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Effects of supplementary protection mechanisms for pharmaceutical products

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Abbreviations

AG	Advocate General
CBG-MEB	College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board)
CJEU	Court of Justice of the European Union
COMP	Committee for Orphan Medicinal Products
DDD	Defined Daily Dose
DTC	Diagnosis Treatment Combination (Diagnose Behandeling Combinatie, DBC)
EC	European Commission
EMA	European Medicines Agency
EPO	European Patent Office
EU	European Union
FDA	US Food and Drug Administration
GMA	Global Marketing Authorisation
GVS	Geneesmiddelenvergoedingssysteem
INN	International Non-proprietary name
MA	Marketing authorisation
Ministry of EZK	Ministry of Economic Affairs and Climate Policy of the Netherlands
Ministry of VWS	Ministry of Health, Welfare and Sports of the Netherlands
NCE	New Chemical Entity
NPO	Netherlands Patent Office (Octrooicentrum Nederland)
NZa	Dutch Healthcare Authority (Nederlandse Zorgauthoriteit)
ODD	Orphan Drug Designation
OTC	Over-the-counter (non-prescription)
PDCO	Paediatric Committee
PPP	Public Private Partnership
R&D	Research & Development
SME	Small and Medium-sized Enterprises
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
ZiN	Netherlands Health Care Institute (Nederlands Zorginstituut)

Executive Summary

Focus of this study

The pharmaceutical industry is among the most R&D intensive industries in the world. Consequently, it is also one of the most intensive users of the patent system. Patent protection provides a pharmaceutical company a time-limited monopoly during which it can recover the costs it had to make for conducting the R&D on the drug. In exchange, it makes the information on the drug publicly available in the patent specifications. After expiry or lapse of the patent, anyone can use this information for production of generic versions of the drug or for further R&D, provided no further protections are in effect.

The pharmaceutical sector is distinct from other R&D intensive industries in several ways. For one, patients need to be able to trust that any drug that comes on the market is sufficiently effective and safe. Therefore, before a drug can receive marketing authorisation, a company needs to conduct extensive clinical trials. This, together with regulatory approval processes and other regulatory procedures, means that the time between the application for a patent and the moment a drug comes onto the market can be many years. This is time that a company loses from its effective term of protection, as during this time it is unable to make a return on investment. Second, as most pharmaceutical innovation is done in the commercial space, it has tended to focus on areas of greatest profit potential. This mean that companies will shun drug development in therapeutic areas where there is a still a need, yet insufficient promise of a financial return. To address these two issues, a set of 'supplementary protection mechanisms' has been created.

In the EU, several such supplementary protection mechanisms exist. These are:

- **Supplementary Protection Certificates (SPCs)**: In 1992, the predecessor of what is now SPC Regulation 469/2009 was introduced in the EU. Its aim is to compensate for loss of effective term of patent and to incentivise pharmaceutical R&D in Europe by bringing European policy more in line with policy in US and Japan. It offers companies the possibility to add up to a maximum of 5 years of protection to their product in addition to the 20 years of patent protection.
- **Paediatric extension**: In 2007, the Paediatric Regulation (1901/2006) came into force. Its purpose is to stimulate research for use of pharmaceutical products for children. The regulation contains a mandatory requirement that for any drug for which a company seeks a marketing authorisation (unless a waiver is granted) it must comply with an approved paediatric investigation plan. In exchange, the regulation offers a reward in the form of a six-months extension to the SPC.
- **Orphan market exclusivity**: In 2000, the Orphan Drug Regulation (141/2000) went into effect. The regulation aims to stimulate development of drugs for orphan diseases. In addition to various other measures, the regulation rewards companies who bring a designated drug to market for an orphan disease with a period of 10 years of market exclusivity during which no other similar products can request or receive a marketing authorisation.
- **Data exclusivity and market protection**: the EU medicines legislation offers holders of a marketing authorisation additional regulatory protection in the form of data exclusivity and market protection. These exclusivities and protections are intended to give companies that have invested in R&D a chance to recover some of these investments before generic competition can enter the market. The basic rule is eight years of data exclusivity plus an additional two years of market protection, which can in certain limited cases be extended with an additional year.

Each of these mechanisms has a clear rationale from the perspective of incentivising pharmaceutical innovation. At the same time, they also have ramifications for the affordability and accessibility of

drugs by delaying competition in the market. These systems thus must strike an appropriate balance between different, and sometimes opposing, interests.

Questions have been asked about whether the systems, as they are today, are in effect achieving that appropriate balance. This study was designed to help answer the question of whether the supplementary protection mechanisms for pharmaceutical products are currently 'fit for purpose', to be understood as whether they are effective in achieving their goals and minimising any negative consequences.

Methodology used

This study has looked at the different mechanisms through three distinct lenses. First, a legal perspective was taken to determine how policy objectives have been translated into statutory provisions; how these provisions have since been challenged and interpreted in the legal system; and what the implications of legal judgements on aspects of the statutory provisions are. This analysis was based on a review of the statutory framework and related documents, the relevant case law and of the legal literature.

Second, this study analysed impacts of the systems from an innovation perspective. Using primary and secondary data sources, including interviews with stakeholders, the effects on R&D intensity and on the therapeutic value of the innovation resulting from that R&D were examined.

Third, by drawing from evidence of seven case studies on drugs that have benefitted from (a combination of) these mechanisms, it was assessed what the impacts of the mechanisms are on the price development of drugs and on the direct costs to the (Dutch) healthcare system. Case studies were based on data on costs and users in the Netherlands, literature and interviews with the pharmaceutical companies. The case studies are illustrative and cannot be used to extrapolate from to the entire Dutch market (or beyond).

Key findings

The systems each are found to have succeeded to a varying degree in achieving their desired objectives. The SPC Regulation offers innovator companies an adequate compensation for their effective loss of patent term. As an incentivising measure, however, the effect is much less clear. First, the SPC Regulation has failed to incentivise pharmaceutical R&D in Europe sufficiently to narrow the gap with the US. Furthermore, the relation between investment incentives and a 'reward' that is not received until many years, or even decades, after the decision to invest in development of a product is made – particularly when the outcomes of that investment decision are highly uncertain – remains unclear.

Meanwhile, the Paediatric Regulation has catalysed much needed paediatric drug research in some therapeutic areas, though it falls short in spurring on drug development for areas of greatest unmet need in children. The Orphan Drug Regulation similarly has been a strong catalyst for development of orphan medicinal products, but this effect has been stronger in certain areas such as oncology than for other truly rare diseases. There thus continues to be a substantial unmet need for pharmacological treatments for paediatric and orphan diseases.

These relative successes must, however, be viewed alongside any drawbacks. It is found that each of the systems has brought with it various unintended effects. Whether these effects are cause for concern is largely a normative judgment, though in many cases it stands to reason that effects that were not intended by the legislator are unlikely to serve the public interest.

Particularly the evolving, and at times inconclusive – if not contradictory –, interpretations of the SPC Regulation by the judicial system have reshaped the system in fundamental ways, adding to its complexity. This is at least partly due to unclear statutory provisions in the Regulation on the one hand, and lack of clarity provided by the Court of Justice of the European Union in adjudicating referrals for interpretation of those provisions on the other hand. As a result, SPCs can now be granted in areas where this was not originally the case, and/or where it was arguably not intended. This study concludes that the system appears in need of a critical review and possibly update, at the level of the

EU, as currently it does not fully provide the legal certainty that users and society should be able to expect from the system, to better align the objectives and effects of the regulation and reduce unnecessary ambiguity.

In the context of the Paediatric Regulation the question arises whether the paediatric extension is the most appropriate instrument to reward paediatric research. There is arguably not always a proper balance between the size of the reward provided and the costs necessary to comply with the regulation.

It has been questioned whether the Orphan Drug Regulation has become the subject of unintended and unfair use via practices such as 'indication stacking' and 'sub-setting'. Such concerns about widespread system failure appear, as yet, unfounded. That is not to say that the regulation is used optimally. It appears that safeguards that were put in place to ensure that the regulation does not offer rewards where these are not needed are insufficiently used. Additionally, it is worth considering whether the statutory framework could be improved to protect against accumulation of periods of exclusivity for medicinal products with the same therapeutic indications.

Conclusions and recommendations

Based on the overall findings, this study concludes that, whilst overall the supplementary protections mechanisms function to a significant extent in the ways for which they were designed, there is ample space for improvement. This involves a combination of actions to: i) improve their effectiveness, ii) resolve remaining uncertainties, and iii) reduce or eliminate unintended and undesired effects. To this effect various recommendations are offered. These have been divided into those recommendations that pertain to specific aspects of the various mechanisms and some more general conceptual measures. Whilst the recommendations mostly would need to be taken up at the level of the EC, they can be used by Member States such as the Netherlands and other parties to advocate for action in these areas.

Specific recommendations

- **Maintain the systems in place in their basic constituent parts**: This study has not found compelling evidence to recommend a complete abolishment of the SPC Regulation, the Paediatric Regulation (more specifically, the paediatric extension), the Orphan Drug Regulation (in particular, the market exclusivity for orphan products) or the data exclusivity and market protection. The objectives set for each are for the most part sound and the systems are, to varying degrees, succeeding in their objectives. There appears to be relatively little (at least visible) outright "abuse" in the legal sense of the word.
- **Tackle the issue of the extent of protection of basic patents**: The issue of defining the scope of protection of the basic patent remains unresolved and should be tackled. Several options for this exist, that each have their own benefits and drawbacks.
- **Establish the extent to which secondary medical use patents, formulation patents, or other derivative patents should be protected by SPCs**: Jurisprudence has paved the way not only for SPCs on indication patents, but potentially also on patents related to formulations or dosages. This may increase the number of SPCs considerably. The lawmaker could contemplate a more sui-generis approach towards this type of patents, somewhat keeping the middle-ground between full SPC protection and no SPC protection at all, for instance by providing a shorter SPC term or some other type of incentive.
- **Consider whether the extent of supplementary protection granted by an SPC can and should be differentiated by the therapeutic value offered by the product**: Whilst tying the degree of innovativeness of a product to the size of the compensation would be in line with the spirit of the SPC regulation, this recommendation is not without its problems. First, there is no agreed definition or metric for what constitutes 'therapeutic added value'. Second, as SPCs are granted at the national level, the assessment of such value could fall on national patent examiners, who are unlikely to have the required expertise to do so. Moreover, leaving this assessment at the national level is likely to introduce substantial divergence of outcomes across Member States. Alternatively, the assessment could be done at

the European level (i.e. by the EMA) or by a national competent authority (such as the CBG-MEB) which then acts as a reference for other Member States.

- **Consider eliminating the possibility of SPC squatting**
- **Re-examine the appropriateness of the 6-month paediatric extension to an SPC as the desired reward for paediatric research**: The existence of zero or negative-term SPCs underscores that the link between SPC protection and the eligibility for the reward for compliance with a PIP is a tenuous one.
- **Consider introduction of alternative or additional incentives to promote R&D for the development of paediatric drugs for which there is no adult indication, and addressing areas of greatest unmet need in children and neonates**: Rather than offering further supplementary protections, this could also be done in the form of, for instance, research and innovation prizes.
- **Explore whether stronger support for basic research into orphan diseases is required**: There remains substantial unmet need for orphan drugs for the treatment of very rare diseases. This may be due to lack of sufficient basic research in this field. Investment in this could be (further) supported via, among others, the EU Framework Programmes or national research funding initiatives. As such support involves investment of public money, it would be important to carefully consider how this can be done in such a way that the affordability of any drugs developed is guaranteed.
- **Consider the introduction of a global marketing authorisation in the context of orphan drugs to ensure that generic entry and competition is not unduly delayed**: However, the Orphan Drug Regulation acts on a very delicate system, as orphan drug development has traditionally not been the natural habitat for pharmaceutical companies who are looking for drugs with significant profit potential. The Orphan Drug Regulation and the incentives laid down therein must achieve the difficult task of sufficiently incentivising investment in the development of drugs with a smaller patient base and profit potential without hampering innovation by foreclosing such markets.
- **Explore whether Member States are sufficiently aware of the derogation options offered under Article 8(2) of the Orphan Drug Regulation** that allow the period of market exclusivity to be reduced under particular conditions. In practice, however, the invocation of this article by individual MSs will likely be complicated due to lack of knowledge at national ministries about exact disease prevalence, or national variations in drug prices, resulting from underlying differences in procurement and reimbursement systems. Yet, the provision offers one of the few possibilities for concerted action against excessive profiteering on orphan drugs at the EU level.

General recommendations

- **Increase expert know-how on supplementary protections and the interface between IP and pharmaceutical regulation**: With know-how in the analysed fields being scarce, managing and improving the know-how base becomes key. This includes proper staffing of patent offices and training of the patent examiners, but also supporting the development towards specialised courts with respective know-how in both IP and regulatory measures.
- **Foster exchange and collaboration between regulatory experts and IP experts**: There appears to be a substantial divide between experts of (pharmaceutical) IP and experts in pharmaceutical regulation. It seems feasible to support an improved institutionalised exchange forum between these two groups of experts to improve awareness of the impacts of decisions taken in one sphere on the other sphere.
- **Improve clarity and ease of use of EU and national data registers on protections and exclusivities for pharmaceutical products**: Whilst most information is in the public domain, registers are not well linked or easy to navigate without expert knowledge. That is, at least in part, because of inconsistent use of product names (e.g. brand names vs INN or chemical formula, variant brand names, language differences). Moreover, different protections

are linked to the actions of different parties (e.g. national patent offices vs national competent authorities for marketing authorisation). The lack of a unified, connected and clear overview makes it hard for non-specialised third parties to see when a drug will become free from protection.

- **Emphasise routine evaluation of the impact of regulations**, not only with a view towards accountability but with an openness to **update and revise regulations** in areas where that is appropriate. Uncertainty about consequences and a fear of upsetting delicate systems should not lead to policy paralysis.

Whilst ultimately it is the responsibility of the legislator (that is, the EU and its Member States) to decide on the appropriate course of action, it is important that this is done with a proper understanding of the needs and interests of all parties involved. Moreover, the consequences of these actions should not only be considered for the short-term (e.g. via cost savings), but also for the long-term (e.g. on the pipeline of pharmaceutical products under development). Ensuring patients' access to innovative pharmacological therapies, yet doing so in a way that is affordable to the individual patient and the healthcare system at large, depends on a pharmaceutical climate wherein both innovation and competition are stimulated, and where the effects of regulatory frameworks on the affordability of healthcare are part of the equation.

Part A

BACKGROUND

1 Introduction

1.1 Pharmaceutical innovation and intellectual property rights

The patent system is designed as a 'social contract' between society and inventors. Inventors, as one 'contracting party', are provided with time-limited monopoly rights in exchange for publication of the working principle behind the invention in patent specifications. The time-limited monopoly rights allow the original inventor to recuperate costs and efforts for R&D, which he or she could otherwise not do, if an imitator could simply copy the proven invention. Society, the other 'contracting party', benefits by being provided with inventions which, after expiry or lapse of the monopoly rights, are freely accessible for further production and follow-up innovations.[1]

At least partly due to the way new drugs are developed, the pharmaceutical industry is one of the most intensive users of the patent system. Pharmaceutical development processes not only require the research and development of new compounds, but necessitate time-consuming and expensive follow-up research in the form of preclinical to phase-III clinical trials to prove, in the regulatory approval processes, the efficacy and safety of the new medications. Only a fraction of promising leads make it successfully through phase-III clinical trials. Therefore, any revenues from the few successful drugs must also cover for the losses incurred through development of drugs that did not make it to market.

Over the years, pharmaceutical companies have faced two major challenges. First, regulatory approval processes have become more complex and demanding. This has narrowed the time window available, within the frame of the maximum term of patent protection of 20 years, to take advantage of the granted monopoly rights. Furthermore, companies have found it increasingly difficult to develop new drugs that can replace their 'blockbuster' drugs that have provided much of their income. There has been, and continues to be, considerable debate as to whether the causes of these difficulties are scientific, technological, regulatory (or any combination thereof), or are due to a lack of proper channelling of investments in innovation. For original inventors, the pressure to extend the life of a patent has therefore increased considerably.

To counter some of the time during which a marketed drug enjoys protection lost due to increasingly long regulatory processes, and to incentivise continued pharmaceutical innovation, additional protection mechanisms have been developed. One such mechanism is the Supplementary Protection Certificates (SPC) system. Under this (European) system, a drug can be granted supplementary protection of up to five years after patent expiry.[2] Furthermore, recognising an unmet need for effective and safe paediatric drugs and for drugs to treat rare and orphan diseases, the European Commission has created two more protection mechanisms: one is the Paediatric Extension and the other a market exclusivity for drugs with a recognised Orphan Drug status respectively. Alongside these a pharmaceutical company can benefit from data exclusivity on the dossier of trial data exclusivity and market protection. An important characteristic of this instrument set is the combination of IP and regulatory approaches to protection.

Whilst the rationales behind these mechanisms align with a societal need to incentivise pharmaceutical innovation, concerns have been voiced about whether the way in which they are currently interpreted and applied is consistent with the underlying intentions and adequately serves the public interest. For society and the health care system the usage of supplementary protections and attempts to effectively prolong patent life of drugs is a double-edged sword: while the system is interested in providing a framework by which original inventors can successfully develop new medications, it must also deal with soaring costs in the health care system and ensure affordable access to medicines. Competition, in particular that provided by generic medicines, is essential to keep public budgets under control and to maintain widespread access to medicines to the benefit of

[1] Bostyn, S.J.R., Enabling Biotechnological Inventions in Europe and the United States. A study of the patentability of proteins and DNA sequences with special emphasis on the disclosure requirement, Eposcript Series, nr. 4, EPO, München, 2001, 32-40.

[2] Or five years and six months when combined with a Paediatric Extension.

consumers/patients. The European Commission estimates that the introduction of generic competition results in a price drop of 25 to 40 percent within two years.[3] In the Netherlands, this effect is even more pronounced.[4] The question is therefore one of finding the right balance: original inventors should have the possibility to duly develop their compounds, but not to unduly benefit from demanding, over exaggerated periods of time, excessive amounts of money for their drugs.

1.2 Problem setting

In early 2016, the minister of Health, Welfare and Sports laid down her vision for pharmaceutical policy in the Netherlands.[5][6] In this vision document, several problems affecting pharmaceutical development and access to medicines are described. In relation to intellectual property and exclusivity rights, specifically, it refers to a report by the Authority for Consumers and Market to state that "industry is sometimes using the protections offered to maximise the profit of products in a way that is undesirable". It is, furthermore, questioned whether the current supplementary European protections in the form of SPCs, paediatric extensions, and orphan drug market exclusivity have failed to hit the mark.

The primary questions underpinning the minister's concern are whether the additional protections granted do indeed contribute to meaningful innovation, by addressing unmet medical needs, and whether these incentives come at an unacceptable societal cost. The present study was launched in response to these questions. It was conducted in parallel to two studies commissioned by the European Commission on economic and legal aspects of the SPC system. Specifically, this study looked at:

- What was the rationale and motivation behind the supplementary protection mechanisms?
- What is the current situation regarding the interpretation and application of SPC legislation at the level of the European Court of Justice?
- What are the main trends in usage of different supplementary protection mechanisms?
- What have been the main impacts of the above supplementary protection mechanisms on incentivising (meaningful) innovation?
- What have been their impacts on the Dutch health care system, in terms of economic costs and access to medicines?
- To what extent is the desired balance of interests achieved?
- To what extent are the current systems fit for purpose?

1.3 Structure of the report

This report consists of four main parts:

Part A describes the background to this study, including its objectives and the methodology that was used.

Part B provides information on pharmaceutical policy in the Netherlands, including details on procurement, pricing and reimbursement. Additionally, it contains a high-level overview of the pharmaceutical R&D landscape in the Netherlands. These two chapters have been included primarily as background information against which the subsequent parts of the report should be viewed.

Part C forms the heart of the study, and includes the comprehensive study findings. This part has been structured into three individual chapters. The first of these provides an in-depth legal analysis of all the different systems and regulations that are the subject of this study, and explores how the

[3] http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_nl.pdf
[4] Autoriteit Consument & Markt (2015). Farmacie onder de loep: Kansen voor toetreding generieke middelen en keuzes voor patiënten.
[5] Schippers, EI (2016) Geneesmiddelenvisie. Ministerie van Volksgezondheid, Welzijn en Sport
[6] Schippers, EI (2016) Kamerbrief Visie op Geneesmiddelen: nieuwe geneesmiddelen snel bij de patiënt tegen aanvaardbare kosten. Ministerie van Volksgezondheid, Welzijn en Sport

interpretation of these has evolved with time as a result of litigation. A second chapter considers how the systems have impacts innovation, both in terms of catalysing or hindering innovation and in terms of the therapeutic value of such innovation. The concluding chapter of this part provides an estimate of economic impacts in the context of the Dutch healthcare system, by drawing lessons from seven case studies on selected drugs.

Part D contains a discussion of the overall study findings and draws conclusions based on these.

2 Methodology

Consistent with the methodology proposed in the response to the Call for Tenders, the study used a number of data collection and analysis methods. In this chapter these methods, and data sources used, have been detailed. An overview of the main methodological limitations is included as well.

2.1 Desk study

The study began with a comprehensive analysis of available background literature relevant to the subject. Literature was identified via, among others, searches in databases for scientific literature such as PubMed, of the websites of governmental bodies and institutions (e.g. Ministry of VWS, Netherlands Healthcare Institute, European Medicines Agency), and of the websites of pharmaceutical industry associations (Vereniging Innovatieve Geneesmiddelen, HollandBIO, Bogin, Health~Holland) and via Google searches. Further relevant literature was identified throughout the entire study.

2.2 Legal analysis

Relevant case law was identified from the following sources:

- Westlaw
- Lexis Nexis
- Hein-onLine
- Kluwer Navigator
- Medline
- Web of Science
- curia.eu (CJEU website)
- bailli.org (website for UK case law)
- rechtspraak.nl (for dutch case law)
- General Internet searches

2.3 Stakeholder interviews

Interviews with a wide range of stakholders formed an important part of this study. Their opinions were thought on the perceived purpose and functioning of relevant aspects of the systems subject to this study and on the observed impacts thereof. Furthermore, where relevant, interviewees were asked to identify other relevant data sources to be included in the analysis. The list of interviewees was prepared in collaboration with the Ministry of VWS. A full list of interviewees has been included in Appendix A.

For all interviews detailed notes were taken. The notes, translated to English, were shared with the interviewees, allowing them to correct factual errors or to elaborate on specific points that were discussed. The approved notes formed the basis for the analysis. All notes were analysed with the aid of Atlas.Ti. An iterative list of codes was developed, against which all notes were coded.

2.4 Economic analysis

2.4.1 Case selection

As a full analysis of economic impact, even in the context of the Dutch healthcare system alone, would not be feasible given the complexity of impact mechanisms at work and the size of the pharmaceutical market, the economic analysis was based on a series of seven case studies to illustrate and outline major strategic approaches and issues arising when using the set of instruments for supplementary and regulatory protection. The cases were purposely selected on a number of criteria:

- Variety of supplementary protection mechanisms applicable (i.e. SPC, Paediatric Extension, Orphan Drug Designation, second and further medical indication patents, data exclusivity and market protection). Within this, one case (Atripla) was selected for a particular issue concerning SPCs, namely that related to combination products.
- Variety of current extent of protection (i.e. drugs that are no longer protected under any of the relevant mechanisms and those that still are) and availability of alternatives and generics.
- Variation across drug prices (high vs low) and sales volumes (high vs low).
- Variation in inpatient and outpatient drugs
- Variation across diseases targeted by the drugs (e.g. chronic vs acute)
- Data availability, as the economic analysis required presence of at least some data on sales volumes and prices in the Netherlands.

Selection of the cases was done in collaboration with the Ministry of VWS, with further input by the Ministry of EZK.

2.4.2 Data sources

The Dutch market data used in the case studies were obtained via the Dutch Ministry of Health, Welfare and Sports. Data on outpatient drugs (Atripla, Cozaar, Glivec (partially), Lipitor and Losec), were obtained from Stichting Farmaceutische Kengetallen (SFK).[7] For each version of the drug on the Dutch market, both from the originator and from generics companies when relevant, it contains information on:

- annual number of defined daily doses (DDD)[8],
- annual number of administrations,
- total costs.

In addition, information was obtained on the total number of users, DDDs and administration of a drug per year, for all versions together. The data set covers the years 2006-2016.[9]

Data on the annual costs and users for the inpatient drugs (Glivec (partially), Myozyme, Revlimid) was retrieved from Vektis.[10]

Representatives for all companies that are the MA holder for the selected products were approached to participate in an interview. Interviews were conducted with representatives of four companies; the remaining companies declined as the products involved had been developed a long time ago and no-one could be identified to provide the requested information within the timeframe provided.

The draft cases were shared with the companies, who were permitted to provide a response and correct factual errors. Where relevant and appropriate, these responses were subsequently incorporated into the final cases presented here.[11]

For all case drugs, a search for any relevant reporting in the Dutch media was conducted via Lexis Nexis.

2.5 Study limitations

The study team has attempted throughout to identify all relevant data sources and triangulate findings across different sources to construct the evidence provided in this report. The possibility remains,

[7] www.sfk.nl

[8] The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, see: https://www.whocc.no/ddd/definition_and_general_considera/ accessed 26-10-2017.

[9] For Atripla, this is 2008-2016, as this drug acquired marketing authorisation in December 2007.

[10] www.vektis.nl

[11] This validation step is currently still in process: 15 January 2018.

however, that important sources were overlooked or that those that were used contained incomplete or incorrect data.

In the selection of interviewees, we have strived to achieve a proper balance of perspectives and interests. However, it is recognised that the selected sample may not be fully representative of all stakeholders. In particular, the patient perspective remains somewhat underrepresented. Although the sample of interviewees was intended to include a sufficient number of stakeholders with specific expertise to cover all aspects of the study properly, in practice it was found that the expertise of most participants was focussed on either patent system issues or on regulatory issues in relation to, in particular, orphan drugs but that few possessed a comprehensive overview of all issues. Moreover, the issues related to data exclusivity were not extensively covered by the interviews.

An additional important limitation lies in the way the economic analysis was approached. By centring the analysis on a set of seven purposively selected cases, a 'survivor bias' was introduced as the selected cases all involve drugs with considerable success in their respective markets. The economic analysis does not take account of the R&D costs that pharmaceutical companies incur for drugs that either fail in the market or that never reach the market. Whilst we acknowledge the limitations of this approach, the focus of the study itself necessitated the selection of drugs that made it to market – to be able to access data on prices and volumes – and that enjoyed one or more of the supplementary protections. The choice of relative 'winners' as case studies implies that no comprehensive conclusion can be drawn vis-à-vis the total costs of pharmaceutical care or the costs and benefits of pharmaceutical investment. Rather, the aim is to see how the supplementary protection mechanisms work out in practice. Furthermore, a full patent landscape analysis for each of the case study drugs was out of the scope of this study, so the focus was on the particular patents and SPCs deemed relevant for the analysis.

Furthermore, as further explained in section 7.1, this study did not consider economic impacts beyond that of the costs to the health care system as a direct result of the costs of the drugs studied. Whilst a welfare economic perspective should certainly be taken into account in a broader discussion on the need to incentivise and reward pharmaceutical innovation, this perspective was beyond the scope of the present study.

Part B

Pharmaceutical R&D and policy in the Netherlands

3 The pharmaceutical landscape in the Netherlands

Pharmaceutical R&D includes the entire chain from early lead discovery through to clinical trials to establish a drug's efficacy, safety and effectiveness. It is a highly resource intensive process, involving many different parties. The introduction of new medicines into the market is the result of lengthy, costly and risky research and development (R&D) process conducted by pharmaceutical and biotechnology companies. By the time a medicinal product reaches the market, an average of 12-13 years will have elapsed since the first synthesis of the new active substance. On average, only one to two of every 10,000 substances synthesised in laboratories will successfully pass all stages of development required to become a marketable medicine.[12]

Discovery and early stage development is often done in public settings, such as academic research groups, or in small-medium enterprises (SMEs). By contrast, late stage clinical trials and further product development are most commonly done by large companies that have the necessary resources and infrastructures.

3.1 Pharmaceutical R&D in academia

In the Netherlands, public investment into R&D in the life sciences comes either directly from the Dutch government, from research funding institutions such as the Netherlands Organisation for Health Research and Development (ZonMW) and the Netherlands Organisation for Scientific Research (NWO), or from, among others, the EU and not-for-profit organisations.[13] Compared to in other countries, universities and public knowledge organisations[14] in the Netherlands receive a relatively high share of their R&D funding from the private sector.[15] In 2015, 9.4% of their R&D funding (across all sectors) came from private investments.[16]

In pharmaceutical R&D, public funding steeply declines when products near the end of the pre-clinical stage; clinical studies are almost fully funded by industry.[17] To facilitate the transition from public to private investments, the Dutch government has invested in a so-called Early Phase Investment tool (Vroegefasefinanciering, VVF) which coordinates loans to small businesses, innovative start-ups and academic start-ups at the national level.[18] Nonetheless, the cost and complexity of drug development often necessitates collaboration between academia and public research institutes with pharmaceutical companies. The current climate of close collaboration between public (academic) research institutes and the private sector has been ascribed as an important reason for private sector companies to settle in the Netherlands.[19]

Knowledge transfer is increasingly recognised as the so-called 'third mission' of universities, in addition to traditional teaching and research roles. Many universities have Technology Transfer Offices (TTOs) to support knowledge co-creation, or, more explicitly, to facilitate the transfer of academic discoveries into start-ups.[20]

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[12] https://www.efpia.eu/media/219735/efpia-pharmafigures2017_statisticbroch_v04-final.pdf

[13] https://www.gezondheidsraad.nl/sites/default/files/200918.pdf

[14] Public knowledge organisations include, for instance, government research agencies, the National Institute for Public Health and the Environment, or the Netherlands Institute for Applied Research (TNO).

[15] Public knowledge organisations combine research with knowledge-intensive services, focusing on a particular topic or field. In 2014, this category comprised 29 institutes employing a total of 15,000 FTEs (from https://www.rathenau.nl/en/page/dutch-knowledge-infrastructure).

[16] https://www.rathenau.nl/nl/page/rd-investeringen-internationaal-perspectief

[17] https://www.hollandbio.nl/uploads/themacategorien/160624_sectorplan_lifesciences2030_leesversie.pdf

[18] https://www.rvo.nl/subsidies-regelingen/vroegefasefinanciering-vff

[19] https://ec.europa.eu/research/innovation-union/pdf/knowledge_transfer_2010-2012_report.pdf

[20] Ibid

3.2 Pharmaceutical R&D in industry

3.2.1 Industry characteristics

Pharmaceutical product R&D is done within two main types of companies. The first are the more traditional, and often (very) large pharmaceutical firms that are usually categorised by a portfolio of products. Alongside these, a newer type of companies has emerged in the form of biotechnology companies. Their products are typically more complex molecules, such as enzymes or antibodies. It is common for biotechnology firms to be considerably smaller and have a portfolio of just one to a handful of products on the market (or none at all, if products are all still in development). However, biotech companies are increasing both in size and in importance. In the 2016 EU R&D Investment Scoreboard, the biotechnology sector reported a one-year growth rate in R&D expenditure of 23.8%, continuing the rapid development of the sector, compared to a 7.2% increase among the traditional pharmaceutical companies.[21]

According to EUROSTAT data, the pharmaceutical industry is the technology sector with the highest added-value per person employed, significantly higher than the average value for high-tech and manufacturing industries. The pharmaceutical industry is also the sector with the highest ratio of R&D investment to net sales. The 2016 EU Scoreboard reports that the pharmaceutical and biotechnology sector amounts to 19.1% of total R&D expenditure worldwide, with an estimated expenditure of over €130b. Recent studies in some countries showed that the research-based pharmaceutical industry generates three to four times more employment indirectly - upstream and downstream - than it does directly.

The landscape in which large pharmaceutical companies operate has undergone profound changes over the last decade. Patent protection on an increasing number of 'blockbuster' products is running out, whilst the market share of generics to replace these products is increasing. Despite the large investments in R&D within the sector, originator companies are increasingly dependent on their existing blockbuster products.[22] Originator companies have responded to this threat by diversifying their risks, through takeovers of smaller biotech- or generics companies.[23] These developments have also led to companies refocusing on ways to increase productivity of their R&D and on streamlining costs in the value chain. The result is an industry in which specialty and niche health care biotech products (as opposed to large-volume blockbusters) are prized for their potential for sustainable health care solutions.

3.2.2 Pharmaceutical R&D in the Netherlands

The traditional pharmaceutical industry in the Netherlands has declined to the point where now it consists primarily of offices of large international pharmaceutical firms, dedicated to sales and clinical trials rather than (earlier stage) R&D.[24] Meanwhile, the last decade has seen an increase in the number of small and medium sized biotechnology companies.

In the Netherlands, the overall pharmaceutical industry consists mostly of small to medium-sized[25] companies. In 2017, there were 420 companies in the pharmaceutical development sector, of which 400 were SMEs versus just 20 'big pharma' companies. Around 38% of the companies are involved in production of pharmaceutical products, 54% represent medical biotech companies and 7% produce

[21] The 2016 EU Industrial R&D Investment Scoreboard, European Commission, JRC/DG RTD. Available at http://iri.jrc.ec.europa.eu/scoreboard16.html#close. Accessed January 2018.

[22] Originator companies are companies that are manufacturers and patent holders on drugs that were first of their kind on the market.

[23] http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_nl.pdf

[24] https://www.cogem.net/index.cfm/nl/publicaties/publicatie/economische-analyse-van-de-nederlandse-biotechnologiesector. Accessed 12 January 2018.

[25] Companies with less than 250 employees

raw materials for pharmaceutical products.[26] The turn-over of the Dutch pharmaceutical production industry in 2014 was around €5.3b.[27]

In 2016 in the Netherlands more than 24,000 people worked in R&D within the life science sector[28]. These companies worked on more than 320 different drugs and diagnostics[29], 60 medical devices and the development of 200 technologies for application in academic and clinical settings. In 2015, the Dutch biotech sector received more than €4.4b in private investments, 70 times more than public investments into this sector[30].

Jointly, the pharmaceutical sector invested an estimated €380m in R&D in the Netherlands in 2017, of which 66% was spent internally and 34% externally (e.g. in collaboration with partners).[31]

3.3 Alternative development models

There is growing criticism of the perceived high drug prices charged by drug manufacturers and a lack of transparency on how development costs relate to the price. In response, a number of alternative pharmaceutical R&D models have emerged. Examples of such initiatives within the Netherlands are Cinderella Therapeutics and Fair Medicine.[32-33] Although these initiatives differ in where in the development chain they operate, they have in common that they aim to re-define (part of) the pharmaceutical development process, reducing the inefficiencies that currently operate in the development chain.

3.4 Generic drug industry

The term 'generic' is widely used but its definition is not always consistent between countries. Generics are usually produced by a manufacturer who is not the inventor of the original product, and are marketed when intellectual property protection rights and other exclusivities are exhausted. The prices and market shares of generics vary widely across Europe. For example, prices charged by manufacturers in Switzerland are, on average, more than 2.5 times those in Germany and more than 6 times those in the United Kingdom, based on the results of a commonly used price index (prices for the Netherlands are not available). In the Netherlands, generic drug substitution is mandatory. In 2015, generic medicines accounted for 16.7% of the pharmaceutical market sales value (at ex-factory prices) in the Netherlands.[34]

[26] https://www.verenigingingnovatievegeneesmiddelen.nl/website/over-de-vereniging/media/publicaties/economische-footprint-nederlandse-geneesmiddelensector

[27] 16% of €33b, from footnote 26.

[28] Not limited to pharmaceutical R&D

[29] Diagnostics are pre-diagnostic tests or screenings

[30] https://www.hollandbio.nl/uploads/themacategorien/160624_sectorplan_lifesciences2030_leesversie.pdf

[31] https://www.verenigingingnovatievegeneesmiddelen.nl/website/over-de-vereniging/media/publicaties/economische-footprint-nederlandse-geneesmiddelensector

[32] https://www.raadrvs.nl/uploads/docs/Recommendation_Development_of_New_Medicines.pdf

[33] http://www.fairmedicine.eu/en/our-approach/how-does-fair-medicine-work/

[34] https://www.efpia.eu/media/219735/efpia-pharmafigures2017_statisticbroch_v04-final.pdf

4 Pharmaceutical policy in the Netherlands

4.1 Regulatory approval and marketing authorisation

Before a drug can enter the market, a company needs to obtain a marketing authorisation (MA) for that drug. For this, it needs to pass through a process of regulatory approval. In the Netherlands, there are several ways in which an MA can be obtained.

Many drugs receive approval through the **Centralised EU Authorisation Procedure**. Under this procedure, pharmaceutical companies submit a single MA application to the European Medicines Agency (EMA) that, if granted, allows the holder to trade the drug in all countries of the EU, Iceland, Liechtenstein and Norway.[35] The scientific assessment of the application is carried out by the EMA's Committee for Medicinal products for Human Use (CHMP). The outcome of the EMA's decision is laid down in the European public assessment report (EPAR). This centralised procedure is mandatory for all biologicals and for new drugs for, among others, cancer, HIV/AIDS, neurodegenerative diseases and diabetes.[36]

The **Decentralised Procedure** is another European registration procedure that can be used to obtain a marketing authorisation in multiple countries if the applicant does not yet have any such authorisation. In this case, one country will act as a Reference Member State (RMS). The majority of drugs in the Netherlands is registered via this procedure. In some cases companies may also opt for the **National Procedure**. Then, the MA is issued by the Medicines Evaluation Board (CBG-MEB) and is valid only for the Netherlands. Similar to the CHMP's role, the CBG-MEB evaluates a drug on the balance between its effectiveness and risks. The assessment procedure should be concluded within 210 days, though can be extended in case companies are requested to provide additional information. A study among companies conducting pharmaceutical R&D found that in the Netherlands the national procedure is hardly used anymore.[37] The national and decentralised procedures are not available if the applicant company has already applied for, or obtained, an MA for the drug in another EU/EER country. In these cases, the **Mutual Recognition Procedure** applies. This means that the MA issued by the regulatory authority of a RMS is recognised in the Netherlands.[36]

Generic medicines can be approved for the Dutch market through a shortened procedure. Here, it only needs to be demonstrated that the drug is biologically equivalent to a reference drug for which an MA is already available (not necessarily within the Netherlands), provided the dossier for the reference drug is complete.

Regardless of the procedure followed, under the current system the MA is issued based on the drug's demonstrated effectiveness and safety for the *(patented) therapeutic indication*, meaning that the drug is approved only for use in patients with the same or highly similar conditions. The indication(s) for which the drug is registered is(are) included in the summary of product characteristics (SmPC). A drug can receive an MA for more than one indication. A company can add an indication by submitting a separate application, accompanied by a full application dossier. Alternatively, a new indication can be added to an existing marketing authorisation as an approved variation, which does not require a full application.

[35] European Medicines Agency. Authorisation of Medicines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp Accessed July 2017.

[36] College ter Beoordeling van Geneesmiddelen. Aanvraag handelsvergunning via centrale procedure. https://www.cbg-meb.nl/mensen/bedrijven-geneesmiddelen-voor-mensen/aanvraag-handelsvergunning/aanvraag-handelsvergunning-via-centrale-procedure Accessed July 2017.

[37] Actal/KPMG (2015) Onderzoek regeldruk geneesmiddelen. https://assets.kpmg.com/content/dam/kpmg/pdf/2015/09/Onderzoek-regeldruk-geneesmiddelen.pdf Accessed 15 January 2018.

A drug that has been patented and authorised for multiple indications eventually will lose protection on one indication, whilst the protection for other indication(s) may still be in force. At that point, generic medicines may only be prescribed for the indication that is no longer patented. To avoid disallowed prescription of generic medicines for patented indications, the (paper-based form of the) SmPC and patient information leaflet may have a so-called 'carve out' of the patented indication. Currently, the CBG-MEB publishes all indications, both those that are off-patent and those that are still patent protected, on its website. This practice is contested by the pharmaceutical industry and is currently still under litigation.[38]

In relation to the scope of this study, it is worth mentioning that in 2015 the Dutch Advisory Board on Regulatory Burden (Actal) found that the regulatory process (in addition to procedures associated with conducting pre-clinical and clinical research) via the centralised procedure is creating unnecessary delays, exceeding the maximum allowed time for the CHMP to assess an application. Also a lack of harmonisation between the requirements from the EMA and the Netherlands Healthcare Institute was said to lead to further delays.

4.2 Pricing and reimbursement policies

Pricing strategies can be roughly classified as those that are cost-based and those that are value-based. In cost-based pricing there is a direct relationship between the cost of development and manufacturing of a product and its price, charged as the price necessary to recover costs plus a moderate percentage margin. Cost-based pricing is the predominant strategy in competitive, mass production markets. By contrast, value-based pricing considers consumers' willingness-to-pay based on their expectations of the value to them, for instance in quality of life or health gains. A complexity here is that for most prescription medicines, most or all of the costs will be reimbursed to the patient (see section 4.2.3). As a consequence, even though the patient benefits from the medicine, patients are extremely price-insensitive as they do not directly bear the costs Products priced on value usually have significantly higher profit margins than those priced on cost. Innovative medicines are commonly priced based on estimations of value. Problematically, however, the pharmaceutical market (just like the broader health care market) is a highly imperfect market, wherein consumers often have few to no alternatives to the offered product.[39] Consequently, there is a need for a degree of market steering to depress prices.

The government of the Netherlands aims to ensure that every Dutch citizen has access to medically necessary healthcare, including pharmaceutical care, at an affordable price. As it needs to do so within a set budget, it relies on various mechanisms to exert influence the prices of medicines. It can do this either directly, by setting maximum allowed prices or conducting price negotiations (or delegating this responsibility to hospitals, health insurers or pharmacies), or indirectly, through the reimbursement and co-payments system. This interplay of different forces that affect pharmaceutical prices has been summarised in Figure 1.

4.2.1 External reference pricing

According to the Medicines Prices Act (Wet geneesmiddelenprijzen, WGP), the price of a medicine may not exceed the maximum price.[40,41] This maximum price, both for inpatient and outpatient drugs, is determined by benchmarking pharmaceutical prices with the market prices of one or several other countries. For the Netherlands, the benchmarking countries are Germany, France, Belgium and the UK. The countries are selected mainly because they are considered comparable with the Netherlands

[38] De Rechtstpraak (2017) Warner-Lambert Company LLC vs de Staat (VWS, CBG). https://uitspraken.rechtspraak.nl/inziendocument?id=ECLI:NL:RBDHA:2016:334. Accessed 15 January 2018.
[39] Although the consumer of a medical product is the patient, in the case of prescription medicines, there are several other parties involved in the procurement process. The decision on what medicine a patient receives is made by physicians, based also on existing guidelines and reimbursement policies.
[40] Ministerie van VWS / Farmatec. Wet geneesmiddelenprijzen. https://www.farmatec.nl/prijsvorming/wet-geneesmiddelenprijzen Accessed July 2017.
[41] For some medicines the government has not set maximum prices but only GVS reimbursement limits (SFK, 2016).

with respect to welfare level, social security system and culture.[42] Each country has a list of maximum prices, which is consulted to select similar medicines to determine the Dutch maximum price. A similar medicine is defined as one with the same working substance, strength and pharmaceutical form. The selection and determination is done as follows:

- Maximum prices of similar medicines are selected from the national list
- A calculated average of the selected maximum prices is determined
- This is done for each country after which they are combined into a single calculated average

If there is no national maximum price for a specific medicine, the maximum price is calculated based on medicines that are listed. The procedure on how this is done differs between countries. In case three or more countries lack the necessary data, a benchmarked maximum price cannot be determined.[43] The maximum prices are evaluated twice a year, and updated if necessary.

4.2.2 Negotiated procurement

Hospitals and pharmacies buy medicines directly from a pharmaceutical manufacturer or wholesaler through price negotiations.[44] They then negotiate with health insurers to get these medicines reimbursed. Negotiations between hospitals and health insurers follow the principle of performance enhancement and selective procurement. Performance enhancement means that hospitals get paid separately for each delivered healthcare service or Diagnosis Treatment Combination (DTC, see also next section). Selective purchasing means that health insurers do not have to buy treatments at any hospital, but may select. Pharmacies do not use DTCs, but negotiate rates for services and medicines individually. These prices are referred to as Pharmacy Purchase Prices (PPPs).[45] The negotiation between pharmacies and health insurers usually result in a reimbursement of the procurement costs (minus a tax rebate, to compensate for the discount that pharmacists imposed on wholesale procurement prices).

The Platform Expertise Purchasing Medicines is a knowledge platform for sharing knowledge and expertise about the procurement of medicines, and is aimed at bringing hospitals and health insurers together to jointly procure expensive medicines.[46] In 2012 the Ministry of VWS introduced so-called 'managed entry arrangements' (financiële arrangementen). These arrangements are price negotiations between the Unit for Drug Pricing Managed Entry Arrangements, part of the Ministry of VWS, and pharmaceutical companies over the price for selected new, unique medicines. A financial arrangement is applied in cases where the financial risks due to budget impact and cost-effectiveness are high, and hospitals and health insurers have insufficient negotiating power due to monopoly power of the manufacturers. The outcomes of the arrangement decide whether a drug is included in the basic health insurance package. The arrangement is concluded for a period until there is a reasonable expectation of competition to arise. Around ten negotiations a year are conducted. Additionally, in a further attempt to curb the costs from very expensive inpatient medicines, in 2015 the 'gate procedure' (sluis) was introduced. Drugs that are subject to this procedure do not flow automatically into the reimbursement scheme. Rather, they too become the subject of price negotiations.

To further strengthen the Dutch position in price negotiations with pharmaceutical manufacturers, in 2017 the BeNeLuxA Connection was established.[47] This cooperation between the Netherlands, Belgium, Luxembourg and Austria will conduct pilots in the coming years on issues such as mutual

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[42] Conquaestor. Onderzoek Wet Geneesmiddelenprijzen: Prijsbeheersing van geneesmiddelen in Nederland. https://www.rijksoverheid.nl/documenten/rapporten/2012/06/25/onderzoek-wet-geneesmiddelenprijzen-prijsbeheersing-van-geneesmiddelen-in-nederland Accessed July 2017.

[43] http://wetten.overheid.nl/BWBR0007867/2013-01-01, accessed August 2017.

[44] Nederlandse Zorgauthoriteit (2014) Martkscan en beleidsbrief Extramurale Farmaceutische Zorg

[45] Nederlandse Zorgauthoriteit (2016) Contractering en inkoop geneesmiddelen in de medisc-specialistische zorg

[46] Ministerie van VWS (2017) Instelling Platform Inkoopkracht Dure Geneesmiddelen. https://www.rijksoverheid.nl/documenten/kamerstukken/2017/09/20/kamerbrief-over-instelling-platform-inkoopkracht-dure-geneesmiddelen Accessed 15 January 2018

[47] http://www.beneluxa.org/

negotiations, horizon scanning and joint health technology assessments. Horizon scanning must ensure that all stakeholders (e.g. patients and hospitals) know early which (new) medicines, or indication extensions, are about to enter the market by providing a public overview of these matters.[48]

4.2.3 Reimbursement

Once a drug has received an MA for the Dutch market, the manufacturing company can request it be included in the Medicines Reimbursement System (Geneesmiddelenvergoedingssysteem, GVS). All drugs listed in the GVS are covered by the basic (mandatory) health insurance package. The National Health Care Institute (Zorginstituut Nederland, ZiN) advises the Ministry of VWS on the inclusion of medicines in the GVS.[49,50] The GVS includes all outpatient medicines that are evaluated positively based on therapeutic value, budget impact and cost-effectiveness. The minster of VWS can also add outpatient medicines that are not yet proven effective.[51] In that case, the admission is temporary and conditional, enabling the collection of further data to demonstrate effectiveness to obtain permanent admission.

In addition to the fact that the GVS functions as a form of package management, the system also sets maximum reimbursement prices. In case a medicine price exceeds the reimbursement limit, the difference is charged in the form of a deductible, if it is not covered by a patient's (optional) supplementary health insurance.[52] To protect their market share, manufacturers may opt to lower their prices to, or below, the GVS reimbursement limit to keep the drug available to a patient at no extra charge. Because the GVS both determines which drugs are included in the insurance package and what the maximum reimbursement is, it enables the government to put some price pressure on pharmaceutical manufacturers.

Inpatient medicines are always covered by the basic health insurance, but a dual reimbursement system applies. The Dutch Healthcare Authority (Nederlandse Zorgautoriteit, NZa) has set a fee for most Diagnosis Treatment Combinations (DTCs), a standard package of care – including pharmaceutical care – based on a patient's diagnosis. The hospital where a patient is treated receives reimbursement based on the DTC fee rates.[53]

When a medicine cannot be an integral part of a DTC product, the NZa determines a so-called 'add-on' performance and related fee rates, to be charged in addition to the DTC product. Most expensive medicines are charged as add-ons. A health insurer and hospital can jointly apply for an add-on performance at the NZa. The add-on structure tackles two issues: (1) that the medicine costs are high with respect to the other costs of the DTC product and (2) that the total costs of a DTC product vary a lot between patients. By carving out expensive medicines from the related DTC, negotiations between hospitals and health insurers are not disturbed.[53]

Health insurers may include further reimbursement terms regarding the procurement of medicines. [54] The 'preference policy' is such a condition, which applies when generic alternatives are available. This policy determines which medicine from which manufacturer is fully reimbursed or whether a deductible applies. In case an insured patient wishes to use a medicine other than the preferred medicine, it will be at own cost. Most health insurers compensate only the cheapest variant of a generic

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[48] https://www.horizonscangeneesmiddelen.nl/, Accessed August 2017

[49] Overheid.nl Geneesmiddelenwet Artikel 13. Available at http://wetten.overheid.nl/BWBR0021505/2016-08-01. Accessed August 2017.

[50] Zorginstituut Nederland. Beoordeling extramurale geneesmiddelen (GVS) https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/beoordeling-extramurale-geneesmiddelen-gvs Accessed August 2017.

[51] Zorginstituut Nederland. Beoordeling voor voorwaardelijke toelating van zorg. https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-voor-voorwaardelijke-toelating-van-zorg Accessed August 2017.

[52] Overheid.nl Regeling Zorgverzekering. http:// wetten.overheid.nl/BWBR0018715/2017-09-08. Accessed July 2017.

[53] Nationale Zorgauthoriteit. (2013) Adviesrapport Bekostiging geneesmiddelen in de medisch specialistische zorg

[54] Overheid.nl. Besluit zorgverzekering. http://wetten.overheid.nl/BWBR0018492/2017-01-01 Accessed July 2017.

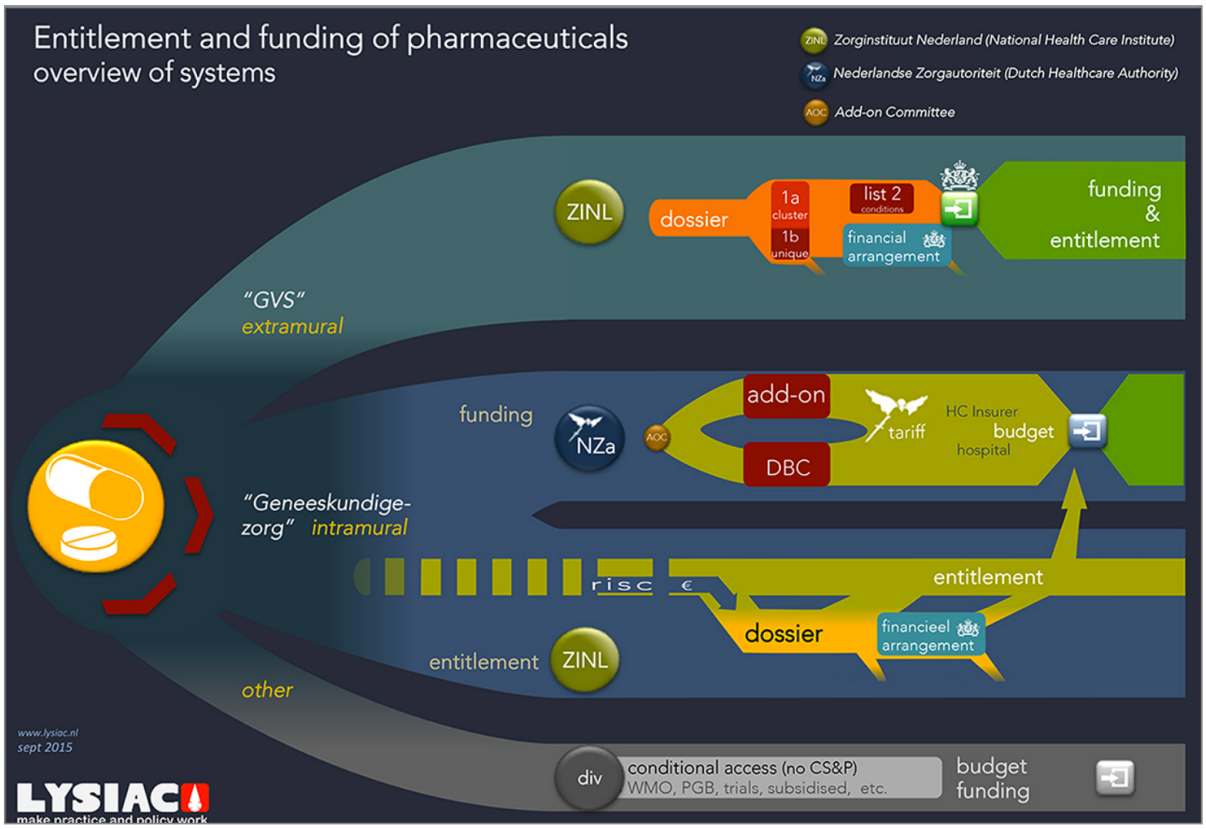
medicine, putting pressure on manufacturers to lower their prices and on patients and health care prescribers to opt for the generic version of a medicine.[55]

A preference policy variant is the 'couvert' preference policy according to which manufacturers negotiate directly with health insurers about the price of a medicine. The manufacturer then offers a direct discount to the health insurer. This means that the pharmacist will charge the pharmacy purchasing price (PPP) to the insurer and that the insurer will receive a discount from the manufacturer.[56] There are other forms of purchasing policy applied by health insurers as well, but these differentiate between medicines by type rather than by manufacturer.

4.2.4 Generic entry

Alongside the above mechanisms, there is a natural market-based mechanism that influences the price of medicines in the form of generic competition. Generic drugs can obtain marketing authorisation once the originator drug loses all its protection. As stated previously, generic entry can and often does have a tremendous impact on the price of originator drugs. As such, it is a key factor influencing both the cost of drugs and overall pharmaceutical expenditures.

Figure 1 Overview of policies, and stakeholders in the Netherlands and their roles in price determination and reimbursement of medicines



Source: Lysiac: Make practice and policy work (2015) http://lysiac.nl/eng/?artikel=overview. Note: the term 'intramural' refers to in-patient products, and 'extramural' to out-patient products.

[55] Nederlandse Zorgauthoriteit (2011). Voorbereiding vrije prijzen apotheekzorg van start. https://www.nza.nl/zorgonderwerpen/zorgonderwerpen/apotheekzorg/nieuws/Voorbereiding-vrije-prijzen-apotheekzorg-van-start/ Accessed July 2017.

[56] Nederlandse Zorgauthoriteit (2014). Marktscan en beleidsbrief. Extramurale Farmaceutische zorg: Weergave van de markt 2010-2014. The Hague: Dutch National

Part C

STUDY FINDINGS

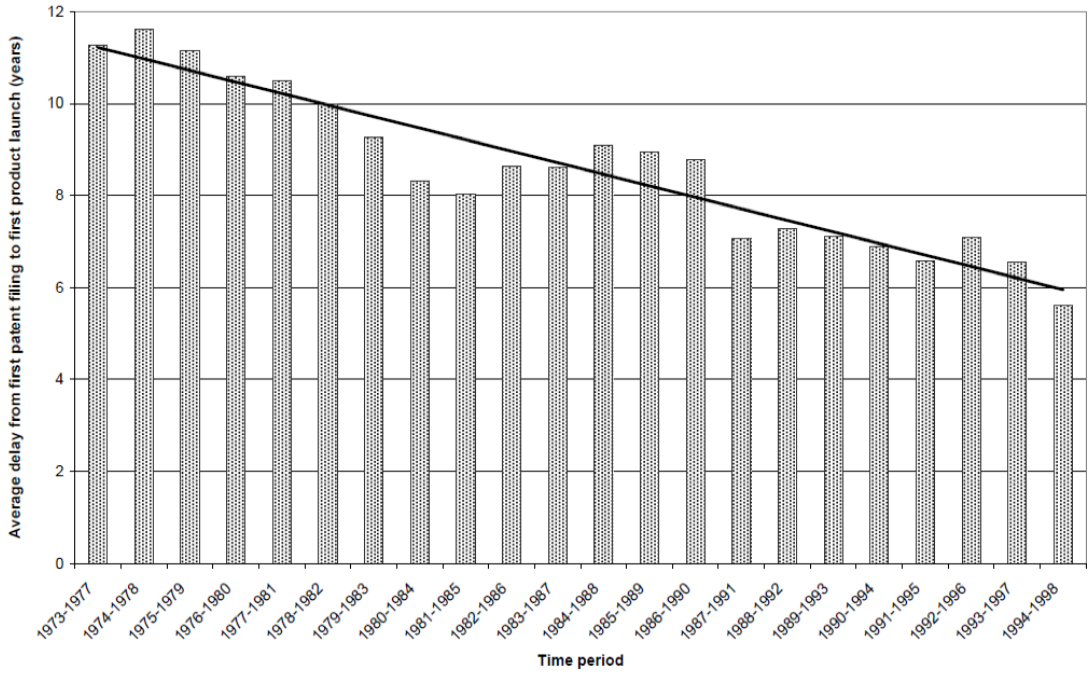
5 Legal analysis

5.1 The SPC system

5.1.1 Introduction

Supplementary Protection Certificates (SPCs) were introduced as a means to effectively prolong the patent life in cases where, most importantly, there have been delays in obtaining regulatory approval.[57] Indeed, pending regulatory approval of the drug, the patent(s) which cover(s) the to-be-approved drug cannot be used or enforced against any third party. That implies that there is a loss of effective term of patent protection compared with less or no regulated product markets. Regulatory approval can take many years, and it is no exception to see a marketing authorisation granted between 8-12 years after the patent has been filed. The Pharmaceutical Inquiry estimated the average delays from first patent filing to first product launch at 8.6 years, though this figure dates back to the period between 1973 and 1998 (Figure 2).[58] The pharmaceutical industry has asked for many years to see some form of compensation introduced, with a view to see effective term of protection to reach an average of about 15 years.[59]

Figure 2 Five-year rolling average delay from first patent application filing to first product launch



Source: Pharmaceutical Sector Inquiry

A European wide SPC system for pharmaceutical products was first introduced in 1992 (Regulation 1768/92, later replaced by Regulation 469/2009). SPCs already existed before that date in some European countries, but there was quite a wide diversity in requirements, conditions and duration. Despite the fact that a European-wide SPC system has been introduced, SPCs are granted at national

[57] The relevant European regulations are council regulations No. 469/2009 for the creation of SPCs on medicinal products and Council Regulation 1610/96 on SPCs for plant protection products.

[58] Staff working paper, at 53.

[59] For more details on the rationale for introducing SPC protection, see Proposal for a Council Regulation (EEC), of 11 April 1990, concerning the creation of a supplementary protection certificate for medicinal products (COM(90) 101 final).

level and are only valid for the country where they have been granted. This has over time led to quite diverse solutions, wherein in one country an SPC is granted, whilst that could potentially not be the case in another country.[60]

SPCs are a form of intellectual property, separate from the underlying patent to avoid conflicts with the maximum term of protection of a patent under Art. 63 of the EPC 2000. The maximum term of SPC protection is five years.[61] A one-off paediatric extension of six months on top of the maximum of five years is possible, provided the applicant has complied with what is called an agreed Paediatric Investigation Plan (PIP).[62]

SPCs combine concepts of patent protection and regulatory concepts for defining the scope, availability and duration of the protection. SPCs do not protect the invention as covered by the patent, but, much more narrowly, 'medicinal products'[63] and 'plant protection products'. Such a product is not only defined by the patent-protected compound per se, its use, production process or formulation, but also by things like physical forms and intended mode of delivery. This results in the underlying patent being not only broader, but also in the patent being possibly parent to many different types of SPCs and, correspondingly, medicinal / plant-protection products.

In order to be **eligible for an SPC,** the European Union (EU) SPC Regulation states in Article 3 that the product must:

- be protected by **a basic patent** that is **in force**
- have been **granted a marketing authorisation (MA)** somewhere in the EU
- **not have been protected by an SPC before**, and
- the marketing authorisation must be the **first authorisation** in the EU to place the product on the market as a medicinal product.

Important terms used throughout this study are defined in Art. 1 (see Table 1 below).

Table 1 Important terms defined in Article 1

Concept	Definition
Product	An active ingredient or combination of active ingredients of a medicinal product
Medicinal Product	Any substance or combination of substances presented for treating or preventing disease in humans
Basic Patent	A patent which protects a product as such, a process to obtain a product or an application of a product, and which is designated by its holder

Application deadline and the additional term obtained

The application for an SPC needs to be filed within six months of the date on which the first authorisation is granted to place the product on the EU market as a medicinal product (or within six months from patent grant if the authorisation is obtained earlier). Also, the required authorisation must be a first authorisation; SPCs are not available for new production processes of making an old product with existing authorisation.

The term of an SPC can be calculated using a formula stated in Art. 13 SPC Regulation, according to which the term is equal to the authorisation data minus the patent filing date minus 5 years up to a

[60] The likelihood of divergent decisions has been partly reduced recently as national Patent Offices' representatives meet regularly to discuss the more contentious SPC applications.

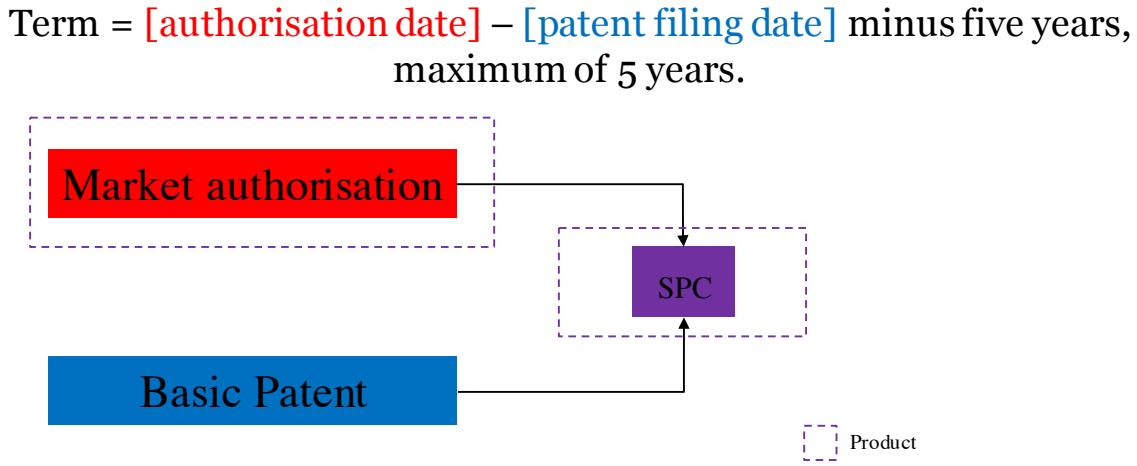
[61] See art. 13 Regulation 469/2009 for the calculation mechanism.

[62] Article 36(1) of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. See also Art. 13(3) Regulation 469/2009.

[63] In this study, we discuss medicinal products only.

maximum of 5 years (see also Figure 3). Figure 3 underlines also the already stated design characteristic of the SPC system, namely that it combines regulatory concepts with IP (patent) concepts. As we will discuss later in the report, this combination is at the heart of many complex issues which may not be apparent given the brevity of the SPC regulation.

Figure 3 The term of SPC protection



Source: Technopolis

Under normal circumstances, therefore, if the period between the patent filing date and the authorisation date is less than five years, no SPC is available. If this period is between five and ten years, an SPC may be granted for the period it took to get marketing authorisation beyond the five-year point. If the period between the patent filing date and the authorisation date is ten years or more, an SPC will have a five-year term.

As already mentioned, there is additionally a possibility to obtain a one-off six-month extension for paediatric use, the so-called **paediatric extension**, provided that there is an approved Paediatric Investigation Plan (PIP) (see also section 5.2). An additional condition for obtaining the paediatric extension is that there is an SPC granted on the basis of which the six months term will be added. The text of the regulation does not provide insight as to why a six-month extension of an SPC was selected as the reward to be offered.

The CJEU has allowed so-called **"negative term" or zero term" SPCs** with a view to be able to claim the six-month term paediatric extension. Indeed, as the paediatric extension requires an SPC, there would have been an issue in situations where no SPC would have been filed for, which would predominantly have been in cases where the difference between the patent filing date and the MA date would have been anything less than five years. In such an eventuality, filing for an SPC would make no sense, as the formula would not provide any useful term extension. At the same time, it would also preclude patent holders from claiming the paediatric extension, in the absence of an SPC. For that reason, the CJEU has allowed zero or negative term SPCs, to allow applicants to benefit of the paediatric extension (see also section 5.2).

The rationales of the SPC system, which were in particular stipulated in the following recitals of regulation 369/2009, are the following:

> ***"[3] Medicinal products, especially those that are the result of long, costly research will not continue to be developed in the Community and in Europe unless they are covered by favourable rules that provide for sufficient protection to encourage such research.***

[4] 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.

[5] This situation leads to a lack of protection which penalises pharmaceutical research.

[6] There exists a risk of research centres situated in the Member States relocating to countries that offer greater protection.

[7] A uniform solution at Community level should be provided for, thereby preventing the heterogeneous development of national laws leading to further disparities which would be likely to create obstacles to the free movement of medicinal products within the Community and thus directly affect the functioning of the internal market.

[8] Therefore, the provision of a supplementary protection certificate granted, under the same conditions, by each of the Member States at the request of the holder of a national or European patent relating to a medicinal product for which marketing authorisation has been granted is necessary. A regulation is therefore the most appropriate legal instrument.

…

[10] All the interests at stake, including those of public health, in a sector as complex and sensitive as the pharmaceutical sector should nevertheless be taken into account. … ”

Apart from the rationale to compensate for lost effective protection time due to prolonged marketing authorisation procedures, there is the explicit goal of fostering European industry and research.

The SPC system tries to strike a balance between various interests. This was emphasised in Case C-130/11 Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents:[64]

> *“Those rules are intended to achieve a balance between the various interests at stake in the pharmaceutical sector.* ***Those interests include, on the one hand, the interests of the undertakings and institutions, some of which pursue very cost-intensive research in the pharmaceutical sector and therefore favour an extension of the term of protection for their inventions in order to be able to balance out the investment costs. On the other hand, there are the interests of the producers of generic medicines who, as a consequence of the extension of the term of protection of the active ingredients under patent protection, are precluded from producing and marketing generic medicines. It is also relevant in this connection that, in general, the marketing of generic medicinal products has the effect of lowering the prices of the relevant medicinal products. Against that background, the interests of patients lie between the interests of the undertakings and institutions conducting research and those of the producers of generic medicines. That is because patients have an interest, on the one hand, in the development of new active ingredients for medicinal products, but, on the other, they also have an interest in those products then being offered for sale as cheaply as possible.*** *The same applies to State health systems in general which, in addition, have a particular interest in preventing old*

[64] Case C-130/11 Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents [EU:C:2012:268].

active ingredients from being brought onto the market in slightly modified form under the protection of certificates but without genuine innovation and thereby artificially driving up expenditure in the health section."[65]

5.1.2 SPC issues

The legal analysis of **national and CJEU cases on SPCs** shows that there are some **recurring key issues under dispute**. Many of these issues seem to arise from the fact that SPCs, while being IP rights, combine IP and regulatory elements (e.g. by referring to marketing authorisation dates) into one instrument and by the difference that exists between patents (patented subject matter) and (medicinal) products. For example, medicinal products can be more complex and consist of several components that can each be patented in their own right, or which can all fall under the scope of one patent, which exact scope first needs to be determined. Some of the components may be active ingredients with therapeutic value, while others have only an assistive function, such as slowing the release of a drug in the body, or making the uptake of the drug in the human body more effective.[66] The question may arise whether a combination product containing both an active ingredient and a non-active ingredient, but with a synergistic effect, can give rise to an SPC, given that the active ingredient was already subject in itself for an SPC.

The behaviour by pharmaceutical companies relating to the various SPC issues must always be seen in the context of the following constellation: A pharmaceutical company has one or more patents covering one or more active substances (in the same or different patents). These patents are filed at an early stage in the R&D development, and no clear view of the later authorised medicinal product may yet be in sight. The Marketing Authorisation (MA) follows at a much later stage. It will be the result of what is feasible from a scientific and safety point of view, and what is commercially possible and desirable. It is not inconceivable that there will be a discrepancy between what, at first sight, is protected by the patent and what is authorised in the MA. A company wishing to obtain SPC protection must try to "marry" what is covered by the MA with what is protected by patents. That is why SPC applicants will at times be "creative" with to make that marriage possible. As is seen in the case law, those attempts are not always successful.

There are two additional layers of complication:

- First, as stated, the SPC system functions on the intersection between patent law and regulatory law in determining whether a specific patent deserves SPC protection. Determining scope of protection of a patent is even in patent law one of the most difficult matters to determine.[67] There are, in fact, two different interpretations:
  - it can cover all eventualities where a third-party product would infringe the patent ('infringement test'), or
  - it covers the concept of 'extent of protection', i.e. it determines what is exactly covered and protection as an inventive concept by the patent. Applying this concept to the SPC system tends to create additional challenges of interpretation, as the result of the exercise in determining scope of protection then needs to be applied to the SPC system with all it is peculiarities.

[65] Para 41 Opinion AG in C-130/11.

[66] These are often called excipients, amongst which adjuvants, which are used in combination with an active ingredient to achieve a specific therapeutic effect of the active ingredient. Some excipients can have a material influence on the functioning of the active ingredient, however.

[67] A patent document consists basically of a description (which gives an overview of the background to the invention, it contains a detailed technical explanation of the invention, and it often contains examples and data to prove how the invention works), the patent claims (in effect the definition of the invention), and where applicable also drawings (which further clarify the invention as claimed). The scope of protection of a patent is determined by the wording of the so-called patent claims. However, those claims have to be read and interpreted in the context of the description and the drawings. See Art. 69 European Patent Convention (EPC). And that is why determining the exact scope of protection can be difficult. It is impossible to always cover all intricacies of the invention in the patent claims. Hence, what is being said in the description can be used to interpret the scope of the patent as defined in the patent claims.

- A second layer of complication is that the SPC statutory framework works with a rather high degree of abstraction. This itself can cause issues, as the very high degree of abstraction always inherently leaves room for interpretation by users and the judiciary. The SPC system is, in that sense, not very different from many other aspects of patent law, which equally work with high levels of abstraction, and which equally lead to many interpretation challenges.

One of the central conclusions which can be drawn from the analysis described in this chapter is that there has been a **rather natural development of the SPC system through case law testing**. A **growing number of issues** seem to have been **settled to a degree** that is perhaps not entirely perfect, but that at least legal uncertainty and the accompanying economic costs are strongly reduced or eliminated. As with any IP protection system, users are going to explore and test the limits of what is possible. At least certain fundamental issues seem to have reached the level of having been largely sorted out.

However, at the same time, **a number of fundamental concepts of the SPC system remain unclear**. We name two to illustrate the reasons for this observation. First, the interpretation of what is protected by the basic patent for determining whether an SPC can be granted remains quite unresolved. Second, the interpretation of what seems at first glance to be a relatively straightforward provision in the SPC Regulation, namely that an SPC can only be granted for a patent covered by an authorised medicinal product provided that it is the first authorisation of that product as a medicinal product, has shifted over time. This, in effect, allows SPC protection in cases where the product had already been authorised as a medicinal product.

We thus see various types of "movement" within the SPC system. On the one hand, there are those concepts that even today have not yet been fully clarified, despite the fact that the system dates from 1992. There are also those at first glance relatively clear concepts and provisions, whose interpretation seems to shift over time, which can also raise questions as to whether that does not make the system less certain.

It appears that, even though large parts of the SPC system and its challenges will likely start to settle slowly, some **fundamental issues remain unresolved and cause legal uncertainty**. **At the same time, we also see that challenges start focussing more on fringe issues**, such as which date needs to be used for calculating the term of SPC protection (see Seattle Genetics Inc. v Österreichisches Patentamt (Case C-471/14))[68], which in practice leads to an additional term of protection of one or two days.

However, in view of the fact that some of the fundamental issues remain unclear, it can only be concluded that the SPC system does currently not provide the legal certainty across the board which could be expected from a system dating from 1992 (=more than 25 years old). Having said that, one must also be realistic and admit that even to this day, some concepts of patent law, a system which in the form as it stands today is closer to 150 years old, are still unclear. That should remind us of the fact that very complex legal systems which have a major impact on society are notoriously slow to "mature". Patent law and SPC law are instruments of economic regulation, wherein a balance is made between the interests of society to see technological innovation flourishing and being publicly disclosed, and the interests of industry developing those innovations to see their R&D investments protected.[69] Such systems lead almost inherently to attempts by the users of it to optimise their interests, which means in effect to see the legal system interpreted in such a manner which coincides with their commercial interests. It is the role of the judiciary to ensure that the legal provisions are applied in accordance with the intention of the legislature. Unclear case law creates a deficit in any legal system, as it means that society as a whole will not benefit in an optimal manner from the legal

[68] C-471/14, Seattle Genetics Inc. v Österreichisches Patentamt, ECLI:EU:C:2015:659.

[69] Sven J.R., Bostyn, Enabling Biotechnological Inventions in Europe and the United States. A study of the patentability of proteins and DNA sequences with special emphasis on the disclosure requirement, Eposcript Series, nr. 4, EPO, München, 2001, 23 et seq.; Sven J.R., Bostyn, Patenting DNA Sequences (Polynucleotides) and Scope of Protection in the European Union: An Evaluation, Luxemburg, European Communities 2004, 11 et seq.

system, whilst at least in the short term, some of the users may benefit, even though that is not an optimal solution in the long term.

Legal certainty is key to every legal system, and therefore also to the SPC system. Any lack of it merits further scrutiny of whether that deficit is to the account of unclear case law, or to the account of flaws within the statutory framework. At least part of the exercise of this study will be to identify of which nature the deficiencies in the SPC functioning are.

In the following, we are looking at the following **set of legal issues**:

- What is a 'product' for purposes of SPC protection – Art. 1(b)?
- What is protected by a basic patent – Art. 3(a)?
- Requirement for having a valid marketing authorisation – Art. 3(b)
- Requirement that the 'product' has not been the subject of an earlier SPC – Art. 3(c)
- The issue of 'secondary uses' with the requirement that there may be no earlier MA for the product as a medicinal product - Art. 3(d)

5.1.3 Definition of a product – Art. 1(b)

5.1.3.1 The issue

- One of the key concepts of the SPC Regulation is the definition of what is a "product". At first sight, Art. 1(b) SPC Regulation provides a relatively straightforward definition of what a product is, i.e., *"'product' means the active ingredient or combination of active ingredients of a medicinal product."*

- A series of cases demonstrates that this at first sight simple concept is in real life not as simple as it looks. There are indeed a number of issues that can create problems. One of the main problems is that the SPC Regulation contains no definition of the expression "active ingredient". How does one decide what constitutes an "active ingredient" within the meaning of Article 1(b)? In particular, what is the position regarding (i) substances which, in one way or another, assist an active ingredient to achieve a particular therapeutic effect and (ii) combinations of such substances and that active ingredient? Some light is shed on this question by paragraphs 11 and 12 of the Commission's Explanatory Memorandum proposing what became Council Regulation 1768/92/EEC, which state:

  - *"11. The proposal for a Regulation therefore concerns only new medicinal products. It does not involve granting a certificate for all medicinal products that are authorized to be placed on the market. Only one certificate may be granted for any one product, a product being understood to mean an active substance in the strict sense. Minor changes to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new certificate.*[70]

  - *12. However, the proposal is not confined to new products only. A new process for obtaining the product or a new application of the product may also be protected by a certificate. All research, whatever the strategy or final result, must be given sufficient protection."*

- The issue seems to be particularly relevant for excipients, amongst which adjuvants, compounds that are used in combination with an active ingredient to achieve a specific therapeutic effect of the active ingredient. As we will discuss further below, an example is the excipient Polifeprosan, which enables the active ingredient Carmustine to be administered in a slow release formulation.[71]

- What seems to be clear is that an excipient or adjuvant is not an active ingredient and can, as such, not form the basis for an SPC. The more complex situation is where the excipient assists the

[70] We will discuss the complexities around second medical indication claims and SPCs, where more than one SPC could potentially be granted for the same product in a later section of this Report

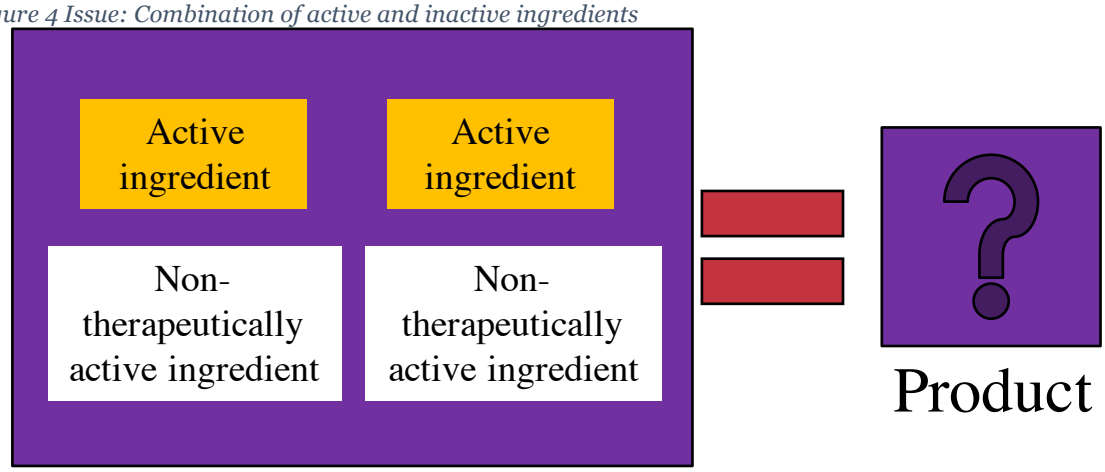
[71] For more details, see the discussion of the CJEU judgement in the case C-431/04 Massachusetts Institute of Technology [2006] ECR I-4089 further below.

active ingredient in having the desired effect or where it has some synergetic effect together with the active ingredient with which it is combined.

- There are two questions to be asked in this regard.
  - Can SPC be obtained for such combination of an active ingredient with an excipient, in particular if the active ingredient has already been the subject of an earlier MA?
  - Can an SPC be granted for such excipient, if such excipient can have a material influence on the functioning of the active ingredient?
- There is now a rather substantive body of CJEU case law on this particular issue, though this has not resolved all doubts about the exact interpretation of what a "product" is.

The typical scenario in which the above questions will arise is when the active ingredient has already been subject of an SPC, and in a subsequent stage, the SPC applicant wishes to obtain SPC protection for the combination of an active ingredient with an excipient, as that combination has not yet been subject of SPC protection. To be successful in such an SPC application, that would assume that the combination of an active ingredient with an excipient falls within the definition of "product" under the SPC regulation (Figure 4). The case law of the CJEU uses a relatively strict and narrow definition of what a "product" is.

Figure 4 Issue: Combination of active and inactive ingredients



Source: Technopolis

- The following CJEU rulings are noteworthy in this context:
- In the **MIT case (C-431/04)**[72] it was concluded that a substance that does not have any therapeutic effect of its own, and which is used to obtain a certain form of the medicinal product, is not to be considered an 'active ingredient' for which an SPC on the corresponding product can be taken out. The fact that the substance without any therapeutic effect of its own renders possible a pharmaceutical form of the medicinal product necessary for the therapeutic efficacy of the substance that confers the therapeutic effects cannot invalidate that interpretation.[73]
- In the **GSK case (C-210/13)**,[74] it was held that Article 1(b) "must be interpreted as meaning that, just as an adjuvant does not fall within the definition of 'active ingredient' within the

[72] Case C-431/04 Massachusetts Institute of Technology [2006] ECR I-4089. This case related to the active substance carmustine, either in combination with a polymeric biodegradable matrix called polifeprosan or alternatively on its own. The applicant relied on a marketing authorisation for the medicinal product Gliadel.

[73] See also, Case C-202/05 Yissum Research and Development Company of the Hebrew University of Jerusalem v Comptroller-General of Patents [2007] ECR I-2839. This case related to the product Silkis ointment. The MA authorisation covered calcitriol as active ingredient, and liquid paraffin, white soft paraffin and alpha-tocopherol as carriers.

[74] Case C-210/13 Glaxosmithkline Biologicals SA v Comptroller-General of Patents, Designs and Trade Marks [EU:C:2013:762]. GSK applied for a SPC for "an oil in water emulsion comprising squalene, DL-α-tocopherol and polysorbate 80", an adjuvant known as AS03 which was protected by European Patent (UK) No 0 868 918. GSK subsequently applied for a SPC for "an

meaning of that provision, so a combination of two substances, namely an active ingredient having therapeutic effects on its own, and an adjuvant which, while enhancing those therapeutic effects, has no therapeutic effect on its own, does not fall within the definition of 'combination of active ingredients' within the meaning of that provision".[75]

- In the **Forsgren case (C-631/13)**,[76] the CJEU held that "the term 'active ingredient', for the purposes of applying Regulation No 469/2009, concerns substances producing a pharmacological, immunological or metabolic action of their own."[77] Furthermore, the Court also dealt with the specific situation where an SPC was not filed for an active ingredient combined with an excipient or adjuvant, but for the combination of an active ingredient with a carrier protein. That is an issue most relevant for the area of vaccines, an explosively growing market in drug development. The question was whether a carrier protein conjugated to a pneumococcal polysaccharide used in a vaccine for paediatric use may be regarded as a 'product' within the meaning of Regulation No 469/2009, that is to say, as an 'active ingredient or combination of active ingredients of a medicinal product'. After having established that such carrier protein did not fulfil the criterion of producing a pharmacological, immunological or metabolic action of its own, it was appropriate to establish whether a carrier protein used in a medicinal product, which does not have an immunogenic effect of its own that is covered by the wording of the marketing authorisation, may be categorised as an 'active ingredient' where – conjugated with a polysaccharide antigen by means of a covalent binding – it produces such an effect. The Court concluded that, in light of the objective of the SPC Regulation, which was that the protection conferred by an SPC is largely intended to cover the cost of research leading to the discovery of new 'products', Article 1(b) of that regulation does not permit an 'active ingredient' to be categorised as a carrier protein conjugated with a polysaccharide antigen by means of a covalent binding, unless it is established that it produces a pharmacological, immunological or metabolic action of its own.[78]

5.1.3.2 Status of issue: largely settled

It is clear from the judgments of the CJEU in MIT, GSK and Forsgren that Article 1(b) is to be interpreted narrowly and cannot cover a substance which does not itself correspond to an "active ingredient" or a "combination of active ingredients". As the law stands, any combination of an active ingredient with another substance which is in itself not an active ingredient, and even if this other substance would have a beneficial therapeutic effect on the active ingredient (and by extension to the patient), will not be interpreted as being a combination of active ingredients, and such combination will consequently also not be able to be the basis of an SPC. As was said in GSK, a combination of two substances, namely an active ingredient having therapeutic effects on its own, and an adjuvant which, while enhancing those therapeutic effects, has no therapeutic effect on its own, does not fall within the definition of 'combination of active ingredients' within the meaning of that provision".

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adjuvanted influenza vaccine comprising an influenza virus component which is an influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak or has the potential to be associated with a pandemic outbreak, wherein the adjuvant is an oil in water emulsion comprising squalene, DL-α-tocopherol and polysorbate 80", a vaccine comprising an antigen and AS03 which was protected by European Patent (UK) No 1 618 889. In both applications GSK relied upon a marketing authorisation for a pre-pandemic influenza vaccine against the H5N1 subtype of influenza A virus marketed by GSK under the trade mark Prepandrix.

[75] C-210/13, paragraph 45.

[76] Case C-631/13 Forsgren v Österreichisches Patentamt [EU:C:2015:13]. Mr Forsgren was the proprietor of a patent relating to Protein D, an IgD-binding protein of Haemophilus influenzae. Protein D was present in a pneumococcal vaccine for paediatric use marketed under the trade mark Synflorix. The marketing authorisation for Synflorix, and in particular the Summary of Product Characteristics ("SmPC"), described Synflorix as a vaccine composed of 10 pneumococcal polysaccharide serotypes which were conjugated to carrier proteins and adsorbed on to aluminium phosphate. In eight of those serotypes, Protein D was the carrier protein.

[77] C-631/13, paragraph 25.

[78] C-631/13, paragraph 54.

The Forsgren judgement has equally provided more details on how an active ingredient is then to be defined. The judgement defines it as a substance which produces a pharmacological, immunological or metabolic effect of its own. It seems that the definition of what constitutes a product under the SPC regulation seems to have been settled, at least for now. It is unlikely that most excipients, adjuvants, carrier proteins etc. will produce a pharmacological, immunological or metabolic effect of their own, which thus excludes them from being the basis for an SPC.

5.1.4 Definition of what is protected by a basic patent – Art. 3(a)

5.1.4.1 The issue

- A second and very crucial requirement for obtaining an SPC is that the product as defined in the previous section must be "protected by a basic patent in force".[79] Art. 3(a) SPC Regulation is very short and is deceptively straightforward in what it tries to achieve: *"A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application – (a)* ***the product is protected by a basic patent in force****."* Closer inspection of the wording of the Regulation opens a plethora of issues of interpretation. The most crucial question is when a product is protected by a basic patent in force. In other words, which criteria need to be applied to determine whether a product as defined is protected by a patent.

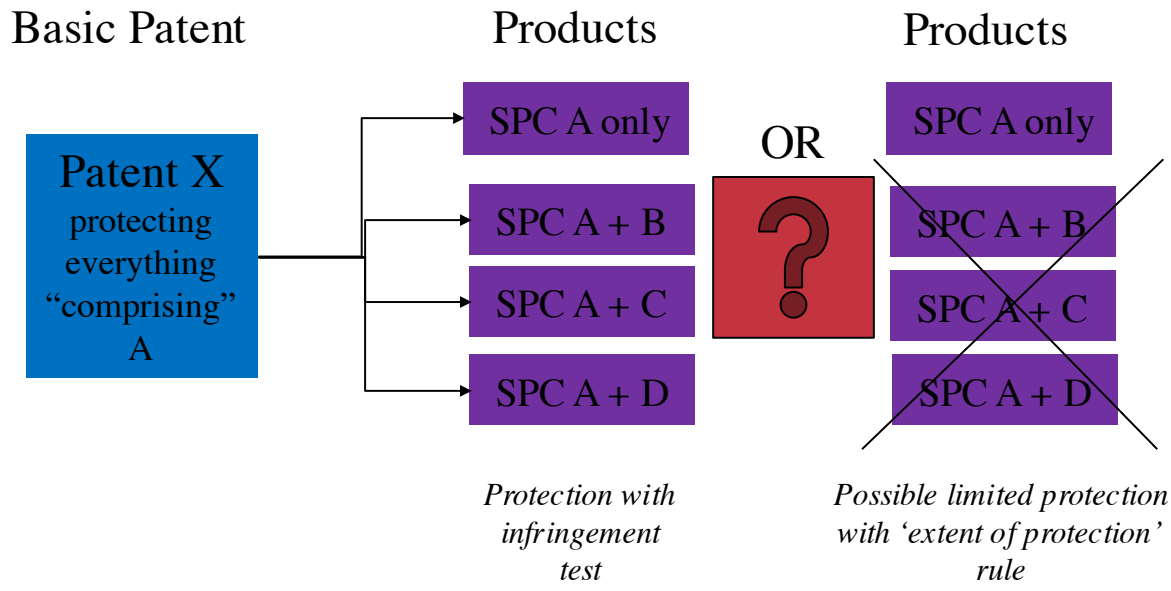
The rule has gained in importance because there is a growing discrepancy between the products that obtain MA, and the products that are protected by the basic patent. It could be expected, as has happened, that SPC applicants attempt to interpret the scope of protection of a basic patent invoked in such a way that it would fit neatly within the boundaries of the MA obtained. For instance, if an MA is obtained for active substances A+B, a successful SPC application would require a basic patent which also protects A+B. The question is now how the wording "protected" by a basic patent should be interpreted.

There are fundamentally two approaches to the question of what is protected by a patent (Figure 5):

- One is the so-called "**Infringing Act Rules**" test, according to which anything is protected if it would constitute an infringement. For instance, if a patent claims a pharmaceutical composition COMPRISING A (which is standard practice in pharma and biotech patents), any combination with A (e.g., A+B; A+C etc) would constitute an infringement of the patent protecting A, as all combinations contain A. Applying that test to the SPC world would imply that the SPC applicant would be allowed to obtain an SPC for any combination of A with something else, as under the "infringement rules" test, all of this would constitute an infringement. That is a very broad interpretation indeed, and the CJEU and many (but not all) national courts do NOT accept this as an appropriate test.
- The second rule is the so-called "**Extent of Protection Rules**" test, which determines the inventive concept as protected by the patent. The two rules may overlap, but that does not need to be the case. It is very well plausible that under the "Extent of Protection Rules", in a scenario of a patent claiming a pharmaceutical composition COMPRISING A, the inventive concept will NOT protect for instance a combination of A+B or A+C. Under this approach, an SPC could only be obtained for any combination that falls within the extent of protection of the patent, which could in at least some cases be limited to A. This could mean that, when an SPC would already have been granted for A, in the strictest case, no further SPC could be obtained for any combination of A with another active substance, if that other substance is not protected by the patent. This is a far more restrictive approach.

[79] See also, Frantzeska Papadopoulou, Supplementary protection certificates: still a grey area?, Journal of Intellectual Property Law & Practice, 2016, Vol. 11, No. 5, 372-381; Mike Snodin, Three CJEU decisions that answer some questions but pose many more, Journal of Intellectual Property Law & Practice, 2014, Vol. 9, No. 7, 599-604,

Figure 5 Issue Nr 2 – What is protected by the basic patent?



Source: Technopolis

The case law of the CJEU and national case law leans towards this more restrictive approach, but there is some legal uncertainty at the moment as the precise boundaries of the "extent of protection rules" test is yet to be precisely determined. The fundamental question is now what is to be understood by "being protected" or for that matter "extent of protection" in the context of SPCs. The CJEU case law has made various attempts to clarify the matter.

- The **Farmitalia case (C-392/97 Farmitalia Carlo Erba Srl)**[80] has for quite some years been the bedrock case relating to the concept of the product being protected by the basic patent, even though, in retrospect, it was a rather unsatisfactory approach to the question of how the wording "protected" is to be interpreted. The then ECJ held that "in order to determine, in connection with the application of Regulation No 1768/92[81] and, in particular, Article 3(a) thereof, whether a product is protected by a basic patent, reference must be made to the rules which govern that patent."[82] The Court stated there were (and still are no) central EU provisions regarding the determination of the scope of protection but that the wording of Art. 3(a) had to be interpreted with reference to "the rules which govern the patent". This does, however, not clarify which rules one would then need to apply.[83]
- In the **Medeva case (C-322/10),**[84] it was said that it is not allowed to obtain an SPC for a combination of active ingredients (e.g., A+B or A+B+C), where any such combination is not as such specified in the wording of the patent claims.

[80] Case C-392/97 Farmitalia Carlo Erba Srl [1999] ECR I-5553. Farmitalia had obtained a German patent for idarubicin. The claims specifically covered idarubicin hydrochloride. Farmitalia had also obtained a marketing authorisation for idarubicin hydrochloride. In Germany, Farmitalia obtained marketing authorisation, under the names 'Zavedos 5mg' and 'Zavedos 10mg', for medicinal products for treatment of acute myelitic leukaemias in humans, in which the active ingredient is idarubicin hydrochloride and the ancillary ingredient is dehydrated lactose.

[81] The predecessor Regulation to current SpC Regulation 469/2009.

[82] C-392/97, paragraph 29.

[83] We refer in this regard to the distinction between "infringing Act Rules" and "Extent of Protection Rules" which we have made earlier in this study.

[84] Case C-322/10 Medeva BV v Comptroller-General of Patents, Designs and Trade Marks [2011] ECR I-12051. Medeva was the proprietor of a patent the specification of which disclosed that a combination of two antigens known as pertactin and filamentous haemagglutinin (or FHA) produced a synergistic effect such that a third antigen called pertussis toxin (or LPF) was not required to produce a vaccine against Bordella pertussis (which causes whooping cough). The claims covered the

- The **Yeda Research and Development case (C-518/10)**[85] ruled upon a situation where an SPC applicant files for an SPC covering one active ingredient (A), whereas the patent claims only specify that active ingredient in a pharmaceutical composition in combination with another one (A+B). The CJEU ruled that "that Article 3(a) of Regulation No 469/2009 must be interpreted as precluding the competent industrial property office of a Member State from granting an SPC where the active ingredient specified in the application, even though identified in the wording of the claims of the basic patent as an active ingredient forming part of a combination in conjunction with another active ingredient, is not the subject of any claim relating to that active ingredient alone."[86] The CJEU did not use the wording *"specified"* in the claim, but referred to *"the subject of any claim"*. It did not clarify why this specific wording, different from that used in the Medeva case, was used, even though it held that, for all intents and purposes, the legal issue and answer were exactly the same as in Medeva.
- The **C-630/10 University of Queensland case**[87] did not add anything new from a legal point of view, but was important for its underlying facts. The case dealt with vaccines, where MAs were obtained for a variety of combinations of active substances (in the case at hand virus particles) of relevance to the vaccines. There were combinations authorised in the MAs that were not in those specific combinations claimed in the patent (for instance, A+B+C+D was authorised, whilst only A+B was claimed in the patent). The case shows that MAs are often granted for combination vaccines, which are more interesting from a commercial point of view, whilst those combinations might as such not be protected under the basic patent. The CJEU ruled that "Article 3(a) of Regulation No 469/2009 must be interpreted as precluding the competent industrial property office of a Member State from granting an SPC relating to active ingredients which are not identified in the wording of the claims of the basic patent relied on in support of the SPC application."[88] Here, the Court used the wording "identified" instead of "specified" without explaining whether it intended to say the same as in Medeva, or whether something else was meant.[89]

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combination of pertactin and FHA. Medeva obtained four marketing authorisations in respect of vaccines each of which was for immunisation against a number of diseases in addition to pertussis and contained between 8 and 11 different antigens. Each of these included pertactin, FHA and pertussis toxin. Medeva filed five applications for SPCs in respect of the medicinal products the subject of the authorisations.

[85] Case C-518/10 Yeda Research and Development v Comptroller-General of Patents, Designs and Trade Marks [2011] ECR I-12209. Yeda obtained a marketing authorisation for cetuximab (a monoclonal antibody specific for the receptor of epidermal growth factor or EGF) authorising its use in combination with irinotecan (an anti-neoplastic agent). Yeda applied for an SPC for cetuximab. The Comptroller-General of Patents refused the application on the ground that it did not comply with Article 3(a).

[86] C-518/10, paragraph 39.

[87] Case C-630/10 University of Queensland v Comptroller-General of Patents, Designs and Trade Marks [2011] ECR I-12231. The patent EP 0595935 related to methods of production of papillomavirus-like particles ('VLPs') of the Human papillomavirus ('HPV') Type 6 (HPV 6) and Type 11 (HPV 11), the VLPs per se and vaccines produced from or comprising VLPs. Relying on that patent and the MA granted on 20 September 2006 by the European Medicines Agency (EMA) to Sanofi Pasteur MSD SNC for the medicinal product Gardasil containing HPV 6, HPV 11, HPV 16 and HPV 18 purified proteins obtained from yeast cells (Saccharomyces cerevisiae). The University of Queensland is also the holder of European patent EP 1359156 B1, entitled 'Vaccine against Human Papillomavirus (Type 18)', the subject of a divisional patent application which was granted on 7 March 2006 and is due to expire on the same date as the parent patent, namely on 19 July 2012. Relying on that patent and on the MA granted for Gardasil, the University of Queensland filed an application with the Patent Office on 8 March 2007 for a SPC covering the HPV 18 VLP. Moreover, relying on the same patent but on the MA granted on 20 September by the EMA to GlaxoSmithKline Biologicals SA for the medicinal product Cervarix containing purified HPV 16 and HPV 18 proteins obtained from insect cells (*Trichoplusia ni*), the University of Queensland applied on 14 December 2007 for two other SPCs. Finally, he University of Queensland is the holder of a third European Patent EP 1298221 B1, entitled 'polynucleotide segment of the HPV 16 genome'. Relying on that patent and the MA granted for Gardasil, the University of Queensland filed an application on 21 February 2007 for a SPC covering the HPV 16 VLP alone. Furthermore, relying on that patent but, additionally, on the MA granted for Cervarix, the University of Queensland applied on 14 December 2007 for a SPC covering the HPV 16 VLP

[88] C-630/10, paragraph 31.

[89] There is no explanation to be found for this different language, and it must also be admitted that it has probably no substantively different effect. It is nevertheless somewhat remarkable that the CJEU is not consistent in the use of language in an area of the law where consistency of language is key.

- In **Case C-6/11 Daiichi Sankyo Co v Comptroller-General of Patents, Designs and Trade Marks**,[90] the patent disclosed only the ingredient olmesartan medoxomil, not that active ingredient in conjunction with one or more active ingredients, such as hydrochlorothiazide. Therefore, the combination of olmesartan medoxomil and hydrochlorothiazide, which was claimed in the SPC application, was not protected by the basic patent. The case did not add anything new to what has been said in Medeva, apart again from the fact that the CJEU used the wording "identified" rather than the word "specified".
- In the **Acatavis vs Sanofi case (C-443/12)**,[91] one of the issues was whether an SPC for two active ingredients, namely Irbesartan and hydrochlotothiazide (a diuretic) was protected by the basic patent claiming Irbesartan and a diuretic, without however specifying in the patent the specific diuretic hydrochlotothiazide. The CJEU did not have to rule on this specific issue, as it ruled that no SPC could be granted, as per Art. 3(c) SPC Regulation, for this combination as an earlier SPC and MA was already granted for Irbesartan. It did say, however, thereby referring to the wording used by the referring UK court, that *"it cannot be accepted that the holder of a basic patent in force may obtain a new SPC, potentially for a longer period of protection, each time he places on the market in a Member State a medicinal product containing, on the one hand, the principle active ingredient, protected as such by the holder's basic patent and constituting, according to the statements of the referring court, the core inventive advance of that patent, and, on the other, another active ingredient which is not protected as such by that patent."*[92] We are left with no further guidance as to this is yet another standard than the one applied in Medeva and the cases discussed above, or whether the CJEU did not intend to deviate from what it said earlier.
- In the **Eli Lilly case (C-493/12)**[93] a problem was addressed where substances are only claimed in functional terms, instead of structural terms. Claiming in functional terms means that one does not claim the substance in its chemical structure, but one claims the substance in terms of what it does or the effect it achieves. This is particularly important for antibodies. Antibodies are rarely, if ever, claimed in terms of the structural characteristics. What one

[90] Case C-6/11 Daiichi Sankyo Co v Comptroller-General of Patents, Designs and Trade Marks [2011] ECR I-12255. Daiichi Sankyo is the holder of European patent EP 0503785, entitled 'Biphenylimidazole derivatives, their preparation and their therapeutic use'. The referring court states that the principle ingredient olmesartan medoxomil is specifically disclosed in the wording of claim 4 of the patent. That active ingredient is an angiotensin II receptor antagonist and is used as a medicinal product for the treatment and prophylaxis of hypertension. A SPC was granted for the active ingredient olmesartan medoxomil. In support of its SPC application, Daiichi Sankyo submitted the MA in force in the United Kingdom for the medicinal product Olmotec, containing olmesartan as the sole active ingredient. Later, Daiichi Sankyo obtained in the United Kingdom a MA for Olmetec Plus, a medicinal product comprising a combination of the two active ingredients olmesartan medoxomil and hydrochlorothiazide. The active ingredient hydrochlorothiazide is a diuretic which can also be used as an antihypertensive agent. Daiichi Sankyo filed a SPC application for the combination of the active ingredients olmesartan medoxomil and hydrocholorothiazide The Patent Office refused to grant that SPC on the ground that the product concerned, namely the combination of the active ingredients olmesartan medoxomil and hydrocholorothiazide, was not, in the light of Article 3(a) of Regulation No 469/2009, protected by the basic patent.

[91] Case C-443/12 Actavis Group PTC ehf v Sanofi [EU:C:2013:833], [2014] RPC 20. Sanofi is the proprietor of European Patent No 0454511 which covers the antihypertensive active ingredient irbesartan. Claims 1 to 7 of the basic patent are based on solely irbesartan, or on one of its salts. Claim 20 of the patent relates to a pharmaceutical composition containing irbesartan in association with a diuretic. However, no specific diuretic is named in claim 20 or in the description of the basic patent. On the basis of that basic patent and MAs granted on 27 August 1997 in respect of the medicinal product Aprovel, which contains irbesartan as its single active ingredient and is used principally to treat primary hypertension, Sanofi obtained its first SPC for that active ingredient on 8 February 1999. That certificate expired on 14 August 2012. Similarly on the basis of its basic patent but, on this occasion, MAs granted on 15 October 1998 in respect of the medicinal product CoAprovel, comprising a combination of irbesartan and a diuretic, namely hydrochlorothyiazide, which is used to treat primary hypertension, Sanofi obtained a second SPC relating to the irbesartan–hydrochlorothiazide combination.

[92] C-443/12, paragraph 30.

[93] Case C-493/12 Eli Lilly & Co Ltd v Human Genome Sciences Inc [EU:C:2013:835]. HGS is the holder of European Patent (UK) No 0 939 804 ('HGS's patent'), which related to the discovery of a new protein, namely Neutrokine alpha (α). The patent discloses and claims, inter alia, that protein. It is apparent from the patent claims that the patent also relates to antibodies that bind specifically to that protein. Neutrokine-α acts as an intercellular mediator in inflammation and immune response, so that too much or too little of that protein is associated with diseases of the immune system. Thus, antibodies that bind specifically to Neutrokine-α may inhibit its activity and be useful in the treatment of autoimmune diseases. Claim 13 of the patent effectively covered any antibody that binds specifically to Neutrokine-α, of which there were potentially many thousands, if not millions. Lilly sought a declaration that any SPC which HGS might be granted in respect of the patent and based upon any marketing authorisation which Lilly had obtained for its own antibody product for use in the treatment of autoimmune diseases, LY2127399, would be invalid. LY2127399 contained as its active ingredient an antibody which bound specifically to Neutrokine-α.

claims is ANY antibody that binds to a defined antigen that is described in the patent. That allows patent holders to obtain protection for all antibodies that bind to a described antigen, instead of claiming a specific antibody that binds to that antigen. In the Eli Lilly case, it was ruled that a functional definition – i.e. the exact antibody is not named in the claims – may be sufficient to obtain SPC protection if the *"…claims relate, implicitly but necessarily and specifically, to the active ingredient in question."* This unclear definition leaves legal uncertainty.

- In the **Actavis vs. Boehringer Ingelheim case (C-577/13),**[94] the problem addressed concerned to some extent a scenario quite similar to the Acatavis vs Sanofi case (C-443/12), i.e., a situation in which an applicant first files an SPC for an active ingredient A protected by the basic patent. While the SPC is running, MA is sought for a combination of A with another well-known and off-patent substance B. This second MA is used as base date for the application of an SPC based on the combination of both active ingredients. The questions to be dealt with were: a) whether such an SPC could be obtained, in case the combination of both active ingredients is protected by the basic patent, and b) how one can determine whether the basic patent covers the combination. The court made a distinction between products/ingredients *"that constitute the subject matter of the basic patent"* and those that do not constitute such subject matter. Only in the former case will SPC protection be granted. The CJEU held in this regard that "Article 3(a) and (c) of Regulation No 469/2009 must be interpreted as meaning that, where a basic patent includes a claim to a product comprising an active ingredient which constitutes the sole subject-matter of the invention, for which the holder of that patent has already obtained an SPC, as well as a subsequent claim to a product comprising a combination of that active ingredient and another substance, that provision precludes the holder from obtaining a second SPC for that combination."[95] This ruling caused confusion as clearly the combination of the two compounds (one new and one known) IS the subject-matter of the invention covered by the patent. Here, the CJEU uses yet another wording to determine whether the product in the SPC application is protected by the basic patent.
- There has been a recent new referral to the CJEU from the UK courts. In **Teva UK Ltd V Gilead Sciences Inc**[96], Arnold J remained deeply dissatisfied about the state of affairs with regard to the interpretation of Art. 3(a) SPC Regulation, and referred the following question to the CJEU: *"What are the criteria for deciding whether 'the product is protected by a basic patent in force' in Article 3(a) of the SPC Regulation?"*[97] He wanted to assist the CJEU by providing his own answer to the question, which in his view should be that *"the answer is that the product must infringe because it contains an active ingredient, or a combination of active ingredients, which embodies the inventive advance (or technical contribution) of the basic*

[94] Case C-577/13 Actavis Group PTC ehf v Boerhinger Ingelheim Pharma GmbH & Co KG [EU:C:2015:165]. Boehreinger's basic patent is entitled 'Benzimidazol derivatives, medicaments containing them and process for their preparation'. It discloses and claims numerous molecules, one of which is telmisartan. Telmisartan is an active ingredient used in the treatment of high blood pressure, namely hypertension, and the reduction of cardiovascular morbidity in adults. Claims 5 and 8 of Boehringer's basic patent relate to telmisartan alone and to one of the salts thereof, respectively. On the basis of that patent and a marketing authorisation granted on 16 December 1998 to one of the Boehringer group companies for the medicinal product Micardis, which contained telmisartan as the sole active ingredient, Boehringer obtained the first SPC for that active ingredient. The telmisartan SPC was granted on 9 August 1999 and expired on 10 December 2013. On 19 April 2002, one of the Boehringer group companies was granted a marketing authorisation for a combination of telmisartan and hydrochlorothiazide. Hydrochlorothiazide is a diuretic that acts by inhibiting the kidney's ability to retain water. That substance is a molecule that has been known to exist since 1958 and is in the public domain. Telmisartan and hydrochlorothiazide are the sole active ingredients of the medicinal product sold by Boehringer under the brand name MicardisPlus. On 6 September 2002, Boehringer filed an application for a SPC for the combination of the active ingredients telmisartan and hydrochlorothiazide ('the combination SPC').

[95] C-577/13, paragraph 39.

[96] TEVA UK LIMITED v GILEAD SCIENCES INC, 13 January 2017, [2017] EWHC 13 (Pat). Gilead obtain SPC protection for the product "Composition containing both Tenofovir disoproxil, optionally in the form of a pharmaceutically acceptable salt, hydrate, tautomer or solvate, together with Emtricitabine". The SPC covers a product which is marketed by Gilead under the trade mark Truvada. Truvada is an anti-retroviral medication used in the treatment of human immunodeficiency virus (HIV). It is a combination product consisting of two active ingredients, namely (i) 245 mg tenofovir disoproxil ("TD") in the form of 300 mg of the fumarate ("TDF") and (ii) 200 mg emtricitabine (also known as FTC) in a single, fixed dose tablet. TD and emtricitabine are both inhibitors of a viral enzyme known as reverse transcriptase. It was disputed whether that product was protected by the basic patent EP 0 915 894.

[97] Now known under the reference Case C- 121/17.

patent."[98] It can be questioned whether this will resolve the matter, as it seems that one source of unclarity has become exchanged for another, namely that we are not sure how to understand the concept of the "inventive advance" of the basic patent.

- The Swiss Federal Patent Court has recently concluded in the **Mepha Pharma v Gilead Sciences case**[99] that the *"Infringing act rules"* approach should be followed, as the *"extent of protection rules"* approach followed to some extent by the CJEU does not provide sufficient legal certainty. It concluded that the various judgements did not provide sufficient clarity and legal certainty on what the standard should be. In contrast, the "infringing act rule" provides in the view of the Swiss Court the necessary legal certainty.

5.1.4.2 Status: only partially solved – extent of protection rule to be applied, but exact modes unclear

The rulings of the CJEU indicate that it is not the 'infringing act rule' test that should be applied when assessing the scope of a basic patent invoked for an SPC. Although it thus seems reasonable to assume that the 'extent of protection' rules applies, the courts leave it open – both in the individual verdicts but as also by using different terms in different rulings – what the 'extent of protection' really should be.

In determining whether the product is protected by the basic patent, the CJEU uses at least six different definitions:

1. is not as such specified in the wording of the patent claims
2. is not the subject of any claim relating to that active ingredient alone
3. is not identified in the wording of the claims
4. constitutes the core inventive advance of that patent
5. claims relate, implicitly but necessarily and specifically, to the active ingredient in question
6. constitutes the sole subject-matter of the invention.

Consequently, legal uncertainty remains. Even though the matter has not yet been sufficiently resolved, what is clear is that the CJEU and national case law here too are inclined to take a rather narrow approach towards what is exactly protected by the basic patent, thereby ridding themselves of wide ranging protection claims invoked by SPC applicants.

There is an issue with legal uncertainty here, which could already have been resolved if it were not that the CJEU seems to struggle with the very concept of extent of protection in patent law, which is not surprising, as this is one of the most difficult concepts in patent law, and the CJEU is not a specialised court, let alone specialised in patent law. A viable option to resolve this matter may be through legislative action, where a definite choice can be made for the interpretation to be applied.

Alternatively, the recent Swiss judgement favouring the "infringing act rule" test has also its clear benefits. It will allow SPC applicants to invoke broadly and widely basic patents to support a multitude of SPC applications, and from that perspective, it may be a less than optimal solution. But, certainly as the law stands now, it offers the benefit of legal certainty. Additionally and not less importantly, **the "extent of protection rule" test will in effect require national patent offices deciding on SPC applications** to determine the exact scope of the basic patent, which can be questioned whether that is a desirable route as many national patent offices might not necessarily be equipped with the required expertise to make that evaluation. Furthermore, this all has to be done in an *ex parte* environment where there is only the SPC applicant and the patent office, which can be expected to lead to a less detailed discussion compared to an *inter partes* environment. This could subsequently also

[98] TEVA UK LIMITED v GILEAD SCIENCES INC, para 97.

[99] Mepha Pharma v Gilead Sciences, Bundespatentgericht, Urteil vom 3. Oktober 2017, O2017_001. This case covers the same patent (EP 0 915 894) and product as the UK TEVA v GILEAD case, i.e., "tenofovir disoproxil fumarate +emtricitabine."

lead to very different decisions in each of the national patent offices. Compared to that is the "infringing act rule" test relatively straightforward to apply with very little risk for national disparities.

5.1.5 Requirement for having a valid marketing authorisation – Art. 3(b)

5.1.5.1 The issue

Art. 3 (b) of the SPC regulation requires a valid marketing authorisation (MA) as a prerequisite for an SPC. Against this backdrop, the relationship between the MA file and the patent specifications can become a subject of interest. For example, a particular MA might cover a multitude of active ingredients, whereas the basic patent referred to in an SPC application only protects a selection of these. Would it then be possible to refer/invoke the MA for filing the SPC?

The following cases are of relevance here:

- In **Medeva BV v Comptroller-General of Patents, Designs and Trade Marks**,[100] the CJEU held that "Article 3(b) of Regulation No 469/2009 must be interpreted as meaning that, provided the other requirements laid down in Article 3 are also met, that provision does not preclude the competent industrial property office of a Member State from granting an SPC for a combination of two active ingredients, corresponding to that specified in the wording of the claims of the basic patent relied on, where the medicinal product for which the MA is submitted in support of the SPC application contains not only that combination of the two active ingredients but also other active ingredients."[101]
- In **case C-422/10 Georgetown University and Others v Comptroller General of Patents, Designs and Trade Marks,**[102] the CJEU held, largely copying what it said earlier in Medeva, that "Article 3(b) of Regulation No 469/2009 must be interpreted as meaning that, provided the other requirements laid down in Article 3 are also met, that provision does not preclude the competent industrial property office of a Member State from granting an SPC for an active ingredient specified in the wording of the claims of the basic patent relied on, where the medicinal product for which the MA is submitted in support of the SPC application contains not only that active ingredient but also other active ingredients."[103]

5.1.5.2 Status: solved – broad interpretation of article

The answer to this question is, given the rulings, basically 'yes', i.e. there is hence a broad interpretation of the article. It is not necessary that there is a double identity between the active ingredients covered by the basic patent and those covered by the MA, as long as all the active ingredients covered by the basic patents are also referred to in the MA. But the MA may contain more active ingredients than the ones protected by the basic patent.

However, it should be reminded that this broad interpretation of Art. 3(b) does not prejudice the relatively narrow interpretation of Art. 3(a) as we have analysed earlier. In other words, even though it

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[100] Case C-322/10 Medeva BV v Comptroller-General of Patents, Designs and Trade Marks [2011] ECR I-12051.

[101] C-322/10, paragraph 42.

[102] Case C-422/10 Georgetown University and Others v Comptroller General of Patents, Designs and Trade Marks [2011], ECLI:EU:C:2011:776, [2011] EUECJ C-422/10, EU:C:2011:776. Georgetown University was the owner of patent EP 0647140 for a human papillomavirus (PV) L1 protein capable of inducing neutralising antibodies against papillomavirus virions. There are many human papillomavirus (HPV) genotypes, which are grouped according to the similarity of their DNA sequences. Types 6 and 11 are responsible for condylomas, whereas types 16 and 18 are responsible for precancerous lesions in the genital region and also cervical cancer. The patent claims include a vaccine for the prevention of papillomavirus infection, comprising at least that protein, or fragment thereof, of, among others, HPV 16, HPV 18 or HPV 16 and HPV 18 together. On 14 December 2007, relying on the MA granted to Sanofi Pasteur MSD SNC on 20 September 2006 for the medicinal product Gardasil, containing HPV 6, HPV 11, HPV 16 and HPV 18 purified proteins obtained from yeast cells (*Saccharomyces cerevisiae*), Georgetown University files four SPC applications, identifying the product as 'the recombinant L1 protein' of HPV 6, HPV 11, HPV 16 and HPV 18, respectively. Moreover, relying on the MA granted to GlaxoSmithKline Biologicals SA on 20 September 2007 for the medicinal product Cervarix, containing HPV 16 and HPV 18 purified proteins obtained from insect cells (*Trichoplusia ni*), Georgetown University filed two SPC applications identifying the product as 'the recombinant L1 protein of papillomavirus type 16 as expressed by an insect cell' and 'the recombinant L1 protein of papillomavirus type 18 as expressed by an insect cell', respectively. All the SPC applications were rejected.

[103] C-422/10, paragraph 35.

is perfectly possible that the MA covers more active ingredients than the basic patent, the product as defined in the SPC must cover only those active ingredients which are protected by the basic patent, as interpreted in the case law we have discussed.

In other words, the SPC system, as far as Art. 3(a) ad (b) is concerned seems to work as follows. Only those active ingredients which are protected by the basic patent (identified or specified in the claims, protected as such by the holder's basic patent and constituting the subject-matter of the invention covered by that patent) can become the subject of an SPC. But it does not matter that the MA makes reference to more active ingredients than the ones protected by the basic patent. The SPC will only protect those of those active ingredients which are protected by the basic patent.

Conversely, if the basic patent protects two active ingredients combined, whilst the MA only covers one of those active ingredients, no SPC can be granted for that one active ingredient, as that active ingredient is not protected as such under the basic patent, as per Art. 3(a) (see e.g., C-518/10, discussed earlier).

5.1.6 Requirement that the 'product' has not been the subject of an earlier SPC – Art. 3(c)

5.1.6.1 The issue

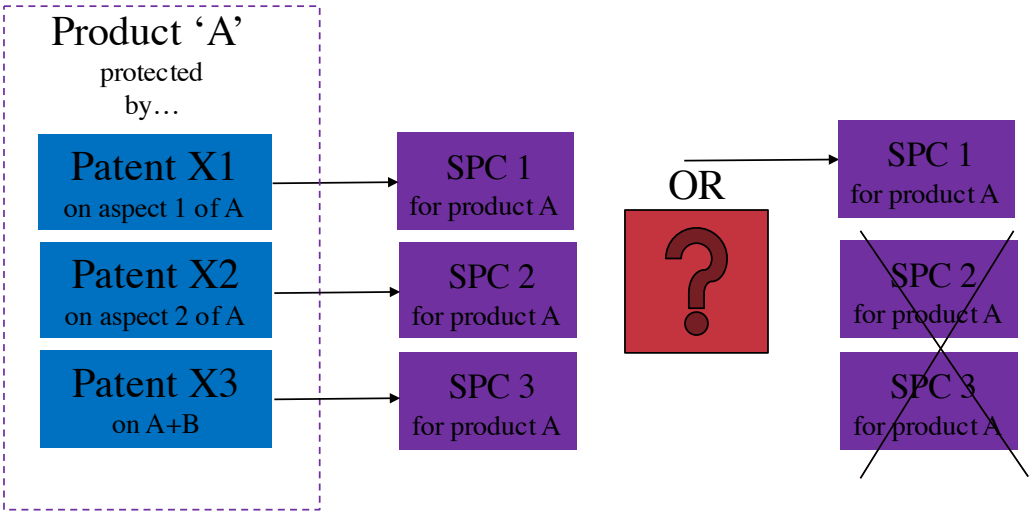
The interpretation of Article 3(a) and the interpretation of Article 3(c) are both interdependent and depend on the interpretation of Article 1(b) (definition of "product"). To date, the CJEU has adopted a fairly narrow interpretation of Article 1(b). In some cases, the CJEU has adopted a correspondingly narrow interpretation of Article 3(a), while in other cases it has adopted a broader interpretation. As the CJEU has recognised, the broader the interpretation of Article 1(b) and/or Article 3(a) that is adopted, the more important it becomes to adopt a narrow interpretation of Article 3(c) if the objectives of the SPC Regulation are not to be subverted.

On the face of it, Art. 3(c) of the regulation seems to make it clear that one cannot obtain an SPC if the 'product' has been already the subject of an earlier SPC. However, this relative straightforwardness is quite deceiving, and the complex reality leads to the conclusion, supported by the CJEU and national case law, that it is possible to obtain more than one SPC for the same product, which seems to contradict the very wording of Art. 3(c) SPC Regulation. Reason for that apparent contradiction is that the complex reality of patenting in the pharmaceutical world is different from the somewhat simpler scenarios the SPC Regulation legislature had probably in mind when drafting it.

Matters become once again complicated in the case of combination products. This refers to situations where, for example, one may find multiple patented ingredients in a product. There are three possible scenarios:

- *Scenario 1*: The first scenario covers the situation where the same product is protected by several different patents. The question then arises whether it is possible to obtain more than one SPC for that same product if one uses a different patent for each such SPC application for that same product?

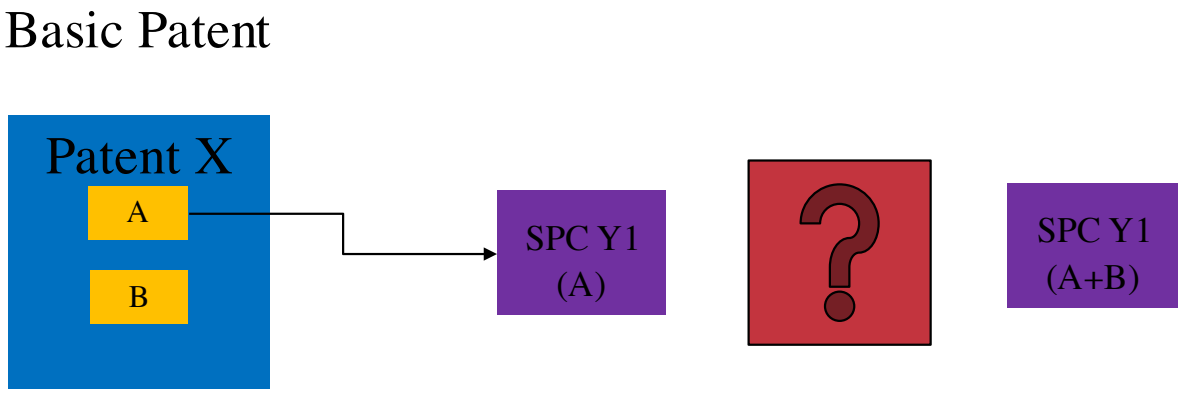
Figure 6 Scenario 1 – Is it possible to obtain more than one SPC for that same product, if one uses a different patent for each such SPC application for that same product?



Source: Technopolis

- *Scenario 2:* This scenario covers the situation where a patent covers multiple active ingredients. Can an SPC still be granted for a different active ingredient, even though that different active ingredient is protected by a basic patent which has already been the basis for an SPC for another active ingredient? The scenario suggests that, for instance, an SPC is filed for B, which is protected by basic patent X. However, basic patent X has already been invoked for an SPC for A+B.
-

Figure 7 Scenario 2



Source: Technopolis

- *Scenario 3:* This scenario arises where an SPC has been granted for an active ingredient protected by a basic patent. The question is then whether it would be possible to obtain another SPC, invoking the same patent, for the combination of the active ingredient which has already been the subject of an SPC and another active ingredient, which combination has been the subject of a MA? That would only be possible if the combination represents a distinct invention protected by the patent. If the combination is a distinct invention, it should not matter whether it is protected by the same patent or by a different patent. In other words, it seems to be possible to grant an SPC for a combination of active ingredients where one of those active ingredients embodies the "core inventive advance" or "sole subject-matter of the

invention" (though the terms remain unexplained by the CJEU) of the basic patent and has already been the subject of an SPC based on that patent, even if the patent contains one or more claims which protect the combination.

The following case law provides respective landmark decisions:

- Regarding scenario 1, in the **Biogen case (C-181/95),**[104] the ruling states that it is in principle possible to obtain more than one SPC for the same product, based on different patents which each may protect that same product. However, only one certificate can be granted for each basic patent, for each product which is covered by that patent. The question in scenario 1 is therefore answered affirmatively. The CJEU ruled that "*Consequently, where a product is protected by a number of basic patents in force, which may belong to a number of patent holders, each of those patents may be designated for the purpose of the procedure for the grant of a certificate. Under Article 3(c) of the Regulation, however, only one certificate may be granted for each basic patent.*"[105]
- The **AHP Manufacturing case (C-482/07)**[106] confirmed further that it is possible to obtain one SPC per patent per product. Hence, multiple SPCs can be granted for the same product, based on different patents. It ruled that "*the answer to the questions referred is that Article 3(c) of Regulation No 1768/92, considered in the light of the second sentence of Article 3(2) of Regulation No 1610/96, must be interpreted as not precluding the grant of an SPC to the holder of a basic patent for a product for which, at the time the SPC application is submitted, one or more SPCs have already been granted to one or more holders of one or more other basic patents.*"[107]
- In the **Georgetown University case (C-484/12)**[108] the situation is analysed where a single patent covers multiple different products (scenario 2). The question whether the same patent can be used different times for SPC applications for the different products covered by the patent is answered affirmatively. The Court confirmed that it is possible to obtain more than one SPC per patent, where such patent covers multiple products, provided that each of those products is "protected" by the patent. In the case at hand, an MA and SPC had been granted for the combination of A+B and the question arose whether a later SPC application for A, invoking the same patent, could be successful. The CJEU held that this is possible, provided that A is "*protected as such*" by that patent: "*in circumstances such as those in the main proceedings, where, on the basis of a basic patent and an MA for a medicinal product consisting of a combination of several active ingredients, the patent holder has already obtained an SPC for that combination of active ingredients, protected by that patent within the meaning of Article 3(a) of Regulation No 469/2009, Article 3(c) of that regulation must be interpreted as not precluding the proprietor from also obtaining an SPC for one of those active ingredients which, individually, is also protected as such by that patent.*"[109] This case confirms the rule that the same patent can be invoked for multiple SPCs, provided that the product used for the SPC application is a different one. It demonstrates that it is possible to obtain SPC protection which may partly overlap in the sense that the product protected by

[104] Case C-181/95 Biogen Inc v SmithKline Biologicals SA [1997] ECR I-357. SmithKline Biologicals marketed Energix-B, a vaccine for Hepatitis-B virus, pursuant to licences granted under patents owned by both Biogen and the Institut Pasteur. Biogen applied for an SPC based on its patents after the Institute Pasteur had obtained an SPC based on its patent.

[105] C-181/95, paragraph 28.

[106] Case C-482/07, AHP Manufacturing BV v Bureau voor de Industriële Eigendom ECLI:EU:C:2009:501. The European Commission granted on 3 February 2000 for the first time an authorisation to place on the market the medicinal product Enbrel, the active ingredient of which is the compound etanercept. On 4 and 6 October 2000 and 30 January 2001, three SPCs for etanercept were granted in respect of the Netherlands, to Immunex Corporation, Hoechst AG and General Hospital Corporation, and Abbott GmbH & Co KG respectively. The basic patents for etanercept had been granted to those undertakings between 1994 and 1998. The three SPCs expire on 1 February 2015. F. Hoffmann-La Roche AG ('Hoffmann'), obtained a European patent for TNF (tumor necrosis factor) binding proteins. On 2 July 2003, Hoffmann lodged with BIE in respect of the Netherlands an application for the grant of an SPC for Enbrel (etanercept). That application was based on Hoffmann's European patent and the abovementioned marketing authorisation. By decision of 22 December 2003, BIE refused that application.

[107] C-482/07, paragraph 43.

[108] Case C-484/12 Georgetown University v Octrooicentrum Nederland [EU:C:2013:828]. This case dealt with the same MA's and SPC applications relating to human papillomavirus (HPV) discussed earlier.

[109] C-484/12, paragraph 41.

such an SPC may be partly identical to another product subject of another SPC, invoking the same patent. It specifies that SPC protection can be obtained for, for instance, more than one product, provided that A is not claimed as such in the different SPC applications, but for instance is claimed in one SPC application as A and in another SPC application as A+B. The latter SPC application will partly overlap with the one for A, but the product A is strictly speaking different from A+B. Consequently, there is nothing to prevent SPC applicants to invoke the same patent, protecting both A and A+B.

- The **Actavis vs. Sanofi case (C-443/12)**[110] provided a negative answer for scenario 3. It held that "*in circumstances such as those in the main proceedings, where, on the basis of a patent protecting an innovative active ingredient and an MA for a medicinal product containing that ingredient as the single active ingredient, the holder of that patent has already obtained an SPC for that active ingredient entitling him to oppose the use of that active ingredient, either alone or in combination with other active ingredients, Article 3(c) of Regulation No 469/2009 must be interpreted as precluding that patent holder from obtaining – on the basis of that same patent but a subsequent MA for a different medicinal product containing that active ingredient in conjunction with another active ingredient which is not protected as such by the patent – a second SPC relating to that combination of active ingredients.*"[111] This is an important decision, in that it attempts to limit, at least to some extent, the potential practice of having multiple SPCs for the same active ingredient in the same patent.[112] The decision is also important, as it to some extent limits the potential effect of Art. 3(a). That is so because it is perfectly possible that the combination of active ingredients might be "protected" by the basic patent, which, as we have seen when discussing Art. 3(a) is not clear what is exactly meant by that. But the CJEU at least seems to suggest that it could be possible that an SPC application for a combination of active ingredients, one of which has already been the subject of an SPC, could potentially fulfil the requirements of Art. 3(a), but would fall foul of fulfilling the requirements of Art. 3(c). However, where it disappoints is in the same areas as we discussed under Art. 3(a), and that is that it makes abundant use of concepts such as "protected as such" and "the core inventive advance", terms that are unclear and which are left undefined by the CJEU.
- The **Case C-577/13 Actavis Group PTC ehf v Boerhinger Ingelheim Pharma GmbH & Co KG**[113] did not add anything new compared to what had already been said Actavis v Sanofi.
- Worth mentioning is the **Dutch escitalopram case**.[114] Lundbeck obtained in 1989 in Denmark a marketing authorisation for the medicinal product Cipramil with the active substance citalopram.[115] In 2001, the Swedish authorities granted a marketing authorisation for the medicinal product Lexapro, with the active substance escitalopram. In the Netherlands,

[110] Case C-443/12 Actavis Group PTC ehf v Sanofi [EU:C:2013:833].

[111] C-443/12, paragraph 43.

[112] A first SPC would have been granted for e.g. active ingredient A, based on a patent where A has been specified. In a subsequent SPC application, based on the same patent, an attempt is made to obtain SPC protection for a combination of the active ingredient (A) for which an SPC has already been granted, combined with another active ingredient (B), which may at least fall within the scope of the same patent. In this combination, B is a known compound and does not constitute the "core inventive advance" of that patent. In such a situation, no SPC for that combination will be granted, as that would extend protection for A (which has already been the subject of separate earlier SPC protection) yet into a further SPC.

[113] Case C-577/13 Actavis Group PTC ehf v Boerhinger Ingelheim Pharma GmbH & Co KG [EU:C:2015:165].

[114] Lundbeck v Alfred A. Tiefenbacher GmbH & Co KG, Centrafarm Services B.V., Ratiopharm GmbH, Court of Appeals The Hague, 24 January 2012, ECLI:NL:GHSGR:2012:BV1963. As far as the part of the judgement concerned with the SPC, the Dutch Supreme Court has confirmed that the reasoning of the Court of Appeal in this regard is solid and comprehensible and presents no issues from a legal point of view (apart from the consequences of the invalidity of claims 1-5 to the SPC) , see Dutch Supreme Court, Lundbeck v Tiefenbacher GmbH & Co KG, Centrafarm Services B.V., 7 June 2013, ECLI:NL:HR:2013:BZ4115.

[115] In 1972 Lundbeck invented the substance citalopram. This substance works as a so called 'selective serotonin reuptake inhibitor (SSRI)'. An SSRI primarily inhibits the reuptake of serotonin, a neurotransmitter, by the cells of the nervous system in order that the concentration of free serotonin is increased. It is generally assumed that the inhibition of the reuptake of neurotransmitters provides for an antidepressant effect. Since the nineteen nineties Lundbeck has marketed citalopram as an antidepressant on a worldwide basis. Citalopram is a racemic substance that consists of two enantiomers, the (-) or (R) enantiomer and the (+) or (S) enantiomer. The latter mentioned enantiomer is also referred to as escitalopram. It became known from research conducted by Lundbeck that escitalopram (hence the (S) enantiomer) has a considerably stronger inhibiting effect on the reuptake of neurotransmitters than the (R) enantiomer of citalopram. The (R) enantiomer even appeared to inhibit the favourable effect of the (S) enantiomer.

a marketing authorisation was granted for the same escitalopram medicinal product on 27 April 2004. Lundbeck is holder of the European Patent with number EP 0 347 066 B1 which covers escitalopram. On the basis of EP 066 Lundbeck was granted a SPC for escitalopram, Alfred A. Tiefenbacher GmbH & Co KG, Hexal AG, Sandoz B.V. and Centrafarm Services B.V., have in 2006 filed to obtain a marketing authorisation for a medicinal product containing the active substance escitalopram.[116] The reference medicinal product referred to in the applications was Cipramil (containing the active substance citalopram). The generics claimed that the SPC for escitalopram was not valid, as a SPC had already been granted for citalopram, which in their view was the same product, and according to Art. 3(c) SPC Regulation, no second SPC could be granted for the same product. The generics argued in this connection that the concept of new chemical substance has a different meaning than the concept of novelty in patent law. A product can be new in accordance with patent law (as a patent had been granted), but can at the same time not be considered as a "new active substance" for regulatory purposes. As their argument was that escitalopram was not a new active substance (which argument has been overruled by the State Council[117]), their view was that with a view to determine whether the active substance was the same (as citalopram had already been subject to a SPC) for purposes of SPC protection, the concept derived from regulatory law had to be used in determining whether a SPC could still be granted. The Court of Appeal did not agree with this reasoning. As SPC protection is an extension of patent protection, concepts of patent law need to be invoked for determining whether the product is the same. As it was held that escitalopram was from a patent point of view novel over citalopram, there was no reason to assume that the escitalopram would be the same product as citalopram for SPC purposes. Consequently, as no SPC had yet been granted for escitalopram, an active substance novel over citalopram, the requirements of Art. 3(c) SPC Regulation had been fulfilled. We would agree with the reasoning of the Dutch Court of Appeal in this.

5.1.6.2 Status of issue(s): rules

The basic rules are thus as follows:

- The same patent can be invoked for more than one SPC, provided the same compound protected by that patent has not yet been subject to an earlier SPC.
- More than one patent can be used for separate SPC applications for the same product. The same product can be protected by different patents. In such a situation, it is possible to have multiple SPCs for the same product, provided they each invoke a different basic patent. That rule is based on the underlying rationale of the SPC system which aims to compensate patent holders for loss of effective patent protection due to regulatory procedures. Each of those patents covering the same product could potentially have been subject to such loss of effective protection.
- An SPC can only be granted for a combination or active substances, even though at least one of these substances has already been the subject of an earlier SPC, and invoking the same patent which was the basis for the earlier SPC on one of the active substances, provided that the combination represents a distinct invention protected by the patent.

The CJEU appears to have realised that the complex reality of pharmaceutical patents has required some adjustment to the, at first sight rather straightforward, wording of Art. 3(c) of the SPC Regulation. However, its case law also makes clear that attempts by the pharmaceutical industry to "re-use" the same patent for multiple SPCs, one for an active substance and one or more subsequent ones for the combination of that active substances with other active substances which would then be "protected" by the basic patent, are likely to be curtailed. These attempts can easily be explained by the corporate behaviour regarding MAs. Companies could file for various MAs covering the same active

[116] Under the so-called abridged procedure of Art. 10(1) Directive 2001/83. For more details on this procedure, see sub 5.3 of this Study.

[117] Lundbeck v College ter Beoordeling van Geneesmiddelen, Raad van State, 6 July 2011, ECLI:NL:RVS:2011:BR0506; JGR 2012/3; AB 2011/272. As a consequence of this judgement, escitalopram was considered to be a "new active substance" for regulatory purposes.

substance in combination with one or more other active ingredients, and look for basic patents which would support an SPC application for such combination. However, there is still a fair level of legal uncertainty for a number of reasons. As Art. 3(c) is closely linked with Art. 3(a), any legal uncertainty in the latter will equally affect the former. Secondly, also in interpreting Art. 3(c), the CJEU avails itself of terms such as "core inventive advance", "protected as such", "distinct invention", which are all left unexplained, and which can in themselves give cause to substantial debate as to what is exactly meant.

5.1.7 The issue of 'secondary uses' and Art. 3(d) with the requirement that there may be no earlier MA for the product as medicinal product

5.1.7.1 The issue

Whereas the preceding examples of legal issues all centre around different forms of inherent complexity arising from multi-ingredient/multi-SPC products, there is another class of legal issues that centres around what is termed 'derivative patents' – i.e. patents for second (and further) (medical) indications. It is yet to be seen whether the teaching of what we now know regarding second medical use patents could extend to new formulations of a known compound, or to new production processes of the same compound. It must be underlined for this discussion that SPCs combine both patent and regulatory elements.

Second medical use patents have been accepted by the legislature and case law. They cover the situation where a patent exists or has existed for the active substance as such, but a further use of that very substance has been discovered or invented. The patent system allows such new uses of an existing substance to attain patent protection. Most common types of second medical use claims are those inventions relating to a novel group of subjects, relating to a new route or mode of administration, relating to a different technical effect and leading to a truly new application, and those relating to a new dosage regime for an existing drug. The era of personalised medicine which we now live in will only make second medical indication patents more important, as in personalised medicine, the use of genetic profiles will allow treatments to be targeted towards patient sub-populations that could benefit from, for instance, a different dosage, or from the use of another active substance.[118]

The fundamental question under Art. 3(d) SPC Regulation is how to interpret the requirement that the product "may not already have been authorised as a medicinal product". Does that mean that once a product has been the subject of an earlier MA in the past (irrespective of whether there has been patent and/or SPC protection or not for that active substance in the past), for whatever use, no SPC can be granted, as the product had already been the subject of an earlier MA, and that MA is not the one invoked in the SPC application? Or does it allow to grant an SPC, despite an earlier MA for the product, for the reason that the SPC application and the MA invoked for such an application refers to a different use of the active substance? The above distinction is relevant in circumstances where the same active ingredient or combination of active ingredients (depending on what is meant by "active ingredient") has previously been the subject of an MA, but the new MA is for a different formulation or a different therapeutic use of that active ingredient or combination of active ingredients. The case law of the CJEU has shifted in this regard. The CJEU has in its Neurim judgement (C-130/11) eventually chosen for the latter approach.

The following case law is relevant:

- **Case C-31/03 Pharmacia Italia SpA**[119] dealt, in the strict sense, with a different issue, more in particular Art. 19(1) SPC Regulation and not with Art. 3(d) SPC Regulation. The ruling

[118] For more details, see Bostyn, S.J.R., Personalised medicine, medical indication patents and patent infringement: emergency treatment required, IPQ, 2016, 151-201; Bostyn, S.J.R., Medical treatment methods, medical indication claims and patentability: A quest into the rationale of the exclusion and patentability in the context of the future of personalised medicine, IPQ, 2016, 203-230.

[119] Case C-31/03 Pharmacia Italia SpA [2004] ECR I-10001. An SPC application had been made in Germany for the active ingredient cabergoline, which was protected by a basic patent filed in 1981. The application was based on a marketing authorisation for cabergoline granted for the human medicinal product Dostinex in Germany in June 1994. By virtue of the transitional provision contained in Article 19(1) of Regulation 1768/92/EEC, an SPC could only be granted for a product if, on

is nevertheless relevant to Art. 3(d) SPC Regulation. In effect, the issue to be decided was about whether it matters that there is an earlier MA for a different use (veterinary use) than the later one invoked in support of the SPC application (human use). The CJEU ruled that the criterion for determining which MA can be relied upon is not the use of the active ingredient in the MA, but the date of the MA as a medicinal product in general. In other words, an earlier MA for a veterinary use can be used against a later MA for human use.

- The **Case C-202/05 Yissum Research and Development Company of the Hebrew University of Jerusalem v Comptroller-General of Patents**[120] was also not about Art. 3(d) as such, but once again its ruling contains relevant statements for the interpretation of Art. 3(d). It can be seen from the Yissum case that the Court of Justice confirmed that the concept of "product" in Article 1(b) of the Regulation was to be interpreted strictly and could not include the therapeutic use of the active ingredient, or even whether the medicinal product was for human use or for veterinary use. As the therapeutic use cannot be relevant for determining whether something is a "product" within the SPC Regulation, it can by consequence also not be relevant for determining whether the MA invoked for that "product" is the first MA for that product as a medicinal product.
- The **Neurim case (C-130/11)**[121] can be, according to some commentators, in this context, considered one of the most influential SPC rulings. It has the effect of liberalising SPC usage and allowing for more situations where SPCs can be validly filed (Figure 8). The focus of attention of the Neurim case is, however, not the basic patent but a regulatory feature, namely, the determination which MA to refer to when filing an SPC. In pre-Neurim times, Art. 3d of the regulation – which stipulates that there may be no earlier MA for the product as medicinal product – was interpreted in such a way that the very first MA for the product in Europe had to be referred to. This rule was to be seen irrespective of the intended use of a drug as described in an MA. In Neurim, the CJEU ruled, however, that the relevant MA can be also a later one tied to a specific use of the drug. Against this backdrop, a situation could ensure where there is an MA m1 for the drug for usage as treatment against condition X, while there is

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the date that Regulation entered into force, it was protected by a basic patent and "the first authorization to place it on the market as a medicinal product in the Community was obtained after" 1 January 1988. The first authorisation for Dostinex in the Community had been granted in the Netherlands in October 1992, but there had been an earlier authorisation for cabergoline as the active ingredient of a veterinary medicinal product called Galastop granted in Italy in January 1987.

[120] Case C-202/05 Yissum Research and Development Company of the Hebrew University of Jerusalem v Comptroller-General of Patents [2007] ECR I-2839. Yissum has since 19 July 1989 been the holder of a European patent entitled 'Cosmetic and dermatological compositions containing l-alpha-hydroxycholecalciferol'. That patent particularly concerns a composition, for use in topical treatment of skin disorders, containing a compound of l-alpha-hydroxycholecalciferol or of 1-alpha, 25-dihydroxycholecalciferol, commonly known as 'calcitriol'. The patent also covers the same composition in conjunction with a carrier suitable for the manufacture of a cream, an ointment or a lotion. On 12 December 2001, Galderma Ltd was granted authorisation in the United Kingdom to place Silkis ointment on the market. That authorisation covers calcitriol as active ingredient, and liquid paraffin, white soft paraffin and alpha-tocopherol as carriers. It also states that the ointment is authorised for 'topical treatment of plaque psoriasis (psoriasis vulgaris) with up to 35% of body surface area involvement'. On 11 June 2002, relying on that authorisation, Yissum applied to the Patent Office for an SPC for calcitriol. Primarily, an SPC was sought solely for calcitriol. Alternatively, Yissum requested an SPC for a combination of calcitriol with an ointment base. By decision of 29 July 2004, the Patent Office refused that SPC application on the ground that the authorisation to place the product on the market on which Yissum was relying was not the first such authorisation for that product as a medicinal product, as required by Article 3(d) of Regulation No 1768/92. Other medicinal products, such as Calcijex and Rocaltrol, containing calcitriol as sole active ingredient, had already been granted authorisation to be placed on the market before Silkis ointment.

[121] Case C-130/11 Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents [EU:C:2012:489]. Following research carried out on melatonin, a natural hormone which has not, as such, been patented, Neurim discovered that appropriate formulations of melatonin could be used as a medicine for insomnia. Neurim subsequently obtained a European patent concerning its formulation of melatonin, in order to sell it in the form of a medicinal product for human use called 'Circadin'. When the European Commission issued Neurim with an MA enabling it to market that medicinal product ('the Circadin MA') on 28 June 2007, the patent protecting that new medicinal product had less than five years to run. Neurim therefore applied for an SPC, basing its application on the Circadin MA which it had just obtained. By a decision of 15 December 2009, after the SPC Regulation had come into force, the IPO refused to grant that request. It had identified an earlier MA, dating from 2001, for melatonin for use in sheep and sold under the mark Regulin. Regulin, which was used as a method of regulating the seasonal breeding activity of sheep, had been protected by a patent held by the company Hoechst since 1987 but which had expired in May 2007. The IPO's refusal was thus based on the fact that, contrary to the requirement of Article 3(d) of the SPC Regulation, the Circadin MA was not the first MA relating to melatonin.

another later MA m2 for the drug for usage as treatment against condition Y. The reasoning of the CJEU was as follows:

- *"22. [...] it must also be noted that the **fundamental objective of the SPC Regulation is to ensure sufficient protection to encourage pharmaceutical research**, which plays a decisive role in the continuing improvement in public health (see Case C-322/10 Medeva [2011] ECR I 0000, paragraph 30 and the case-law cited, and Case C-422/10 Georgetown University and Others [2011] ECR I 0000, paragraph 24).*

- *23. The reason given for the adoption of the SPC Regulation is the fact that the period of effective protection under the patent is insufficient to cover the investment put into pharmaceutical research and the regulation thus sought to make up for that insufficiency by creating an SPC for medicinal products (see Medeva, paragraph 31, and Georgetown University and Others, paragraph 25).*

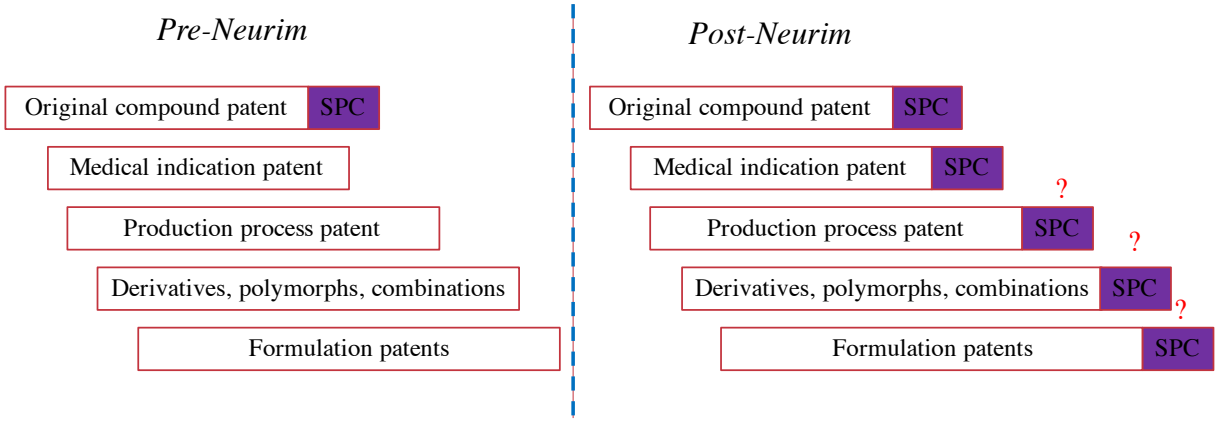
- *24. It is apparent from paragraph 29 of the explanatory memorandum to the proposal for a Council Regulation (EEC) of 11 April 1990, concerning the creation of a supplementary protection certificate for medicinal products (COM(90) 101 final), that, **like a patent protecting a 'product' or a patent protecting a process by which a 'product' is obtained, a patent protecting a new application of a new or known product, such as that at issue in the main proceedings, may, in accordance with Article 2 of the SPC Regulation, enable an SPC to be granted** and, in that case, in accordance with Article 5 of the regulation, the SPC confers the same rights as conferred by the basic patent as regards the new use of that product, within the limits laid down by Article 4 of that regulation (see, by analogy, Medeva, paragraph 32, and order of 25 November 2011 in Case C-630/10 University of Queensland and CSL, ECR I-0000, paragraph 38).*

- *25. **Therefore, if a patent protects a therapeutic application of a known active ingredient which has already been marketed as a medicinal product, for veterinary or human use, for other therapeutic indications, whether or not protected by an earlier patent, the placement on the market of a new medicinal product commercially exploiting the new therapeutic application of the same active ingredient, as protected by the new patent, may enable its proprietor to obtain an SPC, the scope of which, in any event, could cover, not the active ingredient, but only the new use of that product.***

- *26. In such a situation, only the MA of the first medicinal product, comprising the product and authorised for a therapeutic use corresponding to that protected by the patent relied upon for the purposes of the application for the SPC, may be considered to be the first MA of 'that product' as a medicinal product exploiting that new use within the meaning of Article 3(d) of the SPC Regulation.*

- *27. In the light of all the above considerations, the answer to the first and third questions is that Articles 3 and 4 of the SPC Regulation are to be interpreted as meaning that, **in a case such as that in the main proceedings, the mere existence of an earlier MA obtained for a veterinary medicinal product does not preclude the grant of an SPC for a different application of the same product for which an MA has been granted, provided that the application is within the limits of the protection conferred by the basic patent relied upon for the purposes of the application for the SPC**."*

Figure 8 Possibilities to obtain SPCs on different types of patents for the same compound



Source: Technopolis, based on: de Lange M. (2016): Geneesmiddelen, octrooien en aanvullende beschermingsvormen

Because in Europe there is also the possibility to file for second and further medical use/indications patents, the Neurim ruling now allows also for SPCs to be granted for known products based on second medical indications. The economic effect is that – for the same product, but a different indication – there is now also extended effective patent protection. There can therefore be a proliferation of more SPCs for the same compound, for various different medical indications, hereby expanding the scope of possibility for originator firms to exert monopoly powers.

It can also be questioned whether Neurim should be limited to new therapeutic indications. Should in general not ALL second medical indication patents become candidates for an SPC? Why should, for instance, a medical indication patent which relates to a new mode of administration that makes it more effective, not be an allowable candidate for SPC protection? Using the words of the Advocate General in the Neurim case, "*The guiding principle behind my schematic-teleological interpretation of Article 3(d) of Regulation No 1768/92 is the idea that any basic patent should, in principle, be open to an extension of its term of protection under the conditions laid down in Article 3 of Regulation No 1768/92 where the subject-matter of that patent is the result of work which is worthy of protection in the light of the objectives of that regulation.*"

The immediate consequence of the Neurim ruling is furthermore that questions arise whether SPC protection should not also be granted for new formulations, or new processes for making a known compound., etc. The guiding principle behind the decision in the Neurim case was to analyse whether there was so much work put into the patent that there should be – in line with the goals of the regulation – a compensation given for lost patent protection time due to regulatory processes. The line of reasoning is therefore that second and further medical use patents are in no way to be treated differently than the very first patent given for the compound.

That reasoning is now to be tested at least for new formulations of an existing compound.[122] It is not difficult to see that Neurim has opened not one but a variety of "Pandora's boxes", where very similar rationales could be invoked to obtain SPC protection. A number of policy questions can thus be raised here. Is it desirable to grant SPC protection for second medical use patents? Can we conceive a more sui-generis approach towards this type of patents, somewhat keeping the middle-ground between full SPC protection and no SPC protection at all, for instance by providing a shorter SPC term or some other type of incentive? Is there a rationale for not granting SPC protection for other types of invention pertaining to the same active substance, such as for instance new formulations etc.?

[122] ABRAXIS BIOSCIENCE LLC v THE COMPTROLLER-GENERAL OF PATENTS, 13 January 2017, [2017] EWHC 14 (Pat), referring the following question to the CJEU: "Is Article 3(d) of the SPC Regulation1 to be interpreted as permitting the grant of an SPC where the marketing authorisation referred to in Article 3(b) is the first authorisation within the scope of the basic patent to place the product on the market as a medicinal product and where the product is a new formulation of an old active ingredient?" That case is now known as Case C-443/17.

5.1.8 SPC squatting

So-called "SPC squatting" is the phenomenon where one invokes the MA of a third party to obtain SPC protection for one's own patents. Hence, the SPC applicant will not have made any investment in the development of a drug, which is left to another company. Once the MA is there and the work is done, the patent holder identifies a suitable MA which links to a patent stemming from the own patent portfolio, which would then cover the product as authorised in the MA.

It has been argued that this practice should not be allowed, as it defies the purpose and rationale of the SPC system. The SPC system aims at restoring loss of effective patent term protection due to regulatory procedures. The company invoking a third party's MA will not have invested anything in the development of the authorised product. Should such party then be entitled to obtain SPC protection?

The crux in the argument is, however, that the SPC restores loss of effective patent term protection. Even though the SPC applicant who invokes the MA from a third party will not have incurred any costs in obtaining a MA, he will have lost effective patent term protection, as without an MA, the product protected by the patent cannot be brought on the market, and the patent can therefore not be enforced and effectively utilised.

The UK court in Novartis v Medimmune suggested that it might run counter to the objective of the SPC regulation for SPC applicants to use an MA obtained by a third party with a view to obtain patent term extension in the form of an SPC: "*As noted above, in the present case the SPC is based upon a product obtained by means of an allegedly infringing process and upon a marketing authorisation obtained by an alleged infringer of the Patent. It might be thought that it was not the purpose of the Regulation to enable a patent owner to obtain an SPC in such circumstances, since the owner has not been delayed in getting the product to market by the need to get a marketing authorisation, and therefore no extension to the term of the patent is needed to compensate him for that delay.*"[123]

- Even though the point was not raised as a question in the CJEU Lilly v HGS case, the Court did say something that can be deemed relevant for purposes of determining whether such practice is indeed in line with the purpose of the SPC regulation. The Court said in the aforementioned case that: *"[…] In such a situation, if an SPC were granted to the patent holder, even though – since he was not the holder of the MA granted for the medicinal product developed from the specifications of the source patent – that patent holder had not made any investment in research relating to that aspect of his original invention, that would undermine the objective of Regulation No 469/2009, as referred to in recital 4 in the preamble thereto.*"[124]

This is a matter that can be legislated in any future recast or amendment of the SPC Regulation, and in any future Unified SPC. It may assist in this connection to observe that in the US, the Patent Term Extension system under the Hatch-Waxman Act[125] (incorporated in 35 U.S.C. § 156) does not seem to allow this practice.[126]

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[123] Novartis Pharmaceuticals UK Ltd v Medimmune Ltd [2012] EWHC 181 (Pat), [2012] FSR 23, para 61.

[124] Case C-493/12 Eli Lilly & Co Ltd v Human Genome Sciences Inc [EU:C:2013:835], paragraph 43.

[125] Officially called the 1984 Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360; 35 U.S.C. §§ 156, 271)), amended by Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066.

[126] See Manual of Patent Examining Procedure (MPEP), Ninth Edition, Revision 07.2015, Last Revised November 2015, Chapter 2700 Patent Terms and Extensions, 2752 Patent Term Extension Applicant, where it is said: "*If the applicant for patent term extension was not the marketing applicant before the regulatory agency, then there must be an agency relationship between the patent owner and the marketing applicant during the regulatory review period. To show that such an applicant is authorized to rely upon the activities of the marketing applicant before the Food and Drug Administration or the Department of Agriculture, itis advisable for the applicant for patent term extension to obtain a letter from the marketing applicant specifically authorizing such reliance.*"

5.2 Paediatric Regulation

5.2.1 Introduction

Most medicinal products are developed and brought on the market in hopes of treating an as large as possible patient population. Most research is consequently not focussed on paediatric use, as that represents a relatively narrow patient population for most medicinal products. Moreover, there are ethical concerns about conducting clinical trials in children, as well as practical problems (e.g. identifying a sufficiently large patient population to conduct trials). As a consequence, most of the use of medicinal products in paediatric populations have not been developed and researched for that particular use, and no studies are undertaken for paediatric use. The Paediatric Regulation states in that context in recitals (2) and (3) that:

> *"(2) Such 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[127] 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.*
>
> *(3) Problems resulting from the absence of suitably adapted medicinal products for the paediatric population include inadequate dosage information which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations to treat the paediatric population which may be of poor quality."*

The aim of the Paediatric Regulation is to stimulate R&D in paediatric use, as recital (4) confirms:

> *"(4) This 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. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations."*

In order to stimulate R&D in paediatric use, the regulation opted for a number of incentives, set out recital (19) and (26) to (28):

- A six months paediatric extension of SPCs that is the subject of this chapter (Rec. 26)
- A new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), for authorised products no longer covered by intellectual property rights (Rec. 19)

The Paediatric Regulation makes it mandatory to carry out studies and research to be implemented into a so-called Paediatric Investigation Plan (PIP)[128] for all new MA applications filed since the entry into force of the Paediatric Regulation (see Art. 7 Paediatric Regulation). It does in that context not matter whether the medicinal product for which a MA will be applied for is protected by patent or is under SPC protection. The obligation to provide paediatric data exists independent of IP protection.

For those medicinal products that are already authorised, and which are still under patent protection or SPC protection, a PIP is mandatory in case of applications for authorisation of new indications,

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[127] Art. 2(1) Paediatric Regulation defines "paediatric population" as: that part of the population aged between birth and 18 years."

[128] Art. 2(2) Paediatric Regulation defines a PIP as: "'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population."

including paediatric indications, new pharmaceutical forms and new routes of administration. In those cases, the PIP should not only cover the new indications etc, but also both the existing and the new indications, pharmaceutical forms and routes of administration (see Art. 8 Paediatric Regulation).

For off-patent drugs, there is no requirement to produce a PIP. However, a voluntary application to file paediatric data for off-patent drugs can be rewarded with a new type of MA, the so-called paediatric use marketing authorisation (PUMA),[129] which will trigger the common data exclusivity and market protection rules[130] of 8 years of data exclusivity and 2 years of market protection.[131]

For medicinal products that are still under patent protection, the system provides for a one-off six months extension of SPC protection. The condition is, however, that there is SPC protection in place.[132] Furthermore, there has been an agreed Paediatric Investigation Plan (PIP) approved by the regulatory authorities.[133] It is not required to obtain a marketing authorisation for a paediatric use, nor is it necessary to file for one. In many cases, a variation to the existing marketing authorisation is obtained, which does not require a full blown and costly regulatory approval process, even though the variation requires regulatory approval.

There is a separate strand for orphan drug designations. The paediatric extension is not available for drugs with an orphan designation;[134] instead a separate two-year market exclusivity is available for those drugs.[135] An applicant for a product that qualifies as an orphan drug will thus have to make strategic choices. For a specific medicinal product still under patent protection, there will be the possibility to opt for the paediatric extension, provided that compliance can be proven with the PIP. In the alternative, the applicant can choose the orphan drug designation route, in which case there will be no paediatric extension, but an additional two years of market exclusivity is provided.[136]

In this chapter, the discussion will be limited to the paediatric SPC extension.

5.2.2 Paediatric SPC extension scheme in greater detail

The paediatric SPC extension scheme has been implemented into the SPC Regulation in Art. 7 and 8, which reads as follows (only relevant parts):

> *"Article 7 Application for a certificate*
>
> *[...]*
>
> *3. The application for an extension of the duration may be made when lodging the application for a certificate or when the application for the certificate is pending and the appropriate requirements of Article 8(1)(d) or Article 8(2), respectively, are fulfilled.*
>
> *4. The application for an extension of the duration of a certificate already granted shall be lodged not later than two years before the expiry of the certificate.*

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[129] Art. 30 Paediatric Regulation: "1. Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other indications.

2. An application for a paediatric use marketing authorisation shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration for the product, in accordance with an agreed paediatric investigation plan.

The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned."

[130] For more details on data exclusivity and market protection, see chapter 5.3 of this Study.

[131] As per Art. 10(11) Directive 2001/83 and Art. 14(11) Regulation 726/2004. See Also Art. 38 Paediatric Regulation

[132] Art. 36 Paediatric Regulation.

[133] Article 36(1) of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. See also Artt. 7, 8 and 13(3) Regulation 469/2009.

[134] Art, 36(4) Paediatric Regulation.

[135] Art. 37 Paediatric Regulation.

[136] See also Article 8(1) of Regulation (EC) No 141/2000.

5. Notwithstanding paragraph 4, for five years following the entry into force of Regulation (EC) No 1901/2006, the application for an extension of the duration of a certificate already granted shall be lodged not later than six months before the expiry of the certificate.

Article 8 Content of the application for a certificate

1. The application for a certificate shall contain:

[…]

(d) where the application for a certificate includes a request for an extension of the duration:

(i) a copy of the statement indicating compliance with an agreed completed paediatric investigation plan as referred to in Article 36(1) of Regulation (EC) No 1901/2006;

(ii) where necessary, in addition to the copy of the authorisation to place the product on the market as referred to in point (b), proof of possession of authorisations to place the product on the market of all other Member States, as referred to in Article 36(3) of Regulation (EC) No 1901/2006.

2. Where an application for a certificate is pending, an application for an extended duration in accordance with Article 7(3) shall include the particulars referred to in paragraph 1(d) of this Article and a reference to the application for a certificate already filed.

3. The application for an extension of the duration of a certificate already granted shall contain the particulars referred to in paragraph 1(d) and a copy of the certificate already granted.[…].”

To date, not much case law exists relating to the paediatric regulation. However, there is one question regarding the term of a pediatric extension. The question has arisen what the situation would be if an applicant applied for a paediatric extension in a scenario where, were an SPC application filed for the product at hand, the term of the SPC would have been negative. To recall: The main calculation method for establishing the term of an SPC is by taking the difference between the fling date of the patent and the grant date of the MA,[137] minus five years.[138]

The case which to raise here is where the calculation method would lead to a negative number, i.e., the difference between the filing date of the patent and the grant date of the MA would be less than five years. In such a scenario, the patent holder will not file for an SPC, as that would not lead to a useful result. But what would be the situation now if in such a scenario the patent holder would want to benefit from the paediatric extension? As the paediatric extension requires the presence of an SPC, any situation where there is no SPC would preclude the paediatric extension from being successfully applied.

There are basically two ways how to look at this problem, which has become – as could be expected – the subject of an CJEU judgement[139]:

- One approach could be to argue that there would in such a scenario no entitlement to a paediatric extension. The applicant has not lost considerable time due to the regulatory approval, which was the reason why there was no positive term SPC to be granted. Under such

[137] In fact, according to a recent CJEU judgement, for purposes of calculating the duration of an SPC, one is allowed to use the notification date of the grant of the MA instead of the date of grant. The former will be commonly a couple of days later, adding those days to the term of SPC protection. See C—471/14 Seattle Genetics Inc. v Österreichisches Patentamt, ECLI:EU:C:2015:659.

[138] See Art. 13 SPC Regulation 469/2009.

[139] C-125/10 Merck Sharp & Dohme Corp. v Deutsches Patent- und Markenamt, ECLI:EU:C:2011:812.

circumstances it could not be seen why an applicant, who was not entitled to benefit from an SPC in the first place, would be allowed to benefit from a paediatric extension, which is an extension of an SPC after all. This reasoning is, at least partly, based on the statutory provisions in the Paediatric Regulation according to which the paediatric extension requires the presence of an SPC.

- The opposite approach is that there is no reason to assume that in such scenario there would be no entitlement to the paediatric extension. The paediatric extension requires the presence of an SPC, but the SPC Regulation does not state anywhere that an SPC must have a positive term. That line of thinking agrees with the principle that there must be an SPC as a prerequisite for obtaining a paediatric extension. But it argues that, in the absence of any indication in the wording of the SPC Regulation that an SPC MUST be positive, it should in such circumstance be possible to file for SPC protection which would, if granted, lead to a zero or negative term SPC, i.e., an SPC which is subtracting days off the patent term or leads to zero.[140] Following such a reasoning would make it worthwhile for every applicant to file for a zero or negative term SPC if the negative term would be anything less than six months. Indeed, any negative SPC term of less than six months would, if the one-off six months of the paediatric extension is added to that, always lead to an extension of at least one day beyond the standard patent term.[141]

[140] For instance, if the total period between the patent fling date and the MA grant date is 4 years and 9 months, that would lead to a negative SPC of 3 months.

[141] One of the consequences of following this reasoning is that is in effect held that the total patent term would be reduced. A negative SPC term will in effect "eat" patent term away. One can wonder whether the SPC system and more in particular the way how it is interpreted can actually come to such a conclusion without interfering within the legal order of the patent system, not only outside of the realm of the SPC Regulation, but also outside of the direct realm of the CJEU, save as for interpretation of TRIPs provisions, effectively prescribing the same term of protection as the EPC (Art. 33 TRIPs). See in this context the judgement of the CJEU regarding interpretation of TRIPs provisions, C-414/11Daiichi Sankyo Co. Ltd and Sanofi-Aventis Deutschland GmbH v DEMO Anonimos Viomikhaniki kai Emporiki Etairia Farmakon, ECLI:EU:C:2013:520.

Case C-125/10 Merck & Dohme Corp v. DPMA

In Case C-125/10 Merck Sharp & Dohme Corp. v Deutsches Patent- und Markenamt,[142] the latter refused to grant an SPC by decision of 1 July 2008 on the ground that a period of only four years, eight months and sixteen days had elapsed between the date on which the application for a basic patent was lodged and the date on which the first marketing authorisation was issued, so that calculating the length of the SPC would have resulted, pursuant to Article 13(1) of Regulation No 1768/92, in a negative duration of three months and fourteen days. Merck brought an action against the decision before the Bundespatentgericht. It submitted that all the conditions required for the grant of an SPC are fulfilled in this case and the duration of the SPC is not one of those conditions. Merck held that even if the SPC cannot result in a positive duration, it can nevertheless have a zero or negative duration. The reason for its application for the SPC is that it wished to be able to request, at a later date, an extension of the SPC. A paediatric investigation plan was authorised, to that effect, by the competent authority on 27 March 2009 and the studies prescribed in that plan must be completed by 2017. The case was referred to the CJEU.

The CJEU decided to allow negative/zero-term SPCs for purposes of paediatric extensions. It held that *"…if the SPC application had to be refused because the calculation provided for in Article 13(1) of Regulation No 1768/92 results in a negative or zero duration, the holder of the basic patent could not obtain an extension of protection conferred by such a patent, even if it conducted all the studies according to the approved paediatric investigation plan, under Article 36 of Regulation No 1901/2006. Such a refusal would be capable of compromising the useful effect of Regulation No 1901/2006 and could jeopardise the objectives of that regulation, namely, the compensation of effort made to evaluate the paediatric effects of the medicinal product at issue."*[143]

Comments on the judgement

This judgement deserves some critical comments. The Paediatric Regulation clearly states that the paediatric extension can only be granted if there is an SPC (or an application to that effect has been filed). That suggests that the objective was that only those patents that deserved an SPC in the first place should be considered for the extension. That means that patents for which no SPC has been filed cannot file for an extension.

Furthermore, it can be questioned whether the SPC system has ever been devised to allow negative terms of SPC protection, as in the core it is a system for EXTENDING patent protection term, and not for reducing it. The logic of the system is that one is only entitled to an SPC if one has lost considerable effective term of patent protection due to regulatory authorisation procedures. That lost term is to some extent being compensated by the SPC system. If one does not suffer such considerable loss of effective patent term protection, there is no reason for that person or company to avail itself of the system.

Holding that there is no possibility for negative term SPCs would imply that those patent holders who have suffered only a very limited loss of patent term protection would suddenly become excluded from the system. As the AG has suggested, getting an MA one day earlier than a period of five years after the filing date of the patent would then mean that such a patent holder would not be entitled to a paediatric extension, whilst a patent holder who obtains the MA after five years or any later date, would become entitled. This in turn could give the impression that it would create some form of unfairness. In conclusion, even though this is a very pragmatic judgement by the CJEU, it can be questioned whether it is in line with the intent of the system.

[142] C-125/10 Merck Sharp & Dohme Corp. v Deutsches Patent- und Markenamt, ECLI:EU:C:2011:812.

[143] C-125/10, paragraph 37.

5.3 Data exclusivity and market protection

5.3.1 Concepts

Apart from, and in addition to, the patent system, there are also regulatory incentives for stimulating R&D with a similar rationale, i.e. by providing time-limited exclusive rights. Data exclusivity and market protection[144] provide such incentives by granting a temporary exclusive right as a compensation for the development costs of the medicinal product and the generating of research and clinical trial data.[145] It is important to know that patent (and SPC) protection and data exclusivity protection can, and often will, overlap,[146] or can in the alternative be strategically used by innovator companies to optimise the exclusive rights obtained under either of the systems.

The difference between data exclusivity and market protection is:

- **Data exclusivity** is fundamentally a system whereby a generic company cannot refer to the MA dossier of the so-called reference product during the period of data exclusivity.
- **Market protection** refers to the system whereby the MA holder has the sole right to market the medicinal product for which a MA has been granted.

The possibility of generics firms to introduce a generic version of a drug onto the market and offer it at a lower price than the original depends on the ability to avoid the time-consuming and costly different clinical trials.[147] Indeed, the basic principle is that, to obtain an MA for a medicinal product, a wide variety of costly and time-consuming tests and trials must be carried out by the originator company, which is then labelled as the reference product.[148]

For a generic version of the drug, such clinical trials are not necessary as the clinical trials have been already performed by the originator company, provided the generic MA applicant can demonstrate that the medicinal product that is applied for is bioequivalent[149] to the so-called reference originator medicinal product.[150] Generic companies can simply refer to the so-called reference dossier, where all tests and trials relating to the active substance in question have been described.[151] This is a so-called abridged MA.

Data exclusivity denies, for a limited time, generics firms the right to refer to such data of the original drug – the 'reference product' – in their regulatory filings. Hence, during the duration of the data exclusivity, any abridged application submitted referring to the dossier of the reference product will not be accepted. This *de facto* implies that generic companies cannot file for an MA as long as there is data exclusivity on the data of the MA reference dossier.

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[144] Eligibility for data exclusivity and market protection depends on whether the drug triggers a new global marketing authorisation. This can be the case not only for all new active substances, but also for known active substances if a company other than the originator company files a request for authorisation on the basis of a full dossier.

[145] Governed by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67–128. See also Regulation 726/2004/EC for centrally granted marketing authorisations. For the Netherlands, those systems are protected under Art. 42 and 43 Geneesmiddelenwet.

[146] Katarzyna Zbierska, Relations between SPC and data exclusivity, Pharmaceuticals Policy and Law 16 (2014) 73–87.

[147] Article 10(1) Directive 2001/83/EC

[148] See Art. 8(3) and Annex I, Part 2 Directive 2001/83/EC.

[149] See Art. 10(2)(b) Directive 2001/83/EC for the definition of what a generic product is: "'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy."

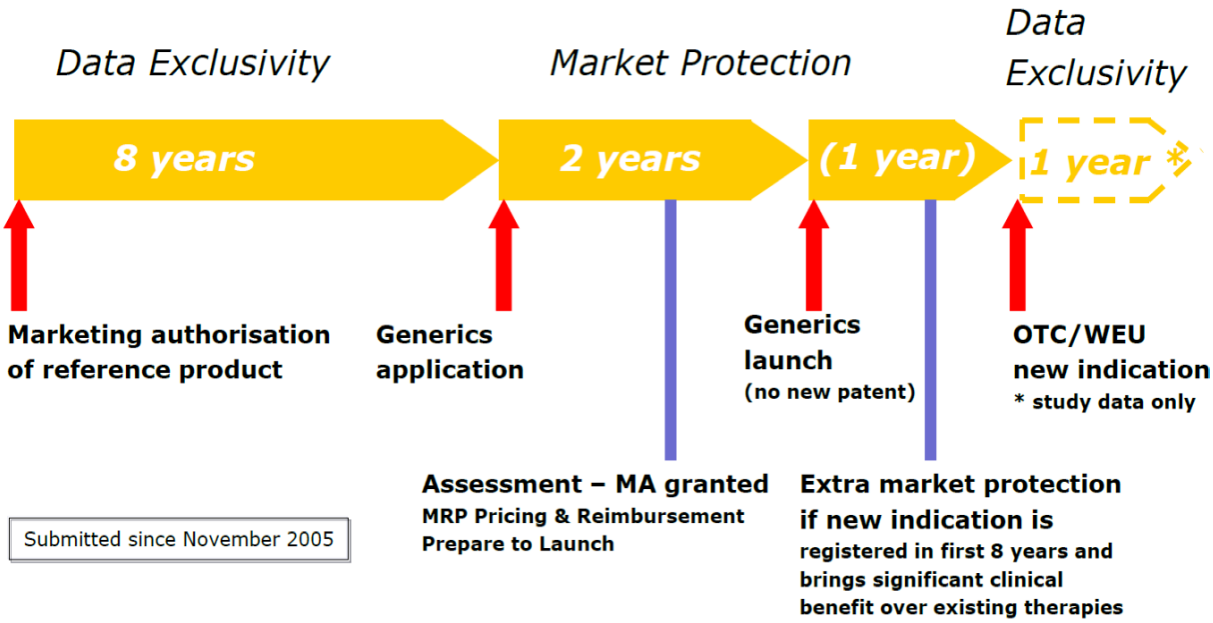
[150] What is a reference medicinal product? Art. 10(2)(a) Directive 2001/83 defines it as "a medicinal product authorised under Article 6, in accordance with the provisions of Article 8."

[151] However, even though the generic company will be able to refer to the dossier of the reference product when filing an abridged MA, the so-called quality part (Chemistry, Manufacture and Control - CMC) of the generic MA dossier must still be produced and submitted. Reference is being made in Art. 10 to Art. 8(3) of Directive 2001/83, which prescribes the requirements for obtaining a marketing authorisation.

Market protection refers to the system whereby the reference product MA holder has the sole right to market the medicinal product for which an MA has been granted. This *de facto* means that during that period, even though generic companies could file for an MA for a bioequivalent product during the period of market protection (provided there is no longer any data exclusivity active on the data referred to), they cannot market the product.

Data exclusivity and market protection overlap in the sense that during the period of data exclusivity, there is also market protection,[152] but there may be (and there is in fact) a period of market protection exceeding the period of data exclusivity, in which case only the former can be invoked, as the latter has lapsed.

Figure 9 Terms of data exclusivity and market protection: the 8+2(+1) formula



Source: European Medicines Agency

The scheme under Directive 2001/83 and Regulation 726/2004 (the latter for centrally granted marketing authorisations), which was the main focus of this study, is applicable to marketing authorisation applications filed as from 21 November 2005. For those filed before that date, a different regime is applicable, but in view of the cut-off date of November 2005, its effects have largely if not entirely stopped having much practical effect today. The term of protection under the aforementioned scheme follows the '8+2(+1)'-rule.[153]

Hence, there is eight years of data exclusivity plus two additional years of market protection. There are three situations where, in addition to the 8+2 years of exclusivity, an additional 1 year of market protection can be obtained. These situations are the following:

[152] This is in practice merely a theoretical matter, as during the period data exclusivity, no third party can even file for a MA for the reference product, let alone prepare to market it. It is, however, important to understand that this market protection is present, as it is calculated from the notification date of the MA, and is hence relevant for calculating until when the market protection lasts, even though during the years of data exclusivity (which has the same starting date) it has no practical effect.

[153] Art. 10 Directive 2001/83; Article 14(11) of Regulation No 726/2004 (for centrally authorised medicinal products).

- One year extension of the 10 year period in Article 10(1) in the case of new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit[154] in comparison with existing therapies[155]
- One year period of data protection for new indications[156] of well-established substances[157]
- One year period of protection for data supporting a change of classification.[158]

It is not possible to cumulate any of the above extensions, which implies that exclusivity cannot extend beyond eleven years. The situation is shown in Figure 9.[159]

The 8 refers to the eight years of data exclusivity, i.e., the period of time during which no generic applicant can refer to the data of the reference product MA in filing its MA for a generic version of the same reference product.

The 2 refers to two years of market protection for the reference product after the eight years of data exclusivity have lapsed. The market protection is in effect ten years from the obtaining of the MA for the reference product. During the period of market protection, but in view of what has been said earlier after the period of data exclusivity, third parties can file for an MA by referring to the data of the reference product, but cannot bring the product on the market pending the market protection.[160]

This means that for a reference medicinal product, the start of the data exclusivity and market protection periods is the date when the first MA was granted in the EU in accordance with the pharmaceutical acquis. New additional strengths, pharmaceutical form, administration routes, presentations as well as any variation and extensions do not restart or prolong this period. All additional strengths, pharmaceutical forms, administration routes, presentations as well as any variations and extensions have the same end point of the data exclusivity and market protection periods, namely eight and ten years after the first MA was granted, respectively. This will apply even if the new presentation has been authorised to the same MA holder through a separate procedure, national or centralised procedure, irrespective of the legal basis and under a different name.[161]

5.3.2 Legal issues identified

In the context of data exclusivity and market protection, five legal issues have been identified:[162]

1. Is there a right to a separate period of data exclusivity and market protection for MA applications based on Art. 10(a) Directive 2001/83/EC (for medicinal products in well-established medicinal use)?
2. The exact confines of the so-called "global marketing authorisation"

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[154] For a clarification of what is meant by "significant clinical benefit", see, "European Commission GUIDANCE ON ELEMENTS REQUIRED TO SUPPORT THE SIGNIFICANT CLINICAL BENEFIT IN COMPARISON WITH EXISTING THERAPIES OF A NEW THERAPEUTIC INDICATION IN ORDER TO BENEFIT FROM AN EXTENDED (11-YEAR) MARKETING PROTECTION PERIOD, November 2007, see at http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf (last visited 12 January 2018).

[155] Art. 10(4) Directive 2001/83; Art. 14(11) of Regulation (EC) No 726/2004

[156] See, GUIDANCE ON A NEW THERAPEUTIC INDICATION FOR A WELL-ESTABLISHED SUBSTANCE. November 2007, see at http://ec.europa.eu/health/files/eudralex/vol-2/c/10%20_5_%20guideline_11-2007_en.pdf , section 3

[157] Article 10(5) of Directive 2001/83/EC. For a definition of well-established substance and use, see Part II of the Annex to Directive 20001/83/EC as amended by Directive 2003/63/EC.

[158] Article 74a of Directive 2001/83/EC, introduced by Directive 2004/27/EC.

[159] There was a rule change in 2005. Before 2005, the period of data exclusivity was not harmonised in the EU and could be in between six to ten years, depending on the country. Directive 2001/83 set the standard to eight years of data exclusivity and introduced the notion and term of the two-year market protection.

[160] See also, NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION, December 2017, section. 6.1.2, p. 40-41.

[161] See NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION, December 2017, section. 6.1.5, p. 43.

[162] This is not an exhaustive list, but constitutes what in the view of the authors of the Study are the most relevant legal issues in this area of the law.

3. When is a medicinal product a new active substance?
4. Can a so-called "hybrid abridged" MA application generate a new period of data exclusivity and market protection?
5. Can a MA holder deregister a drug during or after the period of data exclusivity and market protection, and bring another version of that same drug on the market immediately thereafter?

5.3.2.1 Separate data exclusivity and market protection for MA under Art. 10(a) Directive 2001/83?

Legal issue nr. 1 – Is there a right to a separate period of data exclusivity and market protection for MA applications based on Art. 10(a) Directive 2001/83/EC (for medicinal products in well-established medicinal use)?

As described earlier, the basic principle when filing for a MA is that applicants have to provide results of the preclinical tests and clinical trials that they have conducted. However, Art. 10(a) Directive 2001/83 exempts MA applicants from the obligation to conduct these tests themselves, if they can demonstrate that the active substance of the medicinal product applied for has been in well-established medicinal use[163] in the Community for at least ten years. In such cases, the applicant can instead submit a dossier with relevant data obtained from the literature.

A relevant question is now whether an MA granted under Art. 10(a), and being considered as a reference product, could then trigger a period of data exclusivity and market protection in its own right. The Advocate General (AG) in case C-104/13 Olainfaim[164] discussed the issue in his Opinion in 2014.[165] This case related to the medicinal product NEIROMIDIN – a drug used for conditions of the central and peripheral nervous system.

Before addressing the issue of market protection, it is necessary to know whether the medicinal product for which an MA under Art. 10(a) Directive 2001/83 has been obtained can be considered as a "reference medicinal product" which can be the basis for later generic applications. The CJEU ruled in C-104/03 that such medicinal products can indeed be considered a "reference medicinal product".

The next subsequent question is then to ask whether an MA for such a "reference medicinal product" granted under Art. 10(a) Directive 2001/83 could elicit its own period of data exclusivity and market protection. In his Opinion on the NEIROMIDIN case, AG Wahl argued, that in his view, there would indeed be a separate right to data exclusivity and market protection for medicinal products authorised under the Art. 10(a) procedure. He held that *"Most fundamentally perhaps, where a company wishes to manufacture a generic of a medicinal product which has already been authorised, it can be assumed that the holder (irrespective of the procedure under which the reference product was approved) has had a degree of success in marketing that product. Consequently, if ten-year market exclusivity and the right to challenge decisions to allow generics to be placed on the market during that time were not granted to the holder, companies manufacturing generics would be able to benefit from and free ride on the marketing efforts already made in relation to the reference product."*[166]

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[163] What is to be understood by "well-established medicinal use" can be found in indent (a) in section 1 ("Well established medicinal use") of Part II of the Annex to Directive 20001/83/EC as amended by Directive 2003/63/EC:

"The following specific rules shall apply in order to demonstrate the well-established medicinal use:

a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:

— the time over which a substance has been used,

— quantitative aspects of the use of the substance,

— the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and

— the coherence of scientific assessments." For further details, see NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION, December 2016, section. 5.4, p 34-35.

[164] Case C-104/13, Olainfarm AS v Latvijas Republikas Veselības ministrija and Zāļu valsts aģentūra, ECLI:EU:C:2014:2316.

[165] ECLI:EU:C:2014:342.

[166] Opinion AG Wahl, point 58.

Therefore, even though AG Wahl concedes that there are no data to be protected and there is little innovative activity carried out (as it concerns a well-established product), there are still commercial interests to defend, and he is of the belief that not allowing market protection would give undue commercial advantage to generic manufacturers, who would then *de facto* get a "free ride".

The matter has since been clarified in the Notice to Applicants, which states that "Reference can be made to the dossier of a reference medicinal product for which a marketing authorisation has been granted in the Union in accordance with Articles 8(3), *10(a)*, 10(b) or 10(c) of Directive 2001/83/EC."[167] Because products registered on the legal basis of Art. 10(a) can be a reference product, they can also be the start of a new global marketing authorisation (provided they do not fall within the scope of an existing authorisation), and therefore are entitled to a period of data exclusivity and market protection.

5.3.2.2 Exact confines of the "global marketing authorisation" concept

Legal issue Nr. 2 – The exact confines of the so-called "global marketing authorisation" concept

The concept of "global marketing authorisation" (GMA) is a crucial one as it is the trigger of the regulatory exclusive rights that are the subject of this chapter. Once a medicinal product has been authorised, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions which could become authorised in the future will all fall within the same global marketing authorisation and cannot trigger a separate entitlement to regulatory exclusivity, such as data exclusivity and market protection. All these variations and extensions will not be entitled to their own data exclusivity and market protection, at least in principle.[168]

The global[169] marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures, including in different Member States within the EU, and under a different name, granted to the MA holder of the initial authorisation. Where a product is initially authorised nationally and, subsequently, an additional strength, pharmaceutical form, administration route or presentation is authorised through the centralised procedure, this is also part of the same GMA.[170] The respective major provisions are laid out in Article 6(1) second subparagraph of Directive 2001/83/EC.

It is further noted that applicants and MA holders belonging to the same company group or that are controlled by the same physical or legal entity are to be considered as one entity for purposes of determining whether the concept of GMA will be applicable to that particular set of applicants and MAs.[171] Indeed, the concept of GMA states that all the different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, and hence all are part of the same global MA, provided they all stem from the same MA holder.

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[167] NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION, December 2017, section. 5.3, p 29.

[168] Article 6(1) second subparagraph of Directive 2001/83/EC provides that "When a medicinal product has been granted an initial marketing authorisation in accordance with the first sub-paragraph, 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 sub-paragraph 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)."

[169] The meaning of the word "global" is therefore not in the geographical sense, but in the sense of "applying to a whole".

[170] See NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION, December 2016, section. 2.3, p. 8.

[171] See NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION, December 2016, section. 2.3, p. 8-10.

Generic medicinal products are registered on the basis of Article 10, without a full dossier, and can never be used as a reference product. Generic products cannot trigger a global marketing authorisation and do not qualify for data exclusivity and market protection.

There are some issues that remain somewhat unclear.

- Art. 6(1) simply refers to additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions which will all fall within the global marketing authorisation. However, that remains quite unspecific.
- Art. 10(2)(b) defines a 'generic medicinal product' by saying that it "*shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant.*" That raises some issues relating to the distinction between what is a new active substance and what is a generic product or for that matter a variation of the reference product, both of which do not elicit a new period of data exclusivity and market protection in accordance with the GMA concept. The concept of "new active substance" in the context of the GMA will be discussed in the next section.

To note is also case law C-629/15 Novartis v Europharm.

The issue which is most relevant for the present Legal Issue is the question whether the concept of the same GMA will be applicable in a situation where an originator has an MA for a medicinal product relating to an active substance for certain therapeutic indications. Later, that same company files for a second MA, pertaining to the same active substance, but now for different therapeutic indications. Does this second MA trigger a new GMA, and thus entitlement to a separate period of data exclusivity and market protection, or does the second MA fall within the scope of the GMA generated when the first MA was granted? In the former case, the same active substance would de facto benefit from multiple periods of data exclusivity and market protection, whilst in the latter it would not. The issue was decided in the case of C-629/15 Novartis v Europharm.[172]

Case C-629/15 Novartis v Europharm

On 20 March 2001, Novartis obtained an MA under the centralised procedure for the medicinal product Zometa, the active substance of which is zoledronic acid, for a series of oncology indications. On 15 April 2005, it obtained, also on the basis of Regulation No 2309/93, an MA for the medicinal product resulting from that further research, Aclasta. Aclasta has the same active substance as Zometa, namely zoledronic acid, but its therapeutic indications are different from those of Zometa, and its strength was adjusted in the light of those new indications.

When filing for their MA's (May and June 2011), Teva and Hospira (filing generic so-called "abridged" applications) referred to the results of preclinical and clinical trials submitted by Novartis in the MA applications for Zometa and Aclasta. Novartis claimed to still have regulatory protection for Aclasta.

The CJEU held that all the different medical indications and strengths of zoledronic acid, which in the case of Novartis, had been the subject of two different MA's (for Zometa and Aclasta respectively), belong to the same global marketing authorisation and can consequently not lead to two separate periods of data exclusivity and market protection, but fall all within the same period of data exclusivity and market protection. It held in this context that different therapeutic indications also fall within the definition of "any additional strengths, pharmaceutical forms, administration routes, presentations, as

[172] C-629/15, Novartis Europharm Ltd v European Commission, ECLI:EU:C:2017:498.

well as any variations and extensions" under Art. 6(1) Directive 2001/83, despite not being explicitly mentioned therein.[173] Additionally, the CJEU held that for purposes of establishing whether these variations or extensions fall within the same global marketing authorisation, it does not matter whether these are made within the context of the same MA, or in the context of separate MA's (as was the case here).

The case provides a good illustration of how pharmaceutical companies have tried to limit the interpretation of the concept of "global marketing authorisation" not to include further medical indications of the same active substance, and asserting instead that an MA for further medical indications of an active substance that had already been subject to a MA, but for different medical indications, did generate a new period of data exclusivity and market protection instead.

It also relates to a very frequent practice of having a first MA for an active substance for specific medical indications, and later MAs for the same active substance for other medical indications. If the MA holder would be entitled to obtain a new period of data exclusivity and market protection each time such a new MA for the same active substance but for different medical indications would be allowed, that would in effect imply that generic entry would be delayed for an unspecific time, as there could be a sequence of such MAs for each time different medical indications.

In line with the rationale of the legislature when introducing the concept of GMA, all those further MAs fall under the same concept of GMA, and can thus not generate separate periods of data exclusivity and market protection. Otherwise MA holders could use "salami slicing" strategies to file for MAs each time for different medical indications and then expect to obtain a new period of data exclusivity and market protection for each of those new MAs, all of which relate to the same active substance. It would also be in effect a circumvention of the already existing possibility to obtain a one year extension of data exclusivity for new indications of well-established substances as per Art. 10(5) Directive 2001/83.[174] The current Notice to Applicants clearly states that the "ten year period of marketing protection may be extended by one year in the event of authorisation of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies. The additional year of marketing protection applies to the global marketing authorisation for the reference medicinal product. [...] The overall period of protection cannot exceed eleven years. Therefore, this provision can be used only once per 'global marketing authorisation' within the meaning of Article 6(1) of Directive 2001/83/EC."[175]

5.3.2.3 When is a medicinal product a new active substance?

Legal issue Nr. 3 – When is a medicinal product a new active substance?

As stated previously, Art. 10(2)(b) defines a 'generic medicinal product' by saying that it "*shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant.*"

[173] The AG said in this context: "68. If the authorisation of a new therapeutic indication were to trigger a new data protection period, that would, in my view, go against the above-described objective pursued by the very existence of the abridged procedure in combination with the time limits set by the legislature for the data protection. Instead of benefiting from an additional year, a new therapeutic indication would bring about a full 10-year regulatory data protection period, allowing the holder of the initial marketing authorisation to continue to exploit the respective data and to prevent the producers of the generic products from resorting to the abridged procedure." (Opinion AG ECLI:EU:C:2016:1003.).

[174] This was also noted by the AG in his Opinion in point 68, cited above.

[175] See NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION, December 2017, section. 6.2, p. 44.

That raises some issues relating to the distinction between what is a new active substance and what is a known active substance product or for that matter a variation of the reference product, both of which do not elicit a new period of data exclusivity and market protection in accordance with the GMA concept. Consequently, the notion of what constitutes a "new active substance" becomes of interest, as a "new active substance" will trigger a new GMA and accompanying regulatory protection.

The definition of new active substance can be found in Annex I of Chapter 2 of the Notice to Applicants:

> *"A new chemical, biological or radiopharmaceutical active substance includes:*
>
> *- a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union;*
>
> *- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised;*
>
> *[...]"*[176]

In case law, the distinction between what is to be defined as a new active substance, which elicits a new GMA, and a generic product or a variation of a reference product, has become particularly acute in the area of isomers/enantiomers.[177]

According to Directive 2001/83, an isomer will only be considered a new active substance if it differs significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised, which would then be the racemate[178]. What might constitute a significant difference in safety and/or efficacy to justify new active substance status has been clarified in a number of Reflection Papers.[179] The fact that there have been different Reflection Papers written on the issue demonstrates that it is not an easy matter. At the same time, it is a very important issue for pharmaceutical companies, who often obtain a patent and MA for the racemate, and after further research decide on which enantiomer that has the best properties. Enantiomers have been subject to a decent amount of case law in patent law, and there is also some case law relating to regulatory exclusivities. If an enantiomer, which will normally be brought on the market after the racemate has already received an MA (and has elicited a GMA) can be categorised as a new active substance, it will generate its own new GMA and accompanying regulatory exclusivities. If not, then any MA for an enantiomer will be encompassed by the GMA elicited by the grant of the MA for the racemate.

The Dutch escitalopram case is a good illustration of the issues described above. In the Netherlands, the active substance escitalopram has led to a series of legal proceedings, covering the concept of GMA on the one hand, and the validity of the patent and the accompanying SPC on the other hand. For purposes of this chapter, we will focus on the GMA concept.[180]

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[176] NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation, Annex I to Chapter 2, December 2016.

[177] Most chemical compounds, when they are invented, will be in the racemate version. A racemate consists of equal amounts of spatial isomers called enantiomers, molecules that are mirror images of each other. Due to their spatial orientation, enantiomers are optically active and are characterized by whether they rotate plane-polarized light clockwise (dextrorotatory) or counter-clockwise (levorotatory). Although enantiomers and their racemates have the same chemical composition, they may differ in their physical, chemical, or biological properties.

[178] A 'racemate' is a combination of the different stereoisomers of a molecule.

[179] EMA (2012) "Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance", 18 October 2012, EMA/651649/2010 , Committee for Medicinal Products for Human Use (CHMP); EMA (2015) "Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances", EMA/CHMP/QWP/104223/2015.

[180] For a discussion of the SPC issues, we refer to the discussion earlier in this Study, supra 5.1.6.

Dutch escitalopram case

In 1989, Lundbeck obtained a marketing authorisation for the medicinal product Cipramil with the active substance citalopram in Denmark.[181] In 2001, the Swedish authorities granted a marketing authorisation for the medicinal product Lexapro, with the active substance escitalopram. In the Netherlands, a marketing authorisation was granted for the same escitalopram medicinal product on 27 April 2004.

Lundbeck is holder of the European Patent with number EP 0 347 066 B1 which covers escitalopram. On the basis of EP 066 Lundbeck was granted a SPC for escitalopram. In 2006, Alfred A. Tiefenbacher GmbH & Co KG, Hexal AG, Sandoz B.V. and Centrafarm Services B.V. filed to obtain a marketing authorisation for a medicinal product containing the active substance escitalopram.[182] The reference medicinal product referred to in the applications was Cipramil (containing the active substance citalopram). The generics manufacturers claimed that the SPC for escitalopram was invalid, as an SPC had already been granted for citalopram, which they considered the same product and, according to Art. 3(c) SPC Regulation, no second SPC could be granted for the same product. The generics companies thus argued in this connection that the concept of new chemical substance has a different meaning than the concept of novelty in patent law. That is, a product can be new in accordance with patent law (as a patent had been granted), but can, at the same time, be considered as not being a "new active substance" for regulatory purposes. As the argument was that escitalopram was not a new active substance (which argument has been overruled by the State Council[183]), the companies held that to determine whether the active substance was the same (as citalopram had already been subject to a SPC) for purposes of SPC protection, the concept derived from regulatory law had to be used. However, the Court of Appeal did not agree with this reasoning. It found that, as SPC protection is an extension of patent protection, concepts of patent law need to be invoked for determining whether the product is the same. As it was held that escitalopram was from a patent point of view novel over citalopram, there was no reason to assume that escitalopram would be the same product as citalopram for SPC purposes. Consequently, as no SPC had yet been granted for escitalopram, an active substance novel over citalopram, the requirements of Art. 3(c) SPC Regulation had been fulfilled.

According to parties involved in the actual litigation of the case, the case highlights the following two issues. First, it proves how challenging it is for high courts to decide on matters that deal with both regulatory issues and patent issues. Patent courts may find it difficult to gauge regulatory aspects, while courts with regulatory specialist know-how may find themselves in the opposite position. In the escitalopram case, the Dutch Medicines Evaluation Board concluded that, due to the similarities between escitalopram and citalopram, escitalopram would fall under the much earlier global market authorisation of citalopram. That would have meant that no meaningful SPC protection would have been possible, given the formula for calculating SPC terms. However, Lundbeck used the market authorisation of escitalopram in their SPC applications. The argument of which market authorisation to be used brought forward in the litigation led to questions of what is "new", a concept handled differently in patent law and in regulatory law.

The second issue that emerged from this case is that "...there is no incentive for an originator company to speedily apply for a market authorisation for a line-extension product like escitalopram, even if this would be possible."[184] In case of escitalopram, because of the similarities with citalopram, only limited additional research was conducted. A marketing authorisation could thus have been obtained rather quickly. Instead, the originator company reaped the full monopoly benefits of citalopram and only filed for a marketing authorisation for escitalopram late, which then gave rise to an SPC with a longer term. This behaviour is not illegal, but as stated by one interviewee, "...defies the very idea of the SPC being an instrument to compensate for effective loss of IP protection due to lengthy market approval processes."

[181] Lundbeck v College ter Beoordeling van Geneesmiddelen, Raad van State, 6 July 2011, ECLI:NL:RVS:2011:BR0506; JGR 2012/3; AB 2011/272.

[182] Under the so-called abridged procedure of Art. 10(1) Directive 2001/83. For more details on this procedure, see sub 5.3 of this Study.

[183] Lundbeck v College ter Beoordeling van Geneesmiddelen, Raad van State, 6 July 2011, ECLI:NL:RVS:2011:BR0506; JGR 2012/3; AB 2011/272. As a consequence of this judgement, escitalopram was considered to be a "new active substance" for regulatory purposes.

[184] Interview data

5.3.2.4 *Can a so-called "hybrid abridged" MA application generate a new period of data exclusivity?*

Legal issue Nr. 4 – Can a so-called "hybrid abridged" MA application generate a new period of data exclusivity?

It merits mentioning that there is also a so-called "hybrid-abridged" procedure for those medicinal products that are not generic products of the reference medicinal product, but are variants of the reference medicinal product.[185] For those medicinal products, so-called "bridging data" must be produced.

The question then arises whether an MA holder of a so-called hybrid-abridged MA can invoke data exclusivity for those bridging data, and it should be assumed that the MA for the originator product has already attained regulatory exclusivity. The scenario is then as follows: Originator product A, the reference product has obtained a MA and benefits from regulatory protection. Variant product B has received a MA by filing bridging data. Generic product C is bioequivalent to B. Does generic product C have to respect data exclusivity for product B?

The answer provided by the CJEU is that a hybrid abridged MA does not generate a separate period of data exclusivity and market protection.[186]

- **Case C-106/01 R (on the application of Novartis Pharmaceuticals UK Ltd) v The Licencing Authority established by the Medicines Act 1968 (acting by the Medicines Control Agency) and Others[187] ("Novartis")**. In 1983, Novartis obtained an MA for Sandimmum, an immuno-suppressant. Novartis subsequently developed a related product called Neoral, which was authorised in May 1994 for all the same indications as Sandimmum. Neoral was not the bioequivalent of Sandimmum, and so the application for it was made under the hybrid-abridged procedure. In January 1999, the Medicines Control Agency, the statutory predecessor of the MHRA, granted MAs to SangStat for its product, SangCya, which was the bioequivalent of Neoral. SangStat's application was under the hybrid-abridged procedure. SangStat relied on Sandimmum as the RMP and included bioequivalence data demonstrating bioequivalence between SangCya and Neoral. The MCA relied on Novartis' bridging data for Neoral in granting the authorisation to SangCya. Novartis applied for judicial review of the MCA's authorisation of SangCya; the application was dismissed, but on appeal the Court of Appeal referred questions to the ECJ. The ECJ concluded that Novartis' bridging data for Neoral could not be accorded a further period of protection beyond that protection already afforded in relation to the original product, Sandimmum, and that the competent authorities were entitled to refer to that bridging data provided in support of the application for Neoral, even if Novartis did not consent to that.
- **Case C-36/03, R (Approved Prescription Services Ltd) v Licensing Authority, acting by the Medicines and Healthcare products Regulatory Agency[188] ("APS").** In November 1988 Eli Lilly obtained an MA for Prozac capsules. It then developed Prozac liquid which was authorised in October 1992 under the hybrid-abridged procedure. In 1999, APS applied for an MA under the hybrid-abridged procedure for its own product, Fluoxetine liquid, a generic version of Prozac liquid. APS relied on the similarity between that product and Prozac liquid. The MHRA rejected the application on the basis that Prozac liquid had not been authorised for 10 years or more, and invited a revised application using Prozac capsules as the RMP, requiring APS to supply the appropriate bridging data. APS challenged that decision. The High Court referred questions to the ECJ. By the time the matter came before

[185] Art. 10(3) Directive 2001/83 says in this regard: "In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b), or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided."

[186] The summary of the two ECJ cases referred to here has been taken from the UK case R. (on the application of Napp Pharmaceuticals Ltd) v Secretary of State for Health, [2016] EWHC 1982 (Admin).

[187] Case C-106/01 R (on the application of Novartis Pharmaceuticals UK Ltd) v The Licencing Authority established by the Medicines Act 1968 (acting by the Medicines Control Agency) and Others [2004] CMLR 26.

[188] Case C-36/03, R (Approved Prescription Services Ltd) v Licensing Authority, acting by the Medicines and Healthcare products Regulatory Agency [2004] ECR I-11606 judgment, 9 December 2004.

the ECJ, Novartis had been decided. The Court concluded that an application for an MA for Product C (Fluoxetine liquid) could proceed under the hybrid-abridged procedure on the basis of similarity with Product B (Prozac liquid), where Product B was a new pharmaceutical form of Product A (Prozac capsules) and Product A had been authorised in the EU for the relevant period (at that stage, of six or ten years).

- In the **Napp case**, an argument was made that the two ECJ cases referred to above dealt with situations where the applicants of product A and B were the same (or at least connected companies). Napp argued that this was not the case in its specific application. The UK Court did not consider that fact to make any difference and saw no reason to refer questions to the CJEU in this respect.[189]

In line with the above, the Notice to Applicants now clarifies that "data supporting applications approved under Article 10(3) (e.g new indications, strength, route of administration, pharmaceutical form) do not benefit from periods of exclusivity, except when specifically provided for new therapeutic indications in Article 10(5)."[190]

5.3.2.5 Can a MA holder deregister a drug during or after the period of data exclusivity and bring another version of that same drug on the market immediately thereafter?

Legal issue Nr. 5 – Can a MA holder deregister a drug during or after the period of data exclusivity and bring another version of that same drug on the market immediately thereafter?

An important case to consider here, for historical perspective, is the **AstraZeneca case relating to the drug omeprazole (Losec)**.[191] Even though in this case the core legal issues were abuse of dominant position under Art. 102 TFEU (Treaty of the Functioning of the European Union),[192] the case is relevant for the present study, as the strategies used and found to be abuse of dominant position related to SPC protection and regulatory procedures.

[189] R. (on the application of Napp Pharmaceuticals Ltd) v Secretary of State for Health, [2016] EWHC 1982 (Admin), paras 43-46.

[190] NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation, Chapter 1, December 2017. Section 5.3, p.29

[191] C-457/10 P, AstraZeneca AB and AstraZeneca plc v European Commission, ECLI:EU:C:2012:770.

[192] Art. 102 TFEU states: "Any abuse by one or more undertakings of a dominant position within the internal market or in a substantial part of it shall be prohibited as incompatible with the internal market in so far as it may affect trade between Member States.

Such abuse may, in particular, consist in:

(a) directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions;

(b) limiting production, markets or technical development to the prejudice of consumers;

(c) applying dissimilar conditions to equivalent transactions with other trading parties, thereby placing them at a competitive disadvantage;

(d) making the conclusion of contracts subject to acceptance by the other parties of supplementary obligations which, by their nature or according to commercial usage, have no connection with the subject of such contracts."

The AstraZeneca Losec case

The CJEU has found AstraZeneca abusing its dominant position on account of two different types of practices. One of those was in the field of SPC protection, the other found abuse was in the area of regulatory procedures. For purposes of this Study, we will focus on the issue of abuse of regulatory procedures. The found abuse of the SPC system was a very specific case based on providing deliberately incorrect information to the respective patent offices and can be considered to be in that sense a very exceptional case indeed, as there is very little case law where such practises have been known to have been used.

More interesting for the purpose of the present chapter is the abuse of regulatory procedures, and in particular abuse of the MA approval system and its corollary rights of data exclusivity and market protection.

AstraZeneca had decided, at or even after the end of the data exclusivity period for that drug, to deregister Losec capsules from the market, and replace them with Losec MUPS tablets immediately thereafter. The effect of deregistering the drug Losec was that generics could no longer successfully file abridged MA applications. Indeed, as seen earlier in this Study, in an abridged MA application, the generic applicant will refer to the data of the reference product, provided the drug applied for is bioequivalent to the reference drug. However, if the reference product has been deregistered, the MA is no longer in place. Absent a reference product MA, there are no data to refer to, and hence no abridged MA application can be successfully filed. The only alternative to obtain a MA in such circumstances for the generic would be to produce all the data itself. The question was now whether such strategy constituted an abuse of dominant position. The CJEU ruled it did indeed constitute an abuse.

The CJEU ruled that the strategy used by AstraZeneca of withdrawing the MA for Losec capsules so as to effectively preventing generics to enter the market (by filing an abridged MA application which was now no longer possible as there were no data to refer to anymore) constituted an abuse of dominant position. In particular, the CJEU held that **"in the light of its special responsibility, an undertaking in a dominant position cannot make use of such a possibility in such a way as to prevent or render more difficult the entry of competitors on the market, unless it can, as an undertaking engaged in competition on the merits, rely on grounds relating to the defence of its legitimate interests or on objective justifications, does not constitute either an 'effective expropriation' of such a right or an obligation to grant a licence, but a straightforward restriction of the options available under European Union law."**[193] Astra Zeneca was unable to provide special grounds or an objective justification for the deregistration, apart from commercial reasons, and the CJEU held that such reasons are not enough to meet the threshold it set in the judgement.

Astra Zeneca further argued that the deregistration was carried out in full compliance with the relevant applicable statutory provision, and that strategies which did nothing more than applying the law could not constitute an abuse of dominant position. The CJEU did not agree with that stance and held that the mere fact that one complies with statutory provisions does not by itself imply that those activities cannot fall within the ambit of competition law rules: **"the illegality of abusive conduct under Article 82 EC is unrelated to its compliance or non-compliance with other legal rules and, in the majority of cases, abuses of dominant positions consist of behaviour which is otherwise lawful under branches of law other than competition law."**[194]

Moreover, Astra Zeneca argued that their strategy did not exclude generic companies from obtaining a MA by producing data themselves. The CJEU held that this did not make the strategy less an abuse of a dominant position: **"the fact that the regulatory framework offers alternative means, which are longer and more costly, to obtain a MA did not prevent the conduct of an**

[193] C-457/10 P, para 132.

[194] C-457/10 P, para 149.

undertaking in a dominant position from being abusive where that conduct, considered objectively, has the sole purpose of rendering the abridged procedure provided for by the legislator in point 8(a)(iii) of the third paragraph of Article 4 of Directive 65/65 unavailable and therefore of excluding the producers of generic products from the market for as long as possible and of increasing the costs incurred by them in overcoming barriers to entry to the market, thereby delaying the significant competitive pressure exerted by those products."[195]

Directive 2001/83, which went into effect in 2005, addressed the issue by introducing the concept of the historical reference product. In Article 10(1) it is stated that the applicant can refer to a "reference medicinal product that is or *has been* authorised [...]".[196] The inclusion of the wording 'has been' makes it clear that reference can be made to a product even if this has been withdrawn. This wording has also been included in the Notice to Applicants.[197]

5.4 Orphan drug designation

5.4.1 Basic features

Orphan drugs are drugs for the treatment of rare diseases. In the European Union, a rare or orphan disease has been defined as a disease that affects no more than five in 10,000 people. [198] There are an 5,000 to 8,000 rare diseases[199], affecting some 30 million people living in the EU suffer from such a disease.[198] Because there are so few patients with a specific disease, it is normally economically not worthwhile for companies to develop respective treatments. Against this backdrop, the Orphan Drug Regulation 141/2000EC[200] has introduced an incentive system for spurring R&D efforts, mainly in the form of a stand-alone period of 10 years of market exclusivity for drugs that receive a so-called 'orphan designation'. An additional 2 years of market exclusivity can be obtained in case of a paediatric use. [201]

The rationale for the incentives required for orphan diseases is expressed in Recital 8 of Regulation 141/2000, which reads:

> *"[E]xperience in the United States of America and Japan shows that the strongest incentive for 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; data protection under Article 4(8)(a)(iii) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [OJ, English Special Edition, 1965, p. 20] is not a sufficient incentive for that purpose; Member States acting independently cannot introduce such a measure without a Community dimension as such a provision would be contradictory to Directive*

[195] C-457/10 P, para 154.

[196] DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use. Accessible via: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[197] NOTICE TO APPLICANTS VOLUME 2A Procedures for marketing authorisation, Chapter 1, December 2017. Section 5.3, p.30

[198] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp

[199] Ministry of Health, Welfare and Sports (2013): Strategy of the Netherlands in the Field of rare Diseases, https://www.government.nl/binaries/government/documents/reports/2013/01/24/strategy-of-the-netherlands-in-the-field-of-rare-diseases/strategy-of-the-netherlands-in-the-field-of-rare-diseases.pdf

[200] REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products, OJ 22.01.2000, L 18/1.

[201] Art. 37 REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 378/1, 27.12.2006.

65/65/EEC; if such measures were adopted in an uncoordinated manner by the Member States, this would create obstacles to intra-Community trade, leading to distortions of competition and running counter to the single market; market exclusivity should however be limited to the therapeutic indication for which orphan medicinal product designation has been obtained, without prejudice to existing intellectual property rights; in the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal product which could be of significant benefit to those affected by the condition."

Apart from the 10-year market exclusivity, there are also other incentives that have been made available to drugs with 'orphan designation':[202]

- Protocol assistance, where the EMA provides specific scientific advice to obtain answers, e.g. on the type of studies to be conducted to demonstrate the benefits and risks of the medication.
- Access to a centralised authorisation procedure, which *"...allows companies to make a single application to the European Medicines Agency, resulting in a single opinion and a single decision from the European Commission, valid in all EU Member States."*[203]
- Additional incentives for SMEs developing orphan drugs, such as procedural assistance from the EMA's SME office and fee reductions. [204]
- Possibilities for fee reductions – compared to the fees payable for non-orphan drugs – for regulatory activities. [205]

This study focusses solely on the 10-year market exclusivity period offered by the Orphan Drug Regulation.

A medicinal product can obtain orphan drug status only when the following conditions are fulfilled (see Art. 3(1) Regulation 141/2000):

- *"A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:*
  - a1) 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 in the [European Union] when the application is made,

    or

  - a2) that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the [European Union] and that without incentives it is unlikely that the marketing of the medicinal product in the [European Union] would generate sufficient return to justify the necessary investment,

    and

  - (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the [European Union] or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition"'

[202] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000393.jsp&mid=WC0b01ac058061f017

[203] Ibid. See also Art. 7 Regulation 141/2000.

[204] Art. 9 Regulation 141/2000.

[205] Art. 7 Regulation 141/2000.

There are thus two categories of conditions that could trigger the orphan designation. The first is based on disease prevalence (a1). In the case of the European orphan drug designation system the targeted disease concerns a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the [European Union] when the application is made. The second is based on return on investment (a2), i.e., without incentives it is unlikely that the marketing of the medicinal product in the [European Union] would generate sufficient return to justify the necessary investment. It appears that the vast majority of applications for orphan drug designation status are based on the prevalence.[206]

The standard rule for market exclusivity of 10 years is described in Art. 8(1) of the Orphan Drug Regulation, in that *"Where a marketing authorisation in respect of an orphan medicinal product is granted [...], the [European Union] 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."*

However, if the criteria of Art. 3 are no longer fulfilled, the period of 10 years can be reduced. Art. 8(2) states: "*This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5.*" This should be interpreted to mean that if an orphan designation was granted on the basis of condition a1, any evaluation of whether the product remains eligible should be done on the basis of (a change in) the disease prevalence. Only for products that received a designation on the basis of condition a2 can the market exclusivity period be reduced, if it is found that the product has generated sufficient return on investment (and is not also eligible for orphan designation on the basis of condition a1). However, to date only one product has received a designation on the basis of criterion a2. Therefore, derogation of the market exclusivity due to profitability of a product is unlikely to occur in practice.

Market exclusivity is thus linked to the maintenance of the orphan designation when the medicine receives an MA for the indication concerned. The COMP[207] reviews the maintenance of orphan designation based on the data available at the time and a report on the maintenance of the designation criteria, which the sponsor supplies at the same time as the application for MA.[208]

When the period of market exclusivity for an indication ends, the orphan designation for that indication expires and is removed from the Community Register of Orphan Medicinal Products. Once all of the orphan designations associated with an approved medicine have expired or have been withdrawn by the sponsor, the medicine ceases to be classified as an orphan medicine and no longer benefits from the orphan incentives.[209]

The standard rule relating to market exclusivity states that no other MA application will be accepted during the market exclusivity period. That rule has, however, important exceptions. These are laid down in Art. 8(3), which stipulates that it is possible that a second MA is granted for a similar medicinal product and the same therapeutic indication despite the existing market exclusivity for the first drug for that medical indication, in three circumstances:

1. When the holder of the first (or original) MA has given his consent, or

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[206] Alain Denis, Lut Mergaert, Christel Fostier, Irina Cleemput and Steven Simoens, Issues Surrounding Orphan Disease and Orphan Drug Policies in Europe, Appl Health Econ Health Policy 2010; 8 (5): (343-350) 345.

[207] The Committee for Orphan Medicinal Products. The COMP is responsible for evaluating applications for orphan designation.

[208] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000392.jsp&mid=WC0b01ac058061f019 (last visited 13 January 2018)

[209] Ibid.

2. When the first/original MA holder is unable to provide the medicinal product in sufficient quantities, or
3. When the second MA applicant can establish that the second medicinal product, even though it is similar to the first medicinal product already authorised, is safer, more effective or otherwise clinically superior.[210]

The question then arises what is meant by "similar medicinal product". That is defined as "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."[211]

A "similar active substance" means then "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." It can include isomers, mixture of isomers, complexes, esters, salts and non-covalent derivatives of the original active substance."[212]

"Clinically superior" means that "a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways: (1) greater efficacy than an authorised orphan medicinal product; or (2) greater safety in a substantial portion of the target population(s). In some cases direct comparative clinical trials will be necessary; or (3) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care."[213]

5.4.2 How the system works

In Europe, orphan medicinal products (OMPs) are designated by the European Commission on receipt of a positive opinion from the selected regulatory body – the Committee for Orphan Medicinal Products (COMP) – via a process commonly known as orphan drug designation (ODD). ODD can be granted at any stage in the medicine's development. Opinions for designations are based on the following criteria:[214]

- The rarity of the condition (affecting no more than five in 10,000 people in the EU) or evidence of insufficient return in investment
- Seriousness of the disease/condition
- The existence of alternative methods of prevention, diagnosis or treatment (the EU stipulates that this should be a novel form of therapy for the condition; however, if there is an existing form of therapy, the orphan product must be of significant benefit to the patients and must have an advantage over existing therapies).[215]

The procedure relating to orphan medicinal products consists of two separate phases:[216]

1. Designation – this can take place at any stage of development prior to the submission of a marketing authorisation application, provided that the sponsor can establish that the criteria in

[210] For further procedural details on the application of Art. 8(3) Regulation 141/2000, see Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity, OJ, 23/09/2008, C 242/12.

[211] Art. 3 Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority', OJ 28.04.2000, L 103/5.

[212] Ibidem.

[213] Ibidem.

[214] See Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'.

[215] See for this, Rapulu Ogbah, Orphan medicinal products – A European process overview, Regulatory Rapporteur – Vol 12, No 2, February 2015, 5-11, at 5.

[216] Case T-74/08, Now Pharm AG v European Commission, ECLI: EU:T:2010:376, paragraph 33.

Article 3 of the Regulation are met. Designation has no effect on parallel developments by different sponsors. It is a tool to identify candidate products in a transparent way and to make them eligible for financial incentives. Designation will be confirmed by a separate Commission decision for each candidate product and the designated product will be entered in the Community Register for Orphan Medicinal Products (Article 5 of the Regulation); and

2. Marketing authorisation.

Indeed, the medicinal products are under investigational review, thus positive opinions on orphan drug designations are formed only on the basis of potential activity (i.e., the product's eligibility for an MA via a positive benefit–risk balance, efficacy, good risk management plan, etc). An orphan designation does not obviate the need for a marketing authorisation. Therefore, all drugs designated as "orphans" must demonstrate satisfactory quality, safety and efficacy and undergo regulatory review before they can be granted a marketing authorisation (MA).[217]

5.4.3 Issues

The following issues are discussed among experts and in the literature

- Absent the lack of a concept akin to the global marketing authorisation, there may be a way to extend the effective periods of marketing exclusivity for similar products with ODDs by subsequently applying for orphan drug designations for similar products with at least overlapping therapeutic indications. That can lead to an accumulation of market exclusivity periods for similar medicinal products.
- While outside the immediate scope of the regulatory framework for ODDs, but somewhat linked to it, at least in the case law, there is the following issue: A second applicant who applies for an orphan drug MA by invoking one of the exceptions of Art 8(3) is unsuccessful in establishing entitlement to the exception of Art. 8(3). He has consequently to excise the orphan drug therapeutic applications from the MA which (s)he can otherwise lawfully obtain for other therapeutic applications. However, by not excising the orphan drug applications from the Summary of Product Characteristics (SmPC), it is not inconceivable that the medicinal product of that second applicant will cross-label be prescribed for orphan drug therapeutic applications.
- Some literature discusses that the orphan drug system can be used to 'artificially create' orphan drugs or orphan diseases.[218] This can happen:
  - When drugs are developed for a specific type of patient/disease (a practice called 'targeting')
  - When one disease is split into various subcategories, each of which exhibits its own characteristics (a practice called 'sub-setting').
  - Sub-setting can lead to purported 'salami-slicing', where artificial subsets of a non-orphan disease are created, with a view to qualifying as several orphan diseases.

In the context of legal issues, it is important to note that there is not much case law relating to orphan drugs designations and the accompanying market exclusivity. That is partly informed by the fact that the system is relatively new, and it always take some time before cases make it to the courts. It is likely also partly informed by the fact that there are not that many disputes to be reported.

5.4.3.1 Multiple market exclusivity periods for similar medicinal products

The Glivec case[219] (see also section 7.8) illustrates that companies seem to be willing to avail themselves of the possibility provided under Art. 8(3) Orphan Drug Regulation 141/2000 allowing a second MA applicant to enter the market for a similar medicinal product with the same therapeutic

[217] Rapulu Ogbah, Orphan medicinal products – A European process overview, Regulatory Rapporteur – Vol 12, No 2, February 2015, 5-11.

[218] It is another matter whether all of these strategies can or are effectively used in practice.

[219] C-138/15 P, Teva Pharma BV and Teva Pharmaceuticals Europe BV v European Medicines Agency (EMA), ECLI:EU:C:2016:136.

applications.[220] It also confirms that it is possible to accumulate successive periods of market exclusivity for a similar product with at least overlapping therapeutic indications.

In the Glivec case, the exception that was invoked under Article 8(3) was sub (a), i.e., that the holder of the first MA has given consent to the subsequent applicant to bring a similar product with the same therapeutic applications on the market. On 7 November 2001, the Commission granted Novartis an MA for imatinib under the commercial name Glivec for the treatment of adult patients with CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.

On 19 November 2007, the Commission adopted a decision authorising Novartis (and with the consent of Novartis as the holder of the MA for Glivec) the marketing of Tasigna for the treatment of adult patients with CML in chronic phase and accelerated phase, with resistance or intolerance to prior treatment involving Glivec.

On 5 January 2012, Teva Pharmaceuticals Europe BV applied on behalf of Teva Pharma BV for authorisation to place on the market a generic version of Glivec. That application referred, inter alia, to certain CML therapeutic indications covered by the marketing authorisation granted for Tasigna. The MA application was refused, as there was still market exclusivity for Tasigna, which Teva contested in court.

The Glivec case presents an important issue, which is related to the fact that, under the orphan drug regime, a second MA with at least overlapping therapeutic indications, for which an earlier MA under the orphan drug regime has already been granted (eliciting a 10 year orphan drug market exclusivity) can trigger a new period of 10 years market exclusivity. Under the orphan drug system, there is no such thing as a global MA, as exists under the traditional system of data exclusivity and market protection, as will be discussed in section 5.3. The CJEU in the Glivec case confirmed that a second MA for a similar product with the same indication triggers a separate period of exclusivity: ***"None of the provisions referred to above expressly provides that a marketing authorisation granted on the basis of Article 8(3) of Regulation No 141/2000 is to be denied the benefit of the ten-year period of exclusivity provided for in Article 8(1) of the regulation. The General Court was therefore entitled to state, in paragraph 73 of the judgment under appeal, that there is nothing in that provision concerning whether the authorisation referred to in Article 8(3) of the regulation confers market exclusivity on a similar medicinal product and, in paragraph 78 of the judgment, that there is nothing in the regulation to suggest that application of Article 8(3) precludes the application of Article 8(1)."***[221]

That can present particular problems for generic companies who want to enter the market. Strictly speaking, any generic could enter the market once the period of market exclusivity for the first MA has expired. However, if there are overlapping therapeutic indications between the first MA for which the market exclusivity has now lapsed and the second MA for which there is still orphan drug market exclusivity, the generics company will find itself in a situation that in effect it cannot enter the market until the last market exclusivity covering the therapeutic indications the generic company wishes to bring the medicinal product on the market for has lapsed. That can be 20 years or even more, if there would be an entire string of such subsequent MAs with overlapping therapeutic indications, and provided they all fall within one of the exceptions of Art. 8(3) Regulation 141/2000.

One can question whether that is a desirable effect of the orphan drug system, as it fundamentally allows companies to accumulate market exclusivity periods for similar drugs with identical therapeutic

[220] As said earlier, Art. 8(3) Orphan Drug Regulation stipulates that it is possible that a second MA is granted for a similar medicinal product and the same therapeutic indication despite the existing market exclusivity for the first drug for that medical indication, in three different circumstances, basically being 1) consent from the first/original MA holder, 2) first/original MA holder is not capable of supplying the drug in sufficient quantities, or 3) that the second MA applicant can provide that the medicinal product he wishes to bring on the market is safer, more effective or otherwise clinically superior to the medicinal product of the first/original MA holder.

[221] C-138/15 P, para 30.

indications as the first authorised product. The concept of "global marketing authorisation" was, amongst others, devised with a view to avoid this kind of practices, i.e., that pharmaceutical companies would be able to circumvent the limited maximum period of data exclusivity and market protection by effectively starting the clock again during the period of the exclusivity protection for a medicinal product.

The practice allowed in the orphan drug regulation allows to some extent "evergreening", which will de facto delay generic market entry. Questions can then also be asked about the rationale for Art. 8(3)(a) Orphan Drug Regulation. There is rationale for the other exceptions under Art. 8(3), i.e., the situation where the MA holder for the orphan drug is unable to supply the drug in sufficient quantities (Art. 8(3)(b)) and the situation where the second applicant for a MA for a similar orphan medicinal product can demonstrate that the product is safer, more effective or otherwise clinically superior (Art. 8(3)(c)). Those exceptions clearly have a public health and public interest purpose. The same cannot necessarily be said of the first exception of which Novartis availed itself. There is, nonetheless, a justification for the exception sub (a), as it may be the case that the MA holder would at some point no longer be interested in marketing the medicinal product for commercial reasons and Art. 8(3)(a) provides a remedy for a situation where there would be a risk that the drug would no longer be supplied, even though that already falls under Art. 8(3) sub (b).

The Glivec case illustrates the risks attached to the exception of Art. 8(3)(a). Even if the orphan exclusivity for the reference product's sole indication would have expired, the exclusivity remaining for the second similar product for the same indication would prevent any generic company from entering the market with the first product which is no longer under market exclusivity until the expiry of the orphan exclusivity of the second product, as the therapeutic indication which was already protected under the reference product market exclusivity, is still protected under the AM for the second product. Excision of exclusivity protected information from the label would not be possible as it could in some cases be the only approved indication.

One might consider to review the orphan drug regulation in light of the above. In that regard, various avenues could be taken. One could contemplate to delete the exception under Art. 8(3)(a), as its rationale is not very clear and the risk for less than desirable use is not purely a theoretical matter. As stated previously, the other exceptions under Art. 8(3) seem to have a more straightforward rationale. Another avenue could be to introduce a concept akin to the global MA into the orphan drug regulatory system. That would ensure that generic entry is not delayed. However, the orphan drug system is a very delicate system, as it not the natural habitat for pharmaceutical companies who hope to develop and market medicinal products which have a larger patient base and consequently also a higher investment recoup and profit potential. The orphan drug system and the incentives laid down therein must make the difficult balance between ensuring that there is adequate provision of medicinal products for orphan drugs, whilst on the other hand incentivising commercial enterprises to embark on R&D and commercialisation of drugs which are not necessarily very profitable in view of their very limited patient base.

There is another angle to the Glivec case that deserves attention, and which has been litigated in, at least, The Netherlands. Novartis had MAs for two similar medicinal products, i.e., Glivec (imatinib) and Tasigna (nilotimib), with overlapping therapeutic applications. For Glivec, Novartis had also performed a PIP and had shown interest in obtaining a paediatric SPC extension for its SPC obtained for Glivec (imatinib). As described previously, paediatric SPC extensions are not possible for orphan drugs under the Paediatric Regulation.[222] What is possible is that an additional two years market exclusivity could be obtained for paediatric use.[223] However, a paediatric SPC extension would be possible if the MA holder would deregister its medicinal product as an orphan drug and have it removed from the Orphan Drug Register. That is what Novartis did, which allowed them subsequently to file for an SPC extension and benefit from the six months additional protection under the SPC

[222] See Art.36 Regulation 1901/2006 (Paediatric Regulation).

[223] See Art. 37 Regulation 1901/2006 (Paediatric Regulation).

system. It do that without causing much harm to its orphan drug therapeutic indications, as it had a similar drug, Tasigna, with therapeutic applications overlapping with Glivec. For Tasigna, Novartis maintained orphan drug market exclusivity, which allowed it to benefit from both systems, despite the fact that the intention of the legislature was to not allow MA holders to benefit from both systems. But as, strictly speaking, the medicinal product was not the same – albeit very similar and with overlapping therapeutic applications – the law could not prevent that strategy.

That was further confirmed by the Dutch Court in 2016.[224] In that case, Teva claimed that Novartis was not entitled to an SPC paediatric extension as the medicinal product Glivec (imatinib) had once been approved as an orphan drug, and Teva's reading of the Paediatric Regulation was that this would prevent a patent holder to claim an SPC extension later on. The Court did not agree with this reading, as there was no support for this in the text of the Regulation or in the *travaux preparatoires* that a patent holder who is for the same medicinal product also orphan drug MA holder, would not be entitled to an SPC paediatric extension if the orphan drug status was no longer applicable at the time of filing for the paediatric extension.

5.4.3.2 Not excising orphan drug applications from SmPC despite being unsuccessful as orphan drug second applicant

In the **Orphacol case**[225] a second applicant applied for an MA under orphan drug designation (for the product Kolbam) for the same active substance (cholic acid) which had already been the subject of an earlier MA under orphan designation (Orphacol). The initial MA application by the second applicant was at least partly overlapping with the first MA in the sense that some indications for which the second MA was filed were identical to those listed in the first MA. The first applicant claimed that these indications were still under market exclusivity, and that therefore no MA should have been granted to the second applicant. In a first attempt, the second applicant invoked Art. 8(3) Orphan Drug Regulation 141/2000 sub (c) claiming that its product was clinically superior to the product already on the market.[226] It was held by the Court that clinical superiority was not proven, and thus there was no ground for bringing a similar product on the market for the same therapeutic applications.

The second MA applicant subsequently excised the overlapping medical indications. However, there were still statements of the Summary of Product Characteristics (SmPC), challenged by the first MA holder, relating to the efficacy of Kolbam for all inborn errors of primary bile acid synthesis, including the Orphacol therapeutic indications. The General Court annulled the MA, as there was no justification for the necessity of the statements in both the Commission Assessment Report and the SmPC linking to Orphacol therapeutic indications, and secondly, such statements could influence off-label prescription by physicians to the effect that, in view of the statements in the Commission Assessment Report and the SmPC to that effect, they could consider Kolbam to be therapeutically effective for those therapeutic indications which were the subject of the MA for Orphacol.[227]

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[224] Novartis v Teva, District Court the Hague, 30 March 2016, ECLI:NL:RBDHA:2016:3427

[225] Case T-452/14 Laboratoires CTRS v European Commission, 11 June 2015, ECLI:EU:T:2015:373.

[226] Art. 8(3)(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"

[227] This raises a point in the context of the current policy of the CBG-MEB not to change the on-line version of the SmPC in case of a so-called carve out (i.e., the situation where a MA holder carves out certain therapeutic indications from the MA which are still under patent protection). Whether the CBG-MEB can continue to do that, invoking a public health policy for doing so, is currently the subject of litigation in the Netherlands. See Court of Appeal The Hague, CBG/MEB v Warner Lambert, 4 July 2017, ECLI:NL:GHDHA:2017:1935. It is not excluded that the CBG-MEB would follow a similar approach in a situation such as in the Orphacol case. For information, the Court of Appeal has referred a number of questions to the CJEU: "1) Must Article 11 of Directive 2001/83 1 or any other provision of European Union law be interpreted as meaning that a communication whereby the marketing authorisation applicant or holder for a generic medicine, within the meaning of Article 10 of Directive 2001/83, notifies the authority that he is not including in the Summary of Product Characteristics and the package leaflet those parts of the Summary of Product Characteristics for the reference medicine which refer to indications or dosage forms covered by the patent right of a third party, should be considered as a request to limit the marketing authorisation which must result in the marketing authorisation not applying, or no longer applying, to the patented indications or dosage forms?; 2) If the answer to question 1 is in the negative, do Articles 11 and 21(3) of Directive 2001/83 or any other provisions of EU law preclude the competent authority from making public, by means of an authorisation granted under Article 6 in conjunction with Article 10 of

The case shows a number of issues:

- First, it demonstrates that it is not easy for a second applicant to obtain an MA under orphan drug designation for the same active substance during the market exclusivity period of the first MA for that same active substance, unless it can be demonstrated that 1) it falls under one of the three exceptions of Art. 8(3), or 2) there is absolutely no overlap possible between the two MAs, not even in any of the documentation that is part of the dossier.
- Second, it demonstrates that the Court has shown itself sensitive to any potential risk of off-label use by physicians, and seems to suggest that care must be taken to ensure that nothing in the MA dossier could suggest that the same active ingredient could be used for the therapeutic indications that are the subject of an earlier MA which is still under market exclusivity protection.

Directive 2001/83, the Summary of Product Characteristics and the package leaflet, including those parts which refer to indications or dosage forms which fall under the patent rights of a third party, in a situation where the marketing authorisation applicant or holder has notified the authority that he is not including in the Summary of Product Characteristics and the package leaflet those parts of the Summary of Product Characteristics for the reference medicine which refer to indications or dosage forms covered by the patent right of a third party?: 3) Does it make any difference to the answer to question 2 that the competent authority requires the authorisation holder to include in the package leaflet which the authorisation holder must insert in the packaging of the medicine a reference to the authority's website on which the Summary of Product Characteristics is published, including the parts which refer to indications or dosage forms covered by the patent rights of a third party, whereas those parts, pursuant to Article 11 of Directive 2001/83, are not included in the package leaflet?" The case is pending under reference C-423/17.

6 Innovation impacts

This chapter looks at how each of the supplementary protections or incentives that are the focus of this study relate to innovation impacts. These impacts are discussed first from the perspective of the intent of the underlying regulation. This is followed by a consideration of demonstrated and perceived impacts against two main classes of impacts. First, the study provides an analysis of trends in the research intensity in the area associated with the focus of the regulations. Second, innovation impacts are looked at through the lens of therapeutic added value.

It should be emphasised that the analyses are all limited by the absence of a clear counterfactual scenario. First, although some of the regulations are enacted at national level (i.e. SPCs and paediatric extensions) the regulations themselves have all been introduced at the level of the European Union and pertain to all Member States. Moreover, equivalent regulations in the US predate the European ones, in the form of the Patent Term Restoration Act (equivalent of the SPC regulation), the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act (equivalents of the Paediatric Regulation), and the Orphan Drug Act (equivalent of the Orphan Drug Regulation). This concurrency means that – whilst informative – these regional comparisons cannot offer a true counterfactual. Additionally, the protections and exclusivities offered under each of these mechanisms are potentially accessible to all firms, such that the mechanisms reinforce each other.

In the absence of satisfactory concurrent (regional) comparators, one could consider the use of historic comparators by analysing data (trends) from before and after the introduction of the regulation. This too, however, presents methodological challenges. Pharmaceutical innovation takes place in a complex and dynamic environment: the pace and direction of pharmaceutical innovation is greatly influenced by factors such as economic conditions, corporate consolidation in the pharmaceutical industry, or the emergence of new scientific insights and technologies (e.g. personalised medicine, gene therapy, biotechnology, improved diagnostics). These factors will vary over time and thus introduce substantial confounding into the data.

Whilst the analyses presented in this chapter draw, where possible, on both geographic (concurrent) and historic comparisons, for the interpretation of these observations the investigators thus have made substantial use of other primary (e.g. interviews) and secondary (e.g. articles) data sources.

6.1 SPC Regulation

6.1.1 Intended innovation impacts

To better understand the relation between the SPC regulation and its possible impact on pharmaceutical innovation, it is worth revisiting the rationale for the regulation provided by the European Commission, both in the regulation itself and in its preceding proposal for it.[228,229] The arguments presented therein could be broadly classified as compensatory, incentivising and harmonising.

The compensatory argument is derived from the effective loss of patent life the pharmaceutical industry incurs as a result of the need for extensive tests and trials before a marketing authorisation is obtained, to safeguard the public's interest in effective and safe medicines. The regulation aims to extend the time during which innovator companies can recover their investments, thereby supporting the industry's capacity to continue self-funding research.

[228] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (2009). Official Journal of the European Union. Available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_469_2009/reg_469_2009_en.pdf (accessed 12 January 2018)

[229] European Commission (11 April 1990), Proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products. Brussels.

The above argument itself leads into a further argument in which the regulation is viewed as an incentive for pharmaceutical innovation. At the time of the proposal, both the US and Japan were already offering a form of compensation for effective loss of patent term. In the US this was introduced in 1984 via the Patent Term Restoration Act (also known as the Hatch-Waxman Act)[230], and in Japan a system for Patent Term Extension was introduced in 1987[231]. The lack of a similar compensation system in Europe was seen as a risk to pharmaceutical innovation in Europe, by driving companies away to "non-member countries that offer better protection and an environment more conducive to innovation". The Commission thus expressed a desire to "close some of the gap that has arisen between [the European pharmaceutical industry] and its major competitors in the international market".[232]

A third important reason underpinning the regulation was a recognition of the need to harmonise protection systems not only between Europe and other major international players, but also within the European Union. Purpose of this was to promote proper functioning of the internal market and improve European competitiveness. Whilst the SPC regulation leaves the granting of SPCs a national matter, it offers a standardisation of the duration of protection of medicinal products.

Although the proposal acknowledges that the preparation of the regulation was encouraged by requests of the pharmaceutical industry, it maintains that by incentivising continued pharmaceutical research the regulation also benefits the generic drug industry and the public interest. The Commission expresses the hope that the regulation will lead to "*a possible fall in the prices of the medicinal products covered [...] in light of the extension of the period for recuperation of investments*".

6.1.2 Observed innovation impacts

6.1.2.1 SPCs in the Netherlands

According to the BBP eRegister of the Netherlands Enterprise Agency, in the Netherlands the earliest SPC was published in 1993. Since then, up until November 2017, a total of 1,373 SPCs have been filed, of which 1,247 (91%) are pharmaceutical and 126 (9%) agrochemical. The following analyses pertain only to *pharmaceutical* SPCs.

An average of 50 SPCs have been published each year from 1993 to November 2017, ranging from a minimum of 27 in 2002 to a maximum of 110 in 2014 (Figure 10). By November 2017 there were 98 active SPCs and 124 open applications.[233] Thus far, 440 SPCs published between 1993 and 2017 had already expired because they reached the end of the term. Another 292 SPCs published are inactive because the patent is still in force. On average, about five SPCs are refused each year (Figure 11).[234] Whilst there is substantial variation in this between years, there is no clearly discernible trend. Each year, an average of between one and two SPCs that were previously granted are subsequently invalidated, either because the patent lapsed before its expiry date, the patent was revoked, or because the SPC was invalidated by a court for not meeting the requirements of the regulation. A further three to four SPCs per year are voluntarily withdrawn or renounced.

[230] https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf, accessed 11 January 2018.

[231] From: ((2013). Pharmaceutical Innovation, Competition and Patent Law: a trilateral perspective. Editors: Drexl J, Lee N. Edward Elgar Publishing, Accessed at

[232] As Footnote 229

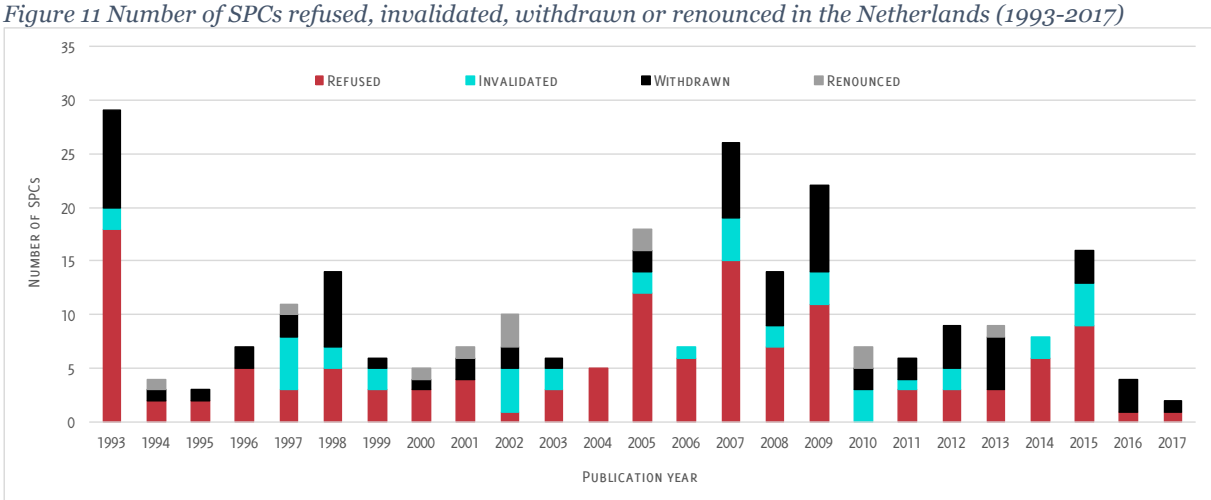
[233] Open applications include both those that have already been published in the journal of the Netherlands Enterprise Agency, and those that have not yet been published.

[234] A refusal herein means that the application was rejected by the Dutch Patent Office because the SPC application did not meet the requirements.

Figure 10 Number of SPCs published in the Netherlands between 1993 and 2017

Source: BPP eRegister. Netherlands Enterprise Agency (data extracted in November 2017)

Figure 11 Number of SPCs refused, invalidated, withdrawn or renounced in the Netherlands (1993-2017)

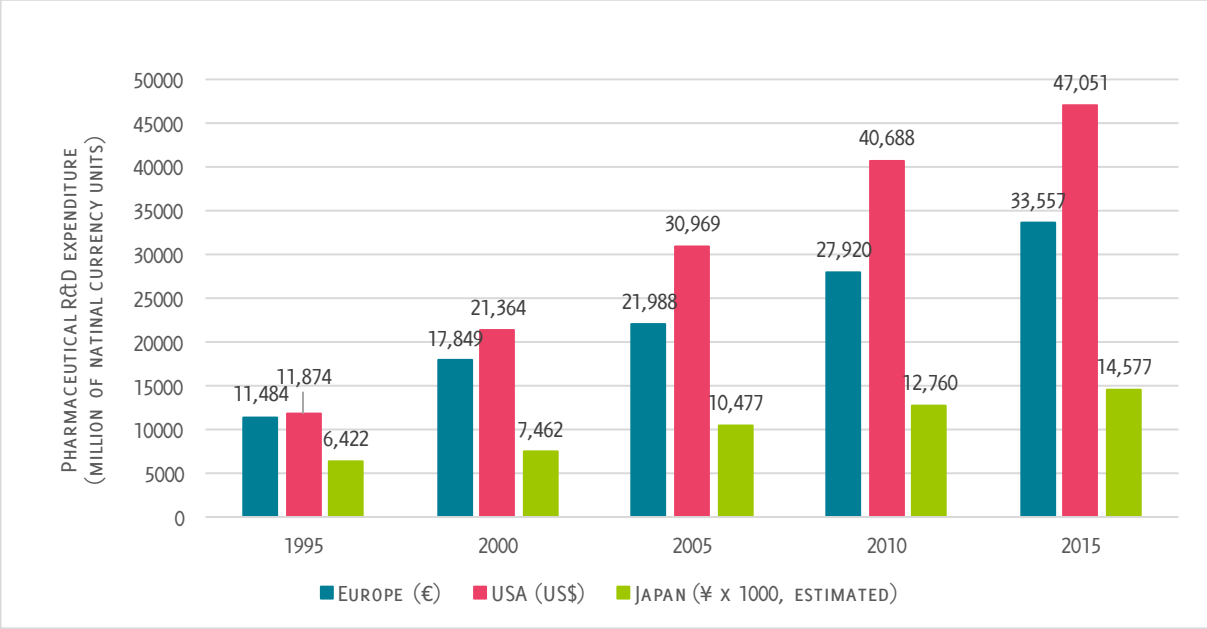


Source: BPP eRegister. Netherlands Enterprise Agency (data extracted in November 2017)

6.1.2.2 *R&D Intensity*

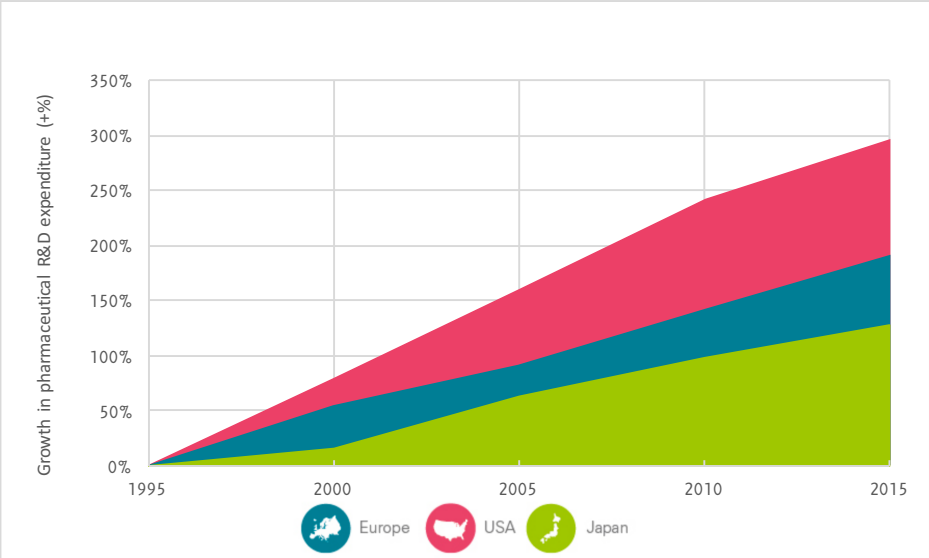
According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), between 1995 and 2015 spending on pharmaceutical R&D in Europe has nearly tripled from €11.4b in 1995 to €33.6b in 2015 (Figure 12). Whilst the rate of growth in Europe has been faster than in Japan, the gap between Europe and the USA in pharmaceutical R&D spending has widened (Figure 13).

Figure 12 Pharmaceutical R&D expenditure in Europe, the US and Japan (1995-2015)



Source: EFPIA Data Center, https://www.efpia.eu/publications/data-center/ Accessed 11 January 2018. Growth is calculated against the base year 1995 (Technopolis).

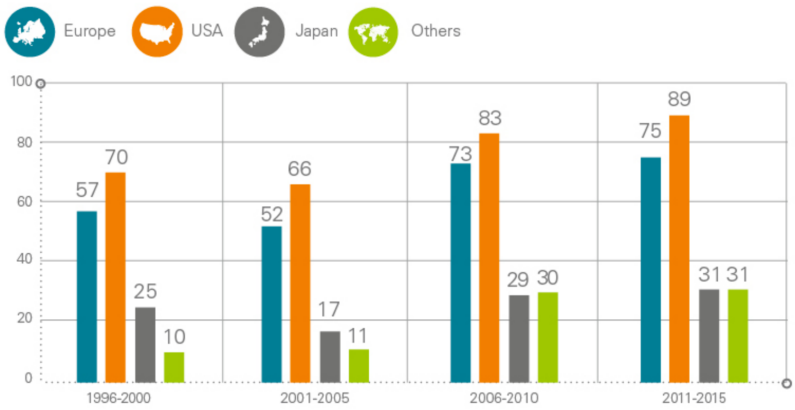
Figure 13 Growth in pharmaceutical R&D expenditure in Europe, USA and Japan, 1995-2015



Source: EFPIA Data Center, https://www.efpia.eu/publications/data-center/ Accessed 11 January 2018. Growth is calculated against the base year 1995, without inflation corrections (Technopolis).

Over the same period, the number of new chemical or biological entities according to nationality of the mother company has increased, both in Europe and in other regions. The relative increase in NCEs in Europe, however, is comparable to that in the USA and Japan (ranging from +25% to +32%), whereas a much sharper increase is seen in other areas of the world (countries not specified).

Figure 14 New chemical or biological entities by region of origin (nationality of the mother company), between 1996 and 2015.



Source: Figure reproduced from EFPIA Data Center, https://www.efpia.eu/publications/data-center/ Accessed 11 January 2018.

Although the above analyses provide no insight into factors driving pharmaceutical R&D expenditure or the successful development of new chemical or biological entities, they at least suggest that the introduction of the SPC regulation has not sufficed to close the pharmaceutical innovation gap between Europe and the USA.

Against this background, it needs to be emphasised that, whilst the SPC regulation clearly embodies an intent to promote pharmaceutical innovation in Europe, it does not contain any provisions to favour innovation originating from Europe over that from elsewhere. Rather, all pharmaceutical innovation is treated equally, regardless of the country where the applicant is based or where the R&D has been performed. Consequently, the greatest economic returns from the SPC regulation appear destined to flow towards where the greatest research and innovation intensity is. The US and Japanese equivalents of the SPC regulation, do not appear to favour national pharmaceutical innovation over foreign innovation either.[235]

In 2015, the Commission issued a communication in which it expressed its intent to consider the introduction of a targeted SPC manufacturing waiver for export purposes.[236] Rationale for this waiver is that, as long as SPC protection on the reference product is still in force in European markets, manufacturers of generics or biosimilars are not allowed to produce in EU Member States. This is said to put EU-based manufacturers at a disadvantage compared to non-EU based operators. The waiver is primarily intended to promote Europe-based manufacturing, and thereby accelerate access to generic products for European consumers, but is also hoped to have a knock-on effect on innovation by promoting increased investment in high skill jobs in Europe.

Data by the Netherlands Patent Office show that, of all SPC applications in the Netherlands between 2011 and 2016, only 46% originated from companies headquartered in Europe (Figure 15).[237] Around half were based in the USA or Japan. Although a similar analysis of all SPCs granted across Europe

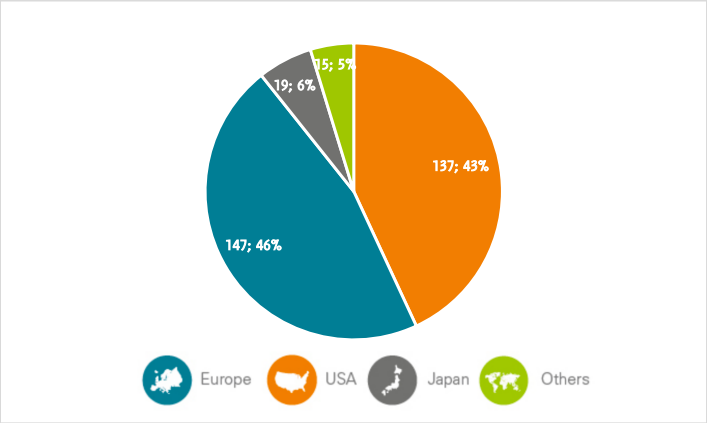
[235] US Drug Price Competition and Patent Term Restoration Act of 1984. (1984) Available at https://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf. Accessed 28 January 2018; Japan Patent Act, Article 67 Available at: http://www.japaneselawtranslation.go.jp/law/detail/?printID=&ft=1&co=01&x=32&y=19&ky=%E7%89%B9%E8%A8%B1%E6%B3%95&page=10&id=42&lvm=&re=02&vm=02 Accessed 28 January 2018.

[236] communication from the commission to the European Parliament, the Council, the European economic and social Committee and the committee of the regions (2015). COM(2015) 550 final. *Upgrading the Single Market: more opportunities for people and business*. Available at https://ec.europa.eu/transparency/regdoc/rep/1/2015/EN/1-2015-550-EN-F1-1.PDF. Accessed 28 January 2018.

[237] Europe here refers to the EU Member States and Switzerland.

was outside the scope of this study[238], it appears reasonable to assume that this pattern will not be substantially different in other countries. Within the applications originating from Europe, the majority comes from just seven countries (Germany (32), Switzerland (32), Great Britain (18), France (12), Denmark (11), Belgium (10) and Sweden (10). Although the available data do not further specify how many of the remaining 22 SPC applications originate from Dutch pharmaceutical companies, the number will be less than three percent. This is not unexpected given the comparatively small size of the pharmaceutical industry in the Netherlands.

Figure 15 Origin of SPC applicants in the Netherlands (2011-2016)



Source: de Lange M (2016), Geneesmiddelen, octrooien en aanvullende beschermingsvormen: presentation to the Ministry of VWS. Netherlands Patent Office

Although there is no direct relationship between the number of SPCs awarded and the total size of the economic reward derived from it, – as this depends on the profits derived from the products covered by the SPCs – the above analysis suggests that a very significant share of the economic reward from the SPC regulation is reaped outside of Europe and certainly outside of the Netherlands.

Despite the limited direct economic benefit to companies in the Netherlands, interviewees working within or close to the Dutch pharmaceutical and biotechnology industries generally consider SPCs a necessary mechanism to reward innovation. However, they typically tend to view the SPC regulation as a compensatory measure – providing companies a 'fair' reparation for the loss of patent term incurred – rather than as a measure designed to further incentivise innovation. Nonetheless, numerous interviewees have suggested that, without the compensation derived from the SPC regulation, the industry would not be able to bring innovations to market in the same way as it has, since the revenues resulting from the SPCs are reinvested in R&D. This claim could, however, not be substantiated with specific examples of innovation that had been enabled or promoted by the existence of the SPC regulation. In the absence of a counterfactual scenario, it also cannot be conclusively deduced whether the SPC regulation indeed has had a positive innovation impact or whether European-based companies would otherwise have relocated their R&D activities outside of Europe.

When considering what factors drive companies' decision to invest in pharmaceutical innovation, and where to locate their R&D activities, interviewees most often referred to other aspects in the broader economic and innovation climate. Several representatives of the pharmaceutical and biotechnology industries were of the opinion that, in that regard, the Netherlands is becoming less attractive for companies by the introduction of what is perceived as increasingly complex, time-consuming and

[238] Concurrent with this study, a study commissioned by the European Commission was performed entitled "study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe. " The study was awarded to Copenhagen Economics. At the time of preparation of the here presented report, the results of this study were not yet publicly available. Further details on the study are available at: https://etendering.ted.europa.eu/cft/cft-display.html?cftId=2025. Accessed 12 January 2018.

strict regulatory hurdles for obtaining market access and inclusion in the reimbursement system. Some feel that the Dutch government's attitude towards the pharmaceutical industry is one of open hostility and have gone as far as to 'threaten' to cease operations in the Netherlands.[239] In public discussion, others have suggested such statements are akin to a game of high-stakes bluff poker and referred to them as "*blackmail politics*".[240] Whilst in these debates, the role of SPCs and other (supplementary) systems to reward and incentivise pharmaceutical innovation is largely undiscussed, it stands to reason that Dutch unilateral decision-making on changes to these systems would be viewed as a further attack on the industry. Whether restrictive action at a European level would have a negative impact on the intensity of pharmaceutical innovation is impossible to predict with any great degree of certainty.

6.1.2.3 Therapeutic Value

Ideally, pharmaceutical innovation should not only be measured in terms of the numbers of new products brought to market but also by the therapeutic added value of such products. Therapeutic added value can be understood as whether a product meets a need in a previously unserved therapeutic area or whether it offers significant benefits over existing products in terms of, for instance, effectiveness, ease of use, or fewer adverse effects. In its proposal to the regulation, the Commission emphasised its desire to award only true therapeutic innovation, noting that "*a large proportion of medicinal products sold on the market have only few innovative features, or none at all. These are not covered by the scope of the proposal*."[241] However, it continues by stating that "*only 50 new medicinal products are authorised worldwide. It is these that are covered by the proposal for a Directive*". This implies that the desired standard for innovativeness is met for any product that receives a marketing authorisation.

In the interpretation of the existing SPC regulation, the aim to reward only meaningful innovation is reflected in the fact that, in principle, only one SPC can be granted per product, thus –at least in theory – excluding the possibility that SPCs are granted for minor variations of existing products that have already benefited from an SPC. However, as previously described in the legal analysis, the seemingly simple criterion of 'one product, one SPC' has since been challenged by further interpretations of what constitutes a 'product' in the legal sense. The Neurim decision in particular could pave the way for additional SPCs for (variations of) a single product. Moreover, the case law shows that SPC applicants try to stretch the scope of what products are protected by the basic patent, fundamentally broadening the realm of potential SPCs. In the same vein, patents covering multiple active substances are also used to obtain multiple SPCs covering a variety of combinations of active substances covered by those basic patents.

As there is no agreed upon definition of therapeutic added value, and one can argue that even relatively minor changes to a product may address some therapeutic need for a particular set of patients, assessing whether or not the SPC system has also unduly awarded innovation of limited therapeutic value involves a normative judgment beyond the scope of this study. Moreover, the high-level data on SPCs awarded to date in the Netherlands do not provide sufficient insight into the underlying arguments for granting the SPC. Without scrutiny of the individual product dossiers, the data cannot easily be broken down into SPCs granted for, for instance, combination products or derivative products.[242] Nonetheless, even without such an analysis, it stands to reason that the SPC regulation is unlikely to counteract the known tendency in the pharmaceutical industry to gravitate

[239] Vaessen T, ten Katen M (2017). Farmabedrijf dreigt Nederland rug toe te keren. Financieel Dagblad 2 October 2017. Available at https://fd.nl/economie-politiek/1220223/farmabedrijf-dreigt-nederland-rug-toe-te-keren. Accessed 12 January 2018.

[240] https://www.tweedekamer.nl/debat_en_vergadering/commissievergaderingen/details?id=2017A02364

[241] European Commission (11 April 1990), Proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products. Brussels.

[242] The authors of this report do not suggest that combination products or derivative products have little to no therapeutic added value. This judgment deserves to be made on a case-by-case basis and is best left to those with in-depth understanding of the product characteristics and its therapeutic benefits.

towards safer, marginal innovations rather than pursue risky, break-through innovation.[243] Rather, with the expanding scope of what can be covered by an SPC, the regulation is more likely to have an amplifying impact on this.

Many interviewees – save for those working in legal affairs – appeared largely unaware of the complexities and evolving legal interpretations of the SPC regulation. The prevailing assumption amongst them is that the granting of a patent and, at a later stage, the marketing authorisation is itself evidence of therapeutic value and inventiveness and that this should therefore justify the award of an SPC. Notable exceptions to this perception are mainly found among those working on issues to advocate for access to medicines, who maintain that SPCs granted on derivative products confer little to no therapeutic benefit and merely represent 'evergreening' strategies.[244] They therefore argue that such SPCs run counter to the intent of the regulation (which itself is contested too). The argument that some combination products do not offer a sufficient inventive advance to merit SPC protection has been upheld by the courts in, for instance, the case of the HIV drug Atripla (discussed in Section 7.6). Nonetheless, the issue has not been conclusively resolved and interpretations of what should be considered as inventive may vary between countries.

The legal analysis has revealed a growing complexity of the SPC system. Seemingly simple concepts turn out to be more complex due to the need to define key terms more thoroughly, due to needs to "marry" regulatory and IP aspects in a well-conceived manner and, – because of the combination of regulatory and IP elements – of the relationship between patents and medicinal products. There are economic and likely also innovation impacts arising: On the one hand, this growing complexity calls for yet further specialisation in a field where there are already few knowledgable experts. On the other hand, the move from seemingly simple to more complex creates additional workload for SPC/patent examiners. These may need now to look at the extent of protection of a basic patent and/or may be confronted in the future with more SPC filings following the Neurim ruling. The increased work-load will entail – absent reforms that simplify the system again – that the patent office be properly resourced; the risk is also that examiners become more inclined to 'rubber stamp' SPCs applications for lack of resources to fully evaluate them.

6.2 Paediatric Regulation

6.2.1 Intended innovation impacts

The Paediatric Regulation was introduced in 2006 in response to a recognition that insufficient research was being conducted to develop suitably adapted medicinal products for children.[245] Drugs developed for and used in adults may not be suitable for children for a number of reasons. For instance, a drug can have different pharmacotherapeutic and pharmacokinetic properties in children, such that simple weight-adjusted dosing does not achieve the intended effect, or there may be an increased risk of adverse reactions. Also, drugs administered to children may require different formulations or routes of administration. For instance, liquid formulations may be easier to swallow for young children than tablets. It was noted that market forces had proven insufficient to stimulate the necessary research for this population group and that intervention was needed to increase the information available on the use of medicinal products in children.[246]

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[243] Munos BH, Chin WW (2011) *How to revive breakthrough innovation in the pharmaceutical industry*. Science Translational Medicine 3(89):89. Doi: 10.1126/scitranslmed.3002273

[244] MSF Access Campaign and European Alliance for Responsible R&D and Affordable Medicines (2017). Open submission on supplementary protection certificates for medicinal products in the European Union. 8 September 2017, Brussels.

[245] EC (2006) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Available at https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf Accessed 14 January 2018.

[246] The paediatric population itself is not homogeneously defined. Different studies may be required in different sub-groups (by age) of this population.

The Paediatric Regulation is based on a system of both obligations and rewards and incentives.[247] It makes it compulsory for drug developers who intend to seek marketing authorisation for their products to submit a Paediatric Investigation Plan (PIP) that specifies "details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population" via high-quality and ethical research. The PIP should be submitted early in the development of the product, such that the necessary studies do not unduly delay marketing authorisation for the product in other age groups. Compliance with the PIP is a condition to obtaining marketing authorisation.

As not all drugs require paediatric investigation, for instance because the indication does not affect this age group, and to avoid unnecessary trials in children, the regulation provides drug developers the option to request a waiver. A waiver can be granted for specific medicinal products or for classes of medicinal products, if there is evidence showing any of the following:

- That the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population
- That the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations
- That the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The assessment of submitted PIPs or requests for waivers (or deferrals, allowing applicants to delay implementation of investigations) is done by the EMA's Paediatric Committee (PDCO).

In exchange for compliance with the PIP, presenting the relevant information of the conducted studies in the product information, and if a product is authorised in all Member States (through the centralised procedure), the marketing authorisation holder receives a reward in the form a six month extension of the SPC. For registered orphan medicinal products a different reward applies: these may receive an extension of the period of market exclusivity by two further years. Companies that fail to comply with the regulation can be financially penalised.

Whilst the underlying intention of the regulation is to increase the number of authorised products with a paediatric indication or of products that have been adapted for paediatric use, the reward itself is not contingent on the nature of the outcomes of the studies. The regulation explicitly states that "because the reward is for *conducting studies* in the paediatric population and not for demonstrating that a product is safe and effective in the paediatric population, the reward should be granted even when a paediatric indication is not authorised".[248]

[247] Ibid

[248] Ibid

6.2.2 Observed innovation impacts

6.2.2.1 R&D Intensity

Annual reporting by the EMA shows that approximately 80 to 100 PIPs are filed each year, nearly all of which are granted (Table 2).[249] Alongside waivers for drugs in specific classes, around 40 to 50 product-specific waivers per year are issued.

Table 2 Outcomes of opinions on paediatric investigation plans and waivers

	2011	2012	2013	2014	2015
Positive opinions on PIP applications	107	87	96	91	71
Positive opinions on product-specific waivers	44	47	51	46	47

Source: EMA Paediatric Committee Annual report 2015.[249]

By the end of 2016, there had been 396 six-month paediatric extensions on an SPC granted, for 41 distinct products.[250] The extensions were granted in 24 different countries, with the distribution pattern varying substantially by drug. The largest numbers of paediatric SPC extensions were granted in Italy (37), Germany (30) and Denmark (30). In the Netherlands, 23 drugs received the extension. In addition to this, there are to-date five drugs with an orphan designation that have qualified for the additional two years of market exclusivity for having completed paediatric studies (Strimvelis, Vpriv, Soliris, Xagrid and Tobi podhaler)

6.2.2.2 Therapeutic Value

Although the main purpose of the paediatric regulation has been to incentivise and reward research to inform paediatric use of medicines, and not to result in a registration for a paediatric indication or a paediatric formulation per se, it is worth considering what impact the rewarded paediatric studies have had in this regard.

In its 10-year report to the European Commission, the Paediatric Committee reports that since the entry into force of the regulation (up to 31 December 2015), 49 new medicines with an agreed PIP in place were centrally authorised for paediatric use.[251] By 2015, nearly all paediatric indications approved in new medicines were linked to the paediatric regulation. Additionally, the regulation was linked to 64 (centralised procedure) new paediatric indications that were added to already authorised medicines, and to 13 new pharmaceutical forms for paediatric use.

A similar analysis of the Summary of Product Characteristics (SmPCs) for the products that received a paediatric extension to an SPC in the Netherlands, shows that in 10 out of 22 cases the studies did not result in a registration of the drug for use in any paediatric age group (Figure 16). In eight cases, at least one indication was added in one or more paediatric age groups. These paediatric indications were commonly accompanied by specific dosing guidelines, based on age or weight. In four cases, an age appropriate formulation was developed, such as chewable tablets or oral suspensions.

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[249] EMA Paediatric Medicines Office. (2016) Report to the European Commission on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation and on the companies that have failed to comply with any of the obligations in this regulation 2015. Accessed 14 January 2018.

[250] EMA Paediatric Medicines Office. Report to the European Commission on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation and on the companies that have failed to comply with any of the obligations in this regulation 2007-2009, 2010, 2011, 2012, 2013, 2014, 2015, 2015 and 2016. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000607.jsp&mid=WC0b01ac0580925b1c Accessed 14 January 2018.

[251] 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. Available at: https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf Accessed 14 January 2018.

Figure 16 Overview of authorised drugs with a paediatric extension to an SPC granted in the Netherlands

Year PE granted	Drug	Company	Outcome
2016	Levemir	Novo Nordisk A	Initial MA
2016	Gardasil	Sanofi Pasteur MSD	Indicated
2016	Corlentor	Les Laboratoires Servier	Initial MA
2016	Menveo	GSK	Initial MA
2015	Ezetrol	MSD	Initial MA
2015	Tracleer	Actelion Registration Ltd	Initial MA
2015	Travatan	Alcon Laboratories	Initial MA
2015	Tygacil	Pfizer	Indicated
2015	Crestor	AstraZeneca	Initial MA
2015	Humira	AbbVie	Indicated
2014	Glivec	Novartis	Indicated
2014[252]	Spiriva	Boehringer Ingelheim	Initial MA
2014	Vfend	Pfizer	Indicated
2014	Rupafin	Uriach y Compañia	Age appropriate formulation (oral solution)
2013	Samsca	Otsuka	Initial MA
2012	Enbrel	Pfizer	Indicated
2012	Remicade	Janssen	Indicated
2012	Viramune	Boehringer Ingelheim	Age appropriate formulation (oral suspension)
2012	Maxalt	MSD	Initial MA
2011	Xalatan	Pfizer	Indicated
2011	Singulair	MSD	Age appropriate formulation (chewable tablets, oral granules)
2010	Lipitor	Pfizer	Age appropriate formulation (oral)

Source: Data on product and company that received a paediatric extensions by year were obtained from the EMA Annual reporting on the paediatric regulation for the years 2007 through 2016.[253] Information on the outcome was extracted from the SmPCs available via the EMA or CBG-MEB.

Whilst the above shows that since the introduction of the paediatric regulation a number of products have been indicated for paediatric use or are available in adapted formulations, most of the applications granted are in therapeutic areas where there is a significant adult indication, and that may be of relatively limited relevance to children. Although there are variations between products, the paediatric use forms only a relatively modest percentage of all use. Moreover, drugs such as Lipitor, Enbrel, Crestor, Remicade, Singulair and Humira are all blockbusters with enormous sales.[254] This has

[252] In the EMA PMCO annual reporting, Spiriva has been listed as having received a paediatric extension in the Netherlands both in 2013 and in 2014. Data by the Netherlands Patent Office indicate that 2014 is the correct year.

[253] EMA Paediatric Medicines Office. Report to the European Commission on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation and on the companies that have failed to comply with any of the obligations in this regulation 2007-2009, 2010, 2011, 2012, 2013, 2014, 2015, 2015 and 2016. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000607.jsp&mid=WC0b01ac0580925b1c Accessed 14 January 2018.

[254] King S (2013) The best selling drugs of all time; Humira joins the elite. Forbes Pharma & Healthcare. Jan 28. Available at https://www.forbes.com/sites/simonking/2013/01/28/the-best-selling-drugs-of-all-time-humira-joins-the-elite/#4c930dfe5110. Accessed 14 January 2018

caused some to question whether for such drugs the reward offered by the paediatric extension is appropriately commensurate to the costs the company has had to incur to conduct the necessary studies. Whilst the total costs of developing and executing costs will vary greatly, a recent study led by Technopolis estimated the average incurred costs per PIP[255] at €19.6m, of which €18.9m were related to R&D costs. For high grossing drugs, the reward will thus far outweigh the costs incurred. By contrast, for less profitable drugs, it is possible that the reward does not even fully compensate.[256]

None of the drugs that received a paediatric extension to an SPC were developed for a paediatric-only condition. This suggests that the regulation has thus far not resulted in significant increased interest in conducting research in paediatric conditions. In its 10-year report the Paediatric Committee has also noted that "*the regulation links the adult indication to the obligation to have a paediatric investigation plan; therefore, matching the adult condition with the one in children is a determinant factor*."[251] The report also notes that especially in neonates, studies are often deferred and that there is a need to address the issue of unmet clinical need in young children. However, as the regulation has been in effect for 10 years – shorter than the average product development cycle –, the full extent of this (lack of) effect remains to be seen.

In addition to an increased number of drugs with a registered indication for paediatric use or an adapted formulation, some interviewees have indicated that the regulation has contributed to greater awareness about the specific issues for paediatric drug use.

6.3 Orphan Drug Regulation

6.3.1 Intended innovation impacts

As already discussed previously, the stated objective of the regulation on orphan medicinal products (EC 141/2000) is "to provide incentives for the research, development and placing on the market of designated orphan medicinal products".[257] The regulation further specifies that:

- Objective criteria for designation should be established. Those criteria should be based on the prevalence of the condition for which diagnosis, prevention or treatment is sought. A prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold. Medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition should be eligible even when the prevalence is higher than five per 10 thousand.
- Market exclusivity should be limited to the therapeutic indication for which orphan medicinal product designation has been obtained, without prejudice to existing intellectual property rights.
- In the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal product which could be of significant benefit to those affected by the condition.

Assessment of the innovation impacts of the orphan designation should thus focus on the one hand on whether the regulation has contributed to the research, development and market entry of new products in the desired priority areas but also whether it has sufficiently safeguarded the interests of patients by not unduly preventing the marketing of other important products for this group of patients.

Whether a compound under development merits designation as an orphan drug is decided by a group of experts and stakeholders from the Member States, represented in the Committee for Orphan

[255] Based on an average of 107 first PIP decisions per year for the period 2008-2015.

[256] Technopolis Group, Ecorys Nederland, empirica (2016) Study on the economic impact of the Paediatric Regulation, including its rewards and incentives Final Report, SANTE/2015/D5/023. https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/paediatrics_10_years_economic_study.pdf

[257] The European Parliament and Council of the European Union (1999). Regulation (EC) No. 141/2000 of the European Parliament and of the Council on orphan medicinal products. Official Journal of the European Communities. 16 December 1999, Brussels

Medicinal Products (COMP) of the EMA. An opinion on the orphan drug designation can be granted by the COMP at any time during the development phase of the product provided the product has not yet received marketing authorisation. The designation needs to be confirmed prior to marketing authorisation before it can receive the market exclusivity reward. Whether a drug is eligible thus is assessed at two main steps in the regulatory lifecycle: at orphan designation (OD) and again at marketing authorisation.[258]

As the orphan designation is awarded at the European Community level and the market exclusivity derived from it does not only apply nationally, our analysis has focused on the European level.

6.3.2 Observed innovation impacts

6.3.2.1 R&D Intensity

Since the regulation for orphan drugs came into effect in 2000, the number of applications submitted to the COMP has risen sharply (Figure 17). Whereas in the first nine years after the introduction, never more than 125 applications per year were received, in recent years in excess of 200 applications are received annually. Between 2014 and 2016 the number of applications peaked. This has been attributed to a Horizon2020 call that provided funding for Phase I/II clinical trials on a therapy for a rare disease for which an orphan designation had been obtained.[259] By late 2017 a total of nearly 3,000 applications had been received. Of these, 1,943 were granted a preliminary orphan drug designation.

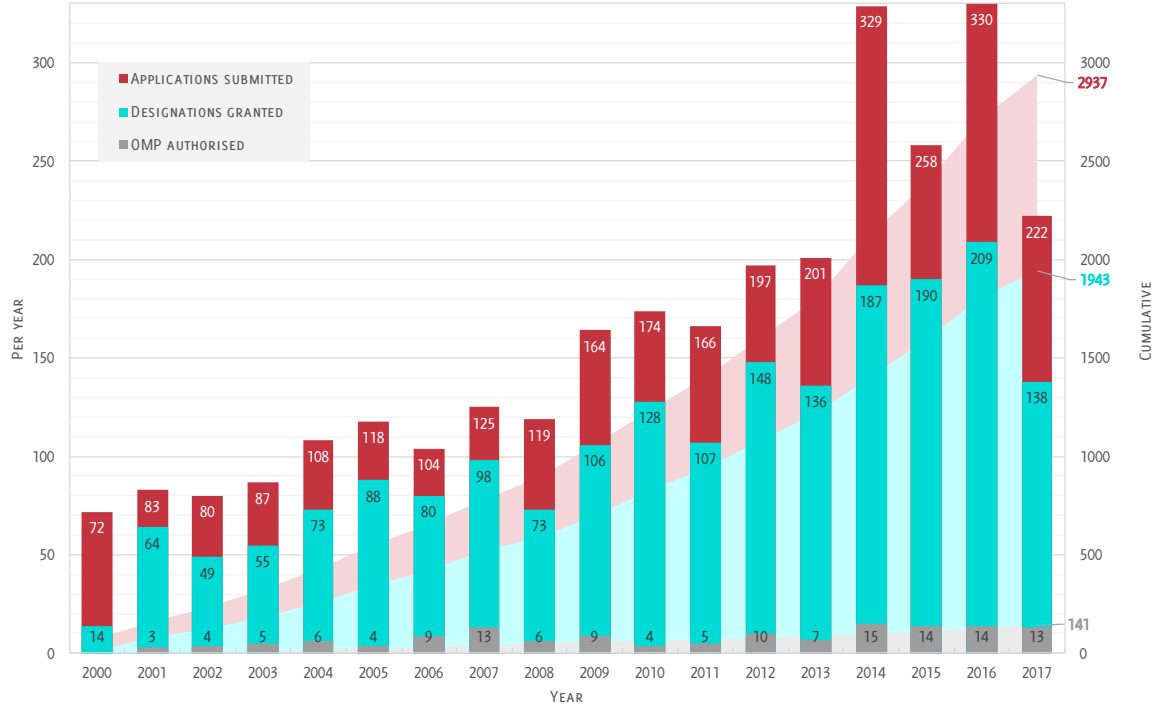
As of late 2017, the COMP had issued just 24 negative opinions on applications (data not shown). This has led some to suggest that the COMP is insufficiently critical of applications and effectively approves all applications. However, in cases where it is likely to offer a negative opinion, companies are informed of this beforehand which enables them to withdraw their applications from consideration.[260] To avoid potential negative press coverage that might be derived from receiving a negative opinion, companies commonly opt to withdraw their application rather than await the COMP's formal decision.

[258] Fregonese L, Greene L, Hofer M et al. (2017) Demonstrating significant benefit of orphan medicines: analysis of 15 years of experience in Europe. Drug Discovery Today. http:// dx.doi.org/10.1016/j.drudis.2017.09.010.

[259] European Commission DG Research & Innovation (2015). New therapies for rare diseases. http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/sc1-pm-08-2017.html Accessed 12 January 2018.

[260] Interview data

Figure 17 Applications, designations and authorisations for orphan medicinal products (2000-2017)



Source: EMA/COMP/685336/2017. Committee for Orphan Medicinal Products (COMP) meeting report on the review of applications for orphan designation 30-31 October 2017

It is difficult to estimate to what degree the observed increase in applications for orphan drug designations reflects an actual increased research intensity in this area. Whilst a degree of impact seems fair to assume, the increase may simultaneously reflect an increased awareness among parties, such as academic research groups and pharmaceutical start-ups, of the regulation and increased capacity to prepare an application.

For funding of basic research, most commonly conducted in academia, other mechanisms for stimulating research in the area of orphan and rare diseases are likely to have had a substantial, if not even larger, impact. These would include both European initiatives, such as targeted calls via the EC's Research Framework Programmes, and national level initiatives. For instance, in the Netherlands academic researchers could apply for funding from the Netherlands Organisation for Health Research and Development (ZonMw) via, among others, the Priority Medicines for Rare Diseases and Orphan Drugs programme.[261]

For early stage clinical development, the catalysing effect on R&D for orphan products is more direct. Various interviewees familiar with pharmaceutical development, particularly that done in the biotechnology sector by small and medium-sized enterprises, signal that obtainment of the orphan drug designation is a key milestone. Hitting this milestone signals the drug's potential and enables companies to attract external investment. Companies with products that receive an orphan designation tend to actively draw attention to this fact, through corporate communications and press releases. A recent study on the impact of the US equivalent, the FDA's Orphan Drug Designation, found that, on average, a company's stock price increases by 3.36% after obtaining ODD for a product.[262] This study is limited to companies that are listed on the US Stock Exchange; for unlisted

[261] ZonMW. Priority Medicines zeldzame ziekten en weesgeneesmiddelen. https://www.zonmw.nl/nl/over-zonmw/internationaal/programmas/programma-detail/priority-medicines-zeldzame-ziekten-en-weesgeneesmiddelen-rare/ Accessed 12 January 2018.

[262] Miller KL (2017). Do investors value the FDA orphan drug designation? Orphanet Journal of Rare Diseases 12:114. https://doi.org/10.1186/s13023-017-0665-6

companies, often smaller and with lower valuations, the effect is likely to be bigger. Whilst increased company valuation need not automatically translate into R&D expenditure, for SMEs with a narrow product pipeline and few or no products on the market yet, external investment usually is a prerequisite for further product development.

Although the EMA Register of designated Orphan Medicinal Products lists the sponsor for each designation, the country from which the sponsor originates is not included. Consequently, these data do not allow for a comprehensive analysis of the breakdown of orphan designations by region or country. Dutch pharmaceutical and biotechnology companies that received one or more orphan designations for products under development include, but may not be not limited to, those shown in Table 3.[263] Companies like Galapagos, UniQure and ProQR are established and publicly listed companies, whereas others are relatively young spin-off companies whose products are all still in early stages of development. Thus far, only UniQure has succeeded in bringing a product to market. However, its gene therapy drug Glybera, for the treatment of familial lipoprotein lipase deficiency, failed to become a commercial success and in 2017 the company announced it would not seek reauthorisation of its market approval in Europe.[264]

Table 3 Dutch companies with products with an orphan designation

Name of company	# orphan designations
Acerta Pharma (part of AstraZeneca)	3
AM-Pharma	1
Amphera BV	1
DCPrime	1
DualTPharma	1
Galapagos	1
ISA Therapeutics	1
Kiadis Pharma	3
Khondrion	2
Neurophyxia	1
ProQR Therapeutics	5
UniQure Biopharma	5
Xenikos	1

Alongside the increase of applications for orphan designation, the number of orphan medicinal products (OMPs) that receives a marketing authorisation has increased. Over the last four years, an average of 14 new OMPs come on the market annually. There are currently 141 orphan drugs on the market that obtained the orphan drug designation, amounting to under five percent of all applications (Figure 17).

6.3.2.2 Therapeutic Value

Therapeutic areas and unmet need

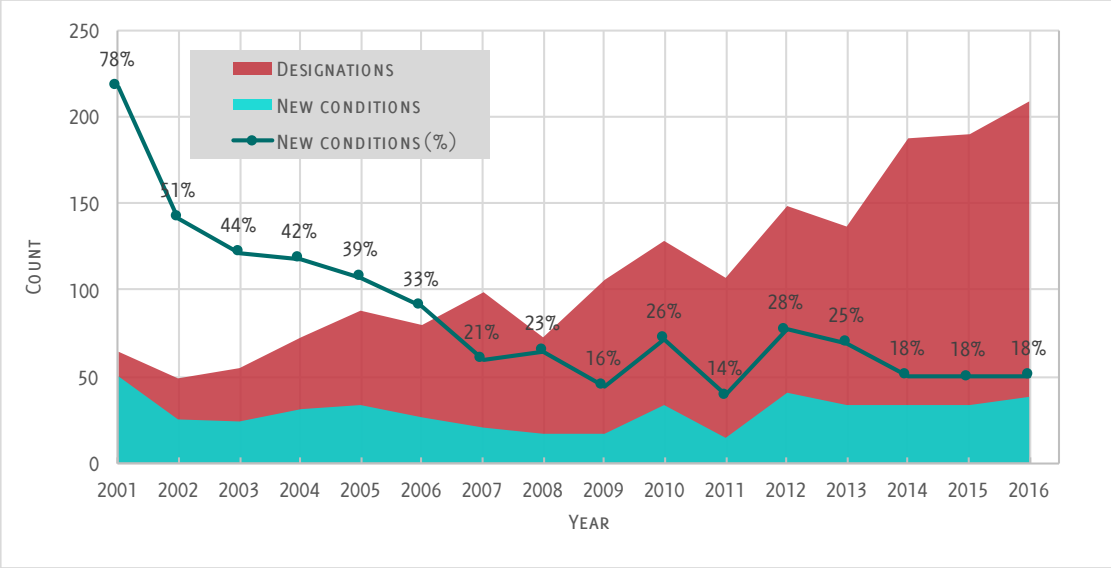
Discussions of the impact of the orphan drug regulation have often centred on the question of whether it has been effective in addressing areas of greatest unmet need. According to an analysis performed by the EMA, in the years immediately after the regulation's introduction, the number of new conditions targeted among awarded orphan designations rapidly declined (Figure 18). This is an expected and natural result, showing that over time the number of areas for which there were viable – based on pre-existing research data –, yet largely unexplored leads declined. In the last decade, this share has been

[263] Dutch herein is defined as a company that originated in the Netherlands and maintains R&D activity here.

[264] uniQure announces it will not seek marketing authorization renewal for Glybera in Europe (2017) http://uniqure.com/GL_PR_Glybera%20withdrawal_FINAL_PDF.pdf Accessed 13 January 2018.

relatively stable at around 21%, with between 15 to 41 new conditions encountered each year. This shows that, whilst the regulation continues to serve areas of unmet need, new applications have tended to cluster in certain therapeutic areas.

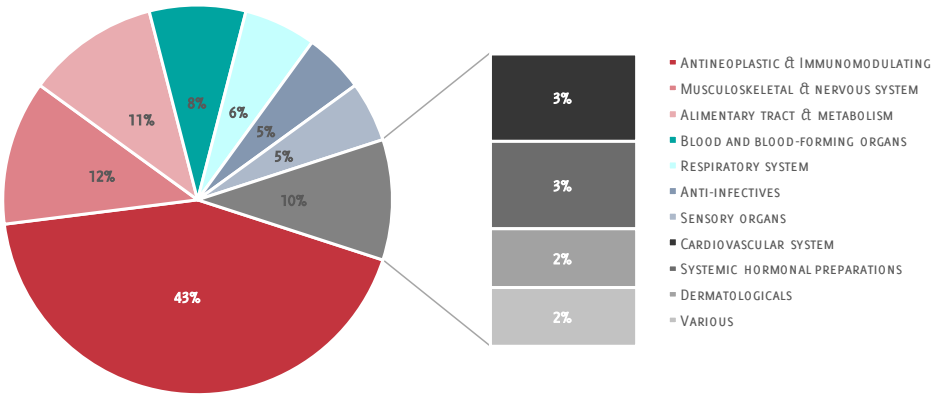
Figure 18 New conditions targets in relation to overall number of products that received orphan designation



Source: EMA. (2016). Orphan Medicine Figures 2000-2016.[265]

The EMA has itself conducted an analysis of positive COMP opinions (most of which result in an orphan designation) by therapeutic area, using the Anatomical Therapeutic Chemical (ATC) classification system (Figure 19).[266] It shows that nearly half (43%) of all positive opinions are for products that have been classified as 'antineoplastic and immunomodulating agents'. This class primarily includes anti-cancer drugs used in chemo- and immunotherapy. Among OMPs that have obtained marketing authorisation, the distribution pattern is very similar (Figure 20). Here too, 43% of all products fall into the category comprising anti-cancer drugs.

Figure 19 Classification of positive opinions by ACT code (2001-2016)

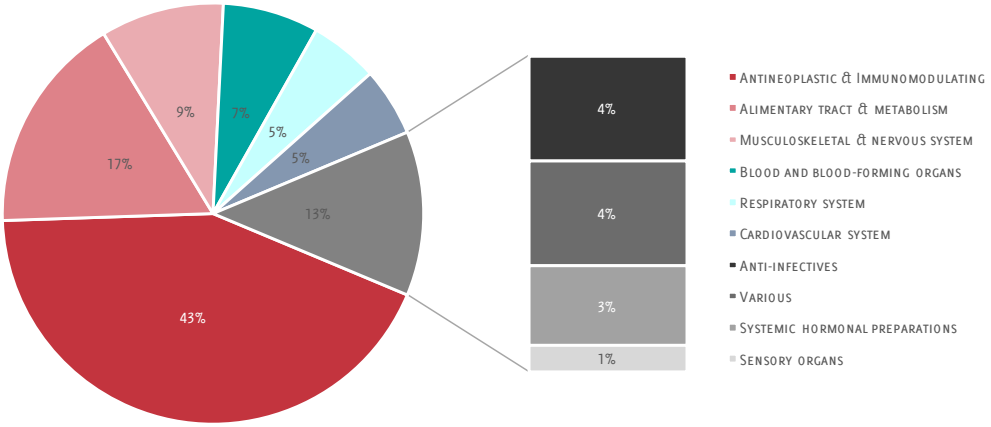


Source: EMA. (2016). Orphan Medicine Figures 2000-2016.[265]

[265] Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf Accessed 12 January 2018.

[266] https://en.wikipedia.org/wiki/Anatomical_Therapeutic_Chemical_Classification_System. Accessed 12 January 2018.

Figure 20 Classification of authorised OMPs by ATC code, excluding extensions of indications (2001-2015)



Source: EMA. (2016). Orphan Medicine Figures 2000-2016.[265]

The demonstrated clustering around oncological indications has caused some to question whether the regulation is sufficiently encouraging drug development in other areas. Indeed, for the vast majority of orphan and ultra-rare diseases there remain at present no drugs in clinical development, assuming that for such drugs an orphan designation would have been sought. A possible explanation for this is that for many such diseases the basic disease mechanisms are not yet sufficiently understood, thus offering no promising starting points for drug development.

Unlike under the US Orphan Drug Act, for a drug to receive an orphan designation in Europe, it must demonstrate 'significant benefit' over existing courses of treatment. This includes both pharmacological and non-pharmacological treatments (e.g. surgery). Significant benefit can include, for instance, greater effectiveness in population sub-sets, better clinical efficacy overall, or a better safety profile. A recent paper by Fregonese et al. also observed that, among 147 authorised OMPs, only 27% did not need to demonstrate significant benefit because they targeted diseases for which there were no alternative treatment options.[267] This too suggests that there are large areas in the orphan disease space that remain virtually untouched, either for lack of basic research or because the incentives are insufficient to encourage activity by the commercial sector.

Nonetheless, EMA data indicate that 40% of all orphan designations are for conditions with a prevalence of less than 1 in 10,000.[265] This highlights that, whilst clearly there remains a substantial unmet need, the regulation has in fact succeeded in targeting drug development for some of the rarest diseases.

Paediatric orphan drugs

The orphan drug regulation is not specifically intended to increase paediatric drug development and contains no obligation for the development of drugs for a paediatric population. Nonetheless, around two-thirds of rare diseases occur in children. It is therefore relevant to consider to what degree the regulation has helped address the needs of this particular population group. Analysis by the EMA shows that over half of all orphan designations granted have been for drugs targeting diseases that occur both in children and adults (53%), followed by designations for adult use only (34%), and a smaller number of designations exclusively focused on conditions affecting only children (13%)(Figure 21). There is no discernible trend over time in the period 2000 to 2016.

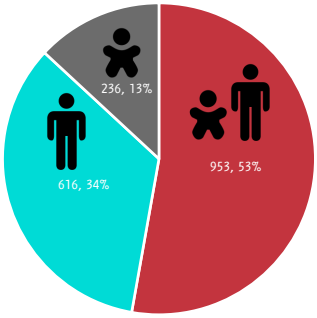
A recent study by Vassal et al. (2017) evaluated the impact of the regulation on the development of oncological drugs for children and adolescents with cancer.[268] It found that only eight out of 26

[267] Fregonese L, Greene L, Hofer M et al. (2018) *Demonstrating significant benefit of orphan medicines: analysis of 15 years of experience in Europe*. Drug Discovery Today 23(1): 90-100

[268] Vassal G, Kearns P, Blanc P et al. (2017) *Orphan Drug Regulation: A missed opportunity for children and adolescents with cancer*. European Journal of Cancer 84:149-158.

oncological OMPs developed for the treatment of a condition occurring both in children and in adults had a recommendation for paediatric use in their first European MA. This shows that companies prioritise the development for the adult indication and that paediatric development is only initiated after the drug is registered for adult use. Less than one percent of all oncological orphan designations concerned a malignancy specific to children. The study concludes that, even though oncology drugs make up a significant share of the OMPs with a marketing authorisation, the voluntary measures of the Orphan Drug Regulation have not succeeded in sufficiently incentivising the development of new drugs for rare cancers in children and adolescents. A similar analysis by Giannuzzi et al. (2017), but of all authorised OMPs rather than only oncological products, found that in Europe nearly half (46%) of approved indications that affect both children and adults had not been approved for paediatric use (as compared to 71% in the US).[269]

Figure 21 Distribution of orphan designations by population group (children and/or adults) affected by the condition targeted (2000-2016)



Source: EMA. (2016). Orphan Medicine Figures 2000-2016.[265]

Indication stacking

There is a growing concern that pharmaceutical companies are increasingly applying a strategy of 'indication stacking' and attempting to seek orphan designation, and by extension market exclusivity, for the same product more than once.[270] This would be achieved by initially obtaining approval for a narrowly defined indication and extending the scope of the registration later on, for instance by registering the drug for use in a different sub-sets of patients. It has even been suggested that excessive stratification and indication stacking has become "the new norm": a study of orphan drugs approved by the US Food and Drug Administration found that "*of the 43 orphan drugs approved whose global annual sales reached more than $1 billion, 18 had only one orphan designation, 15 had two, and 10 had three and more.*"[271]

Data by the EMA, however, do not (yet) show a similarly stark effect.[272] In fact, the number of authorised orphan indications thus far has tallied closely with the number of products (Figure 22). At the end of 2016 there were 14 more authorised orphan indications than there were products (142 and 128 respectively). According to the OMP Community Register, among products that have received marketing authorisation[273], the vast majority (87%) have only a single orphan designation (Figure 23,

[269] Giannuzzi V, Conte R, Landi A, et al. (2017) *Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen.* Orphanet J Rare Dis. 2017 Apr 3;12(1):64. doi: 10.1186/s13023-017-0617-1.

[270] Gagnon MA (2015) Welke prijs betalen we voor nieuwe geneesmiddelen? Geneesmiddelenbulletin. 49(12), 135-142. (translated)

[271] Côté A, Keating B (2012) What Is Wrong with Orphan Drug Policies? Value in Health 15(8), 1185–1191. DOI: http://dx.doi.org/10.1016/j.jval.2012.09.004 Accessed 12 January 2018.

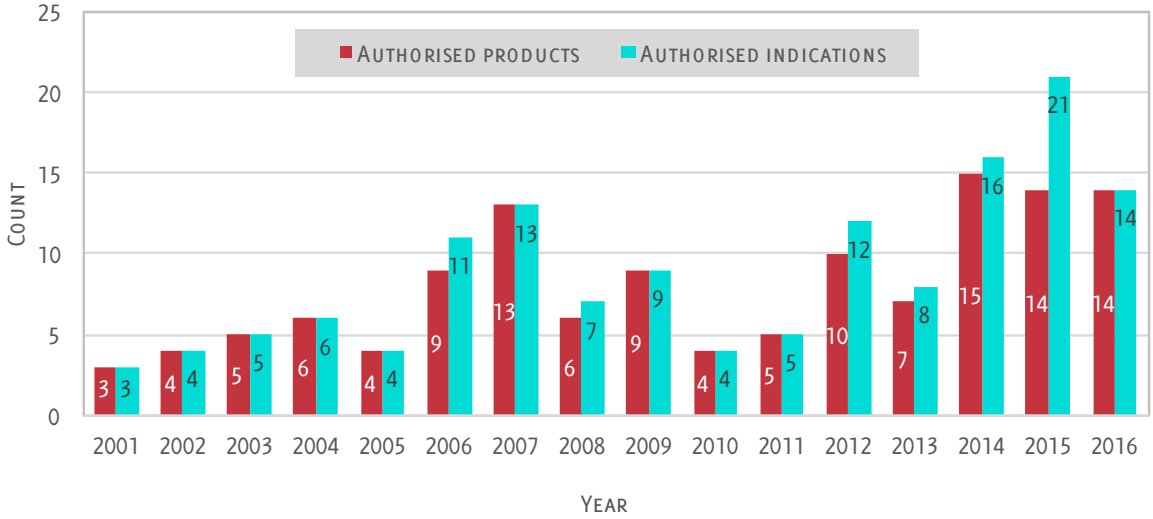
[272] EMA Register of Designated Orphan Medicinal Products. http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm. Accessed 13 January 2018.

[273] Defined here as products for which the register lists a trade name.

left). In total 13 products with two or more orphan designations have been authorised. The product Ravicti, for treatment of urea cycle disorders, stands out with six registered orphan designations. If one considers *all* listed products–that is, both those with a marketing authorisation and those that are still in development– 84% have only a single designated indication (Figure 23, right). Two percent of these products (22 out of 1,213) have four or more registered indications. There is therefore, as yet, no major difference in the extent of 'indication stacking' between products on the market and those that are still in the pipeline. Jointly, these analyses shows that, whilst indeed there are examples of drugs with multiple orphan designations, these represent the exception rather than the norm.

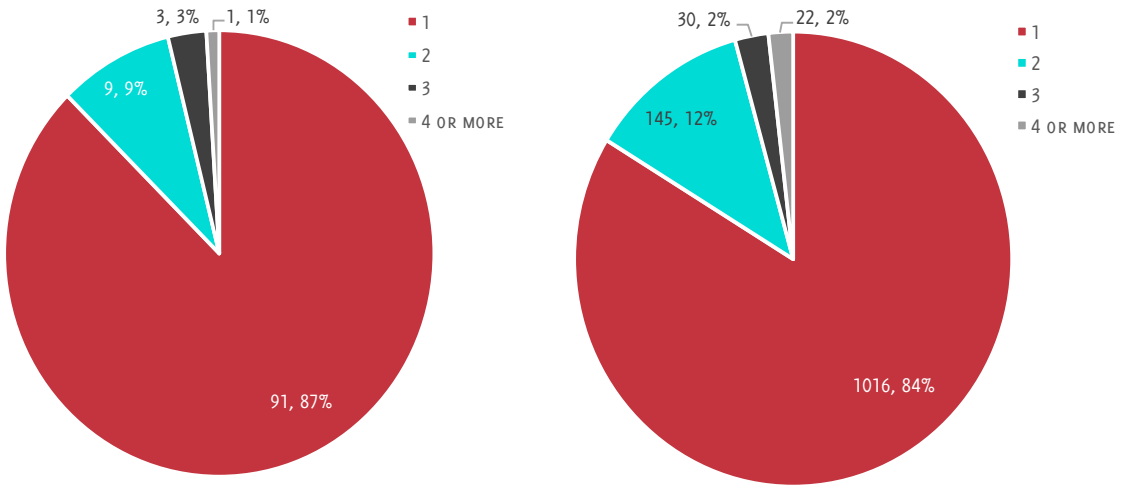
To better understand the phenomenon of indication stacking, an analysis was performed of the classes to which authorised drugs with multiple orphan designations belong. Most (71%) authorised OMPs with multiple designated orphan indications were shown to belong to the class of antineoplastic and immunomodulating agents (Table 4). Here, the designated indications are all distinct sub-types of a form of cancer. For instance, the drug Adcetris is indicated for treatment of anaplastic large cell lymphoma, cutaneous T-cell lymphoma, and Hodgkin lymphoma. Whereas, to the public at large at least, these indications may appear very similar, it should be emphasised that, in its assessment of whether a sub-type of cancer constitutes an orphan disease in the sense intended by the regulation, the COMP relies on the classification of haemato-oncological conditions by the World Health Organization.

Figure 22 Number of orphan products and indications authorised (2001-2016)



Source: EMA. (2016). Orphan Medicine Figures 2000-2016.[265]

Figure 23 Designated orphan indications per product. Left: OMPs with marketing authorisation Right: all registered OMPs.



Source: EMA Register of designated orphan medicinal products.[272]

Table 4 Products with marketing authorisation with multiple orphan designations

Drug	# Designated Orphan Indications	ATC class
Ravicti	6	A
Adcetris	3	L
Carbaglu	3	A
Imbruvica	3	L
Nexavar	3	L
Soliris	3	L
Cresemba	2	J
Gazyvaro	2	L
Iclusig	2	L
Lenvima	2	L
Revlimid	2	L
Rydapt	2	L
Signifor	2	H
Vidaza	2	L

Source: EMA Register of designated orphan medicinal products[274]. A = alimentary tract & metabolism, H = Systemic hormonal preparations, L = antineoplastic and immunomodulating agents, J = Anti-infectives.

There is at least one known example of a drug that received multiple orphan designations for different indications, but for which these designations were subsequently withdrawn. In the case of Glivec (discussed further in the subsequent chapter), the sponsor Novartis withdrew three orphan designations, thereby making the drug eligible for a Paediatric Extension. In the US, Glivec (under the brand name Gleevec) did maintain multiple orphan designations.

[274] EMA Available at http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm. Accessed 13 January 2018.

Opponents of the regulation's possibility to obtain multiple designations for a single product argue that a drug's effectiveness against one sub-type is often a reasonable predictor of effectiveness against another. Therefore, they argue, it is foreseeable that the eventual market for the product is larger than that what would be expect for 'true' orphan diseases and companies should not be allowed to benefit from the orphan drug market exclusivity more than once. This argument has been countered by the observation that registration of additional indications requires substantial follow-on research and development, including costly clinical trials. That obtaining registration for additional indications is not self-evident is demonstrated by, for instance, Revlimid's recent failure in clinical trials which could have led to an additional designation for treatment in diffuse large B-cell lymphoma (DLBCL).[275]

Overall, the here presented data indicate that –whilst the absolute number of products with multiple designated indications has overtime somewhat increased–, there is as yet no evidence to support any claim that this is a widespread phenomenon, at least in Europe. Aside from the question of whether indication stacking is in line with the intent of the Orphan Drug Regulation, it is worth accentuating that, also from a societal perspective, exploring any drug's potential effectiveness in a broader group of patients can in fact be highly desirable: it allows a greater group of patients to enjoy the benefits of a drug that has already undergone substantial clinical testing, thus making the process of development and market access faster and less costly.

Personalised medicine and sub-setting

In discussions with interviewees it is clear that many have questions about the role of personalised medicine in relation to the Orphan Drug Regulation. There is a fear that personalised medicine will permit companies to artificially create strata of patients ('sub-setting') with specific gene mutations in order to qualify for orphan designation. In a recent article, members of the COMP have described their experiences with sub-setting based on the use of biomarkers.[276] The article outlines four eligibility criteria used by the COMP to assess proposals of sub-sets based on biomarkers, namely:

- The subset proposed should fall entirely within a distinct medical condition
- There should be a clear delineation of the subset from the entire of the population
- The subset should have a plausible link to the condition
- The subset should be closely linked to the pharmacological action of the medicinal product in such a way that the absence of these characteristics will render the product ineffective in the rest of the larger population with the same condition.

The article states that the COMP has assessed an unspecified number of unsuccessful applications involving biomarkers to define specific orphan conditions. The details of these could not be revealed as, in all but one cases, the applications were withdrawn prior to the final opinion of the COMP and are therefore confidential. Nonetheless, the paper offers three examples of applications that, based on the aforementioned criteria, were considered ineligible. The authors conclude that, whilst biomarkers can indeed be used to define a valid sub-set of a condition that is eligible for an orphan designation, the need to demonstrate medical plausibility and significant benefit in the defined condition provide a functioning safeguard against unintentional use of the system.

Maintenance of orphan designation at and post-MA

Before a product receives marketing authorisation, the orphan drug status is reviewed again. If a product no longer meets the criteria, for instance because the patient population is larger than initially stated, the orphan designation is revoked. In addition, as outlined previously in section 5.4.1, within the Regulation there is a provision that allows the period of market exclusivity to be reduced to six years if, after five years on the market, the drug no longer meets the criteria for orphan designation. This includes the possibility for reassessment if there is evidence that the product has become

[275] Taylor P (2016) Celgene disappointed as Revlimid fails lymphoma trial. PMLive 27 July 2016. http://www.pmlive.com/pharma_news/celgene_disappointed_as_revlimid_fails_lymphoma_trial_1082856. Accessed 13 January 2018.
[276] Tsigkos S, Llinares J, Mariz S et al. (2017) *Use of biomarkers in the context of orphan medicines designation in the European Union*. Orphanet Journal of Rare Diseases 2014, 9:13. http://www.ojrd.com/content/9/1/13

sufficiently profitable that it no longer justifies maintenance of the market exclusivity.[257] However, there are several issues with this part of the provision. First, it appears unclear what constitutes "sufficiently profitable". In a 2005 report to the Commission, the COMP recommended that further guidance be given on "*the criterion of insufficient return on investment and on the definition of «sufficiently profitable» to review market exclusivity at 6 years. This may imply amending the current Commission Regulation (EC) N° 847/2000 of 27 April 2000 (medical plausibility, criterion of insufficient return on investment) and the Commission Communication of July 2003 (market exclusivity, sufficient profitability).*" In response, the Commission commissioned a study offering considerations on the application of article 8.2.[277] This study outlined several possibilities for how the profitability of an orphan drug could be evaluated, but also cautioned that the possibility of curbing the reward could act as a disincentive to invest in orphan drug development. The report indicates that guidelines should be proposed before August 2006. This study could not confirm whether such guidelines have since been provided. More importantly, though, although this study could not ascertain what the original intent of this particular element of the provision was (that is, whether it was intended to have broad applicability to all designated products, regardless of the basis on which the designation was granted), it has been interpreted to apply only to those products that received orphan designation on the basis of the 'insufficient return on investment' condition (condition a2). As this condition is rarely invoked in applying for orphan designation, in practice this derogation option is rendered ineffective.

More broadly, according to a guideline to the regulation issued in 2008, the Article 8(2) procedure can only be triggered by "*information received from a Member State relating to a specific designation of an orphan medicinal product. The initiation of the procedure established in Article 8(2) is not intended to be systematic for all orphan designated products; on the contrary, Member States should only inform the European Medicines Agency if they have sufficient indications suggesting that the designation criteria are no longer met; in that case, they have to do so. The review procedure under Article 8(2) is therefore expected to be the exception.*"[278]

To date, the Article 8(2) procedure has been triggered only once: in 2016, the UK requested the COMP to assess whether Plenadren, a drug for the treatment of adrenal insufficiency, still met the orphan designation criteria.[279] The COMP concluded that there had been no significant change in the seriousness or prevalence of the condition and that the drug still conferred sufficient therapeutic benefit. It thus recommended that the 10-year period of market exclusivity should not be reduced.

According to a press release on the EMA management board meeting of October 2017, the Chair of the COMP has highlighted that, in light of the increasing number of medicines with an orphan designation and for which access is often challenging, there is a "*need to fully exploit the legal possibilities in the Regulation to reduce protection periods for orphan medicines that do not meet the criteria over time. This also entails the need to generate relevant data for these products after authorisation*".[280]

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[277] de Varax A, Letellier M, Börtlein G, Alcimed (2005) *Study on Orphan Drugs: Phase II Considerations on the application of article 8.2 of EC regulation No. 141/2000 concerning orphan drugs.* Available at: https://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/pricestudy/final_final_report_part_2_web_en.pdf Accessed 2 February 2018.

[278] Commission of the European Communities (2008). *Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: Review of the period of market exclusivity of orphan medicinal products.* Available at https://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/c_2008_4051_en.pdf. Accessed 28 January 2018.

[279] EMA (2016) *COMP assesses whether Plenadren still meets orphan designation criteria.* 28 April 2016. EMA/COMP/263073/2016. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_review/2016/05/WC500205975.pdf Accessed 28 January 2018.

[280] EMA (2017) Press release: EMA Management Board: highlights of October 2017 meeting Available at http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/10/WC500236190.pdf. Accessed 28 January 2018.

6.4 Data exclusivity and market protection

6.4.1 Data exclusivity

The rationale behind data exclusivity is that the party that conducts the clinical trials (which is not necessarily the same as that holding the patent for a drug) necessary for obtaining a marketing authorisation is rewarded for this activity, considering the risk the party and the investments it has to make.[281] As long as the trial data is protected, generic manufacturers cannot refer to the dossier and therefore cannot bring their products to market, even if there is no more patent protection. It does not suffice to demonstrate bioequivalence to the original product, as had been the case before the introduction of data exclusivity under the TRIPS agreement. Whilst data exclusivity can delay the entry of generics, and thus imply additional costs to the healthcare system, the effect on innovation is less clear. Generic drugs themselves are by definition not innovative. However, the trial data dossier can also be used by other parties for further development of derivative, but not equivalent, drugs. Such incremental innovation could thus be delayed by data exclusivity.

Data exclusivity has also been discussed in the context of its impact on 'compulsory licensing'. Under the flexibilities of the TRIPS agreement, governments maintain the right to issue licenses to third parties (or itself) to use an active patent on a drug, in exchange for adequate compensation to the patent holder.[282] Governments decide themselves in what situations it would issue a compulsory license. It can do so, for instance, to force price reductions or increase access. It is, however, widely considered a 'last resort' measure as it violates the social contract between the government and the originator industry. Whilst compulsory licensing enables governments to effectively 'break' patents, a similar exception does not exist for data exclusivity and market protection under EU law. Although from a public health and health systems perspective, data exclusivity could thus have important consequences, there is no obvious direct impact on pharmaceutical innovation. One could postulate that introduction of a waiver to data exclusivity and market protection could disincentivise companies from conducting R&D in the first place, but this would appear unlikely given the nature of their business model and the limited possibility that such a waiver would be used against them.

6.4.2 Market protection and exclusivity

As part of the question of whether the additional protections and exclusivities have stimulated pharmaceutical innovation, it is worth considering any potential negative consequences resulting from these measures. Such consequences would stem from rendering the market less economically attractive for competitors and innovative products.

The question of potential negative impact has been raised primarily around orphan drugs, where the extended market exclusivity granted by the orphan drug regulation potentially poses a barrier for development of other, similar products for that indication. This could in theory negatively impact patients who do not benefit sufficiently from the product that holds market exclusivity and for whom second or third in class drugs are desirable.

This concern has been countered by interviewees in several ways. First, those closely familiar with biotechnological drug development indicated that, because of the high failure rates in drug development, it is not uncommon for more than one company to be working on a drug for a specific indication. The 'race to market' is therefore not an impediment to innovation per se, as slower innovators are not prevented from entering the market all together, though they are delayed in doing so. For instance, the register currently lists five authorised drugs with an orphan designation for the treatment of multiple myeloma.[283] Whilst the exact specifications for patients for whom the drug is

[281] Ragavan S (2017) The significance of data exclusivity and its impact on generic drugs. J. Intell. Prop. Stud. 131. Available at: http://scholarship.law.tamu.edu/facscholar/816. Accessed 14 January 2018.

[282] 't Hoen EFM, Boulet P, Baker BK (2017) *Data exclusivity exceptions and compulsory licensing to promote generic medicine in the European Union: a proposal for greater coherence in European pharmaceutical legislation*. J Pham Policy Pract 10:19 doi: 10.1186/s40545-017-0107-9

[283] These are: Thalidomide Celgene (OD received in 2001), Kyprolis (2008), Imnovis (2009), Ninlaro (2011) and Farydak (2012).

registered may vary between these drugs, it underlines the principle that market exclusivity need not lock out further development for a specific indication.

Second, as explained also in section 5.4.1, the market exclusivity for OMPs extends protection against market competition by "*similar medicines with similar indications*", in which a similar medicine is understood to contain "*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*".[284,285] It therefore does not preclude market entry by products that act via different mechanisms (e.g. gene therapy versus enzyme replacement therapy). A study by Brabers et al. analysed to what extent the orphan market exclusivity hinders the development of so-called 'follow-on' OMPs, orphan products developed for the same indication for which another product has already been approved.[286] Using data on the indications for which the Community Register of OMPs, the authors found that in areas where there are no follow-on OMPs, the main reasons relate to time and market size, rather than to 'monopolies' created by the market exclusivity.

Last, it bears repeating what was stated section 5.4.1, that the regulation (Point 3, Article 8) stipulates that a second marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:[287]

- The holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or
- The holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
- 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.

The case of Glivec / Tasigna described in section 5.4.3 shows an example of the invocation of the first clause, though here Novartis was the MA holder for both drugs and in effect gave itself consent. The study team is not aware of any other examples where any of the above clauses were used to grant an orphan designation for a similar product to a second applicant whilst the market exclusivity still applied. However, as noted earlier, there are several drugs listed with the same designated indication for which this could have been the case.

[284] Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'. Available at https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf. Accessed 13 January 2018.

[285] EMA Marketing authorisation and market exclusivity. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000392.jsp Accessed 13 January 2018.

[286] Brabers AEM, Moors EHM, van Weely S, de Vrueh RLA (2011) *Does market exclusivity hinder the development of follow-on Orphan Medicinal Products in Europe?* Orphanet Journal of Rare Diseases 6: 59. http://www.ojrd.com/content/6/1/59

[287] Ibid

7 Economic impacts

In any analysis of the economic impacts of the additional protections and incentives, one should bear in mind these measures were designed primarily to reward and stimulate pharmaceutical innovation. They were not explicitly designed to have a net positive welfare economic impact, although pharmaceutical innovation itself and increased health can be expected to have positive economic effects, as outlined in this chapter. Nonetheless, as explained previously, in the rationale for the SPC regulation, also the prospect was raised that the regulation would contribute to lower drug prices by allowing companies a longer time to recover their investments. On the other hand, the regulation could have the effect of increasing costs from a health system perspective by lengthening the time of protection and delaying price pressure from generic competition. This chapter explores to what extent and how such economic impacts have occurred.

The chapter centres on a series of case studies on seven selected drugs. Each of these drugs has, at some point in time, benefitted from at least one form of supplementary protection. The cases were chosen on the basis of various criteria, as detailed in section 2.4.1. They all involve drugs that have received marketing authorisation in the Netherlands and have been on the market since, mostly with commercial success. This choice of relative 'winners' as case studies implies that no comprehensive conclusions can be drawn vis-à-vis the total costs of pharmaceutical care or the costs and benefits of pharmaceutical investment. Neither should these cases be interpreted as 'archetypes' of the various supplementary protection mechanisms. Rather, they are intended to illustrate how these mechanisms can work out in practice. Furthermore, as explained also in sections 7.1 and 7.2, the model used to estimate the cumulative costs to the Dutch health care system from the supplementary protection period does not take into account any potential benefits.

The seven cases presented in sections 7.3 to 7.9 can each be read as a stand-alone narrative. A more overarching synthesis across the cases has been included at the end of this chapter, in section 7.10.

7.1 The welfare economic perspective

The supplementary protection mechanisms that are the subject of this study aim to reward and stimulate pharmaceutical innovation. Such innovation is expected to have positive monetary and non-monetary welfare economic effects. The central non-monetary welfare effect of pharmaceutical innovation is of course an intended gain in health (often quantified and monetised in terms of *quality adjusted live years* or *QALY*s). Examples of positive monetary effects are gains in labour productivity if people are healthier and live longer and cost savings on other treatment or care.

From a welfare economic perspective, patent protection and the supplementary protection mechanisms studied here need to strike a balance between such benefits and the costs of protection. For society, these costs consist primarily of the higher prices a pharmaceutical company can charge whilst it does not face competition from generics for a specific drug, and subsequently the higher profits it can make. If a drug is reimbursed under the public health care system, these costs can crowd out other medication or treatment methods, given limited public means. If not, they can affect the accessibility of drugs to lower income groups. In addition, there are the costs of litigation and rent-seeking in relation to the patent system and supplementary protection mechanisms.

Pharmaceutical companies, on the other hand, require expected net profits to justify investment in the development, clinical testing and marketing of a new drug. These investments can run into the billions of euros and, even after such enormous investments, their medical and commercial success often remains uncertain. In 2006, for instance, Pfizer decided to stop the development of Torcetrapib, an intended successor for Lipitor (which will be discussed in a case study later in this chapter), after having spent over €600m on its development and clinical trials. In response, Pfizer lost 11% of its value on the stock market.[288] Just recently, Pfizer announced to halt its quest for new medication for

[288] Pfizer stopt ontwikkeling topmedicijn; Koers daalt met 11 procent, *NRC Handelsblad,* 4 December 2006.

Alzheimer disease and Parkinson.[289] This illustrates that the profits made on successful drugs not only need to make up for the investments costs, but also for the losses made on unsuccessful investments.

7.2 Focus and methodological framework for the case studies

The cases studies in this chapter do not take a welfare economic or social cost-benefit analysis approach, however. They do not aspire to quantify the benefits of specific drugs for public health, let alone social welfare. In general, no comprehensive information is available on the development costs of the drugs in the case studies. Nor do these cases examine the validity of the patent system in itself.

The current debate surrounding additional protections and regulatory incentives appears to have been fuelled, at least in part, by the perceived high prices of certain drugs. This study does not take a normative position on drug pricing per se, nor does it provide a general analysis of price drivers. The aim of the economic analysis in the case studies is to assess to what extent price developments and the total costs of these drugs for Dutch society can be related to patent protection and supplementary protection mechanisms, and what the costs of prolonged protections and exclusivities for the Dutch health care system have been.

In our interviews, opinions vary somewhat on whether there is a direct causal relationship between protections and exclusivities on the one hand, and drug prices on the other. A number of interviewees flag a broader issue with what they refer to as 'monopolistic price setting'. It is felt that pharmaceutical companies price their products based on willingness to pay and that any suggested link between prices and costs of R&D and production are tenuous at best. This results in prices that many perceive as inflated, most notably in the area of oncological drugs.

This perspective concords with what can be expected from standard economic theory:[290] as long as protection mechanisms provide exclusivity for a drug, it can be priced at a considerable mark-up over its marginal production costs while in a competitive situation, such mark-ups would not be sustainable and would result in a loss of market share. In general, the profit-maximising price will *only* depend on these marginal costs and the demand function (that is, the willingness to pay). If demand is high and irresponsive to price changes (inelastic), for instance because the therapeutic effects of a drug in terms of life years saved or quality of life improvements are large in comparison to alternatives (if these exist at all), the profit-maximising price will be high and virtually unrelated to marginal production costs.

Moreover, standard economic theory predicts that profit-maximising prices are unrelated to the investment costs a pharmaceutical company has sunk into the development, clinical testing and marketing of a drug once it is on the market. Also, the term (duration) of protection has no direct effect on pricing while protection lasts. In general, it is against the interests of the shareholders of a pharmaceutical company to charge lower prices if the term of protection is longer, or higher prices if it is shorter. Having said that, prices may be altered *in anticipation of* the expiration of protection. For instance, prices may be lowered even if a drug is still under protection to discourage patients from switching to generics or to discourage generic entry altogether. Alternatively, they may be increased to migrate patients to a follow-up medicine which will be protected for a longer time.

The expected investment costs and the term of protection will, however, affect ex-ante investment decisions in the development, testing and marketing of a drug. The term will determine the expected cash flows from the investment and in general for a commercial company these – discounted – cash flows need to outweigh the ex-ante investments. The effect of discounting is very significant. It depresses the current value of cash flows at the end of the term substantially, and depresses the ex-ante investment incentive of longer protection accordingly. To illustrate this: the net present value (NPV) of 15 annual cash flows of €100m at a 10% discount rate is €760m.[291] The NPV of 16 such cash

[289] Farmareus Pfizer stopt onderzoek naar alzheimer- en parkinsonmedicijnen, *De Standaard*, 10 January 2018.

[290] The framework set out in this section is also in line with that adopted in P. Vernai, K. Farla et al. (2016), *Study on the economic impact of the Paediatric Regulation, including its rewards and incentives*, Ecorys/Technopolis, p. 41-44.

[291] In other words: given this discount rate, a company would be indifferent between receiving €760m at once, or the 15 annual payments of €100m.

flows is €782m. In other words, the NPV of the expected cash flows increases only by 2.9% in this example if the effective term of protection increases from 15 to 16 years. Nevertheless, once a marketing authorisation has been acquired, a company has an incentive to maximise total operational profits and a longer protection period implies higher such profits.

From the argument above, that the term of protection has no direct effect on pricing while protection lasts, it follows that term extension through an SPC or paediatric extension are unlikely to have an effect on the price point at which a drug enters the (Dutch) market. However, they are likely to have an effect on the moment in time when prices drop, provided that there is generic entry after the protection expired. Thus, they have an effect on the overall costs to the healthcare system by prolonging the period during which competition is kept off the market.

In principle, the same holds for orphan drug designations but for orphan diseases, the dynamics can be different in practice. Most of the drugs developed in this space concern biologicals rather than small molecules. The development and production of biologicals is much more complicated and costly. Several interviewees have pointed out that here, even after expiry of all protections on a product, little to no competition may occur, to the effect that prices may remain high even then. This is attributed to both the complexity of drug production itself and to the small market size, which may be too small to be economically interesting for multiple parties. This is particularly the case when one takes into account the fact that the originator can be expected to lower its prices to match an entrant. In fact, interviewees from the pharmaceutical and biotech industries, identify the high costs associated with drug development and production, linked with the small patient base, as the primary reasons that orphan drugs are often priced at a premium. Furthermore, it was suggested that, at least in the area of oncology, the high prices of certain drugs are more associated with that therapeutic area than with their orphan drug status. Although the relationship between orphan drug status and price is thus questioned by some, others have argued that, in exchange for the market exclusivity given to these products, the prices companies can charge for them should be capped at a 'fair' price that takes account of the market size.

The market dynamics sketched for orphan drugs underscores that additional protections and exclusivities are certainly not the sole cost drivers of pharmaceuticals. As mentioned, the price under protection largely depends on the shape of the demand function. In a public health care system this demand function can be, and often is, influenced by policy, e.g. though price negotiations and prescription policies (*preferentiebeleid*). Many interviewees feel that stronger systems for price negotiation for drug procurement are key to containing costs, both at the central level of the ministry of health and at the level of decentralised procurement (that is, at hospitals and pharmacies).

7.3 Lipitor

7.3.1 Background

Lipitor (active substance atorvastatin) is a drug that has been indicated for persons with elevated levels of cholesterol and lipids (hypercholesterolaemia). High cholesterol is associated with an increased risk of heart disease and stroke.[292] A third of all coronary heart disease (also known as ischaemic heart disease) is attributable to high cholesterol. It is the cause of 2.6 million deaths every year, and of 29.7 million years of life lost due to ill-health, disability or early death (Disability Adjusted Life Years). Although raised cholesterol is a major health problem in both developed and developing countries, prevalence is particularly high in Europe at 54% (both sexes). It correlates positively with income. In the Netherlands, nearly a quarter of the population (23.2%) of those between the ages of 30 and 70

[292] http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/, accessed 26 October 2017

suffers from hypercholesterolaemia.[293] The incidence of coronary heart disease and stroke has been increasing steadily and this trend is expected to continue.[294]

Lipitor is a lipid-lowering drug from the class of statins. Statins are used preventatively, either as primary prevention in patients with elevated low-density lipoprotein (LDL) cholesterol and additional risk factors for cardiovascular disease, or as secondary prevention in people who have had coronary surgery, myocardial infarction, stroke, or peripheral artery disease. In the US up to 38 million people are on statins.[295] In the Netherlands, it is reported that only 23% of eligible patients were taking statins for primary prevention and only 69% for secondary prevention.[296] In recent years, in fact, statins have become the subject of some controversy, as it has been suggested that not only is the use of statins in otherwise healthy patients unnecessary but even potentially harmful.[297] Nonetheless, over a third of all people over the age of 65 are taking statins.[298]

Although Lipitor would eventually become the highest-selling drug of all time, it was a late-comer in the statin market. It was first synthesised in 1985 by the pharmaceutical company Warner-Lambert.[299] While Lipitor was still under development, three other statin-based drugs beat it to the market. Consequently, the company considered halting further development. This changed when clinical trials showed the drug to be much more effective than other statins already on the market, resulting in the drug's nickname 'Turbostatin'. Lipitor was first approved in 1997. Commercialisation was through a partnership agreement with Pfizer, who eventually merged with Warner-Lambert in 2000 and acquired the shares for US$90b.

In the Netherlands, the first registration for Lipitor (for film-coated tablets of 10, 20 and 40mg) was granted on 21 April 1997.

7.3.2 Market data

Figure 24 shows global sales of Lipitor from 2000 onwards. During this period, sales increased steadily until hitting a maximum in 2006. Between 2006 and 2011 there was a steady decline. However, the revenues of 2011 were still staggering at almost US$ 9.6b. This was followed by a sharp drop in 2012 when protection expired in many countries (see below). For years, Lipitor was the most profitable drug in the world.[300] One explanation for the decline in global sales between 2006 and 2011 could be competition from cheaper statins in prescriptions.

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[293] https://www.volksgezondheidenzorg.info/onderwerp/cholesterol/cijfers-context/huidige-situatie#node-ongunstig-cholesterolgehalte-hypercholesterolemie, accessed 28 October 2017.

[294] http://www.eengezondernederland.nl/Trends_in_de_toekomst/Ziekten/Hart_en_vaatziekten, accessed 28 October 2017

[295] Adedinsewo, D. (2016): Prevalence and Factors Associated With Statin Use Among a Nationally Representative Sample of US Adults: National Health and Nutrition Examination Survey, 2011-2012. In: Clin Cardiol. 2016 Sep;39(9):491-6. doi: 10.1002/clc.22577. Epub 2016 Aug 9.

[296] Busko, M. (2015): Eight in 10 Primary-Prevention Patients Skip Statins, Dutch Study Finds, https://www.medscape.com/viewarticle/845331

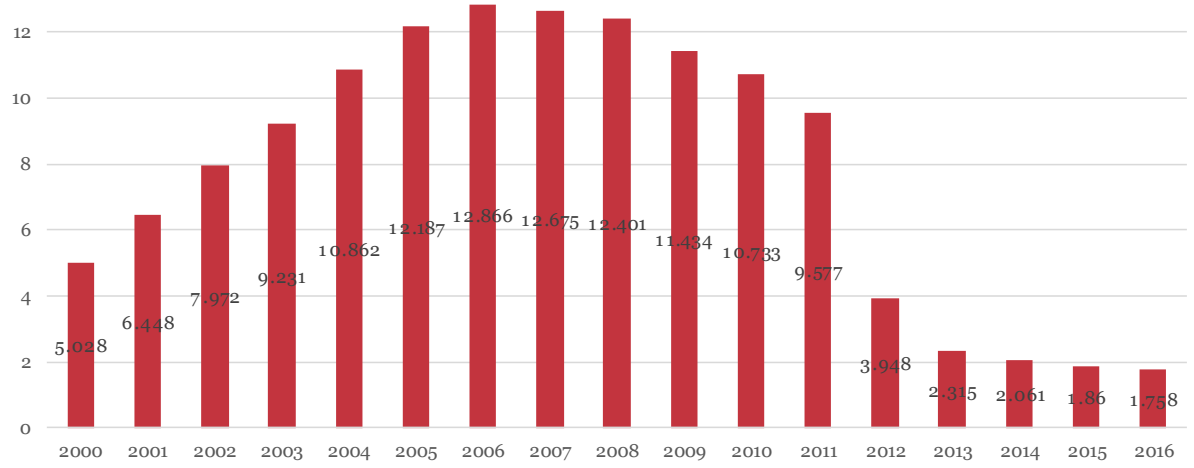
[297] https://www.nrc.nl/nieuws/2017/05/22/statines-zijn-zinloos-voor-vrijwel-gezonde-ouderen-9800369-a1559919 and https://www.nemokennislink.nl/publicaties/statines-de-melkkoe-van-de-farmaceutische-industrie/.

[298] https://www.nrc.nl/nieuws/2017/05/22/statines-zijn-zinloos-voor-vrijwel-gezonde-ouderen-9800369-a1559919, accessed 28 October 2017.

[299] http://theconversation.com/weekly-dose-lipitor-the-highest-selling-drug-of-all-time-55706, last checked 28 Octobetr 2017.

[300] E.g. Omzet medicijnen bereikte in 2004 wereldwijd record, *De Volkskrant*, 20 April 2005.

Figure 24 Global sales of Lipitor, 2000 – 2016 (US$b).



Source: Annual Reports Pfizer

It has been said that the success of Lipitor may not have been due only to its medical properties. The market entry of Lipitor coincided with the moment that the FDA first allowed direct-to-consumer marketing. As a result, Pfizer spent tens of millions on marketing campaigns, aggressively targeting prescribing physicians and giving out free samples. Lipitor was also priced below rival drugs.[301]

7.3.3 Patents and supplementary protections

The drug went off-patent in the US in November 2011. Generics were introduced onto the market in December 2011, and multi-source generic competition began in May 2012.

In the Netherlands, the basic patent (EP0247633) for atorvastatin expired on 29 May 2007 but it was succeeded with an SPC (970034) until 6 November 2011. Subsequently, the period of exclusivity was extended by six months to May 2012 through a paediatric extension, which – following submission of a Paediatric Investigation Plan (PIP) – resulted in an indication for a reduced-dosage formulation of Lipitor for children aged 10 or older.

The paediatric extension on Lipitor made the news in the UK when Teva already delivered generic atorvastatin at the end of 2011. Pfizer sued, and eventually settled with Teva who declared not to sell the generic version until end of May 2012. Pharmacies would not need to fear legal action by Pfizer, provided they ceased selling the generic and would return the remaining stocks for full refund.[302]

Pfizer is reported to have employed a number of strategies to continue reaping benefits from Lipitor after patent and SPC/paediatric extension expiry:[303]

- Pfizer has several authorised generics deals in place. In one instance, the generics firm offering the drug has it produced by Pfizer, and the generics firm had to give 70% of its profits to Pfizer.
- Pfizer has lowered the price significantly and has aggressively discounted it to match any price and maintain brand loyalty (even undercutting most generics prices at the launch of the generics).
- Pfizer offered incentives to customers to stay on the brand product, such as reduced co-payment schemes ("Lipitor for you" in the US).[304]

[301] http://www.businessinsider.com/lipitor-the-best-selling-drug-in-the-history-of-pharmaceuticals-2011-12?IR=T

[302] http://www.pharmaceutical-journal.com/news-and-analysis/news/lipitor-patent-infringement-case-settled-in-pfizers-favour/11086581.article

[303] http://www.patentdocs.org/2011/12/pfizers-lipitor-a-new-model-for-delaying-the-effects-of-patent-expiration.html

7.3.4 Pricing, users and costs in the Netherlands

The first time Lipitor or atorvastatin was mentioned in the Dutch press dates back to 1997 (based on LexisNexis), the year of its marketing authorisation. The article discusses public debate about the high costs of statins for the health care system, and guidelines for the prescription of statins based on the costs per life year saved, which would result in not prescribing Lipitor to men over 70 and women over 75 years old.[305] A little over a year later, Lipitor was mentioned as the number one contributor to the increased costs of medication in 1998.[306] In 1999, Lipitor was the fourth most expensive drug in the Netherlands in terms of its total costs.[307] By 2001, Lipitor had become the most expensive drug for Dutch medicine and it would hold that position for many years.[308] In 2006, the Dutch Society for General Practitioners (Nederlands Huisartsen Genootschap) concluded the annual costs of Lipitor could be reduced by a factor three by prescribing simvastatine instead.[309] Nevertheless, the use and costs of Lipitor continued to increase (

Figure 25). In 2009, limitations were introduced for the reimbursement of Lipitor, to the effect that it could only be prescribed and reimbursed if there were no alternatives.[310] In response, Pfizer sent out a letter to 12,000 general practitioners, specialists and pharmacies stressing the alleged health risks associated with cheaper alternatives.[311]

Figure 25 shows the development of the average costs per defined daily dose (DDD) for atorvastatin in the Netherlands between 2006 and 2016: the red line represents the total market, the dashed blue line that of Pfizer/Lipitor and the dashed black line that of the generics that entered the market in 2012. Until the patent expired in 2012, the red and the blue line are identical. The average price decreased only slowly between 2006 and 2011, but dropped steeply in 2012 when the final protection expired and

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[304] Pfizer has *"...offered a reduced co-payment of $4 a month versus the $10 customers would pay for many generic prescriptions. Pfizer's program, called "Lipitor for You," offers a $4 co-payment card and direct delivery of Lipitor. The program is limited to privately insured customers. However, the discounts can also be applied to many Medicare prescription drug plans, which have agreed to dispense Lipitor even if patients ask for generics. Pharmacy benefit management company CVS/Caremark has notified pharmacies that the generic form of Lipitor would not be covered for 29 prescription drug plans it manages for Medicare Part D. Instead, brand Lipitor will be filled, but only a generic co-pay will be applied. Any prescription claims for generic atorvastatin will be rejected. Pfizer, the benefit managers and some insurers insist all of the new discount will be passed along to consumers, companies and other payers. While this remains to be seen, CVS/Caremark has already lowered its premiums for the government and Lipitor users."* (Ibid)

[305] Cholesterolpil te duur om iedereen te geven, *De Volkskrant*, 20 December 1997.

[306] Nederlanders slikken voor half miljard meer medicijnen, *ANP*, 25 March 1999.

[307] Veertig-plussers slikken duurste medicijnen, *ANP*, 27 April 2000

[308] Borst maakt pillen duurder, *De Volkskrant*, 17 August 2001. Hartpatiënten willen onderzoek naar cholesterolverlagers, *Trouw,* 2 May 2006. Medicijnkosten gestegen tot 4,7 miljard euro, *Trouw*, 24 July 2007

[309] Huisartsen tegen dure cholesterolpil, *ANP*, 3 August 2006.

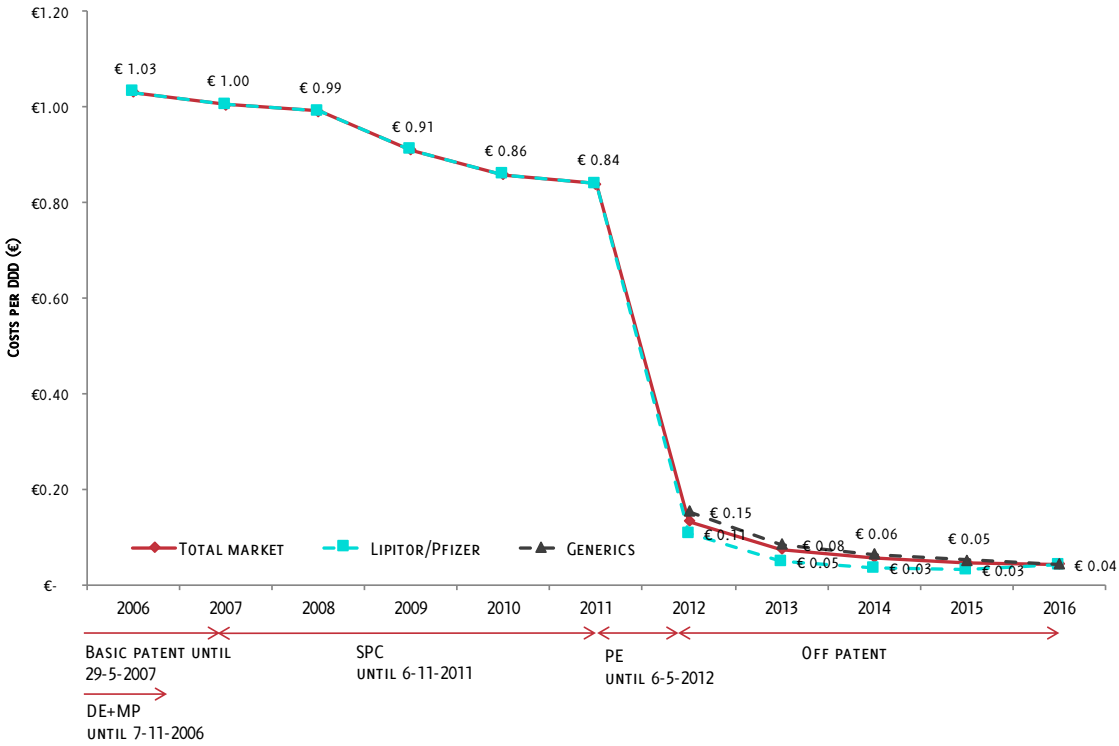
[310] Eindelijk weer een koopmansgeest?, *De Telegraaf*, 30 December 2008.

[311] Pfizer zet huisartsen onder druk; Farmaceutisch bedrijf probeert omzet van dure cholesterolpil te redden, *Trouw*, 3 January 2009.

continued to decrease gradually in the ensuing years. The average price per DDD in the first three years is 21 times higher than the average price in the last three years.

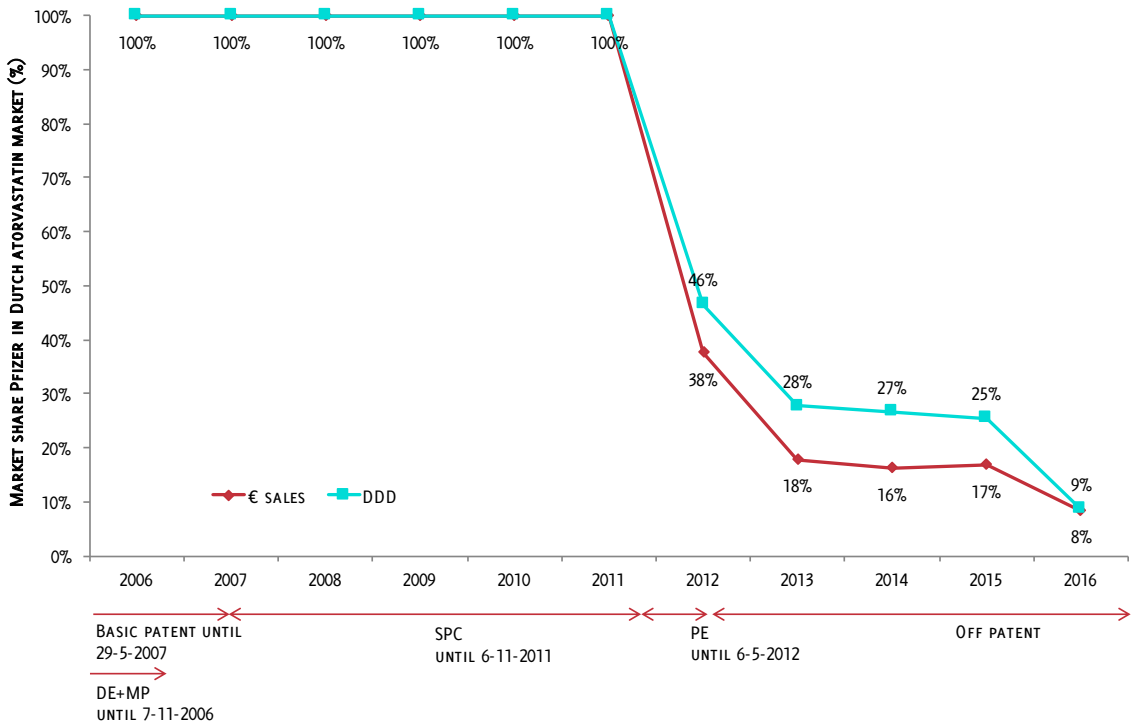
The dashed black line shows that, upon entry of as many as nine to ten generics competitors from 2012 onwards, Pfizer charged a price which was up to 40% below the market average. This corroborates the earlier statement, that Pfizer strived to maintain its market position after 2012 by aggressively undercutting generics competitors. Nevertheless, its market share dropped rapidly, both in € sales and in DDD (Figure 26).

Figure 25 Cost per DDD for atorvastatin in the Netherlands, 2006 – 2016



Source: Data SFK (2017)

Figure 26 Market share Lipitor (in € sales and in DDD) in the Netherlands, 2006 – 2016

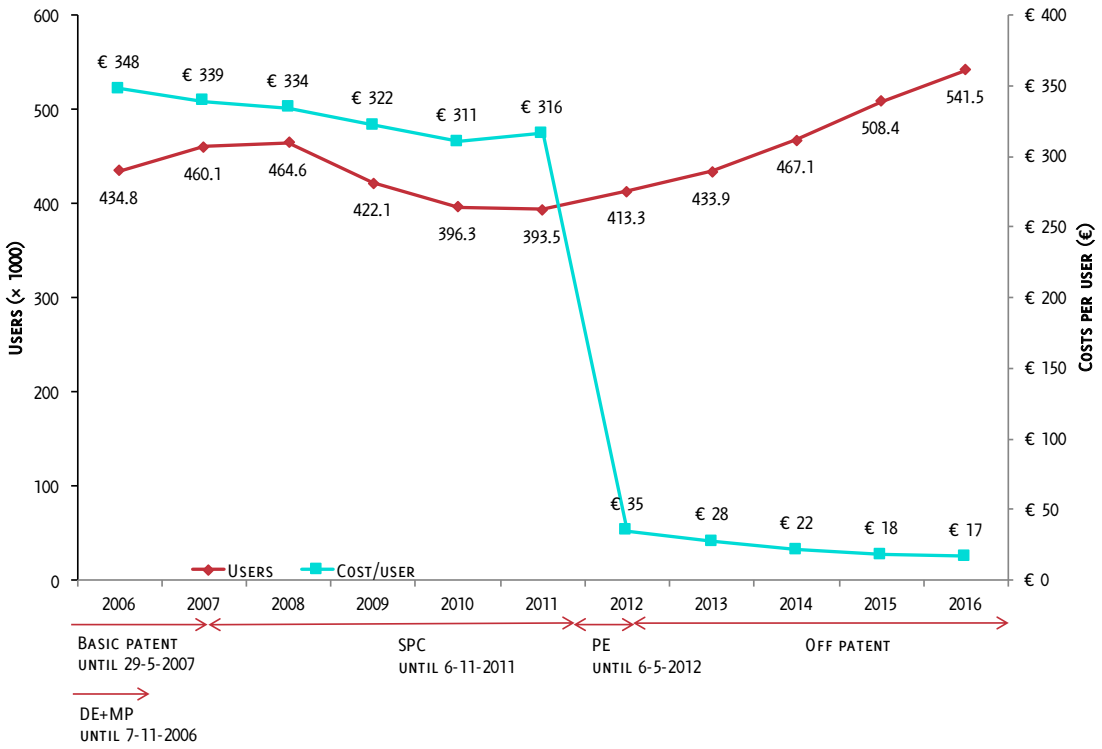


Source: Data SFK (2017)

The drop in the average costs per DDD is mirrored by a similar drop in the average annual costs per patient from €348 in 2006 to €17 in 2016 (Figure 27). Comparing the average costs per user in the last three years to those in the first three years, the difference is a factor 18. During this period, the number of users increased gradually from 435,000 in 2006 to 541,000 in 2016.

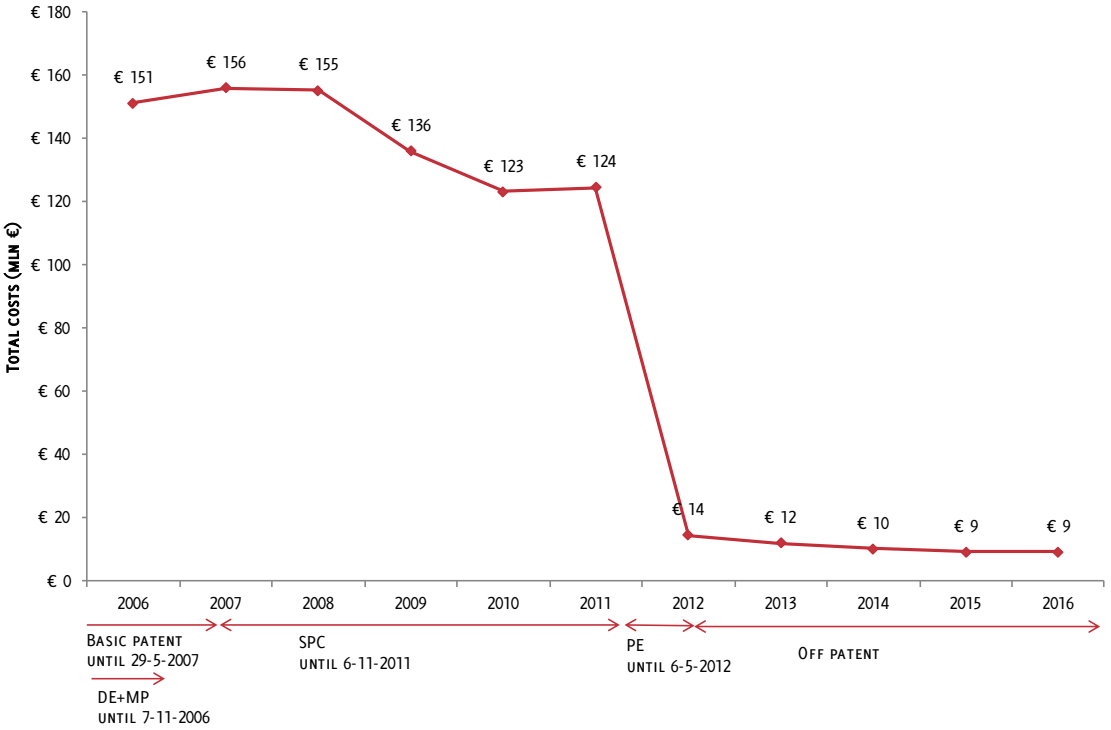
The total costs of atorvastatin for the Netherlands decreased from €151m to €124m between 2006 and 2011, then dropped to €14m in 2012 and continued to decrease gradually to €9m in 2016 (Figure 28). In the years 2006-2011, total costs for the Netherlands were on average 1.7% of global sales for Lipitor.

Figure 27 Users and cost per user for atorvastatin in the Netherlands, 2006 – 2016



Source: Data SFK (2017)

Figure 28 Total costs atorvastatin in the Netherlands, 2006 – 2016 (€m)



Source: Data SFK (2017)

Assuming that the post-2011 prices are still at or above marginal production costs of the medicine and that these marginal production costs have not changed substantially over this time frame, this implies an operational profit margin in the order of 95% on costs or more in the years preceding 2011. In other words: prices were at least 20 times the marginal production costs in the last year before the expiration of the patent.

The figures show that Lipitor benefitted from an SPC between 29 May 2007 and 6 November 2011 (4.44 years) and from a paediatric extension between 6 November 2011 and 6 May 2012 (0.5 years). Thus, SPC plus paediatric extension lasted for 5.04 years and the total time between the marketing authorisation in the Dutch market and the expiration of the paediatric extension was 15.05 years.

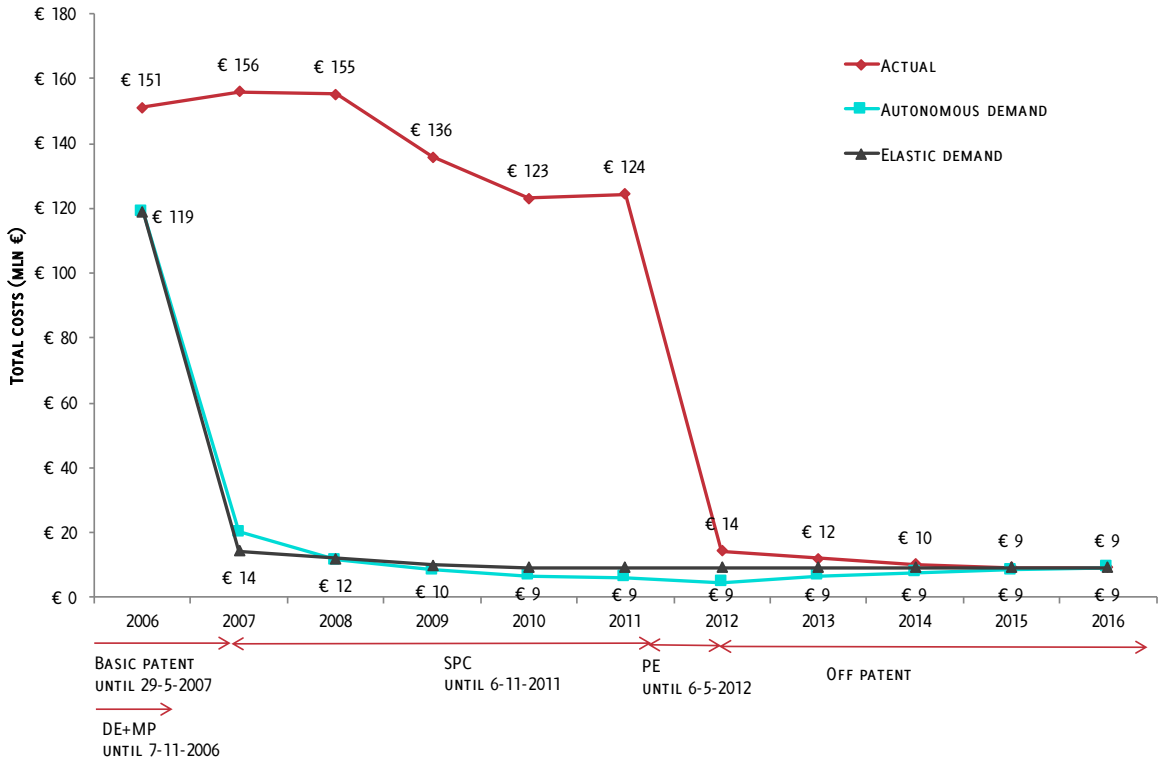
To estimate the additional revenues Pfizer generated in the Dutch market thanks to the SPC and the PE, and subsequently the additional costs for the Dutch health care system, two main assumptions have to be made: one about the price development over time in the counterfactual situation without SPC and PE, and one about the development of the number of users and DDDs in the counterfactual.

In line with the methodological framework discussed at the start of this chapter, it is assumed that the cost development per DDD discussed before would have occurred 5.04 years earlier, if there had been no additional protections at all, and six months earlier had there been no PE. This implies that the gradual decrease in the costs per DDD that is observed between 2006 and 2011 is assumed to be anticipatory of the expiration of protection in 2012. The actual 2016 price level is assumed to remain stable which implies that without SPC and PE, this level would have been reached 5.04 years earlier and would have remained constant since.

For the counterfactual number of users/DDDs, one can either assume it is an autonomous development unrelated to pricing and protection. This would imply it is as observed in the original data. Or, one can assume that there is some elasticity of demand and sales volumes increase as prices drop. This would explain the increasing number of users since protection expired, after a gradual decrease in the preceding years. Following this assumption, the usage data would shift by 5.04 or 0.5 years if there were no SPC and PE.

Figure 29 shows the resulting total costs over the years. The area between the red line and the blue or black lines represents the costs for the Dutch health care system that can be attributed to SPC and paediatric extension protection for Lipitor. Over the years 2006-2016 this amounts to between €681 and €692m, depending on the assumption of elastic or autonomous demand respectively. The additional revenues for Pfizer are in the same range. Along the same lines, the extra costs of paediatric extension for the Dutch health care system are estimated at €73m to €77m.

Figure 29 Actual costs of atorvastatin in the Netherlands, and estimated costs without SPC and paediatric extension, 2006 – 2016 (€m)



Source: Data SFK (2017)

7.4 Losec

7.4.1 Background

The drug Losec (Prilosec in the US, active substance Omeprazole) is the first drug in a class of so-called proton-pump inhibitors (PPI) and designed for the treatment of peptic ulcers. It has been indicated for a variety of uses:

- Gastroesophageal reflux disease (GERD): a long-term condition where stomach contents come back up into the oesophagus. In Europe, the prevalence of GERD is estimated to be between 8.8% to 25.8%.[312] GERD is also a risk factor for the development of Barrett's oesophagus and oesophageal adenocarcinoma. The disease has a high chronicity. A 2002 review on the economic burden of gastrointestinal and liver diseases in the US identified GERD as posing the highest direct costs (US$9.3b).[313]
- Peptic ulcer disease (PUD): a break in the lining of the stomach, first part of the small intestine or occasionally the lower oesophagus. It is mostly associated with the epidemiology of *Helicobacter pylori*. Two studies from the Netherlands found that the prevalence of *H. pylori* was 32% in a group of 1,550 blood donors and 46% in a group of 6,837 pregnant women.[314]

[312] El-Serag HB, Sweet S, Winchester CC & Dent J (2014). Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut, 63(6), 871–880. http://doi.org/10.1136/gutjnl-2012-304269. The epidemiology data available refers to countries like the UK, Spain or Sweden, and robust studies/figures do not seem to be available for the Netherlands.

[313] Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002; 122:1500.

[314] Eusebi LH, Zagari RM and Bazzoli F. (2014) Epidemiology of Helicobacter pylori Infection. Helicobacter, 19: 1–5. doi:10.1111/hel.12165

However, only a minority of persons with *Helicobacter pylori* will develop PUD.[315] The lifetime risk for developing PUD is estimated to be 10%. The incidence of PUD has decreased significantly at the turn of the 21st century, mostly because of the discovery of the role of *H. pylori*, for which the leading scientists obtained the Nobel prize in 2005. In the Netherlands, the incidence of histologically confirmed PUD has halved between 1992 and 2003, and *"…a true decrease is likely. Hospital admissions for peptic ulcer declined dramatically between 1980 and 2003, but remained unchanged or slightly increased for complicated ulcers."*[316]

- Zollinger–Ellison syndrome (ZES): a disease caused by a gastrin-secreting tumour. The prevalence of ZES is estimated at 1-2 cases per million.[317] Without liver metastases, the 10-year survival rate is 90-100%. Howeever, with such metastases – which occur in 65– 75% of patients – the survival rate drops dramatically to 20-40%.

The development of Losec goes back to the 1960s.[318] Building on an increasing understanding of how gastric acid secretion in humans is regulated, scientists from the Sahlgrenska Hospital in Gothenburg, Sweden worked in a partnership with the small Astra-owned pharmaceutical company Hässle AB. Although it would take 22 years for Losec to make it to market, this public-private partnership would ultimately prove to be a resounding commercial success. The drug can safely be considered truly innovative: prior to the development of Losec, peptic ulcers were a very common affliction that frequently necessitated surgery. The development of Losec changed all that.

The success of Losec is due to a combination of extreme effectiveness and a minimal risk of side-effects. This is because the drug itself is an inactive prodrug that is only activated upon reaching the area in the body where it is intended to act. Its effectiveness is aided by a special packaging that allows the drug to pass the stomach intact before its release into the bloodstream. Omeprazole is on the WHO's list of Essential Medicines.

In the Netherlands, Losec (20mg gastro-resistant tablets) has been registered since 9 November 1988.

7.4.2 Market data

Losec was first introduced in 1989 in the US by Astra AB, now AstraZeneca. At the request of the FDA, the company changed the brand name in the US from Losec to Prilosec to avoid confusion with another drug. It was initially a prescription drug, but later (see below) was also sold in over-the-counter (OTC) versions.

In 2002, the drug was one of the best-selling drugs in history, with sales of around US$26b between 1997 and 2001.[319] The drug obtained considerable media coverage, including in case studies on strategic behaviour of pharmaceutical companies, for the employed strategies to manage patent life and deter generic competition.

With a patent expiry in the US in April 2001, in the mid-1990s AstraZeneca allegedly initiated the 'Shark Fin Project', the purpose of which was said to be to 'frustrate' generic competition.[320] Key to the strategy was the development of Nexium (Esomeprazole), a patented drug very similar to Losec, but with a different stereochemistry. Because of this difference, Nexium is not subject to compulsory substitution by generic Omeprazole. A huge marketing effort was started to promote Nexium with physicians, while promotion of Losec was stopped. The price for Nexium was set 15% lower than the older drug and the drug was advertised as 'from the makers of Prilosec'.[321] In addition, via a deal with

[315] Wadie I. Najm, Peptic Ulcer Disease, In Primary Care: Clinics in Office Practice, Volume 38, Issue 3, 2011, Pages 383-394, ISSN 0095-4543, https://doi.org/10.1016/j.pop.2011.05.001.

[316] Post, P. N., Kuipers, E. J. and Meijer, G. A. (2006), Declining incidence of peptic ulcer but not of its complications: a nation-wide study in The Netherlands. Alimentary Pharmacology & Therapeutics, 23: 1587–1593. doi:10.1111/j.1365-2036.2006.02918.x

[317] http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=913

[318] http://www.akademiliv.se/en/2013/12/15747/, accessed 9 January 2018

[319] https://www.wsj.com/articles/SB1023326369679910840

[320] Reena, K. (2013): Interdisciplinary Perspectives on Business Convergence, Computing, and Legality

[321] http://faculty.msb.edu/homak/homahelpsite/webhelp/Content/Pharma_Prilosec_-_Nexium.htm

Proctor & Gamble, Losec meanwhile was made available for OTC distribution. The strategy paid off: Nexium sales soared, while Losec sales (including the generic variants, once available) plummeted.

Although the case of Losec/Nexium is often presented as an example of savvy marketing shenanigans, AstraZeneca has argued that Nexium for certain patients in fact has clinical advantages over Losec. Losec is a so-called racemic mixture, containing both stereoisomers of the drug. In the body, one of these isomers is converted into the other form, which is the active compound. Nexium, by contrast, contains only the active form. It is therefore reportedly more effective in patients who are slow metabolisers. A systematic review and meta-analysis published in 2015 indeed found a significant difference between Esomeprazole and Omeprazole in certain subgroups of GERD patients.[322]

Upon expiry of protection on the original product, and faced with a threat of generic competition and parallel import, AstraZeneca withdrew the marketing authorisation for the capsule administration form of Losec in Norway, Sweden and Denmark. [323] The argument underpinning the withdrawal of the capsule form was that the tablet formulation, using the so-called 'multi unit pellet system' (MUPS), in which the active ingredient is contained in tiny individually coated pellets, allows slower release and better dosing of the drug in the body. Independent (*in vitro*) studies comparing the drug release over time of Losec MUPS tablets against various generic forms of Omeprazole suggest that the tablet formulation of AstraZeneca is more effective.[324] At the same time, however, the withdrawal of the marketing authorisation for the capsule form severely delayed generic competition, as the original product generic manufacturers had to refer to was no longer authorised on the market. The European Commission eventually sued AstraZeneca in 2005 for abusing its market-dominant position and AstraZeneca was fined €60m. In 2010, the CJEU confirmed the position of the EC in most (but not all) parts, which then led to a final fine of €52.5m (Decision T-321/05 of 1 July 2010). Most prominently, it confirmed the EC's allegations i) that AstraZeneca made *"…misleading representations before the patent offices or courts of several Member States of the EEA, to induce them to deliver to it, for Losec, a supplementary protection certificate to which it was not entitled, or only for a more limited period."*[325] and ii) that AstraZeneca could be sanctioned for *"…deregistration of the marketing authorisations for Losec in Denmark, Norway and Sweden, in order to delay or make more difficult the marketing of generic medicinal products."*[326]

Figure 30 shows the evolution of global sales for Losec/Prilosec between 1999 and 2016. One can observe a steep decline in revenues after 2001.

[322] Qi Q, Wang R, Liu L, Zhao F, Wang S (2015). Comparative effectiveness and tolerability of esomeprazole and omeprazole in gastro-esophageal reflux disease: A systematic review and meta-analysis. Int J Clin Pharmacol Ther. 53(10):803-10.

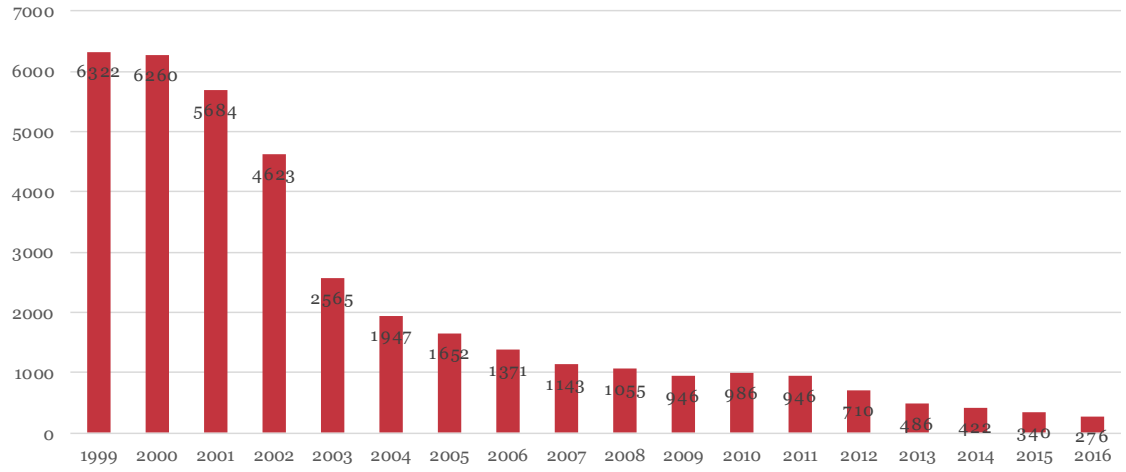
[323] Lehnhausen, A.K. (2017): Studies on Competition and Antitrust Issues in the Pharmaceutical Industry

[324] Tahmassian R, van der Zee PH (2005) De patiënt had toch gelijk. Pharmaceutisch Weekblad 26|27

[325] http://ec.europa.eu/dgs/legal_service/arrets/05t321_en.pdf

[326] Ibid.

Figure 30 Global sales of Losec/Prilosec 1999–2016 (US$m)



Source: AstraZeneca Annual Reports

7.4.3 Patents and supplementary protections

According to an article in the Dutch press, the patent on Losec in the US was to expire in 2001, in the UK in 2002, in Germany in 2003 and in France in 2004.[327] The explains the rapid drop in global sales between 2000 and 2004, as observed in Figure 30.

Losec has been on the Dutch market since 9 November 1988. The basic patent (EP0005129) expired 10.40 years later on 2 April 1999, after which it benefitted from an SCP (EP0005129) until 15 November 2002 (3.62 years). The paediatric extension did not yet exist in the EU at the time.[328]

7.4.4 Pricing, users and costs in the Netherlands

The first mention of Losec/Omeprazole in the Dutch media dates back to 1990, when a Dutch study showed it to be more effective than its competitor Zantac.[329] Five years later, Losec is mentioned as the most costly[330] drug for the Dutch health care system in 1994.[331] It kept that position until 2000, after which it was taken over by Lipitor.[332] By 2001, when the expiration date of the basic patent protecting Losec was nearing, an acclaimed 95% of Losec users had changed to using MUPS, which benefitted from longer protection. A few months before the SPC expired, health insurers announced they planned to procure the production of generics for Omeprazole and various other medicines on the market themselves.[333] A few months later, however, they stated that this plan had failed because of insufficient interest from producers.[334]

AstraZeneca was reported to have lost more than 70% of its market share for Omeprazole in less than a year even though the price of generics was only 10 to 13% lower than that of Losec.[335] However, the

[327] Maagkrampen deren AstraZeneca niet, *Het Financieele Dagblad*, 2 June 1999.

[328] Losec did obtain 6 months paediatric extension in the US. Europese farma niet zonder zorgen, *Tijd Nieuwslijn*, 23 August 2001.

[329] Rustig leven beste middel bij maagzuur, *NRC Handelsblad*, 15 September 1990.

[330] 'Costly' here refers to the overall budget impact (i.e. the price per user (P) x number of users (Q)), and not to the cost per patient.

[331] Paracetamol het meest geslikt, *Algemeen Dagblad*, 21 April 1995.

[332] Medicijnmarkt: truc met duur Losec, *Elsevier*, 6 November 1999. Uitgaven medicijnen stegen vorig jaar iets minder hard, *ANP*, 23 March 2001. Borst maakt pillen duurder, *De Volkskrant*, 17 August 2001.

[333] Zorgverzekeraars willen medicijnen namaken, *ANP*, 24 August 2002.

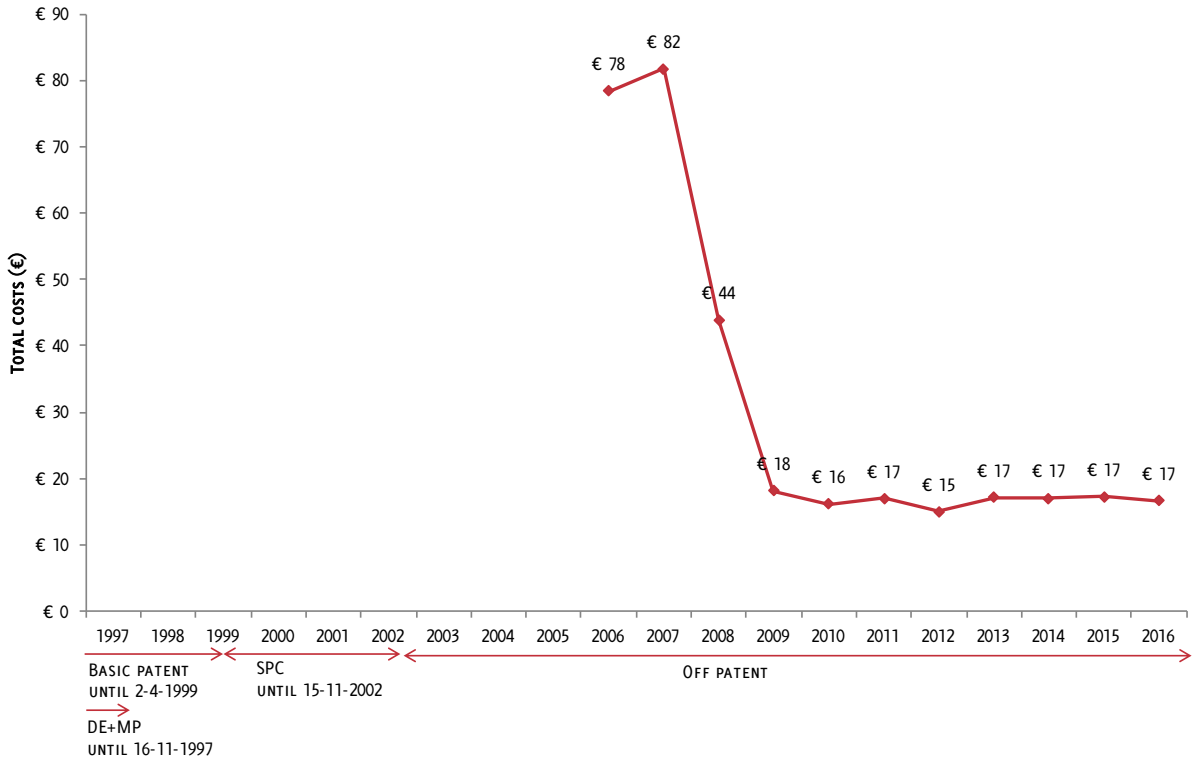
[334] Aanbesteding geneesmiddelen mislukt, *ANP*, 19 December 2002.

[335] Nagemaakte medicijnen vaak nog veel te duur; Generiek middel moet biologisch hetzelfde werken, *De Volkskrant*, 10 May 2003.

market for Omeproazole itself had shrunk in favour of Esomeprazole (Nexium) and Pantoprazole (Prezal) which were still under protection.[336] In the following years, Losec was one of the target medicines for policy to promote doctors and patients to switch to generics once a patent expired, for instance by giving a bonus to GPs.[337] Still, the prices and costs of Omeprazole would only come down gradually.

Detailed data for the usage and costs of Omeprazole are only available from 2006 onwards, a few years after the basic patent protecting Losec expired. By 2006, total costs had come down from over €200m in the early 2000s, to €78m (Figure 31). Between 2007 and 2009, the total costs dropped sharply to less than €20m, where they have since stabilised. Since figures are only available for 2006 and later years, no detailed estimation of the costs of the SPC for the Dutch health care system can be given as it was done for Lipitor. However, a rough estimation is possible. Given the overall decrease in costs from around €200m per year in the early 2000s to around €17m from 2009 onwards, the annual costs of protection were in the order of €183m per year. For the duration of the SPC of 3.62 years, this amounts to a total cost of around €660m.

Figure 31 Total costs Omeprazole in the Netherlands, 2006 – 2016



Source: Data SFK (2017)

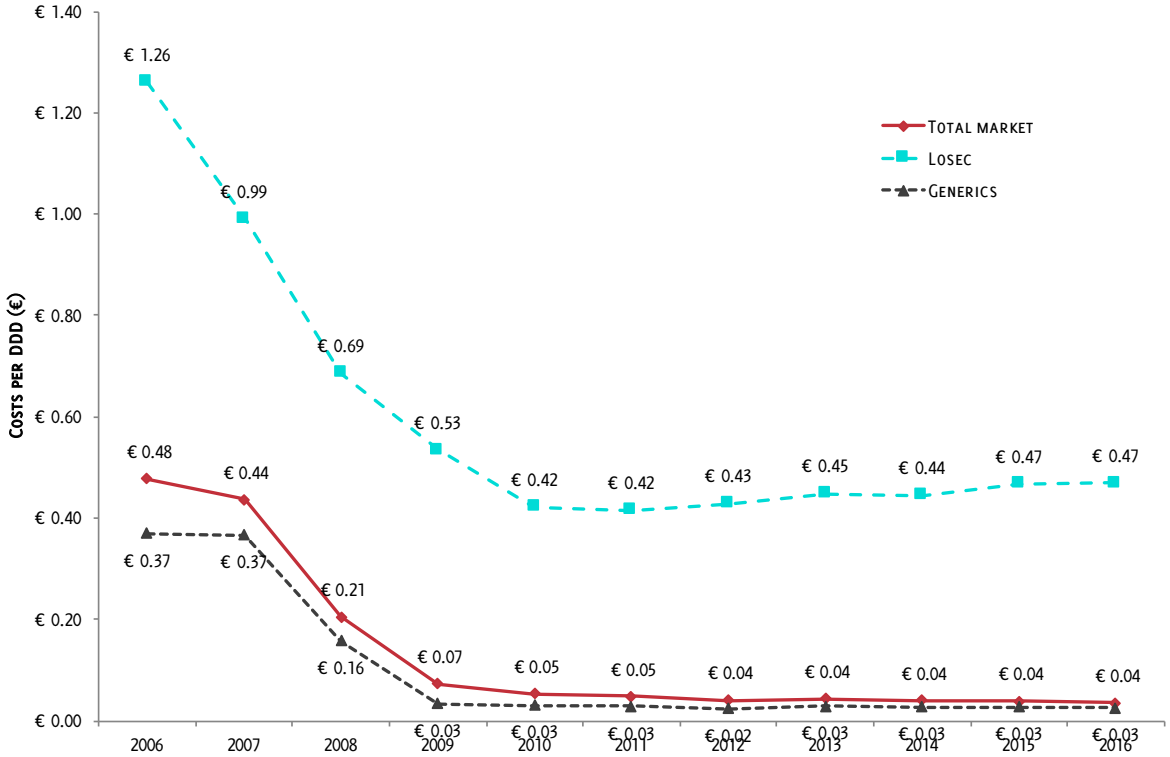
Figure 32 shows the development of the average costs per defined daily dose (DDD) for Omeprazole in the Netherlands between 2006 and 2016: the red line represents the total market, the dashed blue line that of AstraZeneca/Losec and the dashed black line that of generics. Throughout this entire period, Losec was priced well-above the market average: from a factor 2.6 in 2006 to a factor 13 in 2016. Since 2010, the price per DDD for Losec has in fact increased, which is indicative of its strong position amongst remaining users even after the basic patent expired. Moreover, Losec actually regained market share between 2008 and 2009 in € sales (which it lost again in the ensuing years), despite a

[336] Verzekeraars rekenen zich rijk met goedkope pillen; Zware druk om duurdere middelen te verkopen, *Trouw*, 17 May 2013.

[337] Menzis geeft premie aan huisartsen, *Leeuwarder Courant*, 15 September 2005.

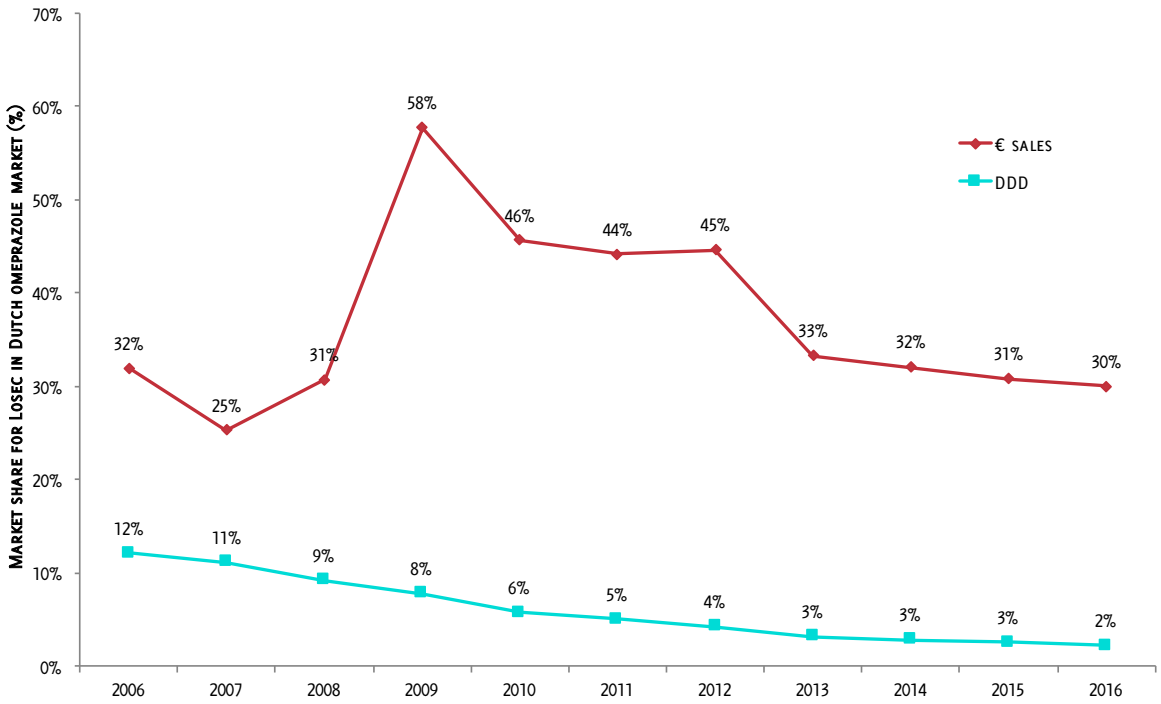
steep drop in the average price of generics between 2007 and 2009 (Figure 33). In terms of DDD, Losec gradually lost market share each year between 2006 and 2016.

Figure 32 Cost per DDD for Omeprazole in the Netherlands, 2006 – 2016



Source: Data SFK (2017) As omeprazole was no longer under any form of protection throughout the entire time period shown, the individual protections are not restated here.

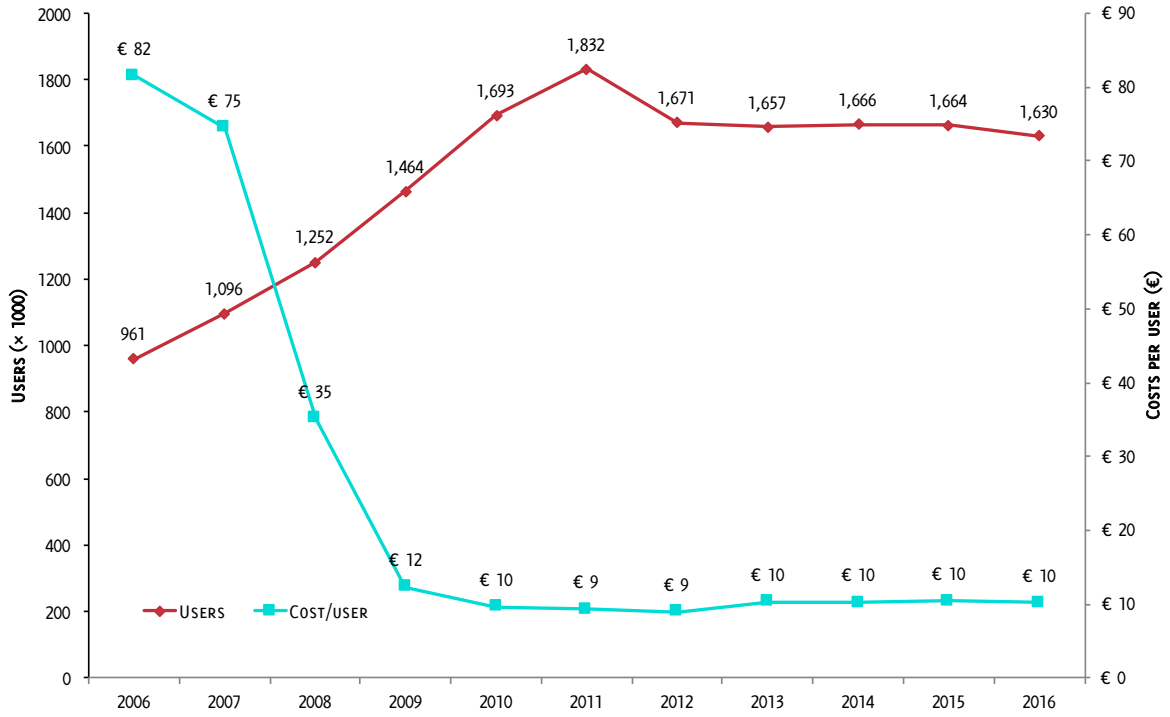
Figure 33 Market share Losec (€ sales and DDD) in the market for omeprazole in the Netherlands, 2006 – 2016



Source: Data SFK (2017) As omeprazole was no longer under any form of protection throughout the entire time period shown, the individual protections are not restated here.

The drop in the average costs per DDD between 2007 and 2009 in Figure 32 is mirrored in a similar drop in the average annual costs per patient (Figure 34), from €82 in 2006 to about €10 from 2010 onwards. The number of users continued to increase until it stabilised at around 1.7 million in 2010.

Figure 34 Users and cost per user for Omeprazole in the Netherlands, 2006 – 2016



Source: Data SFK (2017) As omeprazole was no longer under any form of protection throughout the entire time period shown, the individual protections are not restated here.

7.5 Cozaar

7.5.1 Background

The drug Cozaar (active substance Losartan) is indicated for two distinct uses: the treatment of hypertension (HT) and that of diabetic nephropathy (DN). Hypertension is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. Long-term HT is associated with an increased risk for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease. Consequently, it is a leading cause of morbidity and mortality worldwide; it has been estimated to cause 7.5 million deaths globally.[338] In the Netherlands, around 21% of men and 15% of women suffer from HT.[339] Of these, about 17.9% of men and 38.5% of women receive antihypertensive medication.

Diabetic nephropathy is a condition where patients with diabetes mellitus (DM) experience chronic loss of kidney function. In the Netherlands, at present, some 914,000 persons suffer from DM, most of whom have Type-2 diabetes.[340]. After a stark increase in the number of new diagnoses, since 2013 the prevalence of DM has stayed fairly constant.[341] DN is one of the most serious long-term complications

[338] http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/

[339] Schelleman, H. (2004): Prevalence and determinants of undertreatment of hypertension in the Netherlands, in: J Hum Hypertens. 2004 May;18(5):317-24.

[340] Kleefstra et al. (2016): Dutch diabetes prevalence estimates (DUDE-1), in: J Diabetes. 2016 Nov;8(6):863-865. doi: 10.1111/1753-0407.12370.

[341] Ubink-Veltmaat, L. J., Bilo, H. J. G., Groenier, K. H., Houweling, S. T., Rischen, R. O. & Meyboom-de Jong, B. (2003): Prevalence, incidence and mortality of type 2 diabetes mellitus revisited: A prospective population-based study in The Netherlands (ZODIAC-1), in : European Journal of Epidemiology. 18, 8, p. 793-800 8 p.

of DM and is the leading cause of chronic kidney diseases and end-stage renal disease. A recent study found that 23% of Dutch DM patients develop DN.[342]

The initial development started in the 1980s when a team of researchers, led by Dr. Pieter Timmermans, at DuPont set up an R&D programme for coronary diseases, central nervous systems and anti-inflammatory drugs (and to a lesser degree oncology). Losartan was discovered in 1986. It was the first angiotension II receptor antagonist, representing a new class of therapeutic agents known as 'sartans'.[343,344] The research that led to the discovery of Losartan built upon the earlier discovery of another class of hypertensive drugs known as angiotensin-converting enzyme inhibitors (ACE inhibitors). Whilst the two classes of drugs interact with the same pathway, they do so in different parts of the process and have a different molecular make-up. There were also two patents from Takeda on AT1-receptor antagonists that influenced the development of the drug.

Initially, the marketing department expressed doubts on the possible success of the drug, given that a) the still-needed investments were of considerable magnitude and b) it did not see a chance to differentiate the product from other drugs, such as the ACE inhibitors, and recommended out-licensing to reduce development and cost risks.[345] Researchers, however, disagreed and considered the new drug a scientific break-through, due to its novel mechanism of action. Eventually, DuPont continued development but faced other challenges in the form of lack of experience and capacity to conduct the large, costly clinical trials. DuPont then teamed up with Merck & Co., Inc. – who already had a leading position in the coronary disease market. A collaboration agreement was signed in 1990 for the further development of the drug.

Cozaar obtained FDA approval in 1995. In Europe, it was first introduced into the market in 1995 in Sweden, the UK and France. It became a blockbuster drug as it excelled in terms of efficacy with very few side effects compared to its competitors. As the first of its kind, the drug has become the prototype for numerous other sartan drugs. Since the initial marketing authorisation, Merck has continued the testing and development of Losartan. This has resulted, for instance, in the products Hyzaar, Cozaar Plus and Fortzaar – all combination products containing the diuretic hydrocholorothiazide. In addition, it has developed an oral-suspension formulation of Cozaar, suitable for paediatric use. In addition to its value as a treatment patients with hypertension and renal disease, the drug became a scientific tool for exploring the pathophysiology of the renin-angiotensin system.

Cozaar received marketing authorisation in the Netherlands on 14 March 1995.

7.5.2 Market data

Figure 35 shows the evolution of global sales of Losartan, according to the annual reports of Merck (to be more precise: the combined sales of Cozaar and Hyzaar[346]; a break-down by the two drugs is not available). Reliable data is not available for the time before 2002. Nonetheless, a steady increase of sales, peaking in 2009, – one year before the expiry of the basic patent – can be seen. COZAAR was the leading Angiotensin II Antagonist (ARB) in the Netherlands until the expiry of protections.

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[342] van Herpt TTW, Lemmers RFH, van Hoek, M et al. (2017) Introduction of the DiaGene study: clinical characteristics, pathophysiology and determinants of vascular complications of type 2 diabetes. Diabetol. Metab. Syndr. 9: 47. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5477157/. Accessed 28 October 2017

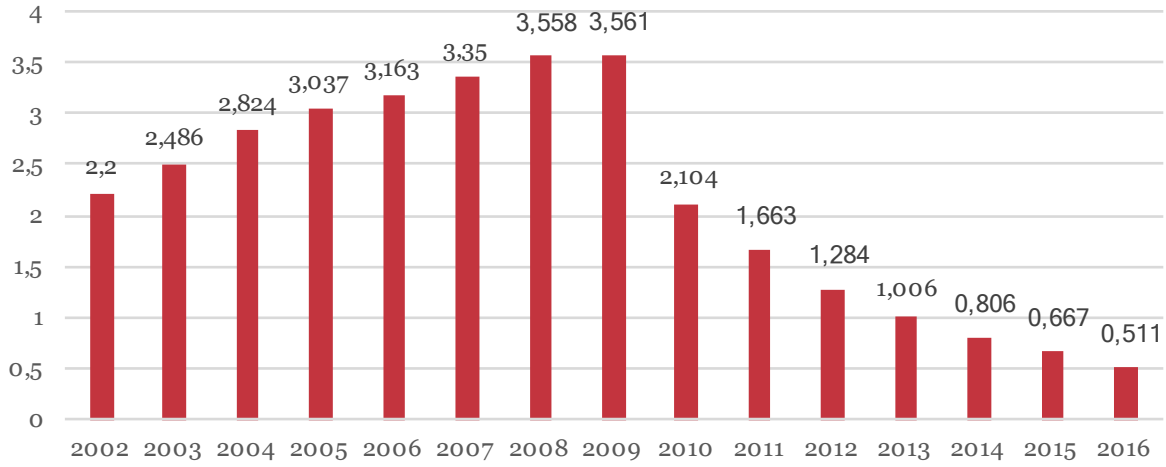
[343] Timmermans PB, Duncia JV, Carini DJ et al (1995) *Discovery of losartan, the first angiotension II receptor antagonist*. J Hum Hyupertens. 9Supp5: S3-18. https://www.ncbi.nlm.nih.gov/pubmed/8583479

[344] Timmermans PB, Smith RD (1994) *A new class of therapeutic agentsL the aniotension II receptor antagonists*. 39(12 Supp1):397-400 https://www.ncbi.nlm.nih.gov/pubmed/7634303

[345] Bhardwaj G (2006). How the antihypertensive losartan was discovered. Expert Opinion on Drug Discovery 1(6). https://doi.org/10.1517/17460441.1.6.609.

[346] Hyzaar is Losartan combined with a diuretic

Figure 35 Global sales of Cozaar (US$b)



Source: Merck Annual Reports

7.5.3 Patents and supplementary protections

Cozaar has been protected by various patents. The basic patent for the final AT1-receptor antagonist was filed in 1988.[347] In November 1989 a patent was filed specifically for the indication of hypertension.[348] In November 1992, another patent was filed for the indication of chronic kidney disease.[349] Another patent followed for a process patent for a new form of producing Cozaar in 1995.[350] In the Netherlands, the basic patent (EP0253310) expired on 8 July 2007, but was followed by SPC protection (950009) until 2 September 2009 and half a year of paediatric extension until 1 March 2010. Combined, this amounts to almost 15 years of protection in the Netherlands between MA and the expiration of the paediatric extension. During the term of protection, MSD sublicensed Losartan to various third parties. After the SPC expiry, Merck globally bought all remaining rights to Losartan from DuPont.

There is an SPC case discussed involving Losartan, in Belgium and in France in 2010.[351] The litigation involved Merck and Du Pont on the one hand, and the generics manufacturer Mylan on the other hand. The case involved Hyzaar, a combination product of Cozaar with Hydrochlorothiazide (HCTZ), a first line diuretic drug of the thiazide class. There were several companies, including Mylan, that prepared for the launch of generic versions of the combination product. Merck wanted to prevent the launch and filed a preliminary injunction action, arguing that an SPC granted for Losartan would also protect this product, even when it is part of a composition with another combination product and even if a different SPC was granted for the combination product. Mylan, however, claimed that *"...the drugs containing only losartan, on the one hand, and those containing losartan combined with HCTZ, on the other hand, constitute different products and that only SPC nr. 96C0020 had obtained a paediatric extension so that the combination product co-losartan was not covered by this paediatric extension."* The Belgian court sided in the first instance with Mylan's argumentation. Therefore the combination product Hyzaar could not benefit from the protection offered by the paediatric extension of the SPC for Losartan. Although upheld also in the second instance, the Court of Appeals said the issue was a matter for the judge to decide on the merits of the case. Despite the failure of Merck to obtain an injunction, Mylan did not launch its generic product in Belgium until after the expiry of the

[347] US patent 5.138.069; However, priority is 11 July 1986. This seems to correspond to patent number EP 0253310 with the same priority. According to the FDA, the expiry date was 11 August 2009.

[348] US patent 5.153.197.

[349] US patent 5.210.079

[350] US patent 5.608.075

[351] http://patentblog.kluweriplaw.com/2010/04/28/the-losartan-case-in-belgium-one-spc-too-far/

extended SPC for Losartan. The French courts ruled differently, in line with Merck's argumentation. In February 2012, the CJEU endorsed the rulings the French Courts.[352]

7.5.4 Pricing, users and costs in the Netherlands

The introduction of Cozaar in the Netherlands was surrounded with some controversy, as the leader of the liberal party, Frits Bolkestein, who was at the time also a member of the Supervisory Board of Merck Sharpe & Dohme B.V. (MSD) was revealed to have lobbied the Minister of Health in May 1995 for acceptance of the drug for reimbursement, stressing that delay could have negative consequences for MSD's Dutch production plant.[353] A few months later the drug was accepted.

For many years, Losartan was one of the drugs with the highest budget impact in the Dutch healthcare system, due to the large number of patients using it on a daily basis. In 1999, Cozaar was one of the medicines (together with Zocor, Selektine, Losec and Imigran) for which the Minister of Health pressured a company to lower its price.[354]

Figure 36 shows the development of the average price per defined daily dose (DDD) for Losartan in the Netherlands between 2006 and 2016. The red line represent the total market, the dashed blue line that of Cozaar (including Entrizen also produced by MSD), and the dashed black line that of the generics that entered the market from 2010 onwards. A very significant price drop occurred between 2007 and 2011, mostly between 2009 and 2010 when the drug came off patent. The average price per DDD in the first three years shown is 20 times higher than the average price in the last three years.

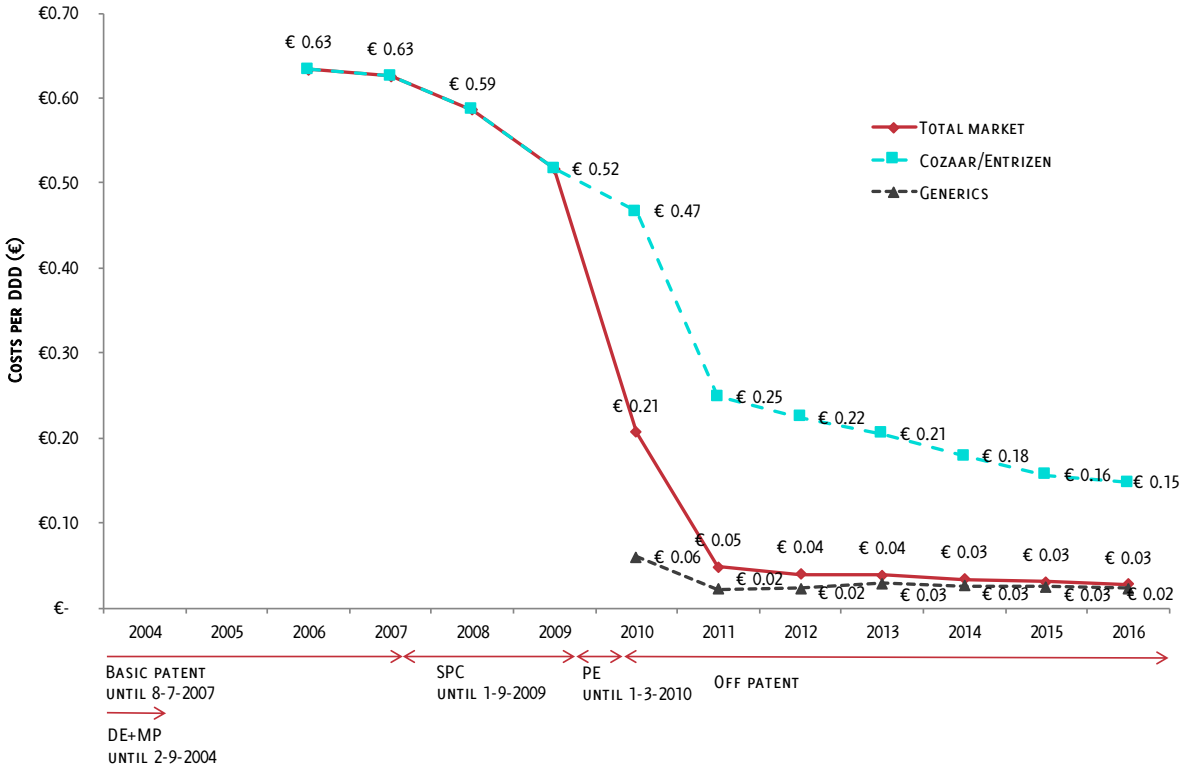
The dashed red line shows that while the price of Cozaar and Entrizen also decreased over the depicted time span, it stayed well above the market average after generic entry and the most significant price drop occurred one year after the expiration of the patent. After protection expired, MSD's market share for losartan dropped significantly, albeit not as rapidly as that of Pfizer for atorvastatin. In € sales, it converged to around 20% which is also higher than that of Pfizer, which suggests there is substantial remaining brand loyalty for this drug and MSDs price strategy pays off. In DDD, MSD's market share dropped to 4%.

[352] Novartis v Actavis, Case C-442/11, Order dated February 9, 2012.

[353] VVD-leider probeerde als commissaris van MSD meermalen minister Borst te beïnvloeden, *Trouw,* 23 September 1996. Passages uit brief aan minister Borst, *NRC Handelsblad*, 23 September 1996.

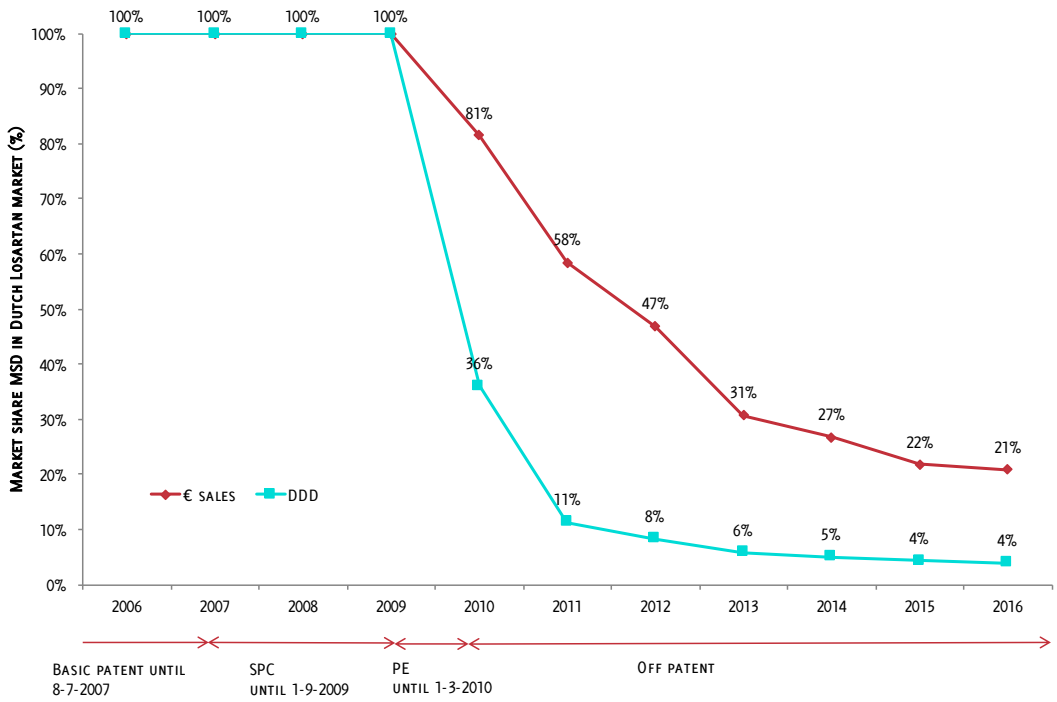
[354] Medicijnenmakers draaien bittere pil voor minister Borst, *De Volkskrant*, 22 March 1999.

Figure 36 Cost per DDD for Losartan in the Netherlands, 2006 – 2016



Source: Data SFK (2017)

Figure 37 Market share Cozaar (in € sales) in the losartan market in the Netherlands, 2006 – 2016



Source: Data SFK (2017) Data exclusivity and market protection expired before the period of analysis and are therefore not shown here anymore.

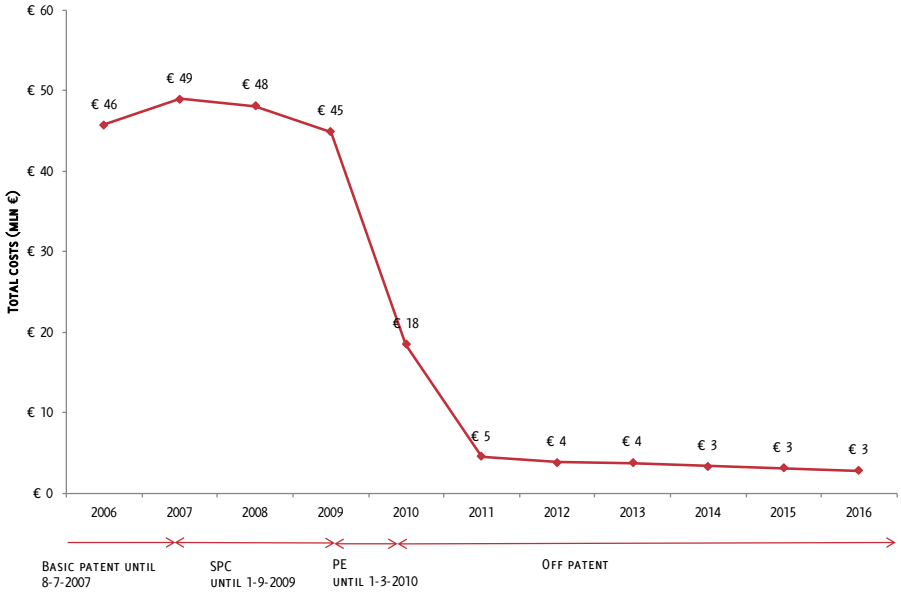
The drop in the average costs per user is mirrored in a similar drop in the average annual costs per patient (Figure 38), from €249 in 2006 to €12 in 2016. During this period, the number of users increased gradually from 183,000 in 2006 to 245,000 in 2016. There is no indication that this increase was affected by the price drop around 2009-2010.

Figure 38 Users and cost per user for Losartan in the Netherlands, 2006 – 2016

Source: Data SFK (2017) Data exclusivity and market protection expired before the period of analysis and are therefore not shown here anymore.

The total costs of losartan in the Netherlands dropped from €45~49m per year up until 2009, to €3~4m per year in the last four years, despite the gradual increase in the number of users (Figure 39).

Figure 39 Total costs Losartan in the Netherlands, 2006 – 2016 (€m)



Source: Data SFK (2017) Data exclusivity and market protection expired before the period of analysis and are therefore not shown here anymore.

Assuming that the post-2011 prices are still at or above marginal production costs of the medicine and that these marginal production costs have not changed substantially over this time frame, this implies an operational profit margin of at least 95% on costs in the years preceding 2009, similar to that of Lipitor. This concords with the point made in section 7.2 that during protection, the price of drugs is related to willingness-to-pay rather than production costs. Prices were at least 20 times the marginal production costs in the last year before the expiration of the patent. After that, several generic versions of Losartan became available and prices dropped due to price competition and the *preferentiebeleid*.

Figure 36 shows that Cozaar/Entrizen benefitted from an SPC between 9 July 2007 and 1 September 2009 (2.14 years) and from a paediatric extension until 1 March 2010 (0.5 years). Thus, SPC plus paediatric extension lasted for 2.64 years and the total time between the marketing authorisation in the Dutch market and the expiration of the paediatric extension was 14.96 years.

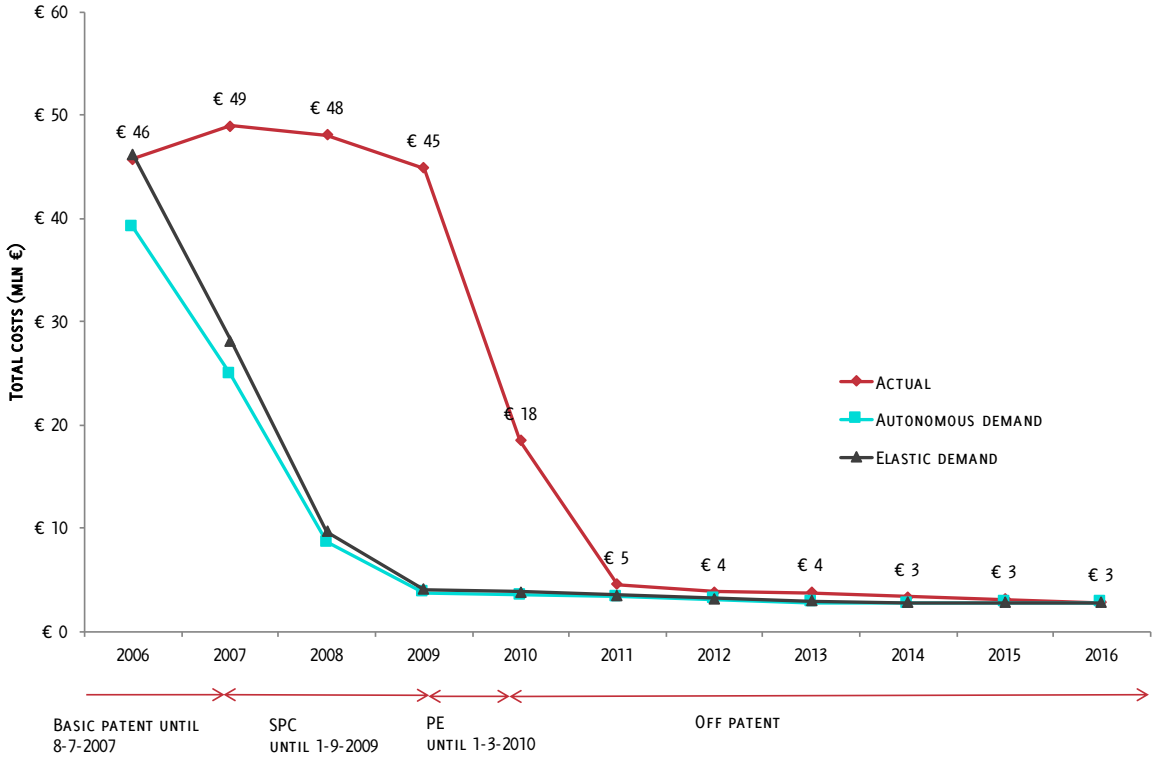
To estimate the additional revenues MSD generated in the Dutch market thanks to the SPC and the PE, and subsequently the additional costs for the Dutch health care system, two main assumptions have to be made: one about the price development over time in the counterfactual situation without SPC and PE, and one about the development of the number of users and DDDs in the counterfactual.

It is assumed that the cost development per DDD depicted in Figure 36 would have occurred 2.64 years earlier if there were no SPC and PE, and 0.5 years earlier if there were no PE. This implies that the gradual decrease in the costs per DDD that is observed between 2006 and 2009 is assumed to be anticipatory of the expiration of protection in 2010. The actual 2016 price level is assumed to remain stable which implies that without SPC and PE, this level would have been reached 2.64 years earlier and would have remained constant since.

For the counterfactual number of users/DDDs, one can either assume it is an autonomous development unrelated to pricing and protection. This would imply it is as observed in the original data. Or, one can assume that there is some elasticity of demand and sales volumes increase as prices drop. This would explain the gradually increasing number of users over time, although no response to the rapid price drop between 2009 and 2011 is observed. Following this assumption, the usage data would shift by 2.64 or 0.5 years if there were no SPC and PE.

Figure 40 shows the resulting total costs over the years. The area between the red line and the blue or black lines represents the costs to the Dutch health care system that can be attributed to SPC and paediatric extension protection for Cozaar/Entrizen. Over the years 2006-2016 this amounts to €118~130m, depending on the assumption of elastic or autonomous demand respectively. The additional revenues for MSD are in the same range. Along the same lines, the extra costs of paediatric extension for the Dutch health care system are estimated at €21~26m.

Figure 40 Actual costs of Cozaar in the Netherlands, and estimated costs without SPC and paediatric extension, 2006 – 2016



Source: Data SFK (2017)

7.6 Atripla

7.6.1 Background

Despite tremendous progress in the fight against HIV, HIV continues to be a major global public health issue. In 2016, there were an estimated 36.7 million people living with HIV (PLHIV), most of whom reside in low- and middle-income countries (LMICs).[355] The Netherlands has seen a steady decline in the number of new diagnosis over the last eight years. As of 2016, there are around 25,000 people with known HIV infection.[356] Of these, 17,721 are on combination antiretroviral therapy (cART).[357] Purpose of cART is to suppress the viral load, halting the progression of HIV infection into AIDS. As such, HIV is now considered to be a chronic disease, but cART needs to be taken for the rest of the patient's life.[358] One form of cART is the drug Atripla. It is a combination drug that consists of three active ingredients as a single tablet regimen (STR):[359]

- Efavirenz (most common brand name: Sustiva) was commercialised by Bristol-Myers Squibb as Sustiva for six European countries, the US and Canada. It was marketed as Stocrin by Merck & Co. in other countries. The drug obtained FDA approval on 21 September 1998, as the 14th approved antiviral drug. It received Marketing authorisation in the EU per 28 May 1999. Its only indication is for HIV-I. On February 17, 2016, the FDA approved the generic tablet formulation produced by Mylan.

[355] https://www.avert.org/global-hiv-and-aids-statistics, based on UNAIDS Data 2017, last checked 22 October 2017

[356] HIV Monitoring Report 2016, *Stichting HIV monitoring*.

[357] https://www.hiv-monitoring.nl/files/8314/7877/7059/SHM_Factsheet_2016_ENG.pdf

[358] Ibid

[359] efavirenz 600 mg/emtricitabine 200 mg/ tenofovir disoproxil fumaraat 300 mg

- Emtricitabine was discovered at Emory University in the US and licensed to the company Triangle Pharmaceuticals in 1996. Triangle was subsequently acquired by Gilead Sciences in 2003, which completed development. The drug obtained FDA approval in 2003 for use against HIV-I and was sold as Emtriva. The drug is similar to Lamivudine in characteristics (and therefore with similar resistance characteristics). The drug was also shown to be clinically active against Hepatitis B virus (HBV), but has no FDA approval for that use. The drug is available as stand-alone, and in combination (together with tenofovir disoproxil fumarate as Truvada; and as part of the four-component STR Stribild)
- Tenofovir disoproxil fumarate (hereafter: tenofovir) is indicated to treat and prevent HIV-I and chronic Hepatitis B. It is sold both by itself and together as emtricitabine/tenofovir (Truvada) and efavirenz/emtricitabine/tenofovir (Atripla). Patented in 1997, it obtained FDA approval in 2001 for use against HIV-I and 2006 for use against Hepatitis B. The drug was developed at the Czech Academy of Sciences already in the 1980s, but its use for HIV-1 was only established later in a collaboration with Gilead.

All three components are, as of end of 2016, on the WHO's list of essential medicines, the most effective and safe medicines needed in a health system.

Atripla, the combination drug, obtained FDA approval in July 2006 and marketing authorisation in the EU in December 2007.[360] For the European market, a joint venture was formed ('Bristol-Myers Squibb, Gilead Sciences and Merck Sharp & Dohme Limited') in Ireland. The drug's only indication is for HIV-I.[361] It was the first single tablet regimen for the treatment of HIV-I in adults. Until 2015 in the US it was recommended as first-line treatment. In 2010 it was reported that one third of people with HIV taking ART were using Atripla. The main advantage of Atripla is its use as single once-daily pill. This reduces pill burden and simplifies dosing schedules, which has potential positive impacts also on adherence to ART therapy by patients.[362] In 2015, Atripla was repositioned to an "alternative" regimen.[363] This followed the appearance of new (combination) drugs from several pharmaceutical companies with less side effects and safer profiles. Gilead themselves launched Genvoya in 2016.

In the Netherlands, Atripla received marketing authorisation on 13 December 2007.

7.6.2 Market data

Figure 41 shows the evolution of global Atripla sales between 2008 and 2016. Sales increased considerably on a year to year basis between 2008 and 2012, peaking in 2013 and subsequently declining again. Between 2013 (total global sales: US$3.6b) and 2016 (total global sales: US$2.6b), there is a drop in yearly sales of nearly 30%. Sales in the US are almost double that in Europe. Other international sales are negligible by comparison, but this is also due to the fact that in LMICs efavirenz is sold at a reduced price. Furthermore, the combination emtricitabine/tenofovir has been licensed to the Medicines Patent Pool and is available cheaply in LMICs.

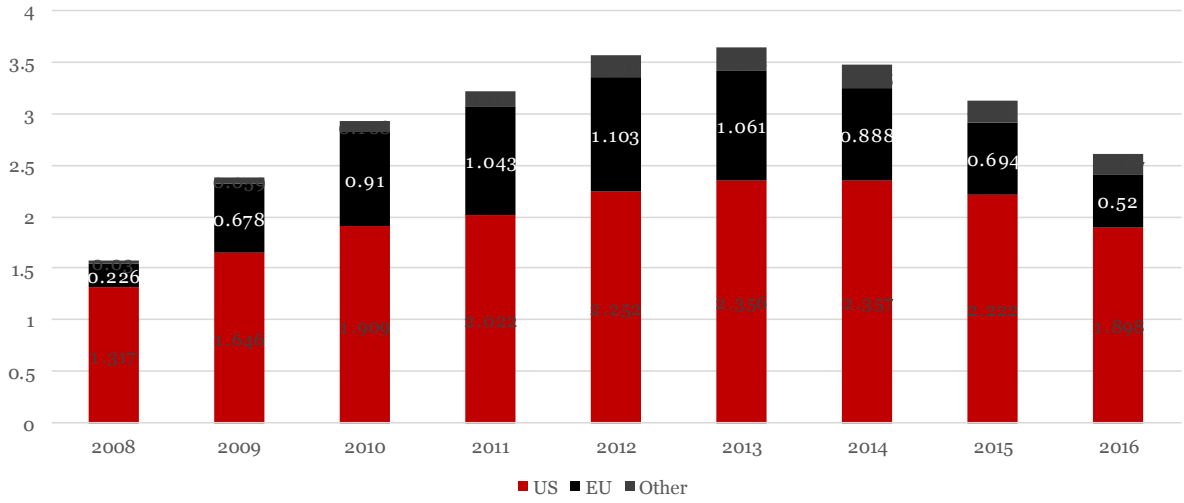
[360] https://news.bms.com/press-release/european-commission-approves-atripla-efavirenz-600-mgemtricitabine-200-mgtenofovir-dis, last checked 22 October 2017.

[361] In fact, there is a warning for use against HBV. http://www.clinicaladvisor.com/atripla/drug/1882/

[362] https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/51/hiv-treatment--the-basics

[363] http://www.fiercepharma.com/marketing/gilead-s-new-launch-genvoya-racks-up-big-script-growth-fastest-hiv-rollout-since-atripla, last checked 22 October 2017

Figure 41 Sales of Atripla, 2008 – 2016 (US$b)



Source: investors.gilead.com, last checked 22 October 2017

In 2017 the global HIV drug market had an estimated value of US$20.4b with an average annual growth rate (CAGR) of 3.7% in the forecast period 2016–2022. Demand for cART is boosted by the prevalence of HIV and rise in treatment and diagnosis rate, as well as by awareness raising programmes.[364] Despite this, with the advent of new drugs, analysts expect Atripla's revenue to continue to decrease to US$2.3b in 2017.[365] Moreover, from 2017 onwards Atripla may face generic competition in some European countries. GlaxoSmithkline (GSK) is Gilead's major competitor in the HIV space.

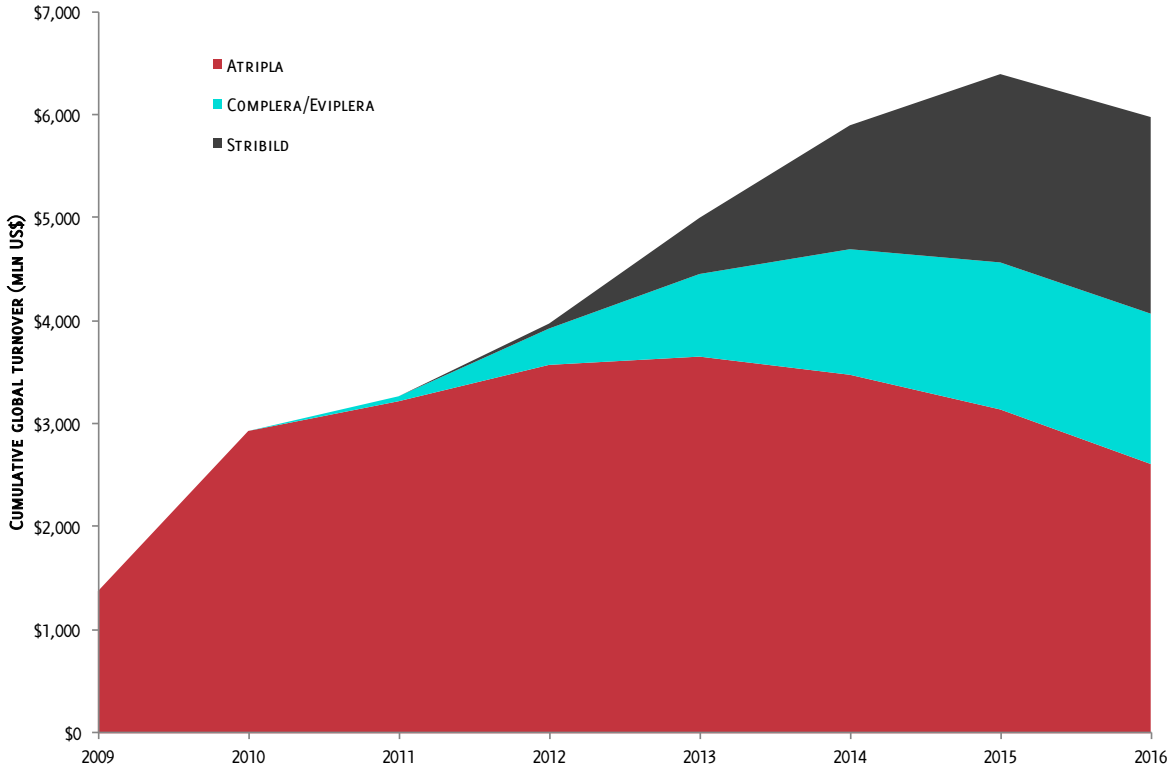
Gilead has continued to add more HIV drugs to its portfolio. By the end of 2011, Gilead acquired marketing authorisation in the EU for a second single tablet HIV-medication: Complera/Eviplera.[366] In May 2013, a third single tablet medication acquired marketing authorisation: Stribild. Also, as mentioned earlier, in 2016 Gilead launched Genvoya. Complera/Eviplera and Stribild have slowly taken over the position of Atripla in terms of global turnover (Figure 42). The combined turnover of these three drugs has continued to increase until 2015.

[364] https://www.alliedmarketresearch.com/hiv-drugs-market

[365] https://beta.marketrealist.com/2016/10/which-of-gilead-sciences-strs-could-decline-in-2017

[366] Gilead krijgt Europese vergunning voor het in de handel brengen voor Eviplera®, een nieuw, compleet eenmaal daags enkel-tablet regime voor hiv-1-infectie bij behandelingsnaïeve volwassenen, in: *Business Wire Netherlands*, 29-11-2011.

Figure 42 Global turnover Atripla, Complera/Eviplera and Stribild, 2009 – 2016 (US$m)



7.6.3 Patents and supplementary protections

According to data from drugpatentwatch.com there are 16 patents protecting Atripla. It furthermore has 21 SPCs in ten countries. In the UK the SPC on Atripla was invalidated, following the case of Teva UK Limited v Merck Sharp & Dohme Corporation. The main issue was whether there would be a valid basic patent covering Atripla and the three active ingredients. It was held that the basic patent invoked by the originator firm extends to two of the compounds, but would not cover the combination of all three active ingredients. Similarly, the contested patent in one of the claims was not seen as a sufficiently distinctive invention compared to efavirenz alone, for which an SPC had already been granted.[367]

In the Netherlands, Atripla was under patent (EP0915894) until 24 July 2017. An SPC application on the basis of this patent was withdrawn in September 2015. However, in a response to the case study, Gilead has pointed out that in the Netherlands it still holds a patent on tenofovir disoproxil fumerate until July 2018 (EP0998480). Also, an appeal against the refusal to allow an SPC on Truvada is still pending in court in the Netherlands. In case allowed, this SPC will in principle also cover Atripla and other medications containing tenofovir disproxil and emtricitabine. So far, there is no generic version of Atripla available either in the US, or in the EU.[368]

7.6.4 Pricing, users and costs in the Netherlands

In the Netherlands, discussions about the price of Efavirenz, one of the components of Atripla, date back to the year 2000.[369] One of the first mentions of Atripla in Dutch newspapers was in April 2009, when it was claimed to be used in the gay scene as a party drug with psychedelic

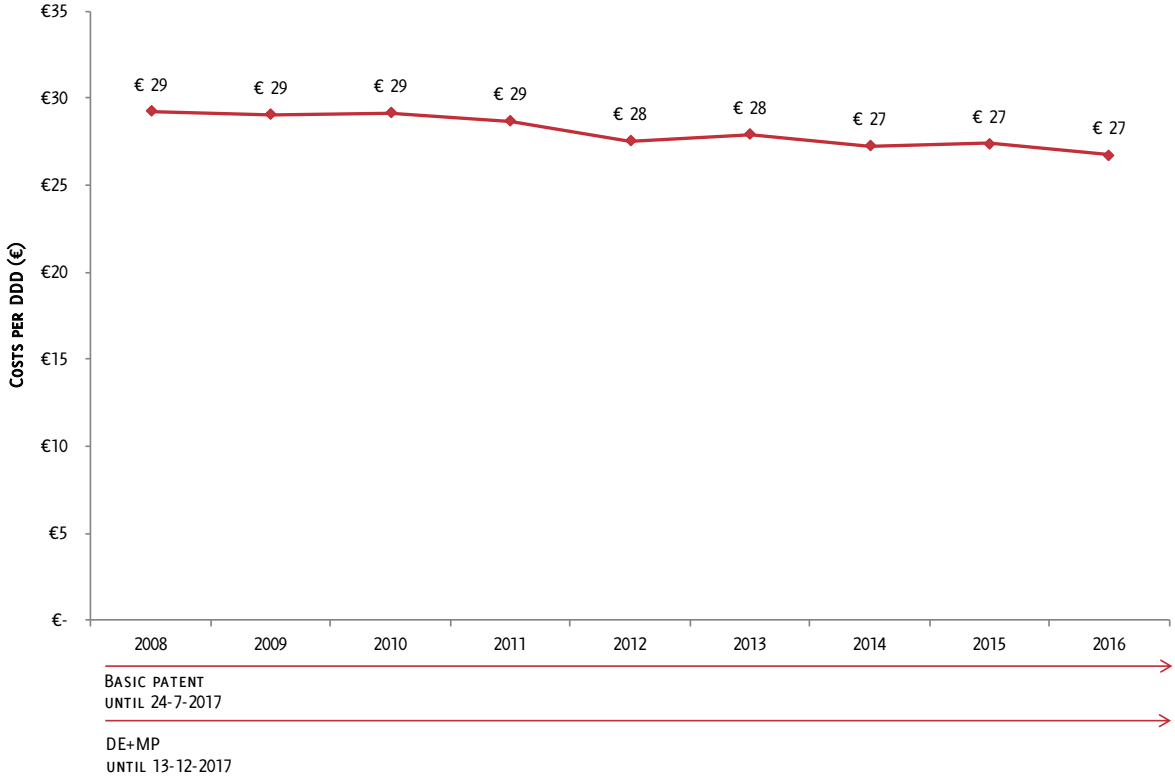
[367] https://www.lexology.com/library/detail.aspx?g=bc80b374-4a5c-43ba-95ef-6f682ce887ac, last checked 22 October 2017

[368] https://www.drugs.com/availability/generic-atripla.html,

[369] Medicijnkosten zware last voor hiv-patienten, in: *Algemeen Dagblad*, 31-1-2000.

effects, at a price of €31 per pill.[370] This matches well with the price per defined daily dose (DDD) from SFK data (Figure 43). Between 2008 and 2016, the nominal price per DDD decreased only slightly, from €29.22 tot €26.73: a 9% decrease over a nine year period. This stable price development can be understood against the background of the fact that Atripla has been under patent throughout this timespan. This also implies no information can be inferred from this concerning the annual costs of protection, since the counterfactual of generic competition has not yet materialised. No impact of the introduction of Complera/Eviplera, Stribild or Genvoya in the price of Atripla in the Dutch market can be observed either: there is neither a price drop, nor a price increase.

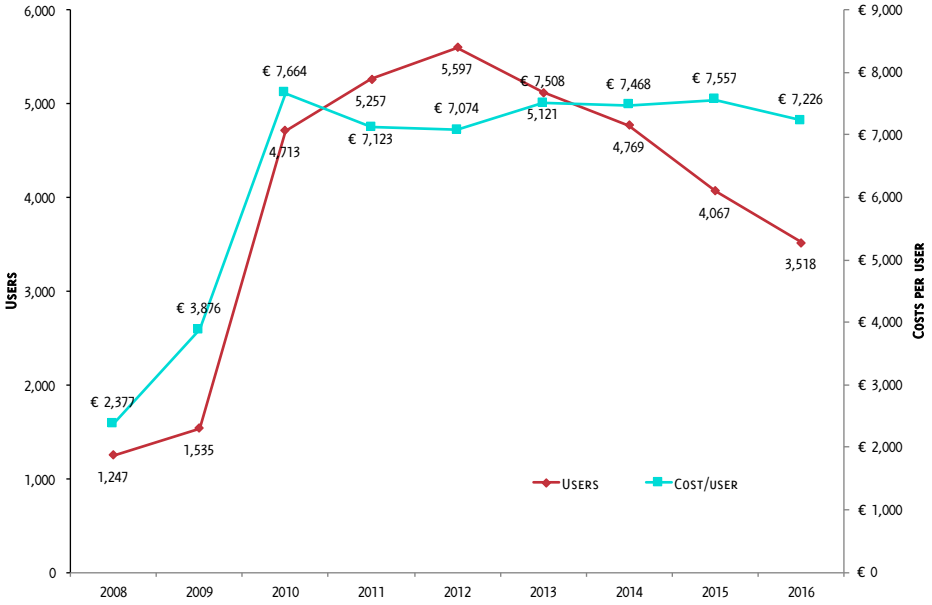
Figure 43 Cost per DDD for Atripla in the Netherlands, 2008 – 2016



Source: Data SFK (2017)

[370] Wilders als product van de emancipatie; Zapkliklees Hans Beerekamp, NRC Handelsblad, 23-4-2009.

Figure 44 Users and cost per user for Atripla in the Netherlands, 2008 – 2016

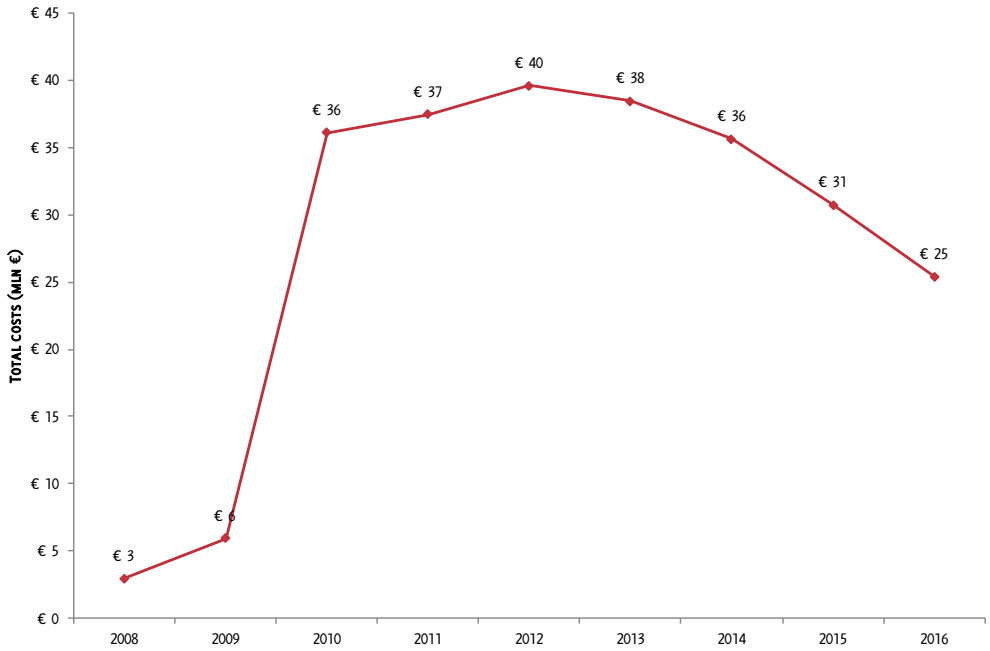


Source: Data SFK (2017) Both the basic patent on Atripla and the data exclusivity plus market protection period were in effect throughout the entire analysis period and are therefore not shown anymore.

In the first two years after market introduction (between 2008 and 2010) the number of users increased rapidly to approximately 5,000. Simultaneously, the average costs per user increased from €2,377 in 2008 to €7,664 in 2010 as a result of increasing dosages. Since then, the costs per user have stabilised, while the number of Atripla users has gradually decreased since its peak in 2012 to 3,518 in 2016 (Figure 44).

As a result of the decline in number of Atripla users since 2012, total costs have decreased from €39.6m in 2012 to €25.4m in 2016 (Figure 45). This development fits the global development in turnover for Atripla, which peaked in 2013. On average, total costs for the Netherlands were 1.4% of global sales for Atripla.

Figure 45 Total costs Atripla in the Netherlands, 2008 – 2016



Source: Data SFK (2017) Both the basic patent on Atripla and the data exclusivity plus market protection period were in effect throughout the entire analysis period and are therefore not shown anymore.

7.7 Myozyme

7.7.1 Background

Pompe disease (also known as glycogen storage disease type II) is a rare and progressive metabolic disease that affects about 1 in every 400,000 babies (0.0025%) born in the Netherlands.[371] Pompe disease is the result of deficiency of acid alfa-glucosidase (GAA), an enzyme that normally breaks down sugar stored as glycogen into glucose as energy by the body's cells. If the enzyme is not present, glycogen progressively builds up in certain tissues, particularly the muscles. This causes a wide range of symptoms, including an enlarged heart, breathing difficulties and muscle weakness.[372-373]

Depending on whether symptoms occur within the first six months after birth or, alternatively, later in life, Pompe disease is classified as infantile-onset or late onset illness, respectively.[374] The infantile-onset illness is rapidly progressive. For an infant born with the disease, the survival rate to age 12 months is estimated to be 26%.[375] Symptoms in the non-typical late-onset form can present at any age, and although the disease progresses more slowly in these cases, the median age of death in this group is 24.5 years (range 0.9–66, n=225).

[371] Ausems MG, ten Berg K, Kroos MA, van Diggelen OP, et al. (1999). Glycogen storage disease type II: birth prevalence agrees with predicted genotype frequency. Community Genetics, 2(2–3), 91–6. http://doi.org/10.1159/000016192
[372] Plotz P. (2013) Pompe Disease. National Organisation for Rare Disorders (NORD). http://rarediseases.org/rare-diseases/pompe-disease/.
[373] Pompe disease. (2016) Genetics Home Reference (GHR). http://ghr.nlm.nih.gov/condition/pompe-disease.
[374] Di Rocco M, Buzzi D, & Tarò M (2007). Glycogen storage disease type II: clinical overview. Acta Myologica : Myopathies and Cardiomyopathies: Official Journal of the Mediterranean Society of Myology / Edited by the Gaetano Conte Academy for the Study of Striated Muscle Diseases, 26(1), 42–4. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2949314&tool=pmcentrez&rendertype=abstract
[375] Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, & Corzo D (2006). A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. Journal of Pediatrics, 148(5). http://doi.org/10.1016/j.jpeds.2005.11.033

Enzyme replacement therapy (ERT) with alglucosidase alfa is disease-specific and the only medicinal product authorized for the treatment of Pompe disease to date.[376] Myozyme is manufactured by Sanofi Genzyme (previously Genzyme). It was designated as an orphan medicine on 14 February 2001, and received marketing authorisation in the European Union in March 2006. Myozyme is produced in Chinese hamster ovary cells using recombinant DNA technology.[377] Before 2006, there was no effective treatment for Pompe disease, despite several decades of studying potential treatments in clinical trials.

In classical (early onset) Pompe disease, treatment significantly lengthens survival and improves motor development and cardiac function.[378] The sooner treatment begins, the better the results will be.[379] In late-onset disease, Myozyme is more effective than placebo at improving both the distance the patients could walk and their lung function over the course of the study.[380] A positive effect on survival chances has also been demonstrated.[381]

The Netherlands has a history of research into Pompe disease, linked to activity of the Erasmus Medical Centre (Erasmus MC). Together with other centres, such as Duke University, the Erasmus MC was involved in the early phase of the development of Myozyme.[382] Currently the Erasmus MC houses the Pompe Center.[383]

Through the centralised procedure Myozyme acquired marketing authorisation in the EU, including the Netherlands, on 29 March 2006.[384]

7.7.2 Patents and supplementary protections

As a result of its orphan drug designation, Myozyme has benefitted from market exclusivity until 31 March 2016, even though the underlying patent has since been revoked. Despite the expiration of the market exclusivity, thus far there is no competition from biosimilar products.

7.7.3 Pricing, users and costs in the Netherlands

The patient population in the Netherlands is well-known, and Myozyme has high market penetration here: of the about 140 patients, 80-90% use Myozyme, as compared to 10-20% in Germany and France.[385] Because of the relatively low number of patients with Pompe disease and the high costs per patient, there have in past been discussions about whether or not Myozyme is to be reimbursed in the Dutch health care system[386], and about Sanofi Genzyme's profit margin on Myozyme. Gerard van Beynum, professor in biotechnology has estimated the profit margin at around 90%[387] and Huub Schellekens, professor in pharmaceutical sciences has claimed to be able to produce a biosimilar

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[376] Kanters TA, van der Ploeg AT, Kruijshaar ME, et al. (2017) Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in adult patients with Pompe disease. Orphanet Journal of Rare Diseases, 12(1), 179. https://doi.org/10.1186/s13023-017-0731-0

[377] https://www.erasmusmc.nl/klinische_genetica/research/lijnen/pompe_center/historie/?lang=en Accessed January 4th, 2018.

[378] Kishnani PS, Hwu WL, Mandel H, et al. (2006). A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. Journal of Pediatrics, 148(5). https://doi.org/10.1016/j.jpeds.2005.11.033. Without treatment, the mortality rate is as high as 92% to 95% in the first year of life (Corzo D, Hwu W, Mandel H, Nicolino M, Yong F, Kishnani P. Natural history of infantile-onset Pompe disease: results from a retrospective chart review study. Mol Genet Metab 2004;81:170). The study from Kishnani et al. shows a median age at death or treatment withdrawal for all patients of 21.7 months.

[379] Chien YH, Hwu WL, Lee NC. (2013). Pompe Disease: Early Diagnosis and Early Treatment Make a Difference. Pediatrics and Neonatology, 54, 219–227. https://doi.org/10.1016/j.pedneo.2013.03.009

[380] van der Ploeg AT, Clemens PR, Corzo D, et al. (2010). A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease. New England Journal of Medicine, 362(15), 1396–1406. https://doi.org/10.1056/NEJMoa0909859

[381] Schoser B, Stewart A, Kanters S, et al.(2017) Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. Neurol J 264(4):621-630. doi: 10.1007/s00415-016-8219-8. Epub 2016 Jul 2.

[382] The patent for Myozyme is held by Genzyme, with the Erasmus MC (among others) receiving royalties.

[383] https://www.erasmusmc.nl/klinische_genetica/research/lijnen/pompe_center/?lang=en

[384] Zorginstituut Nederland (2017), *Monitor weesgeneesmiddelen 2017*. Snyders LL, Link AJ, Delsing MH, Diemen.

[385] Interview data

[386] Pompe wel of niet in het basispakket, dat is de vraag, *NRC Handelsblad*, 22 September 2012.

[387] Tijd voor prijs op levensjaar; Farma-industrie heeft teveel macht, *Leidsch Dagblad*, 22 November 2014.

version of the medicine at only 1% of the costs.[388] By the end of 2017, after the market exclusivity had expired, prof. Schellekens said he was still working on further developing the drug.[389] However, up to now, production at a significant scale has not been reported. In a response to these claims, Sanofi Genzyme has stated that profit or loss is made by a company and not by a product. Furthermore, the company points to the fact that, to ensure the safe and reliable production of Myozyme for less than 3,000 patients worldwide who depend on this enzyme replacement therapy, it has invested around €1.5b and that this investment takes time to earn back.[390]

When Myozyme was introduced in the Netherlands in 2006 it was subject to a special orphan drug policy measure, which required a full reimbursement review, i.e. an assessment of the therapeutic value, a budget impact and cost-effectiveness assessment (so-called 't=0' assessment). The reason for this measure was that the Dutch government would provide additional funding to hospitals for expensive drug treatments, covering 80% of the net market price for these drugs. The cost for Myozyme stayed within the budget impact analysis which was part of the assessment in 2006. The situation changed in 2012, when the orphan drug policy was abandoned and replaced by a structure where insurance companies would directly negotiate drug prices, use and volume with prescribing hospitals.[391] Before and after this policy change orphan drugs were (and are still being) re-evaluated against four criteria: necessity, effectiveness, cost-effectiveness and feasibility. Also in 2012, the so-called 't=4' assessment took place for Myozyme. Myozyme was approved under the condition that strict start and stop criteria would be maintained, and the presence of an indication committee, together with the recommendation that price negotiations should take place. Since January 2014 Myozyme has been subject to a financial arrangement between the Dutch Ministry of VWS and Sanofi Genzyme. The details of the negotiations are confidential, but the former minister of health reported in 2017 that these negotiations are paying off.[392]

Figure 46 shows the number of users and the total costs of Myozyme in the years 2012-2016. These costs increased from €46.6m for 109 patients in 2012 to €56m for 124 patients in 2016. This implies that the costs per patient have gradually increased from €427k in 2012 to €451k in 2016. This is attributed to changes of the prescribed medically required dosage. It should be kept in mind that these numbers are based on the known list prices for Myozyme and do not reflect the aforementioned confidentially negotiated price under the financial arrangement.

[388] Hoogleraar maakt kostbaar medicijn eenvoudig na, *Trouw*, 13 December 2014.

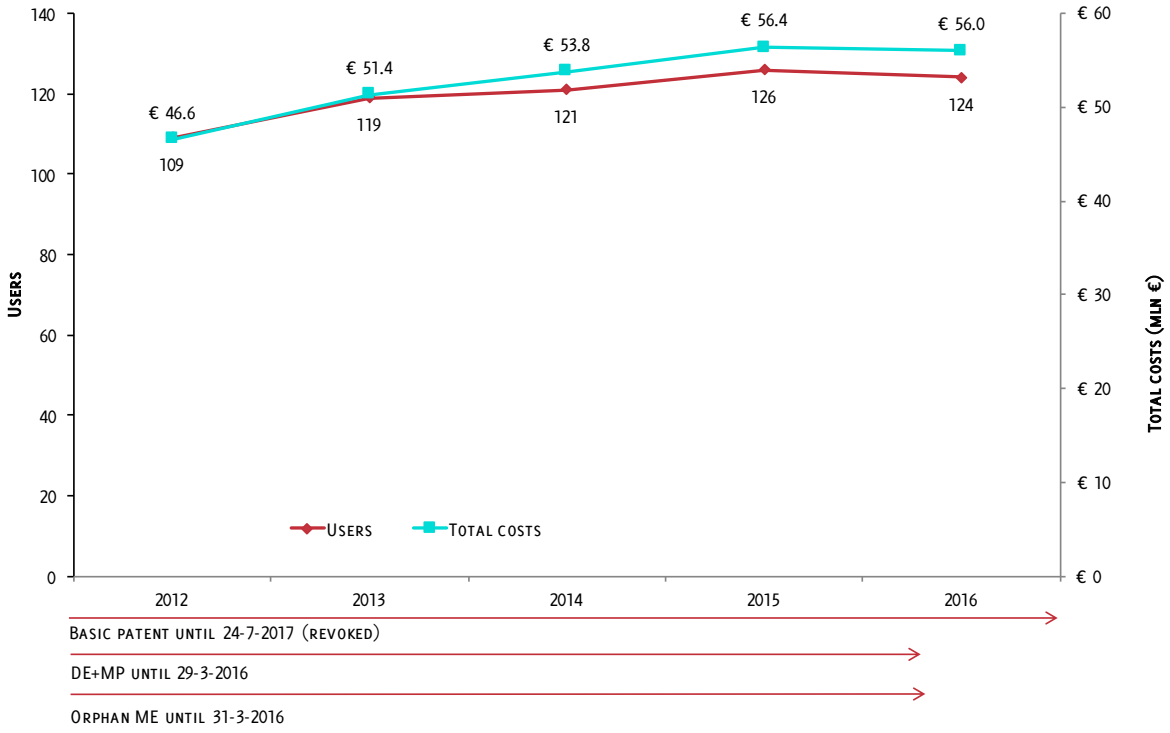
[389] Medicijnen nog peperduur door ontbreken alternatief, *Trouw*, 11 December 2011.

[390] Interview data

[391] Source: https://www.geneesmiddelendebat.nl/toegang-tot-geneesmiddelen/ziekenhuisgeneesmiddelen/beleid-dure-en-weesgeneesmiddelen/

[392] https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/schippers-medicijnen-155-miljoen-goedkoper.htm

Figure 46 Number of users and total costs of Myozyme in the Netherlands, 2012 – 2016



Source: Data Vektis (2017), Snyders et. al. (2017)

7.8 Glivec

7.8.1 Background

Glivec (Gleevec in the US, active substance imatinib), developed by Novartis, is one of the first drugs against cancer specifically designed for that purpose, to repair a specific genetic defect causing cells to produce too many white blood cells. It represents a class of drugs known now as Tyrosine Kinase (TK) Inhibitors. Its development was set in motion by the discovery in the 1960s of the so-called 'Philadelphia chromosome', which was subsequently found to code for a TK, an enzyme involved in signal transduction. However, even once the role of TKs was becoming clear, most companies and researchers were reluctant to develop drugs targeting these enzymes because of their intricate and complex involvement in essential cellular processes.

The first step towards development of what would become Glivec was taken by professor Druker at the Oregon Health & Science University. Ciba-Geigy, the predecessor of Novartis, had started building a compound library on kinase blocking compounds to which it provided the Oregonian researchers access. Imatinib was first determined to work *in vitro* in 1996 and immediately demonstrated outstanding promise in the treatment of Chronic Myelogenous Leukaemia (CML), a rare form of blood cancer. In the Netherlands around 200 people per year are affected by CML.[393] The drug moved into the clinical research in just two years where it resulted in remission in every patient it was tested on. Because of these extraordinary results, Phase 2 trials were stopped early. Glivec was subsequently approved by the FDA in 2001 in a very rapid procedure (two and a half months). The drug was hailed as a 'magic bullet' against cancer and even made the cover of TIME magazine.[394] A study in December 2002 showed Glivec to be five times more effective against CML than other drugs[395]: where before

[393] De geboorte van een 'wees', De Telegraaf, September 6, 2003.

[394] http://content.time.com/time/covers/0,16641,20010528,00.html

[395] Novartis claimt succes leukemiemedicijn, Het Financieele Dagblad, 9 december 2002.

Glivec only 30% of patients with CML survived five years after being diagnosed, with Glivec, that number rose to at least 89%.[396]

The use of Glivec is associated with mild to moderate toxicity, mostly reversible by dose reduction or discontinuation of the drug. Most adverse effects occur within the first two years of starting therapy; however, late effects, are recently being recognised and although the incidence rate is low (<1%) it is recommended that specialists remain cautious about the potential long-term adverse effects.[397]

Glivec received EU marketing authorisation for the treatment of CML on 7 November 2001. Glivec has since been found effective against various other forms of cancer as well and consequently has applied for and been granted additional and extended registrations. Registered indications now include paediatric CML and gastrointestinal stromal tumour (GIST). The company estimates that about 70% of sales of Glivec involve the primary indication of CML, followed at some distance (approx. 30%) by use for treatment of GIST.[398] The other approved indications make up a relatively small part of the use of Glivec.

7.8.2 Pricing and global market development

Since its initial introduction, Glivec has made headlines not only for its therapeutic value but also because of the price at which it is being sold. In the US it was listed at $26,400 per patient per year at the moment of introduction in 2001, but rose to over US$120,000 in 2016.[399]

In the first eight months after its launch, Glivec had a turnover of US$153m and by February 2002, it had been accepted in over 60 countries.[400] Turnover in 2003 $ 1.1 billion (+68%).[401] Turnover in 2005: $ 2,17 billion.[402] 2009: $ 3.5 billion.[403] In 2012, Glivec was Novartis' number one selling drug with a global turnover of € 3.6 billion.[404]

As new indications for Glivec were added, (until the entry of generic competition), and the potential market size grew, there was no significant decline in prices.[405] This has resulted in accusations of 'indication stacking' and profiteering; an accusation that is countered by Novartis by pointing out that registration for additional indications also requires additional trials and thus increased development costs.

7.8.3 Patents and supplementary protections

According to drugpatentwatch.com, there are four US patents on Glivec. One of these is the now expired basic patent that has the same priority as the European basic patent EP0564409, which expired on 25 March 2013. The other three still active US patents are US6894051 and US7544799 (for a crystal modification) and US 6958335 (for GIST treatment). The first two US patents are mirrored in Europe by the patent EP0998473 with an application date of 16 July 1998. The GIST-related patent is mirrored by EP1332137, with an application date of 26 October 2001. These patents remain in force until 2018 and 2021 respectively.

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[396] Pray, L. (2008) Gleevec: the Breakthrough in Cancer Treatment. Nature Education 1(1):37

[397] Mughal, T. I., & Schrieber, A. (2010). Principal long-term adverse effects of imatinib in patients with chronic myeloid leukemia in chronic phase. *Biologics : Targets & Therapy*, *4*, 315–23. https://doi.org/10.2147/BTT.S5775

[398] Based on interview data with representatives of Novartis.

[399] Journey of generic imatinib: a case study in oncology drug pricing (2017). Chen CT, Kesselheim AS. Journal of Oncology Practice 13(6): 352-356

[400] VS motor achter winstgroei Novartis Bazel, Het Financieele Dagblad, 8 februari 2002.

[401] Novartis vergroot belang in sectorgenoot Roche, Het Financieele Dagblad, 23 januari 2004.

[402] Met dank aan Roche, Beleggers Belangen, October 13, 2006.

[403] Overheidsrichtlijnen geen garantie topzorg, Het Financieele Dagblad, 26 juli 2010 maandag.

[404] India weigert patent aan Novartis (2) Algemeen Nederlands Persbureau ANP, April 1, 2013

[405] Journey of generic imatinib: a case study in oncology drug pricing (2017). Chen CT, Kesselheim AS. Journal of Oncology Practice 13(6): 352-356

Upon expiry of the basic patent in the Netherlands, Glivec was awarded an SPC (300086) which was in force between 25 March 2013 and 20 June 2016.

Novartis filed for and was awarded an orphan drug designation for use of imatinib in treatment of chronic myeloid leukaemia in November 2001, which provided it market exclusivity until 2011. Following the initial filing, the company filed additional requests to award the orphan drug designation for several more indications: GIST (2002), acute lymphoblastic leukaemia (2006) and various other cancers (2006). However, Novartis voluntarily withdrew these indications from the community register for orphan medicinal products in April of 2012. This enabled the company to request a paediatric extension instead, having been found in compliance with the PIP requirements the month previous. The paediatric extension was granted, providing Glivec effective protection until 20 December 2016.

With the expiry of protections for its primary CML indication by the end of 2016, the market has opened up for the entry of numerous generic forms of imatinib. Also Novartis, through a subsidiary, markets a generic version under the name Imatinib Sandoz, whilst continuing sales under the brand name Glivec as well. The GIST-indication remains protected, which is why it is in Novartis's interest to participate in the CML-market through a subsidiary instead of lowering its price for Glivec, which would also affect revenues for the GIST-indication. The co-existence of still patented and unpatented indications poses a challenge in the context of implementing compulsory generic substitution for indications where the IP has expired.

7.8.4 Pricing, users and costs in the Netherlands

From its introduction in the Netherlands in November 2001, the number of patients using the drug has risen from 450 in 2002 to more than 1,400 in 2007.[406] This increase in (surviving) patient population was paralleled by an increase in the expenses on Glivec from €6.2m in 2002 to €31.8m in 2007.[407]

In the years 2007 to 2012, the number of *outpatient* users of Glivec and the associated costs continued to increase gradually (Figure 47). [408] Per 2013, the reimbursement policy for Glivec (and other expensive oncology drugs and hormones) was changed due to the so-called '*overheveling'*.[409] The effect of this policy change was that the drug's administration, as well as the concomitant costs, was transferred to hospitals (in-patient). This explains the sharp drop in both the number of users and the costs per 2013, even though Glivec benefitted from SPC protection and a paediatric extension until 20 December 2016.[410] However, Glivec did not entirely disappear from the outpatient data per 2013, which is probably due to the fact that some hospitals have a public pharmacy ('politheek'). As of 21 December 2016, Glivec has been off-patent. By 2017, there were several generic versions on the Dutch market. The limited available data do not allow for an analysis of any price effect of this.

[406] https://www.sfk.nl/publicaties/PW/2008/2008-05.html

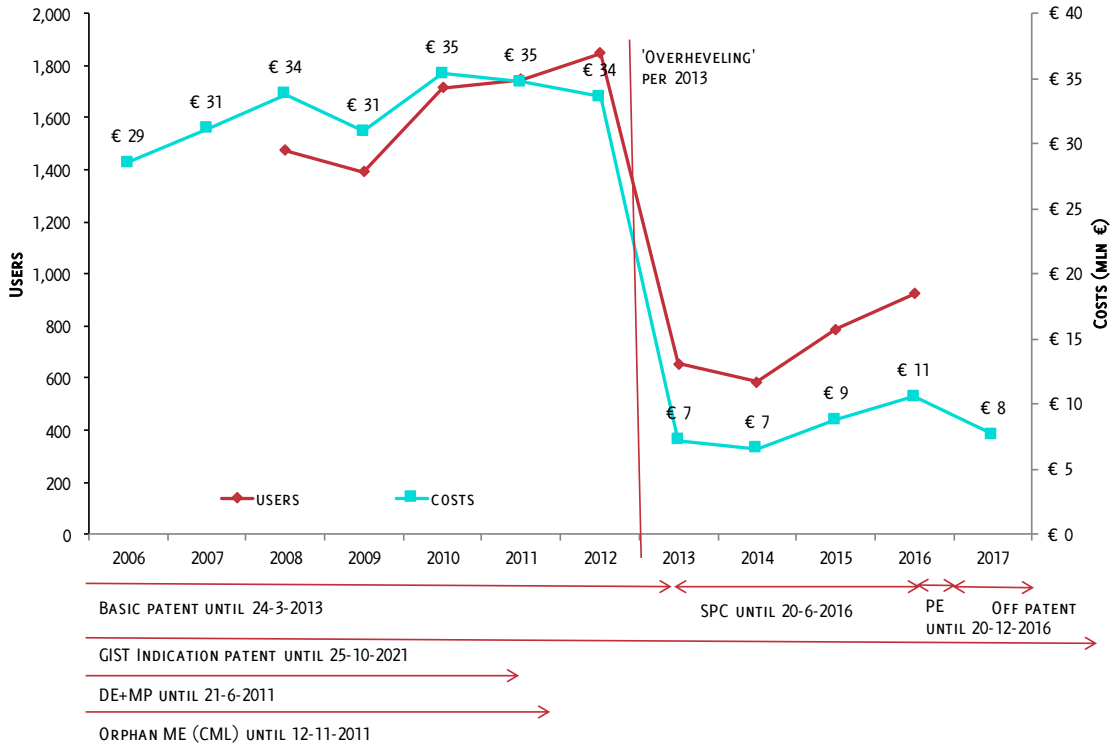
[407] Een weesgeneesmiddel in de eerste lijn, *Pharmaceutisch Weekblad 143(5)*, 31 January 2008, retrieved from https://www.sfk.nl/publicaties/PW/2008/2008-05.html.

[408] No information on DDDs was available and for some years, the number of users is missing.

[409] One of the motivations for this transfer was to decrease the prices of such medicines, thanks to larger buying power for hospitals. See: Kamerstukken II, 2015-2016. 29477 (Geneesmiddelenbeleid), 29248 (Invoering Diagnose Behandeling Combinaties (DBCs)), 370 (Brief).

[410]

Figure 47 Outpatient users and costs of Glivec in the Netherlands, 2006 – 2017



Source: Data SFK (2017)

7.9 Revlimid

7.9.1 Background

Revlimid (with the active substance lenalidomide) is produced by Celgene Europe and used to treat the following conditions:

- *Multiple Myeloma (MM)*, a type of bone marrow cancer. There is currently no cure for MM, and the treatment options available only help manage the disease for several years. According to a study by Verelst et al. from 2011, who surveyed the incidence of MM in the Netherlands between 1989 and 2009, the incidence rose from 631 in 1989 to 968 newly diagnosed cases in 2009.[411] In Europe, some 39,000 people are diagnosed with multiple myeloma, and approximately 24,000 people die from the condition each year.[412]
- *Myelodysplastic syndromes (MDS)* refers to a specific group of bone marrow cancers.[413] The incidence of MDS in the Netherlands was 2.3 per 100,000 in 2001-2005 and 2.8 per 100,000 in 2006-2010, calculated on the basis that there were 5,144 confirmed MDS cases (median age: 74 years) in the Registry. According to Germing et al., the clinical course *"…is highly*

[411] Verelst, S. G., Blommestein, H. M., Karim-Kos, H. E., Huijgens, P. C., & Sonneveld, P. (2011). Trends in Incidence and Survival of Multiple Myeloma in the Netherlands in the Last Two Decades. Results From a National Population Based Study. Blood, 118(21), 5071. Accessed January 08, 2018. Retrieved from http://www.bloodjournal.org/content/118/21/5071.

[412] Ferlay J, et al. Eur J Cancer. 2013;49:1374-1403

[413] According to the latest WHO classifications, these are: MDS with single lineage dysplasia; MDS with ring sideroblasts (MDS-RS); MDS-RS and single lineage dysplasia; MDS-RS and multilineage dysplasia; MDS with multilineage dysplasia; MDS with excess blasts; MDS with isolated del(5q); MDS, unclassifiable. See Arber et al. (2016): The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, in: BLOOD, 19 MAY 2016 x VOLUME 127, NUMBER 20, http://www.bloodjournal.org/content/bloodjournal/127/20/2391.full.pdf?sso-checked=true

variable. About one-quarter of all patients with MDS develop acute leukaemia. The median survival time from the moment of diagnosis is about 30 months."[414]

- *Mantle cell lymphoma (MCL)* is a sub-type of non-Hodgkin's lymphoma (NHL) – a form of cancer of the lymphocytes, a specific type of white blood cell – and accounts for about 6% of NHL cases.[415] In Western Europe, the incidence is reported to be 1-2 per 100,000.[416] The disease has a short remission duration to standard therapies and a median overall survival (OS) of 4-5 years.[417]

Lenalidomide is a thalidomide analogue with improved antitumor efficacy and a reduced – but still significant – toxicity profile.[418] Thalidomide has been known for several decades and was initially sold, in 1957, as a sedative, first in Germany under the trade name of "Contergan". Contergan became infamous for its side-effects, as it caused a risk of significant birth defects if taken by pregnant women.

Lenalidomide was discovered and developed by Celgene. By 2001, there was Phase I clinical trial evidence for efficacy in the treatment of MM. In 2005, the FDA approved Revlimid for MDS and in 2006 for MM. In 2007, the EMA approved Revlimid for MM.

Over the last decade, Revlimid has been approved for additional indications. Some of these indications were extensions of existing indications. Most recently, in February 2017, the EMA approved Lenalidomide as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation (ASCT).[419] Previously, Revlimid as combination therapy was already indicated for the treatment of adult patients with previously untreated multiple myeloma who are *not* eligible for transplant. Furthermore, in combination with dexamethasone Revlimid is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. As a monotherapy, it is indicated for MDS in patients with transfusion-dependent anaemia[420] and for the treatment of adult patients with relapsed or refractory MCL.[421]

Celgene has continued to look for new indications for Revlimid. There has been significant investment in areas of high unmet need where Lenalidomide has not proved beneficial. For example, in 2011, Celgene stopped a large phase three trial in patients with castration-resistant prostate cancer after no survival benefit was found. In 2016, it was reported that Celgene will not expand the indication range of Revlimid as maintenance therapy for patients with diffuse large B-cell lymphoma (DLBCL) based on the lack of a survival benefit reported in the REMARC III clinical trial.[422] In 2017, a phase three trial in previously untreated follicular lymphoma patients did not meet its primary endpoint of superiority over existing treatment options. The current product pipeline shows phase three clinical trials on-

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[414] Germing, U., Kobbe, G., Haas, R., & Gattermann, N. (2013). Myelodysplastic Syndromes: Diagnosis, Prognosis, and Treatment. Deutsches Ärzteblatt International, 110(46), 783–790. http://doi.org/10.3238/arztebl.2013.0783

[415] Skarbnik, AP & Goy, AH (2015): Mantle cell lymphoma: state of the art, in: Clin Adv Hematol Oncol. 2015 Jan;13(1):44-55.

[416] Dreyling et al. (2017):

[417] Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. Am J Hematol. 2017;92:806–813. https://doi.org/10.1002/ajh.24797

[418] http://www.bcmj.org/newsnotes/special-feature-revival-thalidomide-tragedy-therapy

[419] Summary of Product Characteristics. Last updated 5 April 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000717/WC500056018.pdf

[420] Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Summary of Product Characteristics. Last updated 5 April 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000717/WC500056018.pdf

[421] Summary of Product Characteristics. Last updated 5 April 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000717/WC500056018.pdf

[422] https://www.thestreet.com/story/13651230/1/celgene-can-t-expand-revlimid-approval-into-non-hodgkin-lymphoma-just-yet.html

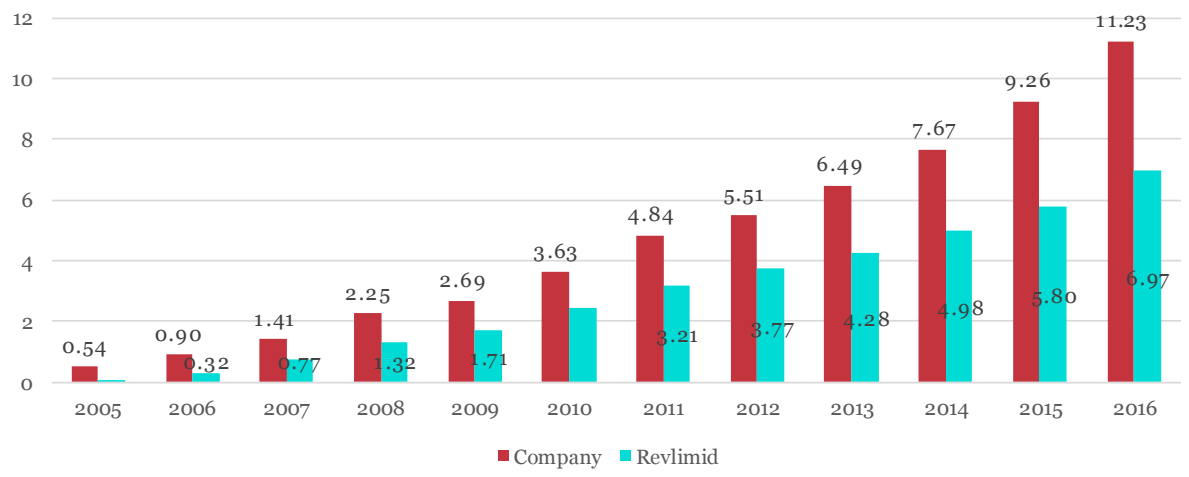
going for diffuse large B-cell lymphoma (ABC subtype): First-line; Indolent lymphoma: Relapsed/refractory; Follicular lymphoma: First-line.[423]

Revlimid acquired marketing authorisation throughout the EU, including the Netherlands, on 14 June 2007.

7.9.2 Market data

Figure 48 shows the development of global sales of Revlimid, according to the annual reports of Celgene. The development of turnover has been constantly increasing since the market launch of the drug and by 2016 had reached global sales of US$7.0b. Noteworthy is also the fact that Revlimid alone accounts for the majority of overall sales of the firm. In 2016, this was 62.1%.

Figure 48 Global sales of Revlimid, 2005-2016 (US$b)



Source: Annual Reports Celgene

According to EvaluatePharma, Revlimid was the top-selling orphan drug in the US. The report forecasts that globally (as well as in Europe) Revlimid will be the number 1 best-selling orphan drug in the year 2022 (with annual average growth rate from 2016 of 12% globally), and that Celgene will be the foremost orphan drug manufacturer in that year in terms of sales.[424] In the US, Revlimid ranked 6th in 2016 in terms of sales among all drugs (including non-orphan).

7.9.3 Patent landscape

In the Netherlands, the original patent on Revlimid expired on 27 July 2017, but was followed by an SPC from 24 July 2017 that will last until 18 June 2022. Celgene has been granted waivers from conducting paediatric trials in all age groups for myelodysplastic syndrome and mantle cell lymphoma. It is protected in Europe with the following three orphan drug designations:

- Orphan market exclusivity for 'Treatment of multiple myeloma' (designation EU/3/03/177) started on 19/06/2007 and ended on 19/06/2017.
- Orphan market exclusivity for 'Treatment of myelodysplastic syndromes' (designation EU/3/04/192) started on 17/06/2013 and will expire on 17/06/2023.
- Orphan market exclusivity for 'Treatment of mantle cell lymphoma' (designation EU/3/11/924) started on 12/07/2016 and will expire on 12/07/2026.

[423] https://media.celgene.com/content/uploads/product-pipeline.pdf

[424] http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf

Several generics firms have challenged patents on Lenalidomide. In the US, several companies have filed Abbreviated New Drug Applications (ANDAs) against Revlimid which triggered a specific type of litigation, known as Hatch-Waxman litigation.[425] In the US litigations, the parties are addressing infringement and the validity of the patents asserted. The US litigations may resolve whether Celgene is able to maintain its patent in the US beyond 2022. There are twelve patents listed in connection with Revlimid in the publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the "Orange Book," that have expiration dates after 2022. Two of those patents, which cover, among other things, crystalline forms of Lenalidomide, have reported expiration dates in 2024 and 2027. In 2015, Celgene reached an out-of-court agreement with Natco under which the generics firm will receive a volume-limited license to sell generic Lenalidomide in the United States commencing in March 2022, and a license to sell an unlimited quantity of generic Lenalidomide beginning in January 2026.[426]

In Europe, the European Patent Office in 2015 revoked a patent covering crystalline forms of Lenalidomide that could have extended the exclusivity by up to two years.[427] Celgene announced it would appeal the decision, which would take at least three years to resolve; until then the patent stays in force. The ruling was based on a technical aspect of EPO law that has no parallel in the United States. Whilst the scope of the ruling is limited, some analysts have argued that the entire family of Revlimid patents may be susceptible to invalidation on the basis that *"...they are based on an older drug and that the use of the drug in the treatment of cancer was obvious"* and that therefore the inventive step criterion for patent protection is not met.[428]

Celgene has also been in the news for purportedly implementing a strategy by which it would register Revlimid for an orphan disease, but anticipating and fostering off-label use of Revlimid by physicians. Physicians are allowed to prescribe drugs for off-label – that is, non-indicated – use, based on their professional judgement and knowing the safety profile of the approved drug. However, drug makers are not allowed to promote off-label usage of their drugs. Off-label use would entail that the drug would be sold to a patient population larger than anticipated, and on the basis of which it qualified for orphan drug status. In July 2017, Celgene agreed to a civil settlement in the US, paying out US$280m, following allegations that the company had engaged in disallowed promotion of off-label usage. The company settled *"to avoid the uncertainty, distraction, and expense of protracted litigation"*, but did not admit any wrong-doing.[429,430]

7.9.4 Revlimid in the Netherlands

Although it currently is one of the world's top selling drugs, Revlimid received very little coverage in the Dutch press. One of the first mentions of Revlimid here quotes haematologist Dr. Peter Huijgens who complained about the slow approval of drugs like this in The Netherlands.[431] Later articles primarily concern its marketing authorisation and the financial performance of Celgene Europe.

Celgene has been supporting the Dutch haematological research collaborative HOVON for doing independent clinical trials. Within these trials several hundreds of patients have been treated with Lenalidomide within The Netherlands. Also, on request of Dutch haematologists, a free of charge

[425] The suing companies were, amongst others, Natco, Dr. Reddy's, Zydus, Cipla, and Lotus Pharmaceutical. See: http://www.ipwatchdog.com/2017/11/21/celgenes-new-revlimid-lawsuits-shows-shifting-tactics/id=90357/

[426] http://ir.celgene.com/releasedetail.cfm?releaseid=947998

[427] https://www.reuters.com/article/us-celgene-patent/eu-patent-office-revokes-celgene-revlimid-patent-appeal-planned-idUSKBN0NS1WB20150507

[428] https://seekingalpha.com/article/3180296-celgenes-revlimid-patent-families-do-not-appear-to-meet-criteria-for-protection

[429] https://www.fiercepharma.com/marketing/celgene-settles-for-280-million-off-label-cancer-marketing-case

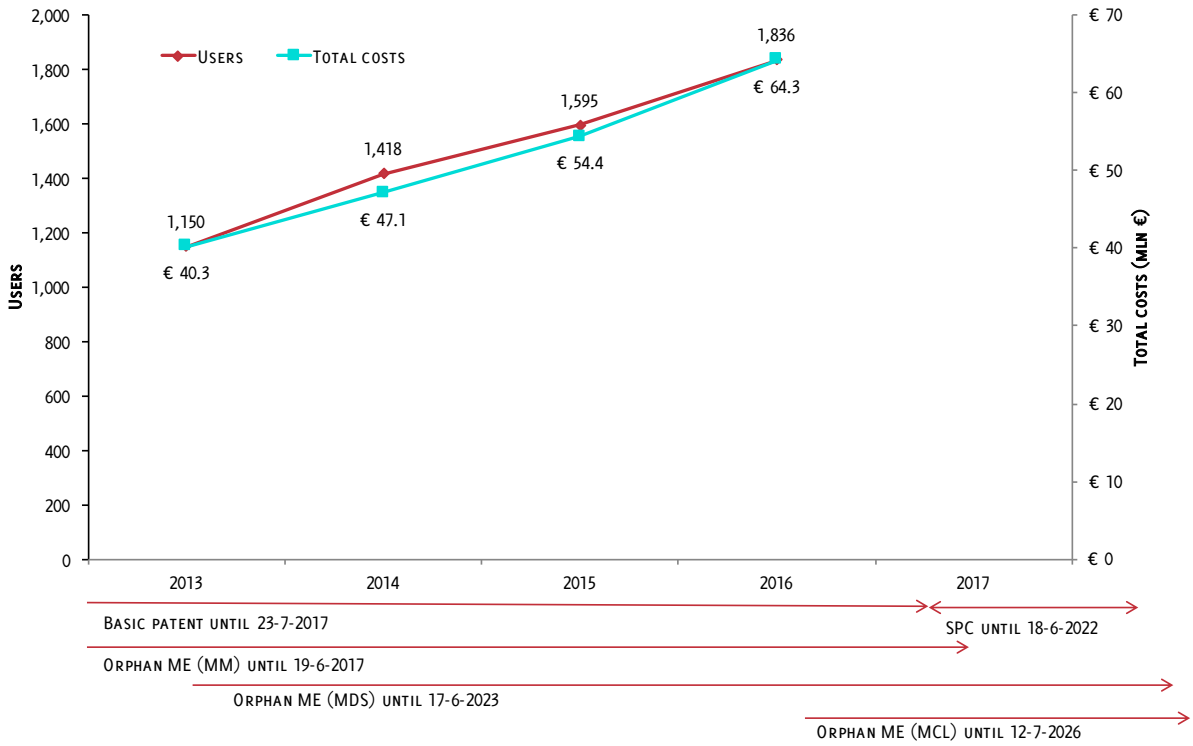
[430] Celgene Corporation Announces Settlement of Civil Litigation (25 July 2017). http://ir.celgene.com/releasedetail.cfm?ReleaseID=1034370. Accessed 31 January 2018.

[431] 'Nederland loopt achter', *Elsevier Weekblad*, 17 November 2007.

access programme was initiated pending the EC approval of the first indication for Lenalidomide in The Netherlands.[432]

Figure 49 shows the number of users and the total costs of Revlimid in the Netherlands in the years 2013-2016. These costs increased from €40.3m for 1,150 patients in 2013 to €64.3m for 1,836 patients in 2016. As can be concluded from the virtually overlapping lines in the graph, the underlying costs per patient remained fairly stable over time at about €35k. In a response, Celgene identified two counteracting forces to the relative stability of costs per patient. On the one hand, as Revlimid gained marketing authorisation in earlier lines of treatment, the average duration of treatment per patient has increased. On the other hand, the list price for Revlimid has decreased.

Figure 49 Number of users and total costs of Revlimid in the Netherlands, 2013 – 2016



Source: Data Vektis (2017), Snyders et. al. (2017)

7.10 Synthesis of case findings

This paragraph contains a synthesis of the key findings that can be derived from across the seven cases. It first reviews how the mechanisms have been used – either in isolation or in combination – and how the companies involved have used these mechanisms to optimal benefit. This is followed by a discussion on whether the chosen strategies have given rise to any particular issues or concerns. Next, we describe the impacts of the supplementary protections on market dynamics and the concomitant costs to the Dutch health care system for these cases. Table 5 contains a summary of these findings.[433]

[432] *Clin Lymphoma Myeloma Leuk. 2010 Apr;10(2):138-43. doi: 10.3816/CLML.2010.n.020. Analysis of efficacy and prognostic factors of lenalidomide treatment as part of a Dutch compassionate use program. Kneppers E1, Lokhorst HM, Eeltink CM, Huls G, Kersten MJ, Koedam J, Minnema MC, van Oers MH, Raymakers RA, Schaafsma MR, Vellenga E, Wijermans PW, Wittebol S, Sonneveld P, Zweegman S*

[433] All data summarised herein are applicable only to the Netherlands.

Table 5 Summary of case findings

Case	MA holder	Authorised indication(s)	Year	Annual cost per user	Users	Supplementary protections	Competition[1]	Estimated additional costs (until 2016)
Lipitor (atorvastatin)	Pfizer	Hypercholesterolaemia	2006	€348	435,000	• SPC: 29/05/2007 – 6/11/2011 (4.54 years) • PE: 7/11/2011 – 6/05/2012	++	€681 ~ 692 m (SPC + PE)
			2016	€17	541,000			
Losec (omeprazole)	AstraZeneca	Gastroesophageal reflux disease, peptic ulcer disease, Zollinger-Ellison syndrome	2006	€82[2]	961,000	• SPC: 3/4/1999 – 15/11/2002 (3.62 years)	++	€660m
			2016	€10	1,630			
Cozaar (losartan)	MSD	Hypertension, diabetic nephropathy	2006	€249	183,000	• SPC: 9/7/2007 – 1/9/2009 (2.15 years) • PE: 1/9/2009 – 1/3/2010	++	€118– €130m (SPC + PE)
			2016	€12	245,000			
Atripla	Gilead	HIV	2006	€2,377	1,247	• Patent on tenofovir disoproxil fumerate in effect until July 2018. • SPC decision pending appeal.	N/A	N/A
			2016	€7,226	3,518			
Myozyme (alglucosidase alfa)	Sanofi Genzyme	Pompe disease	2012	€427k[3]	109	• ME: 31/3/2006 – 31/3/2016	0	N/A
			2016	€451k	124			
Glivec (imatinib)	Novartis	Chronic myelogeneous leukaemia (CML), Gastrointestinal stromal tumour (GIST), acute lymphoblastomic leukaemia (ALL), various other cancers	2008	€23k	1,473	• SPC: 25/3/2013 – 20/6/2016 (3.24 years) • PE: 20/6/2016 – 20/12/2016 • ME: – CML: 12/11/2001 – 12/11/2011 – Other indications: withdrawn	++	Not calculated[5]
			2016	€11k	923[4]			

Case	MA holder	Authorised indication(s)	Year	Annual cost per user	Users	Supplementary protections	Competition[1]	Estimated additional costs (until 2016)
Revlimid (lenalidomide)	Celgene	Multiple myeoloma (MM), myelodysplastic syndromes, mantle cell lymphoma	2013	€35k	1,150	• SPC: 24/7/2017 – 18/6/2022 (4.90 years) • ME: – MM: 19/6/2007 – 19/6/2017 – MDS: 17/6/2013 – 17/6/2023 – MCL: 12/7/2016 – 12/7/2026	N/A	N/A
			2016	€35k	1,836			

SPC: Supplementary Protection Certificate; PE: Paediatric Extension; ME: Orphan Drug Market Exclusivity.
[1] ++ denotes 5 or more generic competitors, + denotes between 1 and 5 generic competitors, 0 denotes no generic competitor even though there are no more protections in effect, N/A denotes that protections are still in effect and no generic competition is allowed yet.
[2] In the base year 2006, there were already generic alternatives on the market
[3] Based on list prices. This does not take into account the confidentially negotiated price under the financial arrangement
[4] Due to the 'overheveling' in 2013 a significant number of users is now treated as in-patient. Data presented here are only for out-patient users
[5] Data were only available for the time period up to 2016, during which Glivec was still under protection due to the paediatric SPC extension

7.10.1 Application of supplementary protection mechanisms in practice

Only two of the included case drugs, Losec and Myozyme, have benefitted from just a single form of supplementary protection (Figure 50).[434] In the case of Losec, it is worth emphasising that the SPC protection expired before the Paediatric Regulation came into effect. For Myozyme, an SPC was granted that would have gone into effect on 6 December 2019 but, according to data of the Dutch Patent Office, the underlying patent has since been revoked thus voiding the validity of an SPC on the basis of this patent.[435] Consequently, to date, the orphan drug market exclusivity has been the only form of supplementary protection in effect in the Netherlands for Myozyme.

By comparison, four of the included case studies illustrate how different supplementary protection mechanisms can interact. Such interactions can either result in consecutive protections, (partially) overlapping protections, or protections that are mutually exclusive. The cases provide examples of each of these three possibilities:

- By design, the SPC extension follows the expiry of the underlying patent on which the SPC is based. This, in turn, can be followed by a further six-month paediatric extension. This series of **consecutive protections** can result in a total prolongation of the effective term of protection of up to 5.5 years. The cases of Lipitor, Cozaar and Glivec each demonstrate this sequence of events, though in none of these cases this maximum period of additional protection was reached.
- The market exclusivity periods granted to Revlimid based on its multiple orphan drug designations **overlap** to a significant extent with the SPC it was granted. These two mechanisms differ in their scope of protection, but effectively prolong the period of protection – for at least one indication – beyond the expiry of the underlying patent with nearly nine years.[436]
- Alternatively, a drug can be eligible for multiple protections that are **mutually exclusive**, namely the paediatric extension to the SPC and the orphan drug market exclusivity. Such a situation forces a company to consider which of these protections offers it the most benefit and to choose accordingly. The case of Glivec illustrates how this may work out in practice: although the company initially obtained orphan drug designation for various indications beyond its original designation for CML, it opted to withdraw these designations to be able to qualify for the six-month paediatric extension. This suggests that the protection offered by the paediatric extension was more economically advantageous to Novartis than the orphan drug market exclusivity.

The above examples show potential forms of interaction between *different* mechanisms. Simultaneously, however, it is also possible to accumulate multiple protections via the *same* mechanism. Two of the orphan drugs included in this study, Revlimid and Glivec, obtained multiple orphan drug designations with separate periods of market exclusivity, even though in the case of Glivec the additional designations were subsequently withdrawn. In this light, it should also be emphasised that the here included cases have only focussed on supplementary protections conferred onto the case drug itself. However, as described in Chapter 5, companies can also benefit from stacking of protections through development of derivatives of these products, particularly in the case of SPCs.

From the above, it can be concluded that the various supplementary protection mechanisms can be used in combination such that the effective period of protection for a product is extended well beyond the duration of the original underlying patent. Companies can extend the protection period by optimising their IP and regulatory strategies.

[434] Excluding data exclusivity and market protection, which applied to all case drugs.

[435] http://mijnoctrooi.rvo.nl/fo-eregister-view/search/detailsType/EP99965162.3/EPV. Accessed January 2018.

[436] Based on the expiry of the market exclusivity for the MCL indication on 12 July 2026.

Figure 50 Effective term of protection for case study drugs

Source: Rijksdienst voor Ondernemend Nederland[437], EMA. The effective term of protection is calculated against the date of first marketing authorisation (t=0). SPC = supplementary protection certificate; PE = paediatric extension; DE+MP = data exclusivity and market protection; ME = orphan drug market exclusivity (for respective indications). Although the patent term for Myozyme has been included here for illustration, this patent has been revoked (indicated with a patterned fill).

7.10.2 Controversy and legal challenges

Several of the included cases have created a degree of controversy or have resulted in legal challenges regarding the strategies chosen by companies to extend their protection.

In response to a challenge from a generics manufacturer, Merck contested that the SPC and the subsequent paediatric extension for Cozaar should be interpreted to extend also to a combination of Cozaar and another product. However, different courts provided different interpretations. Combination products similarly were at issue in the case of Atripla, which itself is a combination of three antiretroviral drugs. Here, the UK Court ruled that there was no valid basic patent that covers the combination of all three active ingredients and that a contested patent was not sufficiently distinctive compared to that for one of the ingredients alone and for which an SPC had already been granted. In the Netherlands, an appeal on the ruling to withhold an SPC on Truvada (containing two of the ingredients of Atripla) is still pending.

Whilst these two cases show how companies may use uncertainty in how to interpret the regulations underpinning the supplementary protection mechanisms to their benefit, they are not as such examples of legally incorrect behaviour. By contrast, AstraZeneca was found guilty on two counts of anti-competitive behaviour involving its drug Losec. The CJEU ruled the company had provided misleading information in its filings for SPCs, and that it had abused its market dominant position by selectively withdrawing the marketing authorisation for a particular form of its product. It was subsequently fined €52.5m.

Glivec and Revlimid both have faced accusations of "indication stacking" and profiteering, due to their registrations for multiple orphan designations and the relatively high prices of these drugs. Although Myozyme has only been registered for a single indication, it too has faced substantial public scrutiny stemming from the high cost per user. Whilst these criticisms are indicative of a perceived 'mismatch' between the costs and benefits resulting from the Orphan Drug Regulation, they do not point at any

[437] BPP eRegister, accessible at http://mijnoctrooi.rvo.nl/fo-eregister-view/search.

outright abuse of the system in the legal sense. Several other forms of controversial behaviour were noted throughout some of the cases, though these relate more commonly to marketing strategies than to (mis)use of supplementary protection mechanisms.

7.10.3 Impacts on competition and costs

The impacts of supplementary protections on delaying of competition from generic or biosimilar versions of the case drugs could only be estimated in five out of seven cases. At the time of the analysis both Atripla and Revlimid remained under some form of protection, such that competition was excluded. For two further drugs the expiry of the protections was relatively recent: the market exclusivity on Myozyme expired in March 2016 and the paediatric extension for Glivec expired in December 2016.

For the three drugs for which the final protections expired several years ago – namely Lipitor (2012), Losec (2002) and Cozaar (2010) – strong generic competition has come in. The available data for Lipitor and Cozaar show that this competition followed almost immediately after expiry of the paediatric extensions. Similarly, even for Glivec, which became free from protection only at the end of 2016, there are already many generic versions on the market. In all cases, costs per user or DDD dropped sharply upon entry of competition, and the manufacturers of the original products dropped their prices substantially. These observations confirm the (expected) result that, in markets where there is substantial commercial potential, the prolonged period of protection is a key deterrent for generic manufacturers and that generic competition is a strong price driver. By contrast, even though the market exclusivity on Myozyme expired several months before the paediatric extension on Glivec, to date no commercial-scale competition has appeared. This likely is foremost a reflection of the limited size and value of the market for a disease with fewer than 200 patients in the Netherlands. The price of Myozyme has been set in a negotiated procurement process, the outcomes of which remain confidential. Therefore, it cannot be determined whether expiry of the market exclusivity has had any impact on price. Such an effect should, however, be considered unlikely in the absence of competitive pressures.

Based on available information about average drug prices, number of defined daily doses and the number of users, we estimated the cumulative costs of the supplementary protections to the Dutch healthcare system for three of the case drugs: Lipitor, Losec and Cozaar. These estimates are based on the assumption of a counterfactual in which the observed price development per DDD upon entry of generic competition would have occurred in the same way, but at the moment where the patent expired and the supplementary protections went into effect. The development in the number of users is assumed to be unrelated to pricing and protection. For Lipitor and Losec, the total costs of the supplementary protections are estimated to have been over €600m each. For Cozaar, the estimate is lower, at around €118 to €130m, mostly as a result of a significantly lower number of users. For the remaining four drugs, no estimates were possible, either because the drugs remained under some form of protection or because no competition has yet come in.

These cases highlight that, for high-grossing drugs, the supplementary protections can represent a substantial amount of additional revenue for companies, which is borne as a cost by the healthcare system.

Part D

Discussion, conclusions and recommendations

8 Discussion of key findings, conclusions and recommendations

This Chapter brings together the key findings of the preceding analytical chapters (Part C) and discusses the implications thereof.

The primary question underpinning all aspects of this study is whether, and to what extent, the supplementary protection mechanisms for pharmaceutical products are, at present, 'fit for purpose'. To answer this question, it is therefore necessary to define what is understood as such. Essentially, whether any system or regulation can be considered fit for purpose depends on the answers to two separate questions:

1. Are the objectives being sufficiently realised? In other words, is the regulation effective in achieving what it was designed to do?
2. Is what is being realised appropriately in line with the objectives of the regulation? In other words, are there any unintended – and potentially unwanted – 'side effects' resulting from the regulation?

Figure 51 illustrates different scenarios, based on the combination of answers to each of these questions.

In the ideal case, all of the objectives of the regulation are satisfactorily realised and none of the observed effects are at odds with the objectives of the regulation or otherwise undesirable (Scenario A). Such a scenario would require an unusually deft piece of policy-making, with full understanding of all the complexities of the systems and stakeholders affected by the regulation and the ability to develop a completely 'bullet proof' regulation that withstands any judicial challenges or other natural system evolutions. Without having conducted comprehensive assessment of all regulations, it would seem fair to assume that, in reality, this scenario is seldom to never encountered.

More realistic therefore is a situation wherein the regulation has succeeded in at least contributing to its objectives, even if these have not been fully realised. Within this, one could imagine two further - scenarios. In the first case (Scenario B), all the realised effects – even though they are insufficient – are at least in line with what the regulation intended to achieve. That is, there have been no side-effects; those who were subject to the regulation have not sought to (or succeeded in) stretching the regulation in ways that its outcomes can be at odds with the intent.[438] A situation such as this would imply that the regulation itself is not fully fit-for-purpose and that additional measures are required to close the gap between the objectives and effects.

The most complex scenario – and one that is arguably the most likely – is that the regulation produces a combination of intended and unintended effects, and that it is only partially effective in the former category (Scenario C). Any adjustment to the regulation should therefore be aimed at both sides of the equation. This adjustment should also take into account what causes the deviation of observed effects from those that were intended.

[438] The assumption is made that unintended effects are negative effects. For positive, yet unforeseen effects, one could argue that these are in line with the regulation's objectives, if not explicitly then at least implicitly.

Figure 51 Different scenarios for alignment between the observed and realised effects of a regulation

Red shapes represent the intended objectives of the regulation; Blue shapes represent the realised effects. (Technopolis)

In the following sections, we will consider how each of the supplementary protection mechanisms studied can be mapped against these different scenarios. Before this can be done, however, it is worth briefly re-examining their connectedness to illustrate that – whilst each of the instruments is assessed separately – their 'fitness for purpose' also depends on how they interact with each other.

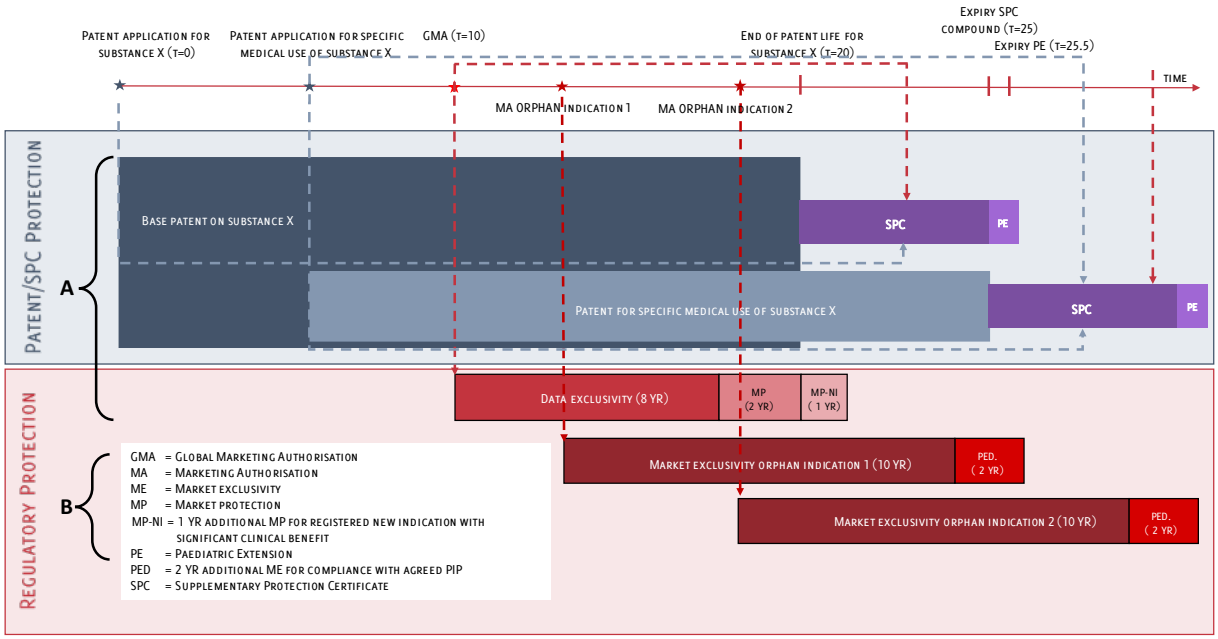
Figure 52 illustrates how the four different instruments (i.e. SPCs, paediatric extensions[439], data exclusivity and market protection, and orphan drug market exclusivity[440]) can co-exist or succeed each other at different points in time. Two hypothetical situations are depicted. Situation A represents a case of a patented (non-orphan) drug. Beyond the basic patent on substance X, the drug enjoys various kinds of supplementary protection. First, as ten years have elapsed between initial filing of the basic patent and the obtainment of the global marketing authorisation (GMA), the drug is eligible for the full five years of SPC protection. In addition to this, compliance with an approved Paediatric Investigation Plan, means that another six months of protection are granted through the paediatric extension. Whilst this is a straight-forward linear sequence of protection periods, two more sets of protections are at play here. The first derives from the fact that the drug has also been granted a specific medical use patent. As a direct consequence of the Neurim ruling, it is now possible to receive an SPC on this too, as well as a further paediatric extension. Because of the GMA, even though it will be a different marketing authorisation that will be referred to for award of the SPC on the specific medical use patent, there will be no new GMA created for this specific medical use. Thus, no new period of data exclusivity and market protection is triggered. Second, the drug also benefits from regulatory protections in the forms of data exclusivity and market protection. Given the drug's registration for a second indication, this period can extend to up to 11 years from the moment the GMA was granted if significant clinical benefit is demonstrated.

A second hypothetical situation (Situation B, parallel to Situation A) is that wherein a drug has been granted market exclusivity thanks to its confirmation of orphan drug designation at the time of marketing authorisation. Subsequently, the same drug receives an orphan designation for a second indication. Absent a Global Marketing Authorisation concept for orphan drugs, the two indications benefit from separate – in this case, partially overlapping – periods of market exclusivity.

[439] Whilst the Paediatric Regulation as an instrument has broader scope than the paediatric extension alone, for the purposes of this study the other elements were not considered.

[440] Similar to the above, the Orphan Drug Regulation comprises multiple elements. However, for the purposes of this analysis, only the market exclusivity incentive was considered.

Figure 52 Relation between the different patent/SPC and regulatory protections for pharmaceutical products



Blue represents patent protection; Red represents regulatory protection. The purple colour for the SPCs indicates the combination of features of patent and regulatory systems. Dotted lines show the relationships between patent application and marketing authorisation dates and how they relate to certain protection mechanisms. The width of the boxes (and the positioning of the two boxes exemplifying the patents) represents the scope of protection provided by the respective instruments. Note that the above depiction is a simplification: the situation could become more complex when considering, for example, the possibility to apply for different SPCs invoking the same basic patent. (Technopolis)

8.1 Key findings

Using the above outlined analytical framework for considering the fitness for purpose of each of the mechanisms that were subject to this study, the following section presents the key findings from this study. It brings together the three separate perspectives: legal, innovation and economic. For clarity, it has been structured around the individual instruments, though as explained previously, these instruments can and often are used in combination. A summary of the findings across all instruments is included at the end of this section in Table 7.

8.1.1 SPC regulation

To assess to what extent the SPC regulation has, first of all, achieved any or all of its intended objectives, this study has primarily looked through the lens of impacts on pharmaceutical innovation.

One of the main objectives of the regulation, underpinning its very existence, has been to offer originator companies a compensation for the time lost of their effective patent protection due to the need to conduct lengthy clinical trials and the regulatory approval procedures themselves (in national contexts further increased by additional conditions set on having the drug included in the reimbursement system). In that respect, industry stakeholders view the regulation as successful. Whilst no in-depth analysis could be conducted of the average duration of SPC protection, anecdotal evidence and several of the case studies suggest that often the period covered by the SPC is less than the maximum of five years. This suggests that the five-year period provides ample compensation.

Alongside the compensatory objective, the SPC regulation was created to incentivise pharmaceutical innovation in Europe with an eye towards closing a gap with the US. The data presented in section 6.1.2 show that in this regard the regulation has not achieved its goal. Although overall pharmaceutical R&D expenditure in Europe has increased, Europe has fallen further behind the US. Moreover, the financial benefits fall mostly outside of the EU and certainly outside of the Netherlands. Whether the

SPC Regulation has overall contributed to pharmaceutical innovation cannot be conclusively stated, in the absence of a counterfactual. Economic theory, however, suggests that it is unlikely that the expectation of a potential, yet largely unknown reward, *ex post* and at the end of the regular term of protection, has a significant direct effect on investment decisions *ex ante*. In the case of pharmaceutical innovation and SPCs this is because, first, the time between the potential reward and the initiation of the research can be as much as several decades. Moreover, pharmaceutical innovation is inherently risky and there is no guarantee that investments will lead to a reward, resulting in a strong discounting of end of term revenues.

To address the question of whether the regulation has simultaneously led to unintended (unwanted) consequences, the study has used several perspectives: the legal, innovation and economic perspective. The different perspectives are substantially intertwined and are therefore discussed jointly.

Since its introduction, aspects of the SPC regulation have given rise to various legal questions and disputes. Many of these issues seem to have arisen from the fact that SPCs **combine IP and regulatory elements** into one instrument and by the difference that exists between patents and (medicinal) products. For example, medicinal products can be more complex and consist of several components that can each be patented in their own right, or that can all fall under the scope of one patent, whose exact scope first needs to be determined.

Over time, there has been a rather **natural development of the SPC system through case law testing.** As with any regulatory system, users are going to **explore and test the limits of what is permissible**. It is important to bear in mind, however, that there is a difference between 1) outright abuse of the system (i.e. breaking the law, or abuse), 2) legally correct behaviour that policy (and society) may not consider in line with the spirit and intents of the underlying system (i.e. 'undesirable strategic use'), and 3) legally correct behaviour that policy considers in line with intents of the system (i.e. 'correct strategic use'). This study has primarily found evidence of the second and third classes of behaviour. That is not to say that the first class of behaviour does not occur, but this study found no indications that this is widespread or insufficiently addressed by the legal systems.

As a result of case law testing, the SPC regulation as it stands today has been interpreted in various ways where one can legitimately question whether these interpretations align with what the regulation intended. Additionally, several fundamental concepts of the SPC system remain unclear. Table 6 summarises the main issues encountered in this study.

Table 6 Key legal issues identified regarding the SPC regulation and their implications

Issue	Implications
Determination of what exactly is protected by the basic patent, i.e. whether to apply the "extent of protection rule"' test or the "infringing act rule" test. (section 5.1.4)	Use of the "extent of protection rule" test will effectively require national patent offices, deciding on SPC applications, to determine the exact scope of the basic patent. Many national patent offices may not have the required expertise to make that evaluation. This could lead to different decisions between national patent offices. By comparison, the "infringing act rule" test is relatively straightforward to apply with very little risk for national disparities, but will allow SPC applicants to invoke broadly and widely formulated basic patents to support a multitude of SPC applications.
Legal uncertainty in the interpretation of the requirement that a product has not been subject of an earlier SPC (in combination with the previous issue). (section 5.1.6)	Current case law shows that it is in fact possible to obtain more than one SPC for the same product by invoking different patents covering the same products or by "re-using" the same patent, covering multiple active substances, for a multitude of SPCs for various combinations of active substances.
Possibility to file for SPC protection based on	The Neurim ruling now allows for SPCs to be granted for

second and further medical use/indications patents ('Neurim ruling'). (section 5.1.7)	known products based on second medical indications. Consequently, there can now be multiple SPCs for the same product, but for different indications. The immediate consequence of the Neurim ruling is furthermore that questions arise whether SPC protection should not also be granted for new formulations, or new processes for making a known compound, etc.
"SPC squatting", whereby one invokes the MA of a third party to obtain SPC protection for one's own patents. (section 5.1.8)	Through SPC squatting an applicant will in effect receive compensation for a loss it has not incurred, as it has not invested in the drug development.

As these issues underline, even though the SPC system already dates back 25 years, it **does not currently provide full legal certainty.** Stakeholders that participated in this study widely agreed that such continued legal uncertainty is undesirable as it translates into costs and litigation. Nonetheless, a growing number of issues seem to have been settled to a degree that is perhaps not entirely perfect, but that at least legal uncertainty and the accompanying economic costs are strongly reduced or eliminated.

The legal challenges and (re)interpretations of the SPC system also directly relate to innovation impacts. In particular the Neurim ruling, that allows one to obtain more than one SPC for the same product, further incentivises companies to focus on marginal innovations that enable them to receive full compensation and minimise the risk and investment needed for product development.

From an economic perspective, the here included case studies give **no indications for any difference in pricing between the time that a drug is under 'ordinary' patent protection and when it is under protection by an SPC.** Price changes typically do not occur before generics enter the market, as illustrated by the cases of Lipitor and Losartan. However, the case studies illustrate that patent and regulatory (supplementary) protections are important factors in the duration during which a certain price is charged for medicines and thereby in the total costs of pharmaceutical care. Drugs that benefitted from protection throughout all or most of the data periods available for this study showed relatively little variation in the price per defined daily dose or per user. Upon expiry of the SPC and entry of generics, however, prices dropped dramatically in some instances. For Lipitor and Losartan, prices dropped by a factor of twenty, causing the costs to the Dutch health care system to decrease by the same order of magnitude. This concords with the prediction from economic theory that drug prices are largely unrelated to the term of protection and determined by a society's willingness-to-pay rather than their marginal production costs. The costs of SPC protection (including the six months paediatric extension) for the Dutch health care system were estimated at around €690m for Lipitor, around €660m for Losec, and around €120m for Cozaar. **The open question, which cannot be conclusively answered within the scope of this study, remains how these additional revenues for the pharmaceutical companies – borne as costs by the Dutch healthcare system – relate to the costs of developing these drugs and to what extent they affect *ex-ante* investment decisions.**

One final, more general observation, stemming from the increasing complexity of the SPC system itself as well as from the extended possibilities to obtain SPCs, is that this appears to be substantially **adding to the workload of patent and SPC examiners**. The increased workload entails a risk that – absent reforms to simplify the system – overburdened examiners may opt to just 'rubberstamp' SPC applications without proper scrutiny of the claims. In general, the study authors note that there is a **shortage of experts with sufficient understanding of both patent and regulatory systems**, particularly within the judiciary and within public bodies dealing with various aspects of pharmaceutical policy. This scarcity of know-how increases the risk of misperceptions.

8.1.1.1 *Unitary SPC*

Whilst it was not within the scope of this study as such, the discussion on the SPC system would not be complete without a brief consideration of the potential creation of a Unitary SPC. Unfortunately, at this stage, there remains considerable legal uncertainty about the Unitary Patent System, and in particular whether and when it will enter into force. Assuming, however, this will at some point be the case, one can consider how this will affect the SPC system.

The current SPC system is based on an EU Regulation, though its application is devolved to the national Member States' patent offices. That thus leaves room for divergent interpretations, which as discussed before, is an undesirable outcome.

The present Unitary Patent system is fundamentally based on the same premises and the same concerns, i.e. a desire to avoid divergent solutions and come to a full harmonisation or even uniformity. A European patent granted by the EPO falls apart in a bundle of national patents, and each, then national, patent can become the subject of litigation in each member state where the patent has been validated. That can lead, and has led, to divergent solutions, where in one country a patent has been held valid and infringed, whilst in another country, based on an almost identical set of facts, that very same patent can be held invalid and not infringed. The Unitary Patent system aims at limiting those divergences by creating a system whereby a patent granted by the EPO will become valid in all participating Member States and will constitute a single right.[441]

A centralised Unified Patent Court[442] will deal with infringement and validity proceedings. The system as it has been agreed upon will not lead to full uniformity of legal rules, as it is a so-called "hybrid" system. That means that, as the system has been set up, there will be a core set of provisions laid down in the respective legislative instruments setting up the Unitary Patent and the Unified Patent Court. However, all provisions relating to substantive provisions of patent law will still be governed by national law. The Unified Patent Court will in each case have to apply national law. Which national law will need to be applied has been laid down in a set of so-called "conflict rules" which determine for all possible scenarios the provisions of which national law will have to be applied.

Introduction of a more uniform SPC system, that could – at least to some extent – be aligned to the Unitary Patent system, would lead to a single examination by one patent office (for instance the EPO), and upon examination, the SPC would be granted for all Member States. Consequently, a Unitary SPC system would create greater legal certainty.

Even though there are no details available yet about an envisaged Unitary SPC system, it can be assumed that such a system would become tied in into the Unified Patent Court. That would mean that, contrary to what is the case today, only one court would take appeals from decisions taken by the Patent Office to grant or refuse the SPC. That too assists in creating more legal certainty, as there no longer would be a risk of having divergent court decisions in each Member state.

One feature that would not change would be the role of the CJEU. If we assume that the Unitary SPC system would be an instrument of European law, then the CJEU remains, as the ultimate guardian of EU law, involved in interpreting and shaping the system.

8.1.2 Paediatric Regulation

By mandating MA holders to develop and comply with an approved Paediatric Investigation Plan (unless a waiver is granted), the paediatric regulation appears to have **succeeded in terms of stimulating paediatric research and improved knowledge of pharmacodynamics/pharmacokinetics in children**, even if the number of new paediatric

[441] Regulation 1257/2012/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32012R1257

[442] AGREEMENT on a Unified Patent Court (2013/C 175/01), OJ, C 175/1, 20 Jun 2013 https://www.unified-patent-court.org/sites/default/files/upc-agreement.pdf

indications and/or formulations remains limited. However, it seems that the regulation has been mostly successful in stimulating paediatric research for drugs that were primarily designed for use in adult populations. Meanwhile, there remains a clear unmet need for R&D for true paediatric drugs, i.e. those for which the need is greatest among children and where there is no (significant) adult market.

From the legal and economic perspective, this study has focussed only on the paediatric extension, part of a broader package of measures that jointly make up the Paediatric Regulation. Here, there are two main observations to be made. The first concerns the **relation between the size of the reward provided by the six month SPC extension and the investments necessary to develop and comply with the PIP**. This study did not by itself consider the second half of that relationship, but a recent evaluation of the Paediatric Regulation commissioned by the EU and led by Technopolis provided insights into this aspect. Our study also did not attempt to estimate the average size of the reward for all drugs for which a paediatric extension was granted. Instead, it considered a limited number of (successful) case study drugs in the specific Dutch context. Nonetheless, these cases together with the broader literature, suggest that, particularly for blockbuster drugs, the reward can be exceedingly generous.

The second observation derives from the legal analysis. To date, not much case law exists concerning the paediatric regulation. However, there is one question regarding the now possible 'negative-term SPC'. The Paediatric Regulation clearly states that the paediatric extension can only be granted if there is an SPC (or an application to that effect has been filed). That indicates that the objective was that only those patents that suffered considerable loss of effective patent term protection deserved an SPC in the first place and should be considered for the extension. It can thus be **questioned whether the SPC system has ever been devised to allow negative terms of SPC protection**, as in the core it is a system for extending patent protection term, and not for reducing it. However, holding that there is no possibility for negative-term SPCs would imply that those patent holders who have suffered only a limited loss of patent term protection would not be allowed to benefit from a paediatric extension. This could be interpreted as unfair. Although the current ruling allowing negative-term protections addresses the potential unfairness, it is debatable whether it is in line with the intent of the system.

Taken together, these two observations could lead one to conclude that **the six months extension to an SPC may be a somewhat uncomfortable and unnatural choice of reward instrument**. The US, by contrast, has chosen a different route, offering a reward in the form of six months of market protection. As this study did not involve a comprehensive comparative analysis of the EU and US systems, the relative merits and drawbacks of these alternative policy choices are here not further discussed.

8.1.3 Orphan Drug Regulation

The Orphan Drug Regulation appears to have been **successful in incentivising much needed R&D for orphan drugs**, as seen by an ever-growing number of products (either on the market or in development) with an orphan designation and an increasing number of orphan diseases for which drugs are becoming available. However, most drugs with an orphan designation are in the space of **oncology** whilst there continues to be an **unmet need for (very) rare diseases in many other areas**. Of note in this regard is also that relatively few orphan products have been brought to market for paediatric diseases for which there is no adult indication.

Various issues have arisen that have become the subject of **debate as to whether the orphan regulation has become the subject of unintended, potentially undesirable, use**. These relate primarily to the practices of so-called '**indication stacking**' and '**sub-setting**'. The former is based on the fact that under the Orphan Drug Regulation, **an MA holder can obtain multiple periods of market exclusivity for the same drug if the drug is authorised as a designated orphan drug for more than one therapeutic indication**. That is because under the orphan Drug Regulation there is no concept of a Global Marketing Authorisation (GMA). Under the 'traditional' system of data exclusivity and market protection each subsequent MA for a new formulation, addition, or medical indication of the same active substance falls within the same GMA. As a result, no new period of data exclusivity and market protection is triggered, thus allowing generic products to enter the market as soon as the period of data exclusivity and market protection for the GMA has lapsed.

In principle, under the Orphan Drug Regulation, during the period the market exclusivity is active, a second marketing authorisation for the same or a similar product for the same therapeutic indication(s) cannot be considered. However, the regulation offers various exceptions, such as when the similar product is safer, more effective or otherwise clinically superior, or if the holder of the first MA gives its consent. In such cases too, the **second MA will elicit a new and separate period of market exclusivity, effectively prolonging the period during which generic manufacturers will be kept off the market for that therapeutic indication**.

Beyond delaying generic entry, it has been **questioned whether indication stacking does not enable companies to unduly benefit from the market exclusivity (and other benefits offered by the regulation) for products for which there is in fact a substantial commercial market**, as with each subsequent indication the total eligible patient population – and thereby the market – grows. This study shows that, there are only 13 designated orphan drugs[443] on the market with two or more indications, suggesting that, to date, the scope and extent of this phenomenon in Europe has been limited. It is worth noting that indication stacking need not be undesirable. In fact, further development of existing drugs to determine whether additional patients can benefit should be a welcomed outcome, both from a public health and an economic perspective. The question rather is whether the protection offered through the market exclusivity, and the ability to stack protections, does not result in undue profit maximisation, as the intent of the regulation has been to incentivise innovation in a space where profit potential is limited. **The regulation provides a theoretical safeguard, in the form of Article 8(2),** that allows the period of market exclusivity to be shortened if it can be demonstrated that a product no longer meets the eligibility criteria. However, this assessment is done against the original criteria on which the product was designated. As an orphan designation is granted for a specific indication for the product, **the assessment only reviews the (change in) prevalence of that indication. It does not consider the cumulative prevalence across all designated indications.** Whilst the wording of Article 8(2) also includes the option to reduce the exclusivity period for products that have become '**sufficiently profitable**', this option is only applied to products that received their designation because they were deemed unlikely to "generate sufficient return to justify the necessary investment". It is therefore deemed **not applicable to products that received their designation on the basis of prevalence, even if they are undoubtedly very profitable**. Importantly also, the derogation procedure offered by Article 8(2) needs to be invoked by at least one Member State. It appears that, in practice, this is seldom done. A certain measure of restraint in the use of such drastic measures is certainly justified, given their potential for undermining the attractiveness of the incentive. However, at a time where certain orphan drugs, such as Humira and Revlimid, are among the highest grossing drugs on the market (nicknamed 'niche busters')[444], it is worth revisiting the interpretation and use of these provisions. After all, the Orphan Drug Regulation was designed to incentivise development of drugs in therapeutic areas where there is insufficient expectation of return on investment.

Concerns have also been raised as to whether the Orphan Drug Regulation is tempting companies to engage in 'sub-setting', that is: **'creating' orphan diseases by targeting sub-sets of patient populations**, based on specific gene mutations, with otherwise non-orphan diseases. Based on the criteria as currently used in the determination of eligibility for the orphan designation, appropriate measures appear to be in place to ensure that any application based on sub-setting is in line with the intent of the regulation. At the same time, it must be acknowledged that this is still a relatively young and developing field of science and that it may in future pose considerable challenges for the assessors at the Committee for Orphan Medicinal Products.

Much of the public discourse on orphan drugs has focussed on their **perceived high prices**. There is a feeling that, in exchange for the exclusivity offered, these drugs should be priced in a way that drugs are sufficiently affordable and accessible. This argument is commonly strengthened by pointing at substantial public investments in early stage R&D for orphan diseases. This study did not focus in any depth on price-setting at the point of market entry, nor on the effects of potentially price-depressing measures such as negotiated entry or joint procurement. Rather, the economic perspective taken was on the impacts of the granted market exclusivity on the price *development* and total costs to the

[443] Designated orphan drugs herein refers to drugs with an orphan drug designation under the EU regulation. This study did not consider which products have received an orphan drug states under the US system.

[444] Kumar Kakkar K, Dahiya N (2014) *The evolving drug development landscape: from blockbusters to niche busters in the orphan drug space*. Drug Dev Res. 75(4):231-4. doi: 10.1002/ddr.21176.

healthcare system. The number of case studies involving orphan products is also too small to extrapolate from with any certainty. Having said that, these cases do illustrate and concur with similar observations by others[445] that, **in the space of orphan drugs, competition by generic drugs or biosimilars tends to be less than for non-orphan drugs**. For instance, although the market exclusivity for Myozyme has expired, no competition has entered the market. One explanation is that the market is too small for multiple products, particularly against the background of an expected price drop for the originating drug once generic competition were to appear. This is particularly true in cases where manufacturing is complex and costly, as is often true for biological drugs. It is this absence of competition itself, including the expectation upfront that competition will be slow or non-existent, that is more likely to affect prices.

8.1.4 Data exclusivity and market protection

Data exclusivity is designed to reward innovator companies for their investment in R&D by granting a period of eight years of protection on the dossier with clinical trial and other test data. After this, a period of two years (in some cases, three years) of market protection applies during which generic companies cannot yet bring their products on the market. Data exclusivity and market protection are regulatory instruments of protection, rather than IP instruments.

Data exclusivity and market protection were infrequent discussion points in the interviews conducted for this study and **no exhaustive analysis was performed of these instruments**. That is primarily because, whilst these instruments have important ramifications from the point of view of *access to medicines* by delaying generic entry, they have only limited direct relation to impacts on pharmaceutical innovation. Moreover, the innovation and economic impacts from data exclusivity and market protection are difficult to separate from the impacts of other instruments such as patent and SPC protections as these largely coexist. Consequently, **this study cannot provide any evidence on whether, or to what extent, the impacts of these exclusivities and protections align with the intended objectives**.

Nonetheless, some broad observations merit inclusion here. First, from the perspective of innovation, **data exclusivity may well represent a double-edged sword**. On the one hand, regulatory data protection provides innovators the security that competitors cannot 'piggyback' on their R&D before they themselves have had a chance to recoup (some) of their investments, whilst being able to provide the necessary disclosure of test data to the regulators deciding on the market authorisation for their product. Some have argued that especially for biological drugs, patent protection by itself is not sufficient to stave off competition as, using the trial data, companies would be able to engineer products with a completely different structure, yet interacting with the same target.[446] This protection thus itself **provides an incentive to R&D**. By logical extension, however, delaying third parties access to this trial data also means that **any incremental innovation based on the drug by such parties is delayed**. **Further study would be needed** to obtain a better understanding of the balance between these opposing effects, as well as on the relative importance between incentivising innovation and delaying access to generics.

Second, market protection and exclusivity was discussed primarily in the context of orphan drugs. Here, the main question is whether the market exclusivity granted by the orphan drug regulation poses a barrier for development of other products for that same indication. This study did not explore underlying reasons for originator companies to invest, or not invest, in (further) development of products for therapeutic indications for which a designated orphan product already exists. It notes, however, that the Orphan Drug Regulation allows for exemptions to the market exclusivity in case of demonstrated superiority of the second product. Additionally, the exclusivity does not extend to products that are not considered similar to the first product, for instance if they are based on a different mechanism of action. Consequently, **it is deemed unlikely that this market exclusivity has a significant negative impact on the development of follow-on orphan drugs**. As noted

[445] A similar observation was included in the *Monitor Weesgeneesmiddelen 2017* (2017) by the Zorginstituut Nederland based on the lack of competition, even after expiry of market exclusivity, for drugs in the treatment of, among others, Fabry disease. Available at: https://www.zorginstituutnederland.nl/publicaties/publicatie/2017/12/21/monitor-weesgeneesmiddelen-2017 Accessed 31 January 2018.

[446] Calfee JE (2008) *When patents are not enough: data exclusivity for follow-on biologics* In: Uncle Sam M.D. AEI Scholars on Health Care and Pharmaceutical Reform. American Enterprise Institute. Available at http://www.aei.org/publication/when-patents-are-not-enough/

previously, the scarcity of competition in the orphan drug space is more probable to be influenced by the dynamics of the market.

Table 7 Summary of key findings regarding the alignment between intended and realised effects

Intended, but not (sufficiently) realised effects	Intended and realised effects	Realised but unintended, effects
SPC Regulation		
• Despite an absolute increase in pharmaceutical R&D expenditure in Europe, the pharmaceutical innovation gap between the EU and the US has widened, both in terms of NCEs brought to market and R&D expenditure. • The implicit objective of encouraging lower prices for still-protected products, by offering pharmaceutical innovators increased time to recoup their investments, appears not to have been realised at all.	• The SPC regulation offers pharmaceutical innovators compensation for the loss of effective patent term they incur due to clinical testing and regulatory approval requirements. There are no indications that the period of 5 years extension is anything less than sufficient. • The SPC regulation has been implemented in all EU Member States. Whether the interpretation of the regulation is sufficiently harmonised was outside the scope of the present study.	• Through case law testing, the current interpretation of the SPC regulation has been significantly broadened compared to what appears to have been the legislators' intent. • By not differentiating the size of the compensation offered by the degree of 'innovativeness' (i.e. therapeutic added value), compounded by the above-mentioned broadened scope, the SPC regulation may be amplifying an industry tendency to focus on safer, marginal innovation at the expense of riskier breakthrough innovation.
Paediatric Regulation		
• There has been no significant increase in the number of products developed for indications that occur only in children. • Thus far, the Paediatric Regulation has not sufficiently stimulated paediatric trials in very young children and neonates.	• For products with both an adult and paediatric indication, the Paediatric Regulation has succeeded in increasing paediatric drug research. • As a result of the regulation, the number of products with an indication for paediatric use or an age-appropriate formulation has increased. • Knowledge on paediatric use of medicines has increased.	• For high-grossing drugs, the financial compensation offered by the Paediatric Regulation in exchange for (mandatory) paediatric trials can be many times over that of the costs incurred by the originator company.
Orphan Drug Regulation		
• There continues to be a great unmet need for products for the treatment of many rare and orphan diseases. • Particularly for orphan diseases that affect only children, there is insufficient development of OMPs. • For diseases with both adult and paediatric populations, the registration of the OMP for paediatric use is often significantly delayed.	• The number of products, both those that are in development and those that have been authorised, for orphan diseases has significantly increased. There are now drugs for many previously untreatable diseases.	• R&D for orphan diseases has clustered in certain therapeutic areas, in particular oncology. This need not be undesirable, yet it potentially diverts resources and attention from other areas of greater unmet need. • The absence of a GMA for OMPs allows multiple periods of market exclusivity on the same product to be stacked if the product has multiple orphan designated indications. The possibility of indication stacking creates the possibility for companies to gain returns on investments for these OMPs that are at odds with the intent of the regulation. • The absence of a GMA also allows successive periods of market exclusivity even for the same therapeutic indications, by invoking exceptions in the regulation.
Data exclusivity & market protection		
• Unknown	• Companies are rewarded for conducting R&D to support pharmaceutical innovation.	• Delayed generic entry and competition increases costs to the healthcare system and delays access. • Data exclusivity could in theory delay incremental innovation of the back of the trial data, though the extent of this in practice is unknown.

8.2 Conclusions

This study comes at a time when pharmaceutical innovators, intellectual property and incentive systems have been the subject of much public debate, commonly negative in tone. The debates involving the (pharmaceutical) patent and supplementary protection systems are substantially polarised and are not always well grounded in evidence. It appears that a share of this polarisation stems from incomplete or incorrect understanding of (parts) of the systems at best, and from a deliberate misrepresentation at worst. Proponents and adversaries of the systems each draw selectively from evidence that supports their arguments. Findings that derive from one particular context, such as the US, may be superimposed on another, such as Europe, even if the underlying systems are substantially different and the data themselves do not always support such comparisons. This study therefore has aimed to provide a non-normative and evidence-supported assessment of different aspects of the supplementary protection mechanisms for pharmaceutical products. It has looked at both intended and unintended impacts from a legal, innovation and health system economic perspective.

It is found that the systems have succeeded to a varying degree in achieving their desired objectives. The SPC Regulation offers innovator companies an adequate compensation for their effective loss of patent term. Yet, it has failed to incentivise pharmaceutical R&D in Europe sufficiently to close the gap with the US. Meanwhile, the Paediatric Regulation has catalysed much needed paediatric drug research in some therapeutic areas, though it falls short in spurring on drug development for areas of greatest unmet need in children. The Orphan Drug Regulation similarly has been a strong catalyst for development of orphan medicinal products, but this effect has been stronger in certain areas, such as oncology, than for other truly rare diseases. There thus continues to be a substantial unmet need for pharmacological treatments for paediatric and orphan diseases.

These relative successes must, however, be viewed alongside their shadow sides. In this regard, this study finds that each of the systems has brought with it various unintended effects. Whether these effects are cause for concern is largely a normative judgment, though in many cases it stands to reason that effects that were not intended by the legislator are unlikely to serve the public interest.

Particularly the evolving, and at times inconclusive, interpretations of the SPC Regulation by the judicial system have reshaped the system in fundamental ways, adding to its complexity. It is not without irony that we note that the proposal for the SPC Regulation included the following wording: *"the proposal for a regulation provides for a simple, transparent system which can easily be applied by the parties concerned. It therefore does not lead to excessive bureaucracy. There is no need for any new administrative body and the patents offices should be able to implement the procedure for granting the certificate without an excessive burden being placed on their administrations."* It is evident that here the regulation has failed to achieve what it set out to do.

Regardless of whether one agrees with the various interpretations as they stand today, the fact that the regulation has in parts effectively been rewritten by the Court of Justice of the European Union should itself be cause for reflection on whether the system is in critical need of realignment. The present imprecise wording of some of the provisions of the regulation has evidently left substantial legal uncertainty. It should then be the responsibility of the legislator, and not the court, to clarify its intent and redraft the provisions accordingly.

Similar concerns arise in the context of the Paediatric Regulation. The question raised by this study as to whether the paediatric extension is the most appropriate instrument to reward paediatric research arises – at least in part – from a lack of clarity of intent on the part of the legislator. Here too, it should be a policy choice rather than a legal verdict that decides eligibility for a reward offered under the system.

Regarding the Orphan Drug Regulation, the issue is somewhat different. Here, the regulation contains various safeguards to protect against use of the regulation in ways that would be at odds with the intent. Yet, these safeguards are not a matter of routine; rather, it is left to Member States to invoke these safeguards and request that action is taken at the European level. Available evidence suggests

that this option is insufficiently used. Here then lies a responsibility for national governments, including the Dutch government, to help ensure the proper functioning of the regulation.

Overall, this study concludes that, whilst overall the supplementary protections mechanisms function to a significant extent in the ways for which they were designed, there is ample space for improvement. This involves a combination of actions to: i) improve their effectiveness, ii) resolve remaining uncertainties, and iii) reduce or eliminate unintended and undesired effects. In the following section, various recommendations are offered.

Whilst ultimately it is the responsibility of the legislator (that is, the EU and its Member States) to decide on the appropriate course of action, it is important that this is done with a proper understanding of the needs and interests of all parties involved. In the interest of this understanding, it will be necessary for all parties to display a greater degree of open-mindedness and self-reflection than we presently observe. On the one side of the debate, there is a tendency to judge an entire industry by its worst excesses. On the other, industry often comes across as unwilling to acknowledge that even legally correct behaviour can be less than socially desirable. Therefore, we urge that the exception not be mistaken for the norm but that, at the same time, there is reflection on whether the current 'norm' is still what was intended when the regulations were developed.

On a final note, we remark that development of actions in any or all of the recommended areas should take a sufficiently long time-horizon. This means that the consequences of these actions should not only be considered for the short-term (e.g. via cost savings), but also for the long-term (e.g. on the pipeline of pharmaceutical products under development). Ensuring patients' access to innovative pharmacological therapies, yet doing so in a way that is affordable to the individual patient and the healthcare system at large, depends on a pharmaceutical climate wherein both innovation and competition are stimulated.

8.3 Recommendations

Against the backdrop of the presented discussion and conclusions, the following set of recommendations is offered. These have been divided into those recommendations that pertain to specific aspects of the various mechanisms and some more general conceptual measures. Whilst the recommendations mostly would need to be taken up at the level of the EC, they can be used by Member States such as the Netherlands and other parties to advocate for action in these areas.

8.3.1 Specific recommendations

- **Maintain the systems in place in their basic constituent parts**: This study has not found compelling evidence to recommend a complete abolishment of the SPC Regulation, the Paediatric Regulation (more specifically, the paediatric extension), the Orphan Drug Regulation (in particular, the market exclusivity for orphan products) or the data exclusivity and market protection protections. The objectives set for each are for the most part sound and the systems are, to varying degrees, succeeding in their objectives. There appears to be little (at least visible) outright "abuse" in the legal sense of the word.
- **Tackle the issue of the extent of protection of basic patents**: As discussed previously, the issue of defining the scope of protection of the basic patent remains unresolved and should be tackled. This can be done either by further specifying the application of the 'extent of protection rule' (e.g. in the text of the Directive or in guiding documents to the Directive); or by allowing for the 'infringement test'. The latter provides more legal certainty, but may also lead to more SPCs.
- **Establish the extent to which secondary medical use patents, formulation patents, or other derivative patents should be protected by SPCs**: The Neurim case has paved the way not only for SPCs on indication patents, but potentially also on patents related to formulations or dosages. This may increase the number of SPCs considerably. The lawmaker could contemplate a more sui-generis approach towards this type of patents, somewhat keeping the middle-ground between full SPC protection and no SPC protection at all, for instance by providing a shorter SPC term or some other type of incentive.

- **Consider whether the extent of supplementary protection granted by an SPC can and should be differentiated by the therapeutic value offered by the product**: Whilst tying the degree of innovativeness of a product to the size of the compensation would be in line with the spirit of the SPC regulation, this recommendation is not without its problems. First, there is no agreed definition or metric for what constitutes 'therapeutic added value' (TAV). Second, as SPCs are granted at the national level, the assessment of TAV could fall on national patent examiners, who are unlikely to have the required expertise to do so. Moreover, leaving this assessment at the national level is likely to introduce substantial divergence of outcomes across Member States. Alternatively, the assessment of TAV could be done at the European level (i.e. by the EMA) or by a national competent authority (such as the CBG-MEB) which then acts as a reference for other Member States.
- **Consider eliminating the possibility of SPC squatting**
- **Re-examine the appropriateness of the 6-month paediatric extension to an SPC as the desired reward for paediatric research**: The existence of zero or negative-term SPCs underscores that the link between SPC protection and the eligibility for the reward for compliance with a PIP is a tenuous one.
- **Consider introduction of alternative or additional incentives to promote R&D for the development of paediatric drugs for which there is no adult indication, and addressing areas of greatest unmet need in children and neonates**: Rather than offering further supplementary protections, this could also be done in the form of, for instance, research and innovation prizes.
- **Explore whether stronger support for basic research into orphan diseases is required**: There remains substantial unmet need for orphan drugs for the treatment of very rare diseases. This may be due to lack of sufficient basic research in this field. Investment in this could be (further) supported via, among others, the EU Framework Programmes or national research funding initiatives. As such support involves investment of public money, it would be important to carefully consider how this can be done in such a way that the affordability of any drugs developed is guaranteed.
- **Consider the introduction of a GMA in the context of orphan drugs to ensure that generic entry and competition is not unduly delayed**: However, the Orphan Drug Regulation acts on a very delicate system, as orphan drug development has traditionally not been the natural habitat for pharmaceutical companies who are looking for drugs with significant profit potential. The Orphan Drug Regulation and the incentives laid down therein must achieve the difficult task of sufficiently incentivising investment in the development of drugs with a smaller patient base and profit potential without hampering innovation by foreclosing such markets.
- **Explore whether Member States are sufficiently aware of the derogation options offered under Article 8(2) of the Orphan Drug Regulation** that allow the period of market exclusivity to be reduced under particular conditions. In practice, however, the invocation of this article by individual MSs will likely be complicated due to lack of knowledge at national ministries about exact disease prevalence, and due to national variations in drug prices, resulting from underlying differences in procurement and reimbursement systems. Yet, the provision offers one of the few possibilities for concerted action against excessive profiteering on orphan drugs at the EU level.

8.3.2 General recommendations

- **Increase expert know-how on supplementary protections and the interface between IP and pharmaceutical regulation**: With know-how in the analysed fields being scarce, managing and improving the know-how base becomes key. This includes proper staffing of patent offices and training of the patent examiners, but also supporting the development towards specialised courts with respective know-how in both IP and regulatory measures.
- **Foster exchange and collaboration between regulatory experts and IP experts**: There appears to be a substantial divide between experts of (pharmaceutical) IP and experts in pharmaceutical regulation. It seems feasible to support an improved institutionalised

exchange forum between these two groups of experts to improve awareness of the impacts of decisions taken in one sphere on the other sphere.

- **Improve clarity and ease of use of EU and national data registers on protections and exclusivities for pharmaceutical products**: Whilst most information is in the public domain, registers are not well linked or easy to navigate without expert knowledge. That is, at least in part, because of inconsistent use of product names (e.g. brand names vs INN or chemical formula, variant brand names, language differences). Moreover, different protections are linked to the actions of different parties (e.g. national patent offices vs national competent authorities for marketing authorisation). The lack of a unified, connected and clear overview makes it hard for non-specialised third parties to see when a drug will become free from protection.
- **Emphasise routine evaluation of the impact of regulations**, not only with a view towards accountability but with an openness to **update and revise regulations** in areas where that is appropriate. Uncertainty about consequences and a fear of upsetting delicate systems should not lead to policy paralysis.

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Appendix A List of interviewees

Name	Organisation
Marcel van Raaij	Ministry of VWS
Huib Kooijman	Ministry of VWS
Jasper Wesseling (in writing)	Ministry of EZK
Martijn de Lange	Nederlands Octrooicentrum
Jean-Luc Gal	European Patent Office
Bert Leufkens	CBG-MEB
Violeta Stoyanova-Beninska Maaike van Dartel Sandra Kruger-Peters	CBG-MEB
Martin van der Graaff Jacqueline Zwaap	Zorginstituut Nederland
Bart Benraad	Zorgverzekeraars Nederland
Peter Bertens Armand Voorschuur	Vereniging Innovatieve Geneesmiddelen
Martin Favié	Bogin
Annemiek Verkamman Wieteke Wouters	HollandBIO
Hans Schikan	Topsector Life Sciences & Health
Cor Oosterwijk	VSOP
Pauline Evers	Nederlandse Federatie van Kankerpatiëntenorganisaties
Carine van den Brink	Axon Lawyers
Marleen van den Horst	BarentsKrans
Rutger Kleemans	Freshfields Bruckhaus Deringer
Martin Klok Otto Oudshoorn	V.O. Patents & Trademarks
Bert de Jong	Sanofi Genzyme
Carla van der Sterren	Synthon BV
Ad Antonisse	AstraZeneca
Martijn Groot Niels Nuland	Gilead
Isabelle Schubert Petra Keil	Novartis
Ellen 't Hoen	UMC Groningen
Marie-Hélène Schutjens	Schutjens De Bruin

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