ENTRY

There are currently four generic versions of Glivec, all of them granted marketing authorisations in 2013. These are Imatinib Teva, Imatinib Accord, Imatinib Actavis and Imatinib Medac.[7]

TASIGNA

In 2006, Novartis received an orphan designation for Nilotinib for the treatment of chronic myeloid leukaemia (CML),[8] an indication for which Novartis had held marketing authorisation for imatinib since 2001.

In 2007, Novartis then gained authorisation for Nilotinib, with the brand name Tasigna.[8]

Tasigna is approved for the treatment of adult patients with newly diagnosed CML in the chronic phase as well as chronic or accelerated-phase CML with resistance or intolerance to prior therapy, including imatinib[9] (which is the active ingredient in Glivec and its generic versions).

When the marketing authorisation was recommended by the CHMP, it noted that the medicinal product was considered similar to Glivec, but that the holder of the marketing authorisation for Glivec (Novartis) had given consent to the applicant (also Novartis).

Note that the CHMP has adopted a positive opinion regarding an extension of the indication to include paediatric use in both indications described above. This follows a paediatric investigation plan that was concluded with a positive compliance check.[10]

MAIN INSIGHTS

The circumstances surrounding Glivec are important as this is the first case involving the withdrawal of a medicinal product from the orphan register in order to apply for the paediatric 6-month extension to the SPC.

The ruling that this is allowed creates judicial precedence for the practice, which has been seen in other cases as well (see case study on Tracleer on pp. 338-339).

This naturally leads to the question of whether or not this access for companies to choose between incentives was, in fact, in line with the intentions behind the legislative framework. This case might be an example of a situation where companies responded to legislation in an unintended way, i.e. withdrawing from the orphan register to obtain an SPC extension. In the case of Glivec, both orphan incentives, SPC and the paediatric extension of the latter, were combined during the life-cycle of the product. In total from 2001 to 2017, total revenue for Glivec amounted to more than USD 50bn.[12]

Cometriq/Cabometyx by Ipsen (1/2)

INDICATIONS

Cometriq and Cabometyx are both cancer medicines containing the active ingredient cabozantinib.[1,2] In Europe, both medicinal products are marketed by Ipsen, under a licensing agreement with Exelixis.[4] Ipsen paid USD 200m upfront, for the rights to cabozantinib outside the US, Canada and Japan, with the possibility of further milestone payments[9]. In 2015-2017 total revenue for cabozantinib was USD 518.6m[10]. What sets these medicinal products apart is the fact that although both medicines contain the same active ingredient and have the same marketing authorisation holder, Cometriq is an orphan medicinal product, while Cabometyx is not.

Cometriq is used to treat adults with medullary thyroid cancer. Specifically, Cometriq is used in cases where the cancer cannot be removed by surgery and has progressed or spread to other parts of the body.[1]

Cabometyx is used to treat adult patients with advanced renal cell carcinoma (cancer of the kidney).[2]

DEVELOPMENT TIME AND PROTECTION

The first patent was filed in September 2004.[3] Where an SPC has been granted, it is due to expire in March 2029.

A (conditional) marketing authorisation for Cometriq was granted in the EU in March 2014,[1] implying a development time of almost 10 years, and an effective protection period from the first patent and SPC of 15 years.

The marketing authorisation was conditional, which means that there is more evidence to come concerning the medicine, which the company is required to provide.

A marketing authorisation for Cabometyx was granted in September 2016,[2] which implies a development period of 12 years, and an effective protection period from the first patent and SPC of 13 years.

As an MA for a second indication bringing significant clinical benefit was obtained within the first 8 years, an additional year of protection is granted to Cabometyx.

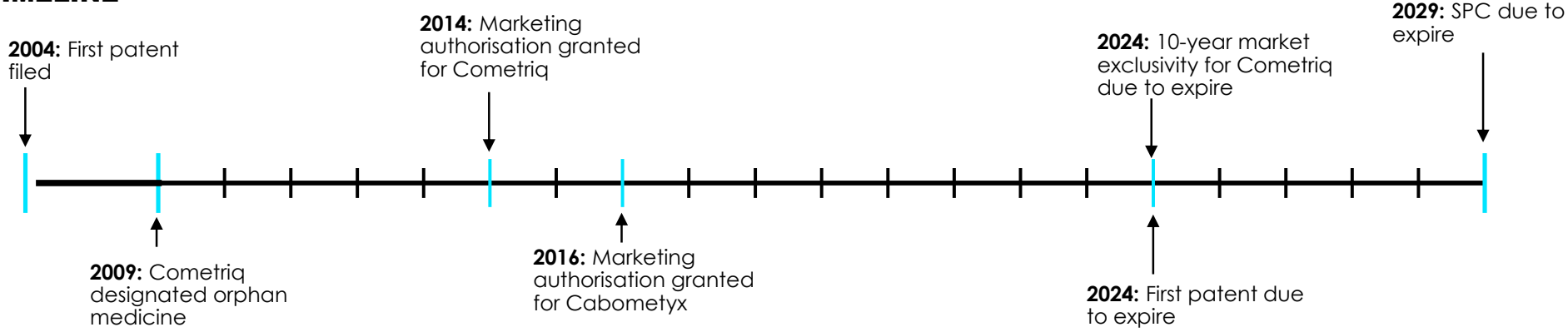
In summary, Ipsen was first granted a marketing authorisation for the use of this medicinal product as an orphan. Then, 2 years later, an additional marketing authorisation was granted for Cabometyx.

PAEDIATRIC USE

A paediatric investigation plan for Cometriq is due to be completed in 2023, after having been granted a deferral by the EMA.[7]

For Cabometyx, the EMA has waived the obligation to submit results of studies with Cabometyx in the paediatric population.[8]

TIMELINE



Cometriq/Cabometyx by Ipsen (2/2)

COMETRIQ: ORPHAN MEDICINAL PRODUCT

In 2009, Cometriq was designated as an orphan medicine due to the rarity of the disease.[1]

This designation means that the company has benefitted from incentives relating to orphan medicinal products, such as fee reductions and scientific advice (protocol assistance).

It is an important point that even though Cometriq and Cabometyx contain the same active ingredient, the benefits described above are specific to Cometriq in the sense that they do not apply to the development of Cabometyx, nor do they directly affect the costs associated with the development of Cabometyx.

The marketing authorisation for Cabometyx does not change the effective protection period from the first patent for Cometriq, as the new medicinal product is covered by the same patent, and the SPC relates to the active ingredient.

Note that according to Article 3(c) of the SPC regulation, it is a condition for the granting of an SPC that the *product* has not already been granted a certificate.[6] In Article 1(b) of the same regulation, the *product* is defined as the active ingredient or combination thereof in the medicinal product.

Since the two medicines in this case contain the same active ingredient, the second medicinal product does not appear to be able to obtain an SPC.[5] In this particular case, the timing of the authorisations further implies that even if an SPC could have been granted for the second medicinal product, it would not have extended beyond the first SPC since the first SPC already had the maximum possible extension of 5 years.

In conclusion, the authorisation of Cabometyx expanded the breadth of the market in the sense that more indications could be treated, but did not extend the effective protection period.

A new indication implies another opportunity to generate revenue for the marketing authorisation holder. It also implies that more patients can be treated using the same medicine.

MAIN INSIGHT

It is worth briefly examining the decision made by the marketing authorisation holder to go for a second indication. On the one hand, since the second medicinal product is covered by the same patent as the first medicinal product and does not seem to be able to obtain a separate SPC, the effective protection period will be shorter by the interval between the marketing authorisations.

On the other hand, some of the costs usually associated with developing a medicinal product have already been incurred in the process of developing the first medicinal product. However, new clinical trials will, of course, have to be undertaken, and these account for a large share of the total costs related to bringing a new medicinal product onto the market.

Furthermore, the ex ante evaluation of the investment changes if the MAH has information indicating that the medicinal product is likely to be effective in treating the second indication. This can be the case, for instance if there is information on effective off-label use. This leads to an increase in the probability that the investment will be successful in the sense that it will lead to a marketing authorisation and therefore additional revenue for the company.

Tracleer by Actelion (1/2)

INDICATIONS

Tracleer contains the active ingredient bosentan and is used to treat patients with pulmonary arterial hypertension (high blood pressure in the arteries of the lungs) as well as the autoimmune disorder systemic sclerosis.[1] In 2016, global sales of Tracleer amounted to USD 1.03bn.[8]

DEVELOPMENT TIME AND PROTECTION

The patent for bosentan was filed in June 1992 by Roche, which is still the owner of the patent.[2]

In 1997, during a restructuring of the cardiovascular therapy area, Roche decided to terminate further development of some compounds. This included bosentan, whose indication was deemed too small for Roche's portfolio strategy.[3]

A number of Roche employees were given permission to spin off the research programme into a separate company that became Actelion.

Roche retained intellectual property rights and out-licensed bosentan to Actelion.[3] Under the terms of the agreement, Roche receives a cut of sales of almost 10%.[4]

The licensing agreement benefitted both parties to the deal. Roche profited from a compound that would have otherwise not been developed, without incurring the usual risk.

Tracleer was granted the first marketing authorisation in May 2002, which implies a development time of almost 10 years.[1]

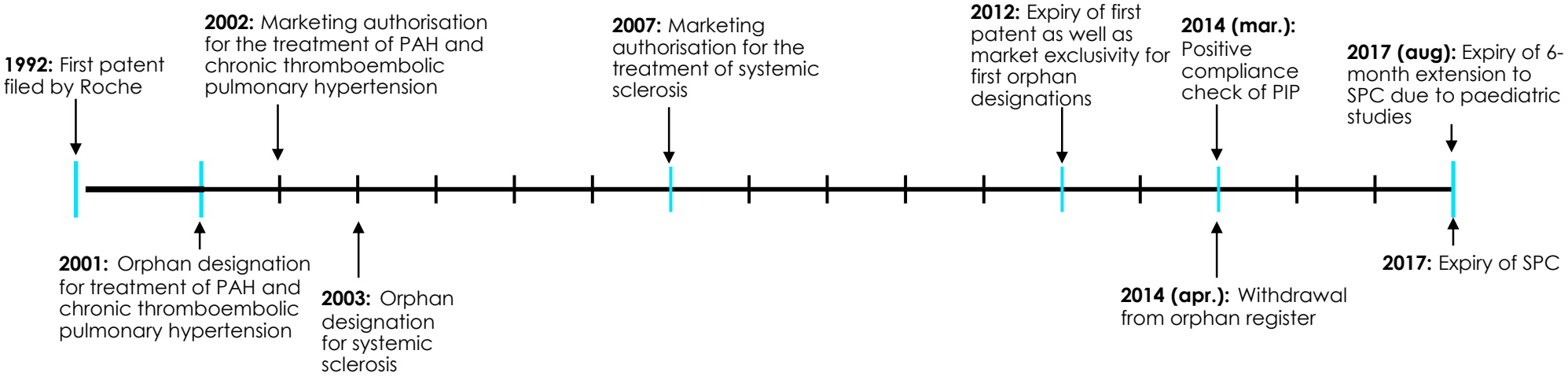
The first patent is set to expire in 2012, however, SPCs have been granted in many Member States. The majority of these expired in February 2017, with the remainder expiring in May or June the same year.[2]

Additionally, Tracleer received 6-month extensions in several Member States due to studies undertaken as part of a paediatric investigation plan. In most Member States, this extension expired in August 2017.[2] This implies a protection period from patent and SPC of around 15 years.

PAEDIATRIC USE

In March 2014, a positive compliance check was adopted by the PDCO. In November, the EMA issued the compliance statement.[7]

TIMELINE



Tracleer by Actelion (2/2)

ORPHAN MEDICINAL PRODUCT

In 2001, orphan designation was granted to Actelion for bosentan for the treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension.[5] A marketing authorisation came the following year.

In 2003, orphan designation was granted to bosentan for the treatment of systemic sclerosis.[6] A marketing authorisation for this indication was granted in 2007.

In 2012, at the end of the 10-year market exclusivity period, Tracleer for the first indication was withdrawn from the orphan register.[1] Tracleer for the second indication was withdrawn from the register in 2014, at the request of the marketing authorisation holder (Actelion).[1]

MAIN INSIGHT

By withdrawing from the register, Actelion was able to benefit from the paediatric extension to the SPC, as per the ruling in the Novartis vs Teva case described in the case study on Glivec. Notably however, the withdrawal from the orphan register happened prior to the conclusion of that case (in 2016).

The reason for the withdrawal before obtaining an extension of the SPC is that the 6-month paediatric extension to the SPC and the 2-year paediatric extension to the market exclusivity period for orphan medicinal products are mutually exclusive.

By withdrawing from the orphan register, and applying for a 6-month extension to the SPC, Actelion thus lost the opportunity to obtain the paediatric 2-year extension to the market exclusivity period afforded by the orphan status. Had they not withdrawn from the orphan register and been granted the 2-year extension, market exclusivity for systemic sclerosis would have extended to 2019, whereas the extension of the SPC expires in 2017.

This might indicate an assessment by the company that the 'wider' protection granted by the SPC (more indications are covered) was more valuable than the 'longer' protection granted by the extension of the market exclusivity period (only treatment of systemic sclerosis covered).

Again, this leads to the question of whether or not this practice of choosing between incentives is in line with the intentions behind the legislative framework.

However, the product has been approved for use in the paediatric population, and as such it seems that the incentive for completing a PIP has worked in this case.

5.4 GENERICS

Losec by AstraZeneca (1/2)

Losec is a proton pump inhibitor (PPI) medicine marketed by AstraZeneca. Losec contains the active ingredient omeprazole.[1] In the US, Losec is marketed as Prilosec.[7]

INDICATIONS

Losec is approved for the treatment of a wide range of indications:[1]

- Duodenal ulcers, including prevention of relapse.
- Gastric ulcers, including prevention of relapse.
- *H. pylori* eradication in peptic ulcers (in combination with appropriate antibiotics).
- NSAID-associated gastric and duodenal ulcers, including prevention in at-risk patients.
- Reflux esophagitis, including the long-term management of patients with healed reflux esophagitis.
- Symptomatic gastro-esophageal reflux disease.
- Zollinger-Ellison syndrome.

In general, Losec and other PPIs slow or prevent the production of acid in the stomach.[2]

DEVELOPMENT TIME AND PROTECTION

Losec (omeprazole) was originally developed by Swedish pharmaceutical company Astra AB,[3] which merged with UK-based Zeneca in 1999 to form AstraZeneca.[4]

The first patent for omeprazole was filed in April 1979.[5] SPCs were granted and expired in late 2002.[5]

The medicinal product was launched in 1988,[6] which indicates a development period of 9 years, which is within the ordinary range, as can be seen by referring to section 1.4.2.

Even though the product was launched before the SPC regulation entered into force in 1993 obtaining an SPC was possible, due to the transitional provision in Council Regulation (EEC) No 1768/92, article 19*.

By 1996 the medicinal product had become the world's best-selling medicinal product, with an estimated 200 million prescriptions and revenue of USD 3.5bn.[3]

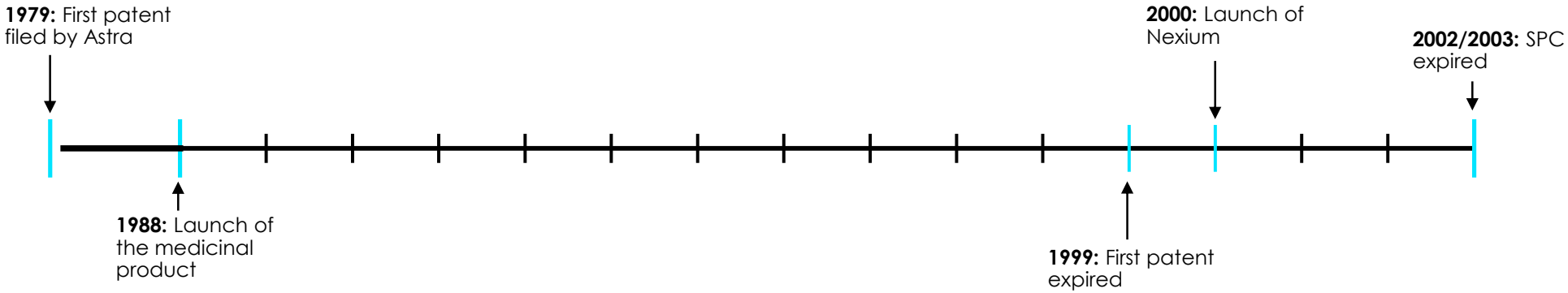
PAEDIATRIC USE

Losec is approved for the treatment of children with the following indications:

- Reflux esophagitis.
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease.
- Duodenal ulcers caused by *H. pylori* (in combination with appropriate antibiotics).

For the two first indications, it is approved for children above the age of 1 weighing more than 10 kg, for the latter for children above the age of 4.

TIMELINE



* See also table on p. 181.

Losec by AstraZeneca (2/2)

NEXIUM

In 2000, AstraZeneca launched the PPI Nexium, containing the active ingredient esomeprazole.[13] Nexium represented an improvement over Losec, and the market protection extended beyond the protection for Losec (omeprazole).[5]

COURT CASE

In June 2005, the European Commission adopted a decision fining AstraZeneca EUR 60m due to infringements of Article 82 of the EC treaty and Article 54 of the EFA agreement. [8] Both these articles prohibit the abuse of a dominant market position.

AstraZeneca was found to infringe these articles in two ways.

The first infringement related to the SPC system. By making misleading representations to the national patent offices, specifically related to the timing of the marketing authorisation that forms the basis for the term of the SPCs granted, AstraZeneca sought to extend the protection from the SPCs beyond what it was entitled to, thereby keeping generic versions out of the market for longer, to the detriment of both buyers and competitors. [8]

The second infringement consisted of the deregistration of marketing authorisations in select countries at the request of AstraZeneca. By doing so, it removed the reference marketing authorisation on which generic firms needed to rely to enter the market. The European Commission found in its decision that by doing so AstraZeneca sought to extend the protection afforded by the patents and SPCs beyond what was provided in the legislation.[8]

The European Court of Justice later ruled that the withdrawal of the authorisation for the reference product did not affect the validity of a marketing authorisation applied for while the marketing authorisation was still in force.[14]

In 2010, the fine was reduced to EUR 52.5m, because *"the Commission failed to prove that the deregistration of the marketing authorisations in certain member states was capable of having an impact on parallel imports"*.[15]

In 2012, the Court of Justice of the European Union upheld the decision made by the European Commission.[9]

MAIN INSIGHT

By inventing and marketing a new improved version of an older product, AstraZeneca can hope to obtain a large share of the market. On the other hand, a new improved version of the medicinal product is also positive news for patients.

The patent protection for Nexium, which was an improvement over Losec, expired in 2014, 35 years after the original patent for Losec was taken out.

5.5 ANTIBIOTICS

Tygacil by Pfizer (1/2)

INDICATIONS

Tygacil is an intravenously administered antibiotic containing the active ingredient Tigecycline.[1]
Tygacil is approved for the treatment of adults and children above the age of 8, for the following infections:[3]

- *Complicated skin and soft tissue infections, excluding diabetic foot infections.*
- *Complicated intra-abdominal infections.*

In 2017 world wide sales of Tygacil amounted to USD 260m.[8]

DEVELOPMENT TIME AND PROTECTION

The first patent for Tigecycline was filed in 1992 and is held by Wyeth Holdings, a subsidiary of Pfizer.[2]

Tygacil was granted a marketing authorisation in the European Union in April 2006,[1] which indicates a development period of 14 years.

The SPC covering Tigecycline expires in late 2017,[2] however studies undertaken according to a paediatric investigation plan imply a 6-month extension,[2] causing the protection period to end in 2018.

This implies an effective protection period from the first patent and SPC of just under 12 years.

The relatively long development period thus means that the company has a shorter time-span than many of the other medicinal products studied in this chapter in which to recoup its R&D investments and make a profit.

Profits are only partly determined by the protection period as prices play an important role as well.

ORPHAN DESIGNATIONS

Tygacil is not designated as an orphan medicinal product.[5]

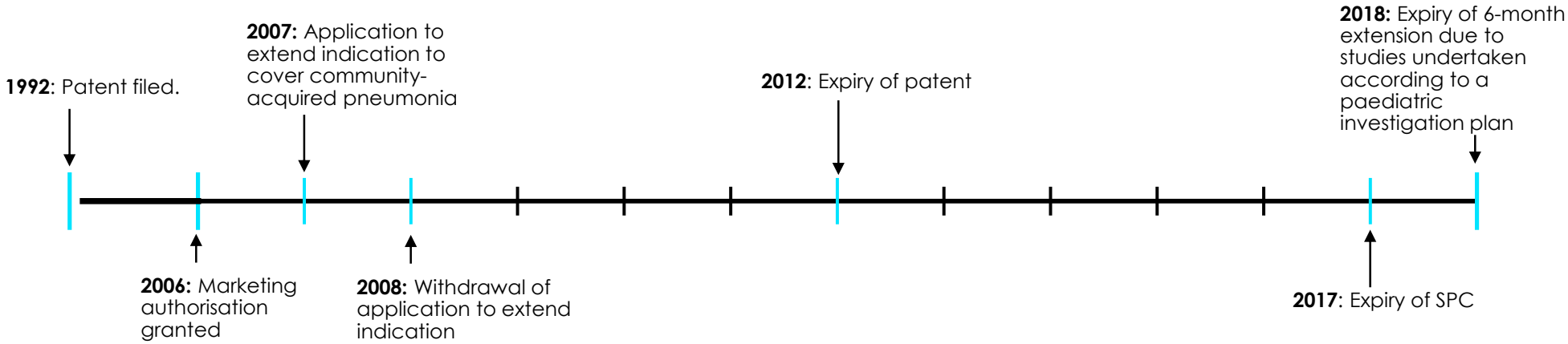
PAEDIATRIC USE

Studies of Tygacil were undertaken according to a paediatric investigation plan. As a result, Tygacil is approved for use in children above the age of 8.[3] However, clinical experience is limited, and use in children is therefore limited to situations where no alternative antibacterial therapy is available.[3]

GENERIC ENTRY (US)

In December 2016, the pharmaceutical company Fresenius Kabi announced the launch of *Tigecycline for Injection* in the US.[6] This is a generic version of Tygacil. No generic versions have obtained a marketing authorisation yet in the EU.

TIMELINE



Tygacil by Pfizer (2/2)

MAIN INSIGHT

In 2007, a year after the MA was granted, Wyeth Holdings submitted an application to extend the indication of Tygacil to include treatment of *community-acquired pneumonia*.[4]

However, in 2008 Wyeth Holdings withdrew this application, stating that the withdrawal was based on the CHMP's opinion that the data provided did not allow the committee to conclude a positive benefit-risk balance.[4]

In the US, the FDA approved the product for the new indication, based on the results of clinical trials[7], however with severe warnings regarding mortality risk[9].

The clinical trials consisted of two randomized double-blind studies including 859 patients in 28 countries.[7]

Naturally, the carrying out of such clinical trials requires an investment on behalf of the company. In this case, the investment did not lead to an extension of the indication in the EU.

This illustrates the inherent uncertainty regarding spending on R&D within the pharmaceutical sector. In many cases, whether the given product will have a positive benefit-risk balance for a new indication, is naturally unknown before studies are undertaken. In this case, the investment in clinical trials resulted in an approval in the US, which yields a return. In the EU there was no extension of the indication and hence, no return on the investment.

During the years 2014, 2015 and 2016 global revenue for Tygacil have been USD 323m, USD 304m and USD 274m respectively[10].

Dificlir by Astellas Pharma

INDICATION

Dificlir contains the active ingredient fidaxomicin, an antibiotic used to treat adults with certain infections of the gut.[1] Dificlir is marketed in the US as Dificid[10]. Dificlir was discovered by Optimer Pharmaceuticals, which entered into a collaboration and license agreement regarding sale of Dificlir in Europe, the Middle East and Africa, with Astellas Pharma in 2011[14]. The agreement included a USD 68m payment from Astellas to Optimer Pharmaceuticals, with options for additional payments of up to USD 156m, depending on achievement of agreed regulatory milestones[14].

Dificlir is approved for the treatment of adult patients with *Clostridium difficile* infections, also known as *C. difficile*-associated diarrhoea.[7] Clostridium difficile is a bacterium that causes severe diarrhoea and is resistant to most antibiotics. The infection often arises subsequent to antibiotic treatment for another infection.[10]

A major challenge when treating the infection is the risk of recurrence, a risk which clinical studies indicate Dificlir reduces, compared to the alternative treatment Vancomycin. [10,11] This is a crucial fact as Vancomycin is no longer patent-protected.

Total revenue for Dificlir in Europe, the Middle East and Africa was € 14m and € 20m in 2014 and 2015 respectively[13].

DEVELOPMENT TIME AND EFFECTIVE PROTECTION PERIOD

Originally developed by Optimer Pharmaceuticals, fidaxocimin was first patented in 2003.[2] In 2011, Optimer entered into a partnership with Astellas Pharma to develop and market fidaxocimin in Europe.[3] A marketing authorisation was granted in the EU the same year,[4] implying a development time of 8 years.

Optimer was acquired by Cubist in 2013, which was again acquired by Merck the following year.[5]

SPCs have been granted in most member states, and are due to expire in 2026.[2] This will imply an effective protection period from the first patent and SPC of 15 years.

PAEDIATRIC USE

The safety and efficacy of Dificlir in the paediatric population has not yet been established, and a deferral has been granted.[6,7]

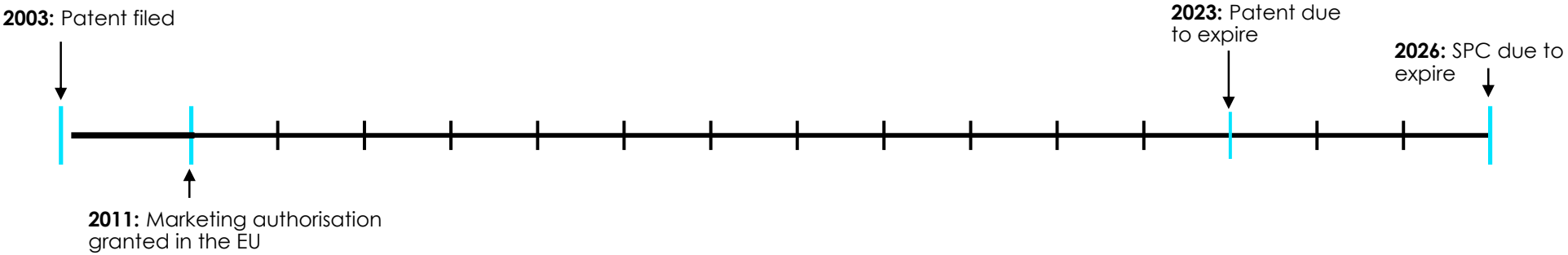
ORPHAN DESIGNATION

Dificlir has not been designated as an orphan medicine in the EU[8], however paediatric use was orphan-designated in the US in 2010, but Cubist as the sponsor of the designation has not yet been given a marketing approval.[9]

MAIN INSIGHT

In a sense, Dificlir is approved for the treatment of a disease for which a treatment already exists, namely Vancomycin, which is, in fact, no longer patented. However, it is important to keep in mind that by performing better in terms of the risk of recurrence, it is possible that Dificlir might be cost-effective even if the price is higher than for the alternative.

TIMELINE



5.6 VACCINES

Cervarix by GSK Pharma (1/2)

INDICATIONS

Cervarix is a vaccine, containing human papillomavirus (HPV) type-16 and type-18 L1 proteins.[1] Cervarix is approved from the age of 9 years for the prevention of premalignant ano-genital lesions and cervical and anal cancers causally related to certain oncogenic HPV types.[1]

DEVELOPMENT TIME AND PROTECTION

The patent behind Cervarix was filed in October 1999.[2] Cervarix was granted a marketing authorisation in the EU in September 2007,[3] implying a development time of almost 8 years.

The SPC for Cervarix is due to expire in September 2022,[2] leading to an effective protection period from the first patent and SPC of 15 years.

Vaccines represent a case where multiple SPCs have been applied for, relating to the same vaccine. For Cervarix, a total of 162 SPC applications have been filed, relating to 5 distinct products, and 7 distinct basic (European) patents.[9]

ORPHAN DESIGNATIONS

Cervarix does not carry an orphan designation.

PAEDIATRIC USE

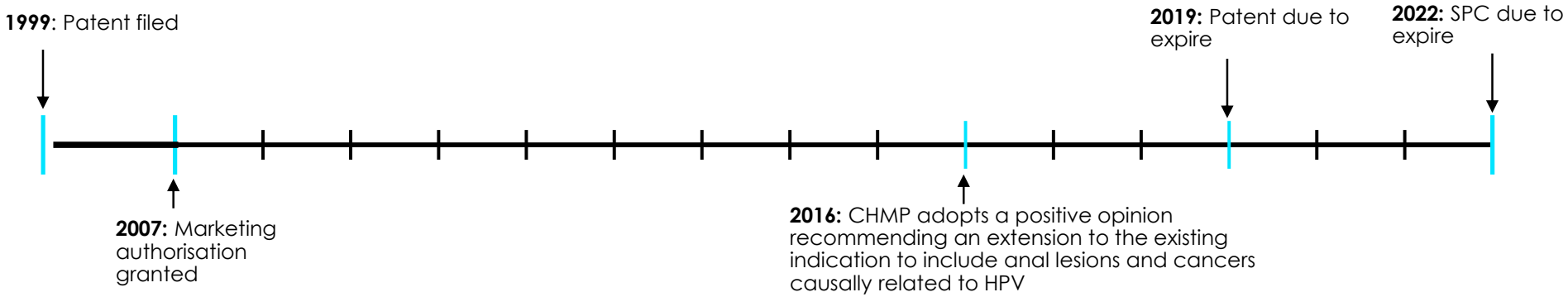
Cervarix is not recommended for use in children below the age of 9.[1]

MULTIPLICITY OF SPCS

There are seven distinct basic European patents related to Cervarix, and a total of 162 SPCs have been applied for in 18 countries.[9] This highlights how vaccines seem to be distinct from other medicinal products, where usually it is only possible to obtain one SPC per country.

In many cases, vaccines are combinations of active ingredients while likewise including adjuvants to enhance the effect. This has presented challenges for the IP-system regarding the granting of SPCs. The issue has been debated extensively in the literature[12]. The combination of more active ingredients as well as adjuvants in the same vaccine is the reason for the multiplicity of SPCs.

TIMELINE



Cervarix by GSK Pharma (2/2)

COMPETITION WITH GARDASIL

In the market for vaccines for type-16 and type-18 HPV, Cervarix is in competition with Gardasil produced by Merck.[4]

Gardasil was given a marketing authorisation in the EU in September 2006, a year prior to Cervarix.[5] In addition to type-16 and type-18 HPV, Gardasil is used for the prevention of type-6 and type-11 HPV.[5]

While global sales of Cervarix were EUR 90m in 2016 and EUR 98m in 2015,[6] sales of Gardasil were approx. EUR 1.8bn and EUR 1.3bn in the two years respectively.[7]

As of 2016, GSK no longer markets Cervarix in the US.[8] Gardasil was patented in 2000,[2] with the SPC due to expire in 2021.[2]

MAIN INSIGHT

The research underlying the vaccines Cervarix by GSK Pharma and Gardasil by Merck was initially developed by four different institutions; three universities located in Australia and the US, and the National Cancer Institute (NCI) in the US.[11]

Each institution filed patent applications in their respective countries, and the IP rights were initially licensed to Merck and MedImmune, while GSK later acquired the IP rights related to HPV vaccines from the latter. [11]

By 2005, Merck and GSK entered into a cross-licensing agreement, which gave both parties the right to the patent rights related to HPV held by the other. [10]

Under this agreement, GSK received an upfront payment as well as royalties from Merck based upon sales of the vaccine. Details of this financial arrangement are not public.[10]

This shows how licensing agreements are used in the pharmaceutical sector to bring products from initial discovery to the commercial market.

Furthermore, it is interesting that 162 SPC applications relating to Cervarix has been filed. This is due to the fact that vaccines often are combinations of active ingredients as well as adjuvants. This has presented certain challenges for the IP-system regarding the granting of SPC and is the reason for the multiplicity of SPCs for vaccines[12].

Infanrix Hexa by GSK Pharma

INDICATIONS

Infanrix Hexa is a vaccine containing the following active substances:[1]

- Toxoids from diphtheria and tetanus
- Parts of Bordetella pertussis
- Parts of hepatitis B virus
- Inactivated polioviruses
- Polysaccharides from the bacterium Haemophilus influenzae type B.

The vaccine is used to protect infants under 3 years of age from diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis (polio) and diseases caused by Hib (e.g. bacterial meningitis)[1].

Infanrix Hexa is a combination of vaccines previously available in the EU.

DEVELOPMENT TIME AND EFFECTIVE PROTECTION PERIOD

The vaccine was first patented in 1993.[2] In 2000, a marketing authorisation was granted to GSK.[1] This implies a development time of 7 years.

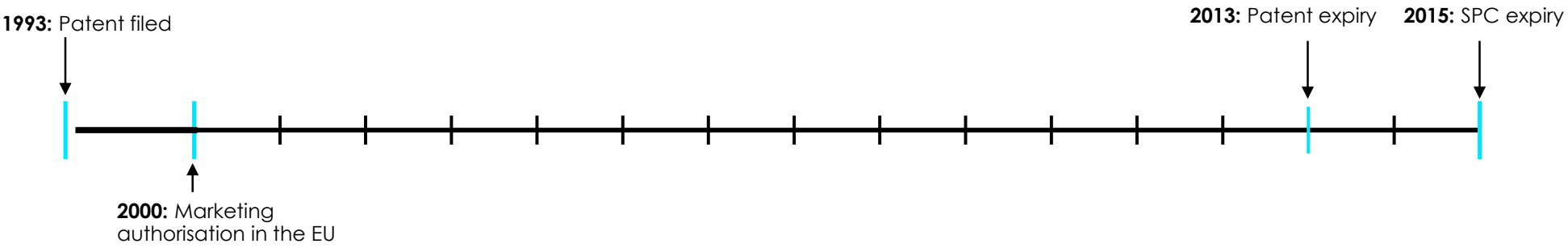
The SPCs granted expired in 2015,[2] leading to an effective protection period from the first patent and SPC of 15 years.

MAIN INSIGHT

There are three distinct basic European patents related to Infanrix Hexa, SPCs have been filed in 14 different Member States, and a total of 36 related SPCs have been applied for.[3] This highlights how vaccines seem to be distinct from other medicinal products where it is usually only possible to obtain one SPC per country.

As described on pp. 348-349, vaccines are often combinations of active ingredients as well as adjuvants, to enhance the effect. This has presented challenges for the IP-system regarding granting of SPCs and is the reason for the multiplicity of SPCs[4].

TIMELINE



5.7 CONDITIONAL MARKETING AUTHORISATIONS

Sutent by Pfizer (1/2)

INDICATIONS

Sutent is a medicinal product containing the active ingredient Sunitinib.[1] Sutent is approved for the treatment of gastrointestinal stromal tumour (GIST), metastatic renal cell carcinoma (MRCC) and Pancreatic neuroendocrine tumours (pNET), as described in the 'summary of product characteristics' by the EMA.[3] Sutent was discovered by Sugen, which was bought by Pharmacia in 1999 for USD 650m[6]. In 2003 Pfizer bought Pharmacia for USD 60bn[7]. In 2016 total revenue from Sutent amounted to USD 1.10bn.[5]

DEVELOPMENT TIME AND PROTECTION

The first patent was granted in the EU in February 2001.[2] In July 2006, Sutent was granted a conditional marketing authorisation in the EU, which was switched to a full marketing authorisation in January the following year.[1] This implies a development time of 5 years (albeit until a *conditional* MA). This is a relatively short development time, as can be seen by comparing to section 1.4.2.

The granted SPC is due to expire in 2021, implying an effective protection period from the first patent and SPC of 15 years. Note that since the development period is only slightly longer than 5 years, the SPC is relatively short. This in turn means that in this case the SPC expires in the same year as the patent.

Including all patents and protection schemes, the average effective protection period for Sutent is 16 years, which is not out of the ordinary, when comparing to the histogram in section 1.4.2.

According to the EMA, Sutent was initially given a conditional marketing authorisation *"because there was more evidence to come about the medicine, in particular in the treatment of renal cell carcinoma."*[1]

Conditional marketing authorisations are used for medicinal products where the benefits of immediate availability outweighs the risk of less comprehensive data than usually required.[3]

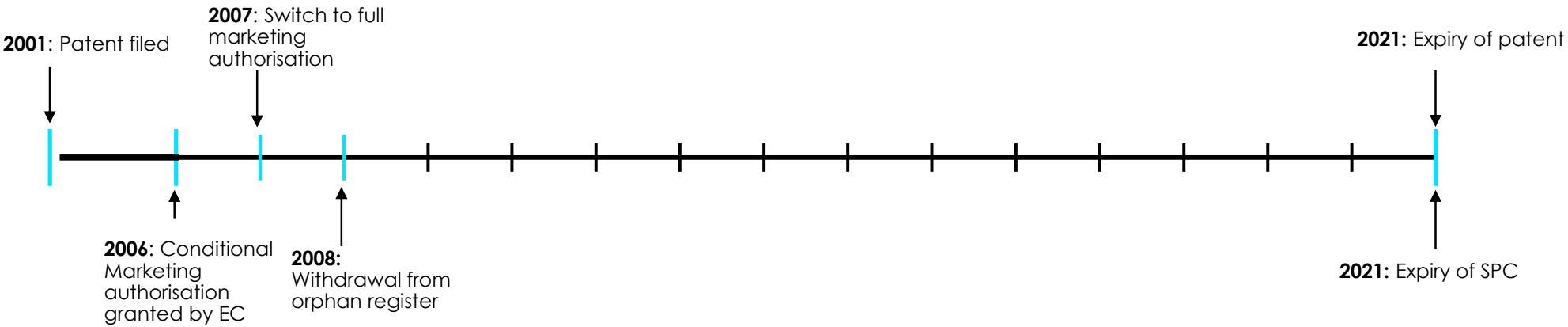
PAEDIATRIC USE

Only limited data regarding the use in children has been produced, implying that the safety and efficacy of the medicinal product in the paediatric population have not yet been established.[4] However, a paediatric investigation plan has been initiated. This may explain the motivation behind the withdrawal of Sutent from the orphan register since the 6-month extension of the SPC cannot be applied for in the case of orphan medicines, where a 2-year extension of the market exclusivity can be obtained instead.

ORPHAN DESIGNATIONS AND AUTHORISATIONS

Sutent was originally an orphan medicine approved for the following indications: *Treatment of renal cell carcinoma* and *treatment of malignant gastrointestinal stromal tumours*. However, Sutent was withdrawn from the register of orphan medicinal products in July 2008, at the request of the marketing authorisation holder.[1]

TIMELINE



Sutent by Pfizer (2/2)

The 2-year market exclusivity paediatric extension and the 6-month paediatric extension of the SPC are mutually exclusive. Because of the chronology of this particular case, the 2-year market exclusivity paediatric extension would not have caused the effective protection period to be longer since it runs from the expiry of the basic 10-year orphan market exclusivity period.

An extension to the SPC on the other hand does imply an extension of the effective protection period.

MAIN INSIGHT

It is important to realise that the initial approval of a conditional marketing authorisation does not extend the effective protection period for products with a development time of 5 to 10 years, since the SPC compensates fully in this period. Rather, it allows the company to market and generate revenue from the medicinal product earlier than it would otherwise have been able to. Correspondingly, patients benefit by having access to treatment sooner.

In exchange for the earlier market access, the company forfeits protection for an equivalent period in the final stage of the protection period.

Since future profits are typically discounted to some extent (i.e. EUR 1 today is worth more than EUR 1 in a year's time), this is for the benefit of the company.

As a 15-year time period would typically lead to heavy time discounting, the conditional MA can therefore represent a significant benefit to the company.

A conditional marketing authorisation implies earlier market access without affecting the effective protection period as long as the development time is between 5 and 10 years, and this highlights an important feature of the way the term of the SPC is calculated, namely that the SPC compensates one-to-one for the development time spent between the fifth and the tenth year of development.

5.8 PAEDIATRIC-USE MARKETING AUTHORISATIONS

Buccolam by Shire (1/2)

INDICATIONS

Buccolam is approved for the treatment of prolonged, acute, convulsive seizures in patients between 3 months and 18 years of age, and is exclusively to be used by patients diagnosed with epilepsy.[8] There are four age-specific products with the same solution, but varying in terms of the amount contained in the syringes. In 2017 world wide sales of Buccolam was USD 47m.[12]

PATENTS AND MARKETING AUTHORISATION

Buccolam contains the active ingredient Midazolam.[4] Midazolam was originally patented by Roche and marketed as Hypnovel.[5,6] The final protection for Midazolam in the EU expired in 2005.[5]

Buccolam was developed in a collaboration between the two pharmaceutical companies Auralis and Therakind. Auralis was acquired by ViroPharma in 2010 prior to the submission of the PUMA application in August 2010.[1]

In 2013, ViroPharma was then acquired by Shire.[7]

The PUMA for Buccolam was approved in September 2011,[1,4] 4 years after the regulation allowing for a PUMA was introduced into the regulatory framework.

PAEDIATRIC-USE MARKETING AUTHORISATION

Buccolam was the first paediatric-use marketing authorisation (PUMA) to be approved in the EU.[1] The PUMA was introduced by the Paediatric Regulation entering into force in 2007.[2] As of 2017, only three paediatric-use marketing authorisations have been granted.[2]

The stated goal of the PUMA concept is to incentivise research into existing compounds that are off-patent and/or to help transform off-label use into authorised use that is safer and better-framed through the marketing authorisation.[2]

A PUMA approval requires the following three criteria be met:[3]

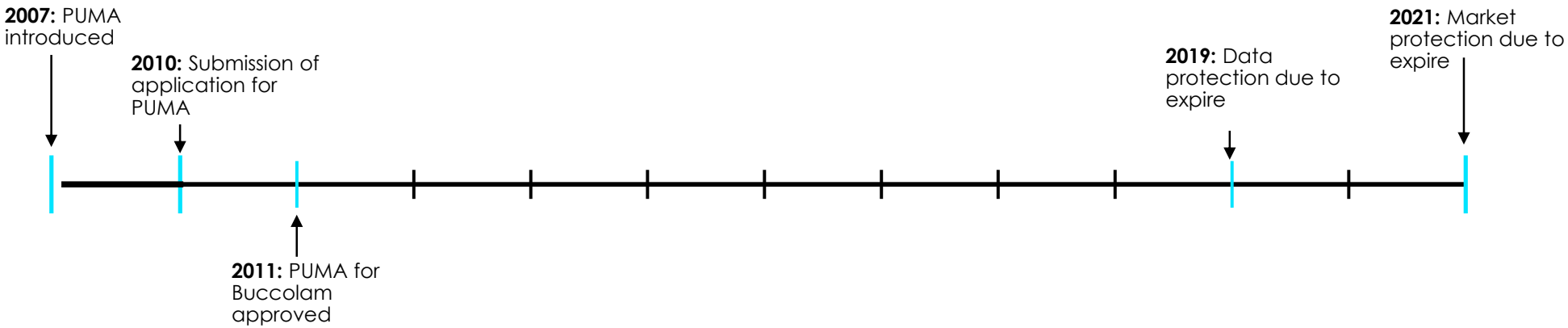
- The medicine is already authorised
- The medicine is no longer covered by a patent or an SPC
- The medicine is exclusively developed for use in children.

As described in section 1.1, a PUMA approval confers an 8-year period of data protection, and a parallel 10-year period of market protection.

PROCEDURE OF APPROVAL

The application was submitted in August 2010. The centralised procedure began in September the same year. The CHMP adopted a positive opinion in June 2011, and the PUMA was issued in September 2011. This means that the centralised procedure took approximately 12 months from application to approval.

Timeline



Buccolam by Shire (2/2)

MAIN INSIGHT

In October 2017, the European Commission published a 10-year report on the implementation of the Paediatric Regulation.[9] In this report, it is described how the number of PUMA approvals (3) is below expected levels. Furthermore, the report outlines certain issues related to encouraging companies to invest in additional research in known compounds. The first of these is the worry that a PUMA might not prevent physicians from prescribing off-label competitor products with the same active ingredient, but authorised for other indications. Secondly, national healthcare payers are seen to be hesitant in paying a premium price for products authorised under the regulation regarding PUMA products.[2]

As an example of this, in 2013 a medicines management team within the National Health Service (UK) recommended that practitioners continued to prescribe the unlicensed medicinal product Epistatus, which is similar to Buccolam.[10]

This recommendation may have partly reflected the fact that the British National Institute for Health and Clinical Excellence (NICE) estimated that the price of one administration of Epistatus was 84% of the equivalent price for Buccolam.[11]

5.9 SPCs across countries

SPCs across countries

On the following two pages we present tables with information regarding SPCs across countries.

The tables present information on the expiration date of SPCs in the individual countries, if an SPC has been granted. If a granted SPC has a paediatric extension, the expiration date of the extension is presented. If an SPC has been applied for, but not yet granted, this information is given in the table, along with information stating whether an SPC application has been rejected.

The data is extracted from the Alice de Pastors dataset on SPCs based on the trade name of the product.

ALICE DE PASTORS DATA

The information presented on the two following pages is extracted from the Alice de Pastors database on SPCs, which spans the period 1991 to April 2016.

The Alice de Pastors dataset contains data on SPCs, published or made available to the public, by the National Patent Offices in Patent Registers. The database combines information from a range of sources, such as patent journals, bulletins and registers publicly available, in the individual countries, to produce a coherent database, containing information on SPCs.

The variables included in the database are e.g. the name of the product, the given country, patent number, date of patent commencement, SPC number, SPC expiration date, whether the SPC has a paediatric extension and if so, when it expires.

CAVEATS

Only countries where SPCs have been granted or applied for, for at least one of the products in the case studies have been included in the tables.

In some instances, more than one SPC in a given country were recorded in the dataset. In these cases only the SPC with the latest expiration date has been included.

Only SPCs that were marked as "Granted", "Applied" or "Rejected" have been included[1]. Paediatric extensions that where applied for, but not yet granted, have not been included. In these instances, the expiration date of the SPC is presented.

In some cases the SPCs have a different 'titular' across countries. A titular is the 'owner name published in the SPC'[2]. However, as some products e.g. might have been developed in collaboration between several entities, might have changed owner several times during their lifetime or be part of a licensing agreement, we have not used the 'titular' as a selection variable. As such, there is a risk that some included SPCs are not necessarily the ones held by the company given in the case study as the company marketing the medicinal product.

We have included all entries in the dataset which had the exact given tradename of the product. E.g. the product Infanrix has several entries with suffixes such as 'Hep', 'Penta', 'Tet' and 'Hex'. However, we have only included entries where the recorded name exactly matched 'Infanrix Hexa'.

Furthermore, some entries in the database have the tradename missing. This is a challenge, as it is not possible to infer from other variables which product the information pertains to. E.g. both Humira and Trudexa have the international non-proprietary name Adalimumab. As such, if the tradename is missing, we do not know whether an observation with Adalimumab as the international non-proprietary name in the dataset covers Humira or Trudexa. Observations with missing tradenames have hence not been included in the following tables.

As such, there is a risk that some SPCs are not included in the table, because of missing information regarding the tradename. Especially for the vaccines Cervarix and Infanrix Hexa where other studies have shown a rather large number of SPCs[3] it is obvious that not all SPCs are identified using the Alice de Pastors dataset.

1 Some were marked with a "W", which had no explanation in the documentation accompanying the dataset.
2 Documentation for the Alice de Pastors database.
3 See the individual case studies for a review of this.

	Humira	Sovaldi	Herceptin	Enbrel	Revlimid	Imbruvica	Viagra	Tobi Podhaler	Glivec
Austria		17/01/2029		01/08/2015*					
Belgium		Applied for SPC							
Switzerland									
Cyprus			28/08/2015			Applied for SPC			
Czech Republic		Applied for SPC			14/06/2022	Applied for SPC			
Germany	SPC application rejected	Applied for SPC		01/08/2015*					21/06/2016
Denmark	Applied for SPC	Applied for SPC				23/10/2029	22/06/2013	Applied for SPC	
Spain	16/04/2018		29/07/2014	03/08/2015*	14/06/2022		14/09/2013		07/05/2017*
Finland									
France		17/01/2029							
United Kingdom	SPC application rejected	Applied for SPC		31/07/2015*	17/06/2022				
Greece	09/09/2018	17/01/2029	30/08/2015	02/08/2015*	15/06/2022		23/06/2013		22/06/2016
Croatia		Applied for SPC							
Hungary		Applied for SPC			Applied for SPC	Applied for SPC			21/12/2016*
Ireland		16/01/2029		31/07/2015*	13/06/2022				
Iceland		16/01/2029							
Italy	15/04/2018	16/01/2029	28/08/2015	01/08/2015*	13/06/2022	23/10/2029	14/09/2013	08/05/2026	21/12/2016*
Luxembourg	16/04/2018	17/01/2029		01/08/2015*	14/06/2022				
Latvia		Applied for SPC				23/10/2029			
Malta		17/01/2029							
Netherlands		16/01/2029							
Norway	16/04/2018	Applied for SPC			14/06/2022				
Poland		Applied for SPC			14/06/2022	Applied for SPC			
Portugal	08/09/2018	Applied for SPC	29/07/2014	01/08/2015	14/06/2022	Applied for SPC	19/01/2014	Applied for SPC	21/12/2016*
Romania									
Sweden									
Slovenia		17/01/2029							
Slovakia									

* Paediatric extension

	Cometriq	Tracleer	Losec	Tygacil	Dificlir	Cervarix	Infanrix Hexa	Sutent
Austria								
Belgium								
Switzerland								
Cyprus		14/05/2017				20/09/2022		
Czech Republic	26/03/2029			30/09/2017	Applied for SPC			Applied for SPC
Germany							SPC application rejected	
Denmark	Applied for SPC		SPC application rejected		Applied for SPC			
Spain		15/11/2017*		21/02/2018*		20/09/2022	SPC application rejected	19/07/2021
Finland								
France								
United Kingdom								
Greece		01/03/2017		22/08/2017		Applied for SPC	04/10/2015	
Croatia								
Hungary	Applied for SPC			02/04/2018*	Applied for SPC	Applied for SPC		19/07/2021
Ireland						07/03/2019		
Iceland								
Italy	22/03/2029	15/11/2017*		21/02/2018*	07/12/2026	19/09/2022	02/10/2015	18/07/2021
Luxembourg		28/02/2017	16/11/2002	21/08/2017		20/09/2022	02/10/2015	19/07/2021
Latvia	26/03/2029							24/07/2021
Malta								
Netherlands								
Norway				02/10/2017		Applied for SPC		19/07/2021
Poland				02/10/2017		SPC application rejected		19/07/2021
Portugal	Applied for SPC	28/08/2017*		21/02/2018*		20/09/2022	02/10/2015	24/07/2021
Romania								SPC application rejected
Sweden		27/08/2017*					SPC application rejected	
Slovenia								
Slovakia		28/08/2017*						

* Paediatric extension

CHAPTER 5 APPENDIX

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