Supplementary Protection Certificate for medicinal products
An assessment of European regulation

Management, Policy Analysis and Entrepreneurship in Health and Life Sciences
Internship 1

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“We can't solve problems by using the same kind of thinking we used when we created them.”

Albert Einstein
Preface
This research is commissioned by the Dutch Ministry of Health, i.e. het Minsterie van Volksgezondheid, Welzijn en Sport (VWS). Civil servants at the department of Pharmaceutical Affairs and Medical Technology, i.e. Geneesmiddelen en Medische Technologie (GMT), are working on the innovation policy of the Netherlands. They have identified several mechanisms to stimulate, promote and, or filter innovation. The supplementary protection certificate (SPC) for medicinal products (Regulation (EC) 469/2009) is an example of such a mechanism in the European Union. The idea of this regulation is that it should stimulate innovation. This research is conducted in order to gain insights into this particular mechanism that should stimulate innovation.

I would like to thank several people who helped me with this master thesis. First of all, my two supervisors, Frank Flier of VWS and Marianne Benard of the VU, for all the patients and good feedback that helped to improve my thesis significantly. In addition, I would like to thank Bram van Houten en Maaike Vermunt who also looked at and helped me to improve the text. Secondly, I would like to thank Margreet Schreurs who helped to get all the data from the SFK database. In addition, I would like to thank Martijn de Lange and his colleague who made a perfect overview of all the SPCs in the Netherlands. Finally, I would like to thank all my interviewees who also were kind to give up some of their valuable time and share their views with me for this research.

I am a master student at the Free University, Vrije Universiteit (VU), in Amsterdam. This is the first master thesis of my two-year master of Management, Policy Analysis and Entrepreneurship in Health and Life Sciences.

Enjoy reading!

Rens
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Executive Summary

Subject matter
The subject of this research was the supplementary protection certificate (SPC) for medicinal products in the European Union. The SPC was implemented in 1993. The primary reason and rational behind the implementation of the SPC regulation was to increase the patent life of medicinal product after market authorisation, also called effective patent life (EPL). The extension of the patents should stimulate innovation in the pharmaceutical sector. The purpose of this research was to assess this effect and collateral effects of the SPC regulation on the pharmaceutical sector.

Methods
The reasons and rationales behind the SPC regulation came from document analysis, in particular the explanatory memorandum on the SPC regulation (COM (90) 101 final). Six topics were determined with this analysis concerning effective patent life; research productivity and innovation; relocation; competition; drug prices; and interests. The research questions were derived from these topics. In addition, the research question on research productivity was assessed with the understanding of the concept of research productivity, which is defined by Paul et al. (2010).

Thirty-two experts in the field of pharmaceuticals and health policy were contacted with the network of the Dutch Ministry of Health, and fifteen experts were able to participate for interviews. Fourteen semi-structured interviews were conducted; one interview was conducted with two participants. Interviews were transcribed and summarised. All participants validated their summaries. Transcribed interviews were coded and analysed to get answers for the research questions.

In addition, a quantitative analysis was done towards the topics of effective patent life and drug prices. The database of the Dutch patent office (RVO) was consulted to get quantitative insights in how the SPC prolongs patents of medicinal products and to find certain trends in granted SPCs over time in the Netherlands. Also, the database of the Foundation of Pharmaceutical Statistics (SFK) was consulted to get quantitative insights in how the SPC affects drug prices of extramural medicinal products after basic patent expiry and after SPC expiry in the Netherlands.

Results and conclusions
Results of the interviews suggest that extensive R&D periods that lead to patent erosion, are the result of strict market access regulation by governments. The SPC compensates this erosion of basic patents and standardises the EPL to 15 years in 50% of the cases. In the other cases patent erosion has still occurred due to extensive R&D periods of more than 10 years. In addition, an increasing trend of granted SPCs is found in the Netherlands when SPCs are ranked to their basic patents. These quantitative results are, therefore, in line with the statements of the interviewees.

This study could not find evidence for the other presumed positive effects that were stated in the explanatory memorandum. First, the SPC has limited effect on research productivity. The SPC only affects the economic value of a medicinal product. Hence, the SPC
is likely to skew innovation more towards economically attractive medicines. Hence, this study provides evidence that patent extension, i.e. the SPC, stimulates incremental innovation, because therapeutic value and radical innovations are not particularly rewarded. Second, the SPC is no solution for possible relocation of innovative companies; moreover, the SPC forces generic companies to relocate outside the EU. This study indicates that the (re)-location of a pharmaceutical company is based on business climate of a certain region, and the business climate is far more complex than only patent extension. Third, this study found no evidence for lower drug prices; moreover, patent cliff is delayed, because generic entry is delayed. Hence, the SPC has implications on health budgets, in particular for blockbuster drugs, because the monopoly with a high price is extended. Finally, this study shows that the SPC regulation is not in the interest of the European generic industry. The SPC regulation creates unfair competition between European based generic companies and non-European based companies. Hence, it forces generic pharmaceutical companies to relocate to outside the European Union. This has an effect on labour in the EU and export out of the EU. In addition, the SPC delays the opportunities to enter the market with a generic medicinal product.

This research shows that the extension patents skew innovation towards economically attractive medicinal products and large markets, neglecting some markets and medicines, which have an unmet medical need. Moreover, the extension of patents in the European Union has other implications that affect the whole pharmaceutical sector in the EU.

Recommendations
This study has shown that patents and patent extension regulation stimulates economically attractive innovation. Solely patents and patent extension are, therefore, not applicable to stimulate the development of medicines that are therapeutically valuable and economically not valuable, leaving pharmaceutical gaps. Therefore, other mechanisms are needed to stimulate innovations towards these kinds of medicinal products. Research is needed to find which mechanisms are favourable. In addition, it is recommended to conduct an assessment towards the implications of the SPC on relocation in the pharmaceutical sector in the European Union and on the national health budget of the Netherlands and other European countries.

Limitations and strengths
This research was a master thesis. Hence, the researcher was inexperienced. This could have lead to an increased risk of missed information. However, two PhDs supervised this research. In addition, the interviewees were key opinion leaders in the field of pharmaceuticals and health policy. Hence, all the experience of the supervisors and interviewees made it less likely that valuable information was missed. Moreover, the combination of quantitative and qualitative research added extra validity to the results of this research. The quantitative data added extra insights towards the statements of the interviewees and gave additional illustrations towards specific statistics.

Key words
Innovation, Pharmaceuticals, Medicinal product, Patent extension, SPC, Supplementary protection certificate
1. Introduction

Innovation in the pharmaceutical sector towards new medicines and treatments has made diseases curable and eradicated, for example, smallpox (Fenner et al. 1988) and rinderpest (Gosh 2010). However, many diseases remain incurable. Kaplan and colleagues (2013) have identified these pharmaceutical gaps, and concluded that prioritisation is needed for the development of new medicines towards these unmet medical needs, because these needs, or gaps, could be resolved with further innovation within the pharmaceutical sector.

This means there are many innovation opportunities in the pharmaceutical sector. In addition, there are several regulations, such as tax reductions or research and development funds, which stimulate innovation. The regulation with the longest history to stimulate innovation is the patent system (Boulet et al. 2003). With a patent, the owner can exclude others from employing the knowledge that is covered by the patent. This exclusivity lasts for twenty years and can be seen as a reward for the research and development (R&D) investments and for sharing the knowledge. The shared knowledge stimulates innovation and with the monopoly the owner can set such a price to have a guaranteed return on investment.

In the late 1980s, however, it seemed that the guaranteed return on investment was in jeopardy. Research of DiMasi and colleagues (1991) stated that R&D towards new medicinal products had become increasingly expensive and time consuming. These researchers stated that almost 12 years of the 20-year patent was lost on R&D, leaving 8 years for commercial exploitation of the patent on the market. This is called patent erosion. This erosion seemed to be responsible that the 20-year duration of the monopoly of a patent was becoming more of a burden than a privilege, which could hamper innovation in this sector.

A simple, and straightforward, solution for patent erosion is to extend the patents for medicinal products. Patent extension was implemented in the European Union by regulation in 1993. This regulation is called the Supplementary Protection Certificate (SPC) for medicinal products and extends the effective patent life and the guarantee for a ROI. Though, it remains unknown whether this regulation actually stimulates innovation. The purpose of this study was to get insights in how patent extension affects innovation in the pharmaceutical sector and the pharmaceutical sector itself. Furthermore, the Dutch Ministry of Health wants to know whether patent extension provides the right incentives to innovate in the fields where there is still an unmet medical need (Kaplan et al. 2013).
2. Research objective

The SPC regulation is a European regulation implemented in January 1993. The regulation should be a solution for the patent erosion and extends the patent life with a maximum of 5 years. Several additional positive effects were stated in the explanatory memorandum of the SPC regulation (COM (90) 101 final) for example the improvement of productivity in the innovative pharmaceutical sector. However, the question remains if these presumed effects have worked out.

The research objective was to find how the Supplementary Protection Certificate (regulation (EC) 469/2009) affects the pharmaceutical sector in general and research productivity in specific, by assessing the rationales behind the SPC regulation stated in the explanatory memorandum of the SPC regulation (COM (90) 101 final).

This objective leads to the main research question:

To what extent does the Supplementary Protection Certificates (EC Regulation 469/2009) stimulate innovation and what are additional effects of patent extension in the European Union?
3. Contextual background

The pharmaceutical sector and the world of medicinal products are complex. This chapter highlights the most important aspects of the pharmaceutical sector. The understanding of these aspects was necessary for this research.

3.1 Market authorisation for medicinal products

A new medicinal product has to obtain market authorisation (MA) by the medicine evaluation authorities in order to enter the market (Directive 2001/83/EC). This directive obligates a pharmaceutical company, i.e. applicant for market authorisation, to conduct clinical tests in order to provide scientific data that proves efficacy and safety of the medicinal product. All these data are combined in a dossier. This dossier includes the results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests and clinical trials (Art. 8(3) 2001/83). This dossier, which must accompany an application for MA for a medicinal product, has to demonstrate that potential risks are outweighed by the therapeutic efficacy of the product. In addition, the holder of the granted MA has to conduct further trials to assess long-term effects. However, MA is not granted if the medicine evaluation authorities are not convinced about this risk benefit balance.

A copy of a medicinal product, a generic medicinal product (i.e. identical and bioequivalent product), does not need its own (pre-)clinical trials. The dossier of a generic product can refer to the data of the (pre-)clinical trials of the reference product, the original medicinal product (Directive 2001/83/EC article 10(1)). However, according to that article, the owner of a generic product is only allowed to use the data of the reference product the following 8 years after MA of the reference product, i.e. Regulatory Data Protection (RDP) and can get MA not until 10 years have lapsed after the MA of the reference product, i.e. market protection. This 2-year market protection can be prolonged with 1 year if the reference product has gained an extra indication during the first 8 years after MA (art 10(5) 2001/83).

3.2 Research and development - preclinical and clinical trials

The clinical trials are the most time consuming. In order to get an understanding of this phase an elaboration is given in this section. The research and development of a new medicinal product has five phases. These five phases can be divided in two categories, i.e. the preclinical and clinical phases (Angell 2004b, Dissel et al. 2013).

3.2.1 Preclinical trials

The nature of a disease has to be understood on a very detailed level before a medicinal product can be developed and tested (Angell 2004b). With the understanding of the disease researchers can identify a link in the chain that a medicinal product will target. The research towards the understanding of a disease is mostly done at universities or government research labs (Angell 2004b).

Promising medicinal product candidates for the targeted disease are identified before the preclinical trials. The molecules can be screened by computerised methods to see if they will target a link in the chain of the disease. Thousands of different molecules are identified. In addition, these new molecules can be synthesised or extracted from animal, plant or mineral sources. These drug candidates are tested in animals and cell cultures during the preclinical
Approximately five to ten potential medicinal products can be tested in the clinical trials (Angell 2004b).

### 3.2.2 Clinical phases

Clinical phase 1 starts after the preclinical trials. Phase 1 is to see if there are some minor or more severe side effects, therefore tests are done with healthy subjects, except for oncolytics (Angell 2004b). Healthy subjects can be students who are recruited via universities. Phase 1 last for 3 to 4 weeks. That is enough time to see some short-term side effect of the tested medicinal product. Probably no evidence will be obtained if a medicinal product is effective. The medicinal product will continue to the next phase if there are no severe side effects.

Two more phases need to be completed after phase 1. These are to determine effectiveness of the medicinal product on patients (phase 2) and to determine the right dose (phase 3), respectively. These phases are bigger than the 3 to 4 weeks and 100 subjects of phase 1. Some hundred subjects are involved in phase 2. The potential medicinal product is tested against a placebo and lasts 1 to 2 years. Tests in phase 3 needs to confirm safety and efficacy of the potential medicinal product for large patient groups. Thousands of subjects participate in these phase 3 tests, which lasts also 1 to 2 years (Angell 2004b, Dissel et al. 2013). A pharmaceutical company will continue with clinical 4 trials after MA to determine long-term effects and to update the clinical dossier for the medicine evaluation organisations.

After each phase a percentage of drugs will not pass to the next phase (Pammolli et al. 2011), in other words every phase has an attrition rate. The higher the attrition rate, the more potential drug candidates will fail. A pharmaceutical company can apply for MA for a particular medicinal product if all these phases are successful, discovery up to phase 3 clinical trials (Angell 2004b).

### 3.3 Push and pull mechanisms to stimulate innovation and productivity

These clinical phases and testing of medicinal products are time consuming and expensive. Therefore, governments have tried with numerous ways and policies to stimulate the pharmaceutical industry to develop new medicinal products. These ways can be divided in push and pull mechanisms (Mossialos et al. 2010). With these mechanisms companies or research projects are helped directly to start innovation (push), or companies/research projects are stimulated indirectly with a possible return on investment (ROI) when an innovation is completed (pull).

#### 3.3.1 Push mechanisms

Mossialos et al. (2010) has given the following definition of push mechanism, also called push incentives:

> “Subsidies to help to fund research. By reducing the cost of inputs and advancing the state of basic science, push mechanisms aim to make drug development cheaper.” (p17)

Since 1984 the European Union (EU) tries to stimulate, support and encourage research and innovation in all sectors of the European Research Area, including the pharmaceutical sector (Arnold et al. 2011). The EU encourages research and innovation with Framework Programmes for Research and Technological Development (FPs). The most recent FP, FP8, is known as
Horizon 2020. Horizon 2020 is the biggest EU Research and Innovation programme ever with nearly €80 billion of funding available over 7 years, from 2014 to 2020. Researchers, from profit and non-profit organisations, from all over Europe can apply for funding and education for their research projects.

These framework programmes are considered push mechanisms to encourage research (Mossialos et al. 2010). The first FP was initiated in 1984 and lasted until 1988 and had a budget of €3.75 billion euro. The eighth FP, Horizon 2020, is started in 2014 and has a budget of €80 billion. Other push mechanisms described by Mossialos and colleagues (2010) are, for example, R&D wage tax reductions or better infrastructures to enhance collaboration, e.g. consortia. Push mechanisms are also used on national levels.

### 3.3.2 Pull mechanisms

Mossialos et al. (2010) has given the following definition of pull mechanism, also called pull incentives:

> “Offer of a financial reward upon delivery of a specified product.” (p. 17)

Research and innovation are also stimulated by pull mechanism (Mossialos et al. 2010). Intellectual property rights (IPR) are considered pull mechanism. The most important that is discussed for this research are the patent rights. When a patent is granted on an invention it gives the inventor exclusive rights to work with that invention. In addition, the inventor can prohibit others to copy, make, use, or sell that invention (Rijksoctrooiwet 1995). Therefore, the inventor will have a monopoly when he or she will sell this patented invention on the market. This specific monopoly for a medicinal product is expected to be a guaranteed return on investment (ROI) because there will be limited competition until the patent expires. Innovative pharmaceutical companies can prevent generic competition with a patent in force. This protection has duration of 20 years after the day of patent application. A more detailed explanation about patents will be given later on.

Another European pull mechanism is the supplementary protection certificate (SPC) for patented medicinal products (Regulation (EC) No 469/2009). This regulation is a revision of regulation (EC) No 1768/92. This certificate can increase the patent life of up to 25.5 years. A detailed elaboration will be provided below. There are more pull mechanisms described by Mossialos et al. (2010), but these will not be described because they go beyond the scope of this report.

### 3.4 Intellectual property rights to create and increase market share

The site of the World Intellectual Property Organisation (WIPO) provides a detailed description of intellectual property (IP):

> “Intellectual property (IP) refers to creations of the mind, such as inventions; literary and artistic works; designs; and symbols, names and images used in commerce. IP is protected in law by, for example, patents, SPCs, copyright and trademarks. These laws enable people to earn recognition or financial benefit from what they invent or create. By striking the right balance
between the interests of innovators and the wider public interest, the IP system aims to foster an environment in which creativity and innovation can flourish.¹

The pharmaceutical industry uses the rights of intellectual property to protect their medicinal products and uses the rights for commercial purposes. They act like any other commercial and private company. They use trademarks and copyrights on their brand names so that customers will recognise their products. Furthermore, pharmaceutical companies use patents, like tech-giants Google and Apple, to ensure a return on investment of their R&D efforts by (partially) blocking competition. A short explanation will be given in the next paragraph.

3.5 Patents and effective patent life of medicinal products

In this part an explanation is provided about how pharmaceutical companies use patents to ensure a return on investment (ROI). There are key events in the life of a patented medicinal product. Figure 1. shows a schematic representation of these key events.

The date of patent application is, retrospectively, the first day of the patent life. However, there is no guarantee that a filed patent will be granted. In short, if the invention is considered novel, inventive, industrial applicable and is described in great detail it will be granted a patent (Rijksoctrooiwet). At European level it takes between 3 to 5 years to investigate if the patent meets these requirements and to grant a patent. However, there is an example that it can also take up to 19 years, e.g. Medeva case. In this case the patent was filed in 1990 and was granted in 2009 and then the patent expired in 2010).² A granted patent will expire 20 years after patent application. In addition, a patent will be disclosed in the public patent database 18 months after patent application.

The effective patent life (EPL) of a (medicinal) product is the part of the patent life where the commercial benefit of the monopoly can be exploited. Exploitation of a (patented) medicinal product can be done when the authorities have granted market authorisation (MA) and after a positive reimbursement decision is made. The European authority that grants MA is the European Medicines Agency (EMA), the Dutch authority is “het College ter Beoordeling van Geneesmiddelen” (CBG), i.e. Medicines Evaluation Board. Revenue is created during the effective period of a patent. This revenue is the return on the investment for a pharmaceutical company.

¹ http://www.wipo.int/about-ip/en/
² Medeva et al. case C-322/10 C-422/10
Figure 1. A schematic representation the life of patented medicinal product. The time between patent application and patent expiration is 20 years. The date of MA is used to determine EPL. However, there is no return on investments if a medicine is not included in the insurance, i.e. a negative reimbursement decision. Time to market (i.e. cycle time) is defined as the time between patent application and MA.

3.6 The Supplementary Protection Certificate

The Supplementary Protection Certificate (SPC) for medicinal products in the European Union (Regulation (EC) 1768/92) was implemented in January 1993. Prior to the implementation, during the late 1980s and the beginning of the 1990s, the European Federation of Pharmaceutical Industries and Associations (EFPIA) lobbied for patent extension in Europe (Permanand 2006). EFPIA convinced DGIII to implement the SPC regulation that could extend the patent life of medicinal products. Together, they produced a draft version of the regulation.

Two contextual factors were working in favour for the implementation of this regulation, i.e. the completion of the single market in the European Union (COM (85) 310 final) and similar patent extension regulations in other countries (Permanand 2006). The single market in the EU made it possible for goods and products to move more freely from one European country to another. Prior to the completion of the single market, several European countries, e.g. Italy and France, had already implemented similar national patent restoration acts for medicinal products. A discrepancy in patent lengths in different European countries would hinder free movement of goods. Moreover, other countries outside Europe, the US and Japan, had also similar patent term restoration regulations for medicinal products. These two contextual factors have probably helped EFPIA and DGIII to successfully implement the SPC regulation (Permanand 2006, chapter 5).

The SPC is an additional pull incentive that extends the rights of a basic patent. A basic patent can cover the medicinal product itself. However, the basic patent may cover, for example, a process for obtaining the medicinal product. However, only one SPC may be granted to one medicinal products according to article (3) of the SPC regulation. In addition, a medicinal product needs to fulfil several criteria to obtain an SPC. These criteria are described in Regulation (EC) 469/2009.
A medicinal product needs to have both a granted (basic) patent and MA in order to obtain an SPC (article 3). The SPC application shall be lodged within 6 months after MA date if basic patent grant is prior to MA. Notwithstanding, an SPC application shall be lodged within 6 months of the basic patent grant if the date of patent grant is after date of MA (articles 7(1) and 7(2), respectively). An extension of the SPC, i.e. paediatric investigation plan (Regulation (EC) No 1901/2006), shall be lodged after the SPC is granted and not later than 2 years before expiry of the SPC. The owner of the basic patent shall lodge for an SPC (extension) application at the national patent office(s). The Dutch patent office is the Netherlands Enterprise Agency (Rijksdienst voor Ondernemend Nederland, RVO). The civil servants at the RVO will review the application and finally grant or reject the SPC. The owner of a Dutch SPC is required to pay annual fees. These fees are increasing from 1600 euro in the first year of a granted SPC to 2400 euro in the last year of a granted SPC.\(^3\)

3.7 Supplementary Protection Certificates and effective patent life of medicinal products

The effective patent life (EPL) of a medicinal product is the time of a monopoly of a medicinal product on the market, in other words the time between market authorisation (MA) and the date of patent expiration. Multiple authors describe in the literature that the time to conduct R&D, also called cycle time, is increasing and therefore EPL is decreasing (BCG 2001, DiMasi et al. 2003, Paul et al. 2010, Morgan et al. 2011), this phenomenon is called patent erosion. DiMasi and colleagues (2003) describe that this cycle time has increased from an average 4 year in the 1980s to an average of 12 years in 2000. This means that the EPL has decreased from 16 to 8 years.

The SPC extends the monopoly rights and increases the guarantee of a standardised EPL. The length of the SPC is determined by the following formula:

\[
\text{SPC length} = (\text{date of market authorisation}) - (\text{filing date of original patent}) - (5 \text{ years})
\]

Note: 0 years \(\leq\) SPC length \(\leq\) 5 years

An SPC can increase the EPL to a maximum of 15 years. Figure 2 schematically shows the effect of an SPC on the EPL. A Paediatric Investigation Plan (PIP) is an addition to the SPC. When one (e.g. a pharmaceutical company) files for an SPC and also has conducted clinical trials with children during R&D, one can obtain a PIP certificate. A PIP certificates prolongs the SPC with 6 months, as set out in Article 36 of Regulation (EC) No 1901/2006. A paediatric extension can increase the EPL to a maximum of 15.5 years. The regulation concerning the PIP certificate is made to encourage pharmaceutical companies to also tailor their medicines to children.

\(^3\) http://www.rvo.nl/onderwerpen/innovatief-ondernemen/octrooien/octrooi-merk-model/octrooirecht/tarievenoverzicht
Figure 2. Three scenarios (A, B, C) that shows how the SPC and PIP affects the EPL. The date of "MA and patent application (at '0') are used to determine the length of the SPC and EPL. However, there will be no return on investment if a medicinal product is not reimbursed. Hence, a positive reimbursement decision is very important as well. The white box in scenario's B and C is the cycle time longer than 5 years. This time is added in the form of an SPC after patent expiration.

The length of the SPC is determined with the filing date of a patent, i.e. patent application, and the date of the corresponding market authorisation: less than 5 years means no SPC; between 5 and 10 years means an SPC between 0 and 5 years, accordingly; more than 10 years of R&D means an SPC of 5 years.

3.8 Research productivity of the pharmaceutical sector

The SPC has been implemented to stimulate innovation and research productivity. This and the following paragraphs elaborate on the current views about this aspect of the innovative pharmaceutical sector. The pharmaceutical sector has, generally, two types of industry: innovative and generic. The innovative pharmaceutical companies create new or improve existing (patented) medicinal products. The generic pharmaceutical companies manufacture generic medicinal products when the original medicine comes off patent.

The innovative pharmaceutical sector suggests it faces big challenges, because innovation comes with a price (DiMasi et al. 2003) and risks (Pammolli et al. 2011). Literature suggests a success rate of research and development (R&D), i.e. (pre-)clinical tests, in the pharmaceutical sector between the 4 and 10 per cent (DiMasi et al. 2001, Farnoud et al. 2010, Paul et al. 2010, Pammolli et al. 2011). Furthermore, pharmaceutical companies claim that in recent decades it has become increasingly expensive and time consuming to develop new
drugs. For example, in the 1980's, the average cost to develop a drug were around US$ 100M and the time to get from an idea to an approved drug was around 4 years. In addition, in the mid 2000’s, the average cost to develop a drug exploded to US$ 800M and the average time to market increased to around 12 years. Furthermore, this trend of increasing cost was quantified by Rawlins (2004) and was believed to grow annually by 7.4% above general price inflation. Moreover, Scannell et al. (2012) and Fernald et al. (2013) have described a productivity gap.

This gap means that the amount of new drugs, (i.e. new chemical entities (NCE) or new molecular entities (NME)), developed by the pharmaceutical sector annually is not increasing, nor decreasing, while the cost of total R&D is (Morgan et al. 2011). It can be expected that the amount of R&D money invested by the pharmaceutical sector should be positively linked with the amount of NCE created by that sector, in other words more money should pay off. However, studies of Forbes done by Herper (2013) have shown such a relation is not easy to make. Moreover, he has suggested that bigger pharmaceutical companies spent on average more on R&D per new medicinal product, i.e. new chemical entity (NCE), than smaller pharmaceutical companies.  

3.9 Research productivity of the pharmaceutical sector - the other side of the story

There is a wild debate in the literature about the R&D productivity, especially about the cost and cycle time of drug development. One side of the story has already been described in the previous paragraph. These authors, e.g. DiMasi, who work for or in the pharmaceutical sector, claim that cycle time and cost are increasing heavily over time (BCG 2001, DiMasi et al. 2003, Paul et al. 2010, Morgan et al. 2011). In contrast to that, other authors (Angell 2004a,b, Light and Lexchin 2004, Light and Warburton 2011) claim that these examples about increasing cycle time and cost are exaggerated. For sake of brevity these authors are called ‘opposition authors’.

The opposition authors reject the statements made by the pharmaceutical sector by addressing topics used to support the industry’s point of view. The topics that are engaged are: sample representativeness and the way of presenting data (Angell 2004a,b, Light and Lexchin 2004, Light and Warburton 2011); and capitalisation and tax benefits (Light and Lexchin 2004, Light and Warburton 2011). These two points will be addressed in the following paragraphs.

3.9.1 Sample representativeness and presentation of data

DiMasi et al. (2003) presented characteristics of a selected medicinal product portfolio, i.e. self-originated new chemical entities (NCE) (Light and Warburton 2011). This is the most expensive and time consuming R&D project for a pharmaceutical company. Only 22% of all the drugs developed are self originated NCE (i.e. radical innovation), in contrast to the 65% of all drugs that are already existing-molecule drugs (i.e. incremental innovation), the cheapest form of drug development. On the other hand, almost 75% of the total R&D budget in spent on self-originated NCEs. This explains a big difference between mean and median average cost of almost 35%.

By presenting the mean cost the problem seems bigger, according to Light and Warburton (2011).

3.9.2 Capitalisation and tax benefits
There are two more artifices that BCG (2001), DiMasi et al. (2003) and Morgan et al. (2011) use and present to make the cost of R&D look higher than it actually is. First of all, they do not deduct the tax benefits. In the end, when a profit is made, out of pocket R&D cost are deductible, making the net out of pockets cost lower than the gross out of pocket cost. Light and Warburton (2011) suggests that tax savings are 50%, so their estimation of R&D cost (201 million US dollars) is half compared to, for example, DiMasi et al. 2003, not capitalised out of pocket cost.

Secondly, the authors who wrote for the pharmaceutical sector incorporate capitalisation, i.e. opportunity cost. This is the money that would have been made if R&D funds had been invested in equities, so this is a presumed profit (Light and Lexchin 2004). By multiplying the gross R&D cost with an interest rate (11%) for a couple (11.8) of years, DiMasi et al. (2003) estimated that the mean capitalised R&D cost are 800 million US dollars for a self originated NCE. This is a big difference compared to the mean 201 million US dollar tax reduced and not capitalised cost Light and Warburton (2011) suggest. This shows that there is a big difference in the perception of R&D cost and much uncertainty about the cost. The real R&D cost of a drug is very hard to determine (Morgan et al. 2011), it depends on the type of R&D, i.e. self originated NCE, licensed in NCE or existing-molecule, and what needs to be included.
4. Conceptual framework

4.1 Rationales and presumed effects of the SPC regulation

The actors, the process and the context of the SPC regulation were described in the contextual background. This chapter elaborates on the content of the SPC regulation. Several reasons were given for the implementation of the SPC regulation. These reasons are stated in the explanatory memorandum of the SPC regulation (COM (90) 101 final – SYN 255) 1990) and in the SPC regulation ((EC) 469/2009).

The objective of this study was to evaluate these reasons of SPC regulation. In other words, the objective is an assessment of the rationales and presumed effects of patent extension. The European Commission has implemented the regulation with help of the industry and gave various different reasons why patent extension was needed. These reasons are listed below.

1. The SPC regulation is an intervention for the problem of patent erosion.
   *Regulation (EC) 469/2009 articles (3), (4), (5), and COM (90) articles (7), (15) and (25)*

2. The SPC regulation will have a positive effect on the research and development productivity. Hence, the regulation will be an encouragement for innovation.
   *COM (90) articles (5), (7), (8) and (25)*

3. The European Union might risk that innovative pharmaceutical companies would relocate to countries with sufficient protection, i.e. the US and Japan. Therefore, a similar regulation is needed for the European Union.
   *Regulation (EC) 469/2009 article (6)*

4. The SPC regulation should lead to a proper functioning of the internal European market and should not have a negative effect on the competition. In fact, the SPC regulation would enhance the competition.
   *COM (90) articles (8) and (25)*

5. The implementation of the SPC regulation favours the possible fall in the prices of medicinal products covered by the SPC.
   *COM (90) article (24)*

6. The SPC regulation is in all the interest of consumers, the innovative and the generic pharmaceutical companies.
   *Regulation (EC) 469/2009 article (10) and COM (90) article (25)*

4.2 Conceptual model of research productivity

The civil servants at the Dutch ministry of Health, Welfare and Sport are, as stated in the preface, particularly interested in how this regulation affects innovation and R&D productivity. Therefore, an understanding of the concept of research productivity (Paul et al. 2010) was
needed for this research. The definition of this concept is given below. The SPC is discussed in respect to every aspect of research productivity in the following chapters.

\[ P \sim \frac{WIP \times p(TS) \times V}{C \times CT} \]

Figure 3. Model of R&D productivity derived from Paul et al. 2010.

The concept of R&D productivity \((P)\) is influenced by five different factors. Each of these parameters can be conceptualised and analysed on the level of one project, i.e. a single drug, to the level of a particular medicine group, i.e. multiple projects of multiple companies, e.g. all oncology drugs. This conceptual framework provides an understanding of research productivity and this understanding is needed for how patent extension has affected research productivity.

4.2.1 Work in progress
The amount of research being done is considered as work in progress \((WIP)\). This can be one medicinal product (i.e. \(WIP=1\)) or multiple medicinal products simultaneously (i.e. \(WIP>1\)). More work in progress means a higher productivity. Large innovative pharmaceutical companies, also called Big Pharma\(^5\) test multiple medicines simultaneously; all the work in progress combined is called the pipeline. Each medicinal product can be in a different phase of (pre)clinical testing.

4.2.2 The probability of technical success
Productivity will increase proportional to an increase in the probability of technical success \((p(TS))\) of the work in progress. The probability of technical success is related to the risk of development and also the attrition rate. As described in the contextual background, some drug candidates will drop out in each phase of clinical testing. If \(p(TS)\) of a medicinal product is higher, the chances of failure will be lower. Therefore, innovative pharmaceutical companies want to control success rates as much as possible. However, bringing this into practice is more complicated than it seems. In addition success rates differ between different fields of drugs. For example, the average success rate of medicines for the nervous system is 2.85%; in contrast, the average success rate of medicines for the genitourinary system is 11.75% (Pammolli et al. 2011).

4.2.3 Value
The economic and/or health impact value \((V)\) is also proportional to \(P\). A higher value will mean a higher probable return on investment. If a company develops a medicinal product for a large patient population the economic value is probably higher than the economic value of a medicinal product for a disease which has small patient group. For example, a drug for high cholesterol (i.e. statin), Pfizer’s Lipitor, was a product with a relatively high (economic) value. On the contrary, an orphan disease, which is a disease with a prevalence of less than 5 patients per

\(^5\) http://www.mckinsey.com/insights/health_systems_and_services/a_wake-up_call_for_big_pharma)
10,000 persons, might have a lower economic value. However, the health impact value for the patients with this orphan disease may be substantial.

4.2.4 Cost
Cost (C) is inversely proportional to the productivity (P) of the R&D work. A rise of the cost in R&D of one or more projects will decrease the productivity. Recourses as money can only be spent once; therefore, a rise of cost will have both an effect on productivity as on the work in progress.

4.2.5 Cycle time
Cycle time (CT) is the time it takes to develop a drug, and is defined as the time between basic patent application and market authorisation. Also, CT is inversely proportional to the P of the R&D. If cycle time to develop a drug increases, it will take more time to get to the market, i.e. time to market. Hence, CT has a negative effect on the effective patent life (EPL) of a medicinal product. This EPL of a medicinal product also has a relation with the economic value of that product. Hence, cycle time of drug development, EPL and patent erosion are three intertwined concepts in the pharmaceutical industry.
5. Research question and sub questions

The research sub questions of this study were formulated with the detailed contextual background, the understanding of the conceptual model (see Figure 3), and the knowledge of the content of the SPC regulation. Six research questions were derived from the content of the SPC regulation. The sub-sub questions were derived from the conceptual model of Paul et al. (2010) in order to answer the sub question of innovation and research productivity (1.2):

5.1 The main research questions
To what extent does the Supplementary Protection Certificates (EC Regulation 469/2009) stimulate innovation and what are additional effects of patent extension in the European Union?

5.2 The research sub questions
1. To what extent is the SPC a successful intervention for the phenomenon of patent erosion?

2. What are the effects of SPCs on innovation and research productivity?
   2.1 To what extent does the SPC affect the work in progress?
   2.2 To what extent does the SPC affect the risks of development?
   2.3 To what extent does the SPC affect the value, economic and/or therapeutic, of a medicinal product?
   2.4 To what extent does the SPC affect the cost of development?
   2.5 To what extent does the SPC affect the cycle time of development?

3. To what extent could a relation be verified between patent extension and relocation of innovative and generic pharmaceutical companies?

4. To what extent does the SPC affect the competition within the pharmaceutical market?

5. To what extent does the SPC affect drug prices, during and after patent extension?

6. To what extent were innovative and generic interests considered?
6. Methodology
The research aim of this study was to assess the rationales behind the SPC regulation. Qualitative and quantitative methods were used in order to provide answers to all the research questions. Both approaches were used in order to get insights on the statistics concerning the SPCs (quantitative approach, for insights to questions 1, 3 and 5) and on the effects of the SPC regulation (qualitative approach, for insights to questions 1 - 6). The answer to the main research question was derived with the answers of the sub research questions.

6.1 Qualitative analysis: Interviews, participants, coding and analysis

6.1.1 Interviews
Qualitative methods such as interviews are useful in gathering actual data and first hand perspectives on a specific topic. This study used semi-structured interviews (Appendix A). A semi-structured interview was chosen due to several reasons. First, this study had an exploratory nature. This study was the first qualitative, and quantitative, assessment of the rationales behind the SPC regulation. And second, interviews were done to get an understanding of patent extension in relation to the complexity of the pharmaceutical sector.

The questionnaire had different topics with open-ended questions. The topics were derived from the research questions and the conceptual framework. In addition, the interviewer and interviewee could diverge from these questions during the interview to examine an idea in more detail. Each interview was done at a quiet setting at the work location of the interviewee or at the Dutch Ministry of Health. Each interviewee was asked for an informed consent to record the interview for further analysis. The interviewees were transcribed and a summary was sent for validation.

6.1.2 Participants
Participants were identified and contacted with the help of network of the Dutch Ministry of Health. The goal was to interview participants with various backgrounds. The various backgrounds would reduce the chances of a biased perspective on the topic of patent extension with regard to research questions. Thirty-two potential participants were contacted. All contacted potential participants were experts in the pharmaceutical sector and/or health policy. Fifteen key opinion leaders and experts in the pharmaceutical sector were able to participate for interviews in this study. The others were not interested or were not able to make time.

The goal was to interview participants with various backgrounds including public (7 participants) and private sector (8 participants). In addition, the generic industry was represented by 2 participants and the innovative industry was represented by 4 participants. A list of all the participants can be found in below. Participants are ranked alphabetically. Some interviewees requested to stay anonymous, in these cases the organisation they work for are named.

Antonisse, A., - Director Economic Affairs (market access & public affairs) at AstraZeneca
Calles Sanches, A. - Policy Officer, Industrial Property, DG Internal Market & Services, European Commission

Prof. Claassen, E.* - Founder of Erasmus Centre for Valorisation, professor of entrepreneurship in health sciences and professor of knowledge valorisation

Prof. Cohen, A. - CEO of Centre for Human Drug Research and Professor in Pharmacology

Den Exter, A. - Lecturer in Health law at the Erasmus University of Rotterdam (public)

Drs. Favie, M. - Chairman of Bogin, Dutch branch organisation generic pharmaceutical industry, Director at Dienstapotheek Westfriesland-Hoorn, Chairman of supervisory board of Rabobank Hoorn-Midden Westfriesland

‘t Hoen, E. LLM - Consultant Medicines, Law and Policy

Murray, J. - Former DG of the European Consumers Organisation

Drs. Posthumus, R.* - Senior Legal Counsel at Erasmus Centre for Entrepreneurship

Drs. Vijn, I. - Senior Policy Advisor at Holland BIO

- Civil servant at Unit Food and Healthcare Industries, Biotechnology of Directorate-General for Enterprise and Industry

- European Generic Medicines Association

- Dutch Medicines Evaluation Agency

- Pharmaceutical Sector Specialist at a Dutch bank

- Professor industrial property law at Utrecht University

* These interviewees participated together in one interview.

6.1.3 Coding and analysis

The recorded interviews were transcribed and coded. Each interview was coded with the final coding scheme (Appendix B). The initial coding scheme was derived from the research (sub)questions and the conceptual model. Open coding resulted in a, more detailed, final coding scheme, which was used to code all the interview transcripts. Hence, transcribed interviews were coded multiple times to reduce the chances of missed information. Coded texts were ordered according to the research questions. Subsequently, all the ordered and coded texts were compared in order to find similarities or contradictions.
6.2 Quantitative analysis

Two databases were consulted in order to get answers for the sub questions 1, 3 and 5. These were the SPC database\(^6\) of the Netherlands Enterprise Agency (RVO) and the database of the Foundation for Pharmaceutical Statistics’, i.e. Stichting Farmaceutische Kentallen (SFK). Civil servants at the RVO and VWS helped to obtain these data.

6.2.1 SPC statistics

Information of all medicinal products that filed for an SPC in the Netherlands, between January 1993 and May 2014, were gathered in an excel file. This file contained the following information of all these SPC applications:

- SPC number, status of SPC, application date, granting date, expiration date
- Basic patent number, status of patent, application date, granting date, expiration date
- Title of basic patent, owner company, town owner company, country owner company

With these data the following calculation (1) was made in excel:

(1) \[ \text{Duration SPC in months} = \text{‘expiration date SPC’} - \text{‘expiration date basic patent’} \]
\[ = (\text{JAAR}(\text{date1})-\text{JAAR}(\text{date2}))*12+\text{MAAND}(\text{date1})-\text{MAAND}(\text{date2}) \]
\[ = (\text{YEAR}(\text{date1})-\text{YEAR}(\text{date2}))*12+\text{MONTH}(\text{date1})-\text{MONTH}(\text{date2}) \]

The duration of the SPC was determined with this calculation. These statistics were used to make further analysis. SPCs that were included for analysis had the status ‘in force’, ‘granted’ or ‘expired due to the end of the lawful term’. Four different analyses were done in which all these SPCs were ranked according to (a) duration, (b) SPC application date, (c) basic patent application date and (d) country of the owner company.

These statistics provided quantitative support for the research sub questions 1 and 3. Statistics (a) and (b) were produced to get an understanding of the quantity of the SPC applications. Statistics (c) was used for sub question 1 about patent erosion and (d) for sub question 3 about relocation.

Analysis (c) has extra considerations. The SPC regulation was implemented in 1993 and all patented medicinal products that were granted MA after 1985 could file for an SPC. However, not all the years of basic patent were included in this analysis. Only the statistics of the years of basic patent applications that will not change were included for this analysis. This meant all basic patents filed before 1988. The statistics of basic patents filed after 1988 could change, because SPC longer than 5 years, or patent could still be in force. This means that these SPCs or basic patents could still be ruled invalid. SPCs with such status were not incorporated in this study. This analysis was done in May 2014. Basic patents filed after 1988 with a granted SPC of 5 years were still in force in 2014. In addition, basic patents filed after 1994 were still in force, too.

\[^6\] http://register.octrooicentrum.nl/register/searchform
6.2.2 SFK Statistics

The SFK statistics were gathered to gain insights for sub question 5 concerning drug prices. The SFK database, which was accessed by an authorised civil servant of VWS, entails the information of the total amount of reimbursed cost (RC) (i.e. materiaalkosten gedeclareerd) and total amount of defined daily dose of all extramural medicinal products (#DDD) ranked by the Anatomical Therapeutic Chemical classification system (ATC-code) and by year.

Twenty-one medicinal products were selected of which the SPC expired in 2010. A (price) patent cliff could only occur after SPC expiration, since generic competition can start after SPC expiration. It was assumed that the statistics of the years 2011 up to 2013 would show this (price) patent cliff, due to generic competition.

First, corresponding ATC-codes of these medicinal products were found on the site of the World Health Organisation\(^7\). Thereafter, full and complete data of these medicinal products were derived from the SFK database, i.e. RC and #DDD. SFK statistics were gathered between 2005 and 2013. Data prior to 2005 was not available, and data from 2014 was not complete. With these data the following two calculations (2) and (3) were made in excel to determine (2) the cost per DDD (cDDD) and (3) the standardised cost per DDD (%cDDD):

(2) \(cDDD = \frac{RC}{#DDD}\)

(3) \(%cDDD \text{ (year)} = \left(\frac{cDDD \text{ (year)}}{cDDD \text{ (year patent expiry)}}\right) \times 100\%\)

These statistics of calculation (3) were put in a graph to see if a price patent cliff has occurred after SPC expiration. Standardised prices were used to compare the different medicinal products, because it is likely that RC differs substantially between different medicinal products. In addition, the course of price development could be seen because analysis is done from the year 2005.

\(^7\) http://www.whocc.no/atc_ddd_index/
7. Results

The aim of this study was to assess the rationale and the assumed effects of the EU regulation on SPCs (Regulation (EC) 469/2009 and COM (90) 101 final - syn 255). This assessment was done studying the content of the SPC regulation, in combination with conceptual understanding of research productivity (Paul et al. 2010). The results are discussed according to the topics of the research sub questions as described in chapter 5, starting with the question concerning patent erosion.

7.1 Is the SPC an intervention for patent erosion

7.1.1 Patent erosion

Numerous participants elaborated on patent erosion in the pharmaceutical industry as the result of the demands of the regulatory system for market authorisation (MA) and reimbursement (ID 1, 2, 10, 11, 13). They elaborated that these demands of the regulatory system, as described in the contextual background, are the probable causes of the lengthening of the research and development time. Moreover, according to three interviewees (ID 2, 5, 13), patent erosion is the result of the increasing demands of society: every new medicine needs to be safer or more effective than medicines already on the market. Two interviewees have stated that this has resulted in a progressive decrease of effective patent life (EPL) (ID 2, 13).

This progressive decrease is caused by requirements set for market authorisation (MA). These requirements mean that sufficient clinical trials are needed in order to gain MA, also stated in article 8(3)(i) of Directive 2001/83/EC. This means, according to ID13 that medicinal products need to be out in the open during these clinical trials. Medicinal products are tested on patients and participants and are in the hands of physicians, as described in the background. Hence, two participants elaborated that pharmaceutical companies probably need to file for patents at least before the beginning of the (clinical) R&D stage (ID 2, 13). According to them, the needed early filing of patents in combination with the clinical tests could be the cause of patent erosion.

Four participants mentioned that if a medicinal product is not patented, ‘third parties’ could relatively easily copy the product, because a medicine is just a chemical substance (ID 2, 6, 7, 13). Moreover, a copy of a medicinal product, a generic (i.e. identical and bioequivalent product), does not need its own (pre-)clinical trials and may refer to the data of the (pre-)clinical trials of the reference product, the original medicinal product (Directive 2001/83/EC article 10(1)). However, this Directive also describes that the owner of a generic product is only allowed to use the data of the reference product 8 years after MA of the reference product and can get MA not until 10 years have elapsed after the MA of the reference product. However, this 10-year period is shorter than the 15 years standardised EPL as the result of most granted SPCs.

This argument has illustrated the possible phenomenon of patent erosion. However, it was also stated by three participants that patent erosion in the pharmaceutical industry has increased over time. Three interviewees stated that this was caused by the increasing demands of the society concerning the effectiveness of medicinal products and their side effects (ID 2, 5,
13). The following quotes of two persons who work in the innovative pharmaceutical sector exemplifies this:

“New medicines have to be safer than medicines that are already on that market.” (...) “More extensive tests are needed to create a better and a safer medicine.” (ID2)

“Extra studies are needed due to safety demands. These studies were probably not needed a couple of years ago.” (ID13)

7.1.2 SPC statistics

Three interviewees suggested (ID2, 5, 13) that patent erosion has increased over time. Other interviewees just acknowledged that patent erosion exists in the pharmaceutical sector. If these statements of increasing demands and development time were true, i.e. more medicinal products that had a development time longer than 5 years, an increasing number of granted SPCs is expected. In addition, the duration of the granted SPCs could increase as well. The SPC database indicates that an increasing amount of patents were granted an SPC.

More than a thousand SPC applications (1021) were filed at the Dutch patent office (RVO) between January 1993 and May 2014: with an average of 50 applications each year. Figure 4 shows the statistics of all the granted SPCs. The SPCs were ranked according to their duration. This figure shows that almost half of all the granted SPCs are longer than 5 years (SPC 60+), i.e. scenario C of figure 2 of chapter 3.7. Five SPCs had the length of 66 months, i.e. 5.5 years, which means that these medicinal products have filed for an SPC and for a PIP-certificate, i.e. SPC extension. An SPC of 60 months or longer indicates that the time between basic patent application and the associated MA for these medicinal products is equivalent or longer than 120 months, i.e. 10 years. The EPL of the prolonged patents in these cases is 15 years or less. This indicates that the SPC was not adequate to compensate for the entire patent erosion.

The other 53% of the granted SPCs had a duration between 0 and 59 months, including 59 months, i.e. scenario B of figure 2. This means that the time between basic patent file and the associated MA for these medicinal products is between 60 and 120 months. In these cases, the granting of the SPCs resulted in a standardised EPL of at least 15 years. In these cases the SPC seemed an adequate intervention for patent erosion.
All SPCs, granted, expired and in force, between January 1993 and May 2014, on the 23rd of May, in the Netherlands. The length of these SPCs is ordered into 7 categories. One granted SPC had the duration of -4 months and is excluded from this analysis, 5 SPCs had the length of 66 months. Data retrieved from the RVO database. Corresponding data is public. Corresponding table can be found in appendix C.

Figure 5 shows the development of all the SPCs granted in the Netherlands between 1994 and 2013 ordered by the year in which these were filed, excluding the SPCs granted in the year 1993 and the year 2014. Inclusion of the SPC grants of 1993 might give a wrong impression, because the number of SPCs granted in 1993 is the sum of a period of medicinal products that received a MA between 1985 and 1992, i.e. 8 years. The number of granted SPCs in 2014 is not presented in this figure, because the data was only up till May 2014. This means that this number, 7 SPCs, will probably increase. This figure shows an erratic number of SPCs granted each year in the Netherlands.

Figure 5 does not indicate an increasing number of granted SPCs. However, as these SPCs are referring to a basic patent, the application dates of the basic patents can vary substantially for all the SPCs filed in 2011. Therefore, figure 6 shows all the SPCs ranked according to the corresponding basic patent term.

Figure 6 shows all the SPCs ranked corresponding to the term of the basic patents. The numbers of the specified categories of SPCs are somewhat erratic. However, the total number of granted SPCs, ranked by the date of basic patent application, might give the impression of an increasing number of SPCs. This could confirm the statements about the increasing patent erosion and cycle time of three interviewees (ID 2, 5, 13). The cause of patent erosion, however, cannot be confirmed with just these numbers.

This chapter has elaborated on patent erosion in the pharmaceutical industry. Many interviewees have stated that patent erosion has occurred. Some interviewees stated that patent erosion has increased in the past decades. In addition, the Dutch SPC database was consulted. These results have suggested that an increasing amount of SPCs were granted. This could give some evidence to the statements about the increasing cycle times of drug development made by the interviewees.
Figure 5 Number of SPCs, total granted (SPCtotal, blue), 60 months or longer (SPC 60+, green) and shorter than 60 months (SPC <60, red), on the 23rd of May. The numbers of 1993 and 2014 are not in this figure. Inclusion of these numbers might give a wrong impression. All the SPCs granted in 1993 represent the sum of the period between 1985 and 1993. For that period, in 1993, 108 SPCs were granted (32 SPCs 60+ months, 76 SPCs < 60 months). Between January and May 2014 7 SPCs were granted (6 SPCs 60+ months, 1 SPC <60 months). Corresponding table can be found in appendix D.

Figure 6 The numbers of SPCs that were granted in the Netherlands ranked by corresponding basic patent term. SPCtotal (blue), SPC<60 (red) and SPC 60+ (green). Corresponding tables can be found in appendix E.
7.2 Research productivity and innovation

The perspectives on the relation between research productivity and the SPC vary substantially. One general finding from the interviews needs to be considered before going into the concepts of Paul et al. (2010). Some interviewees mentioned the different types of innovation, i.e. incremental and radical (ID1, 2, 6). Incremental innovation is innovation in small steps. Radical innovation, in contrast to incremental innovation, is innovation with bigger steps or into total new directions or fields, as described in the background chapter.

Both types of innovation may lead to therapeutic improvements. However, according to interviewees 1 and 2, radical innovations are more likely to lead to medicinal products for diseases with an unmet medical need. In addition, numerous interviewees stated that not every new (patented) medicinal product, or NCE, has a therapeutic advantage (ID 1, 6, 7, 8, 12) this is discussed in the value paragraph. Therefore, this number of NCE is not adequate enough.

The results on how the SPC have affected the different aspects of research productivity are described in the next paragraphs. These five concepts are discussed according to how much these were mentioned in the interviews, cost, cycle time, probability of technical success, value and work in progress, respectively.

7.2.1 Cost

The perspectives about the cost of (new) drug development varied among the interviewees. This illustrates the difference outlined in the contextual background (paragraphs 3.8 and 3.9). The interviewees could roughly be divided into two groups. One group believed and mentioned the high cost of drug development. Most of them named the amount of one billion dollars for developing a new medicinal product (ID 2, 4, 10, 11, 13). Cost is the biggest barrier for innovation, claimed by several interviewees (ID 2, 10, 11, 13). The quote of ID2, professor in knowledge valorisation and expert in health sciences, illustrates the perception of high cost.

“I know for sure that I will have to invest a billion dollars if I develop a new medicine.” (ID2)

The other interviewees mentioned that amount. However, these interviewees were more sceptical. They believed that the industry is a black box when it comes to cost of drug development (ID 1, 3, 5, 6, 7, 8, 9). One interviewee (ID 6), a professor in pharmacology, stated that effectively one group of scientists has done research to the cost of R&D (DiMasi et al. 1999, 2001, 2003 and 2007). The calculations that were made are probably extremely complex and the data they have used are confidential. Hence, according to the interviewee, it is not possible to replicate these studies. No additional information was gathered with regard to paragraphs 3.8 and 3.9.

7.2.2 Cycle time

The first paragraph of this results section has elaborated on patent erosion. Many interviewees acknowledged that the time to develop a drug, including the demands of regulatory approval, is the cause of patent erosion in the pharmaceutical industry. Moreover, this increasing cycle time was one of the primary reasons of implementing the SPC regulation (COM (90) 101 final).

A majority of interviewees mentioned that the demands of regulatory approval and society are the cause of the increased cycle time (ID 2, 3, 4, 5, 6, 13). The primary reason, according to these interviewees, is that each new medicine has to be either equivalent and safer
or better than other approved treatments. This is the case for incremental innovations, according to these interviewees. Two interviewees stated (ID 1, 2) that incremental innovations lead to similar medicinal products for the same treatment in an already existing market. Hence, larger, longer trials or more trials are needed in order to prove (extra) efficacy. This would result in a longer cycle time.

7.2.3 Technical success and risks
The pharmaceutical business is considered as a risky business by several interviewees (ID 2, 3, 5, 6, 13). Roughly 1 out every 9 to 10 innovations or ideas make it to the market, according to two interviewees who work in the pharmaceutical sector (ID 2, 13). This low success rate is the result of several steps that need to be succeeded in order to get to market. These steps include pre-clinical and clinical phases, regulatory approval and a reimbursement decision. As stated by ID 2 and 13, a medicinal product will not recoup the investments if one of these steps has failed, i.e. (pre-) clinical trials or regulatory approval.

Incremental innovations are considered far less risky compared to radical innovations according to two interviewees (ID 1, 2) and innovative pharmaceutical companies want to control these risks as much as possible (ID 2). Hence, innovative companies probably prefer to conduct incremental innovations to radical innovations.

7.2.4 Value
Three interviewees mentioned that the value of the (patented) medicinal product could be defined in two ways (ID 1, 2, 6): therapeutic value and economic value. According to these interviewees, a high economic value is not necessarily related to a high therapeutic value, considering the large number of different statins or antacids, also called me-too’s (ID 1, 2, 6). In addition, a high therapeutic value is not necessarily related to a high economic value, for which a good example is a new antibiotic. The following quote of someone who works at a big pharmaceutical company illustrates this example.

“We brought a new antibiotic to the market 2 years ago. 2 patients have used our antibiotic in these past two years, which means that we have sold 6 boxes of this antibiotic drug. These patients survived.” (ID 13)

The more a new antibiotic is used, the faster antimicrobial resistance will occur, according to ID 13. Therefore, new medicinal products, e.g. new antibiotics, could have a high therapeutic value, e.g. the patients survived with the antibiotic treatment. However, such a medicinal product does not necessarily have a high economic value, e.g. only 6 boxes were sold in two years.

Two interviewees (ID 1, 6) provided the example of a new treatment for hepatitis C. This example illustrated that it is very likely that a product with a high therapeutic value is sold at a high price, which might lead to a high economic value if the volume is high. This medicinal product in this example is made by Gilead and is named Sovaldi (generic name Sofosbuvir). This medicine is sold for about US$ 1.000 a day and the treatment lasts for 3 months (ID 1, 6). Hepatitis C is in many cases curable with this new treatment; prior to that this was hardly the case, according to these interviewees. This is an extreme example of a medicinal product that has both a high therapeutic and a (very) high economic value.
These examples above have illustrated that therapeutic value is not always rewarded with an economic value (ID 1, 6, 13). That economic value is needed to recoup the investments including interests and failed investments, according to several interviewees (ID 1, 2, 3, 8, 13). Therefore, it is more likely for a private party to invest in new medicinal products with a high potential economic value, and the SPC will probably only increase that incentive. Hence, according to several interviewees, increasing effective patent life probably does not stimulate all innovations (ID 1, 2, 3, 6, 12).

7.2.5 Work in progress and concluding remarks
Two interviewees (ID 2, 13) mentioned that a pharmaceutical company would only conduct R&D for a certain medicinal product if the mechanism of the disease is known. This is the case for all incremental innovations. The development of medicinal products, for radical innovations, is, therefore, likely following state of the art scientific knowledge or fundamental research (ID 2, 13).

However, it seems that SPC does not change the existing incentives to conduct R&D, which were already present in the pharmaceutical industry due to the patent system. Those incentives that were mentioned were: a probable preference for the development of economically attractive medicinal products and an aversion of (unnecessary) risks. Moreover, economically attractive medicinal products would become even more attractive due to the SPC, because the EPL is extended. The answers of the interviewees or the data provided no link between the SPC on one hand and cycle time, risks or cost of R&D on the other. In addition, as illustrated above, not all economically attractive medicines have had a therapeutic (added) value. Therefore, as stated by three interviewees (ID 1, 2, 6) it is plausible that the SPC shifts the focus even more to low(er) risk, incremental innovations, because the chances of a reward, the pull factor, are higher.

7.3 Effects of SPCs on relocation of pharmaceutical industry
The following paragraphs present the results about the question concerning relocation. The results are presented in two perspectives. First the probable effects of the SPC on relocation of innovative pharmaceutical companies, and second the probable effects of the SPC on relocation of generic pharmaceutical companies.

7.3.1 Relocation of innovative pharmaceutical companies
Five interviewees mentioned various factors that might have an effect on (re)location. These are factors that affect business climate of a region or country. These interviewees provided several examples of these factors that are important for a good business climate such as tax incentives, good infrastructure, and opportunities to recruit high-educated personnel (ID 2, 4, 5, 6, 13).

In addition, perspectives varied substantially regarding the relocation of innovative pharmaceutical companies in relation to patent extension. Two interviewees (ID 5, 6) suggested that this is due to the fact that the question about relocation is far more complex than a direct and single relation between adequate patent protection and possible relocation. Some interviewees agreed that there would be a risk of relocation if there were other countries with greater protection (ID 3, 11, 13). Others who had doubts about these statements (ID 2, 5, 6, 7) said that these assumptions are used by the industry in order to convince governments to
implement additional regulations, beneficial to the innovative industry. In addition, most big pharmaceutical companies are multinationals. Therefore, according to some interviewees (ID 1, 2, 13), these companies could do their R&D and production anywhere in the world. Relocation depends on a variety of factors; one of those could be adequate protection in forms of patents or SPCs.

Statistics of all the granted SPCs indicate that the SPC regulation does not take away a presumed relocation incentive: 48% of granted SPCs belonged to EU based patent holders, whereas 52% of the granted SPCs belonged to non-EU based patent holders. A full list is provided in appendix F. Hence, European based and non-European based patent holders can profit from the European SPC regulation. This would mean that EU based patent holders and companies could still relocate, for any reason, and benefit of the European SPC regulation. This means that the SPC is not an intervention for this proposed threat. The opinions varied substantially concerning a(n) (in)direct effect between patent extension and relocation of innovative companies. On the contrary, the opinions are far more consistent about the effects of the SPC on relocation of generic companies.

7.3.2 Relocation of generic pharmaceutical companies
According to five interviewees, generic companies based outside the EU can start commercial activities, including production, during the period of supplementary protection, because the (European) SPC regulation affects only EU based pharmaceutical companies (ID 7, 8, 10, 11, 12). This means that non-EU generic companies can have a substantial advantage compared to EU based generic companies (ID 1, 3, 7, 8, 12). This advantage occurs, in a simplified example, when the patent of medicinal product ‘A’ has expired and the concerning SPC is in force and Regulatory Data Protection (RDP) after market authorisation has expired. This example of one interviewee (ID12), employee at EGA Generics, states that a non-EU generic company may start commercial activities, including stockpiling and preparing for export to the EU before the SPC expires. The EU generic company may not start during SPC protection and can only start when the SPC has expired. Therefore, the SPC is a significant factor for generic companies to relocate to non-EU countries with no regulation similar to the SPC regulation, according to the EGA. This relocation of generic pharmaceutical companies has, according to three interviewees (ID 10, 11, 12), an effect on employment within the EU, on import into the EU, and export out of the EU as a whole.

The European Parliament (EP) has acknowledged that the SPC regulation may have been an important factor for the generic pharmaceutical companies to relocate to countries outside the European Union. The following text was posted on the site of the EP:

“The European Parliament,

(…)

66. Calls on the Commission to propose legislation which will enable European companies to manufacture generic and biosimilar medicines in the EU during the supplementary protection certificate (SPC) period, following the expiry of patent protection, in order to prepare for immediate launch following expiration of the SPC or to export to countries where no patent or SPC is in place; believes that such provisions could help to avoid the outsourcing of production
and to foster job creation in the EU, as well as to create a level playing field between European companies and their competitors in third countries;\(^8\)

It seems that the SPC is not a solution for the possible relocation threat of innovative companies posed in the regulation. Any basic patent holder, located anywhere in the world, may file for an SPC. Moreover, it is believed that (re)location incentives are affected by more than just patent extension regulations. In addition, the SPC does provide an incentive for the generic industry to relocate to places outside the European Union.

7.4 Competition
The question about competition was be addressed in two ways, like the questions concerning innovation, value, and relocation. In this case this concept could be seen as competition between innovative pharmaceutical companies, and as competition between innovative and generic pharmaceutical companies. Both aspects are presented respectively.

The explanatory memorandum on the SPCs referred to competition between innovative companies. It was stated that this competition is not affected negatively by the regulation (COM (90) 101 final, articles 8 and 25). Competition between innovative companies is a result of more than one patented medicine with MA for the same disease, each manufactured by a different pharmaceutical company. This includes the me-too medicines according to several interviewees (ID 1, 2, 13). The SPC extends the rights of the basic patent, meaning that the regulation extends the time, i.e. EPL, in which this, innovative, competition could occur. Therefore, the SPC should probably not have a negative or positive effect on the competition between innovative companies.

All the interviewees confirmed that generic competition is delayed, because the SPC extends the rights of the basic patent. However, the explanatory memorandum on the SPCs did not refer to competition between generic and innovative companies, probably because this regulation has a significant effect on generic competition. Besides, the whole rationale behind the regulation is to increase EPL, in is an positive intervention for the patent erosion. Therefore, generic competition needed to be delayed. This delayed generic competition probably has a significant effect of drug prices.

7.5 Drug prices
7.5.1 The relation between effective patent life and drug prices
The explanatory memorandum stated that drug prices could decrease, due to an increased EPL. Several interviewees (ID 1, 2, 3, 5, 6, 12) were surprised about this statement. Three interviewees have stated that pharmaceutical companies need to recoup their investments, including the failed investments and interests (ID 1, 2, 13). One interviewee suggested that this would probably only work the other way around, meaning that it is plausible that drug prices need to be higher if the time to recoup the investment, i.e. EPL, is shorter (ID 6). Moreover, the rationale of a patent is to create a specific monopoly. According to several interviewees (ID 1, 2, 5, 6, 7), innovative pharmaceutical companies could almost ask any price with this monopoly.

7.5.2 The price patent cliff, drug prices after SPC expiry

All interviewees mentioned that the SPC has a big effect on the so-called patent cliff. It was argued that this occurs when the patent-rights are expired. After patent or SPC expiration generic companies could enter the market, creating fierce competition according to four interviewees (ID 2, 7, 12, 13). The SPC delays generic competition according to the previous paragraph, therefore, delaying the generic competition and the patent-cliff. It was stated that this (fierce) competition could cause a price drop of 80-95% (ID 1, 2, 7). Patent cliffs on a global scale can be enormous. One interviewee, a professor in valorisation, provided two examples of two economically valuable drugs, e.g. blockbuster drugs Lipitor and Plavix, which are experiencing enormous revenue patent cliffs for these innovative companies⁹.

The analysis that is done in this study is not based on the revenues of an innovative company. This analysis is done toward the prize per defined daily dose (DDD) of a particular medicinal product. This price-patent cliff on a national level, i.e. for the Netherlands, is partially illustrated in Figure 7. The price developments of several medicinal products are in this figure. These medicinal products, with granted SPCs, were extramural products of which the SPC expired in 2010. It was assumed that the start of the price-patent cliff would occur in that year in which the patent rights of the basic patent expire, this year of basic patent expiry is between brackets. The corresponding data can be found in appendix I.

The price-patent cliff is not always visible in these cases as shown in Figure 7. Only data was obtained for eleven medicinal products. Adalimumab was excluded because it was moved from intramural to extramural in 2012, giving a wrong image of the amount and cost. Therefore, only ten were incorporated in the analysis. In six cases an expected price patent cliff is observed, i.e. (Lercanidipine (green triangle), Mycofenolzuur (blue +), Desloratadine (blue square), Levetiracetam (light green), Becaplermine (blue asterisks) and Losartan (purple asterisks). In four cases it seems there is no or no delayed price patent cliff, i.e. Enfuvirtide (orange), Mizolastine (purple diamonds), Barnidipine (dark blue), Nebivolol (red). In two cases, Mizolastine and Barnidipine there are probably other patents pending or in force. These other patents prolong the EPL of these products as well; therefore no price patent cliff is observed. The price per DDD of Enfuvirtide (orange) has not decreased. However, the total amount of DDD and price volume has decreased with 80% between 2006 and 2008, during SPC protection. This could mean that generic competition is not likely to start because the market in the Netherlands for Enfuvitide is commercially probably not interesting. In the case of Nebivolol it seems that the price patent cliff has started well before patent/SPC expiry. However, the patent cliff in revenue is in the year of SPC expiry. The manufacturer has increased market share in volume in the Netherlands by lowering the price per DDD. Hence, the early start of the price patent cliff is probably a strategic decision.

These results, both qualitative and quantitative, show that there is, so far, no support that patent extension could lead to lower drug prices. However, it is believed and showed that the SPC delays the lowering of drug prices due to delayed generic competition. This could lead to less access to vital drugs in some specific cases.

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⁹ http://www.drugdevelopment-technology.com/features/featuretop-5-expired-blockbuster-drugs
7.6 Interests

It was assumed in the explanatory memorandum that the SPC regulation was in the interests of generic companies and innovative companies. The rationale was that the SPC would stimulate innovation. Hence, more innovative medicinal products would lead to more opportunities for generic companies. However, it is debatable whether the SPC has stimulated innovation. Moreover, already mentioned in the introduction, only two parties created a draft version of the regulation. One identified third party that was involved was the European Consumers Organisation (BEUC) (Permanand 2006). This means that the generic companies did not have (any) substantial influence in this policy forming process.

The EGA, the branch organisation for the generic industry, confirmed that they were...
established as a reaction to the implementation of the SPC regulation. Since then, they wrote several position papers in order to create awareness at European level that the SPC regulation is not in their interest. First, because the SPC causes unfair competition with generic pharmaceutical companies outside the European Union, as stated in chapter 7.3.2. Secondly, because the EGA, just like the BEUC, advocate that the SPC should only be granted for true therapeutic innovations and not just any (incremental) innovation. And finally, because it is possible to receive more than one SPC for one medicinal product according to their last published position paper\textsuperscript{10}.

\textsuperscript{10} This position paper was written by the EGA and can be obtained via EGA or the corresponding author of this research.
8. Conclusion

The aim of this study was to verify the rationales behind the implementation of the supplementary protection certificate (SPC), which can be found in the regulation on SPCs and the explanatory memorandum. The most important reason to implement SPCs was to resolve the problem of patent erosion. In addition, it was assumed that this would lead to the enhancement of innovation. Besides, other beneficial effects were stated, i.e. no relocation of the innovative pharmaceutical industry, no reduction in competition and a possible decrease of drug prices. The actual effects of the SPC after implementation are concluded below.

Firstly, the problem of patent erosion has partially been resolved with the SPC. The SPC, without further extension, prolongs the EPL to a maximum of 15 years. These compensated years are valuable, because generic competition is delayed. However, the SPC regulation is not sufficient to compensate cycle times of longer than 10 years. Hence, the SPC regulation is not adequate to compensate all the patent erosion.

Secondly, this extended EPL did not translate into more NCEs annually, as this annual output has not changed (Munos 2009, Fernald et al. 2013, Moors et al. 2014). This could be explained in several ways. One explanation, from literature, is that the cost of developing one NCE has increased in the past decades (Morgan et al. 2011, Light and Warburton 2011, Scannell et al. 2012). Another explanation, from this study, is in the context of risk aversion. This research indicates that the SPC only rewards economic value and not therapeutic value. This means that innovative companies tend to invest more in lower-risk incremental innovation, which leads to follow-on drugs for existing markets. Moreover, this study hints that clinical testing has increased in size and budget because a follow-on drug has to be safer than existing competitor drugs due to regulation. This effect is called the ‘bigger than the Beatles’ problem (Scannell et al. 2012).

Thirdly, any basic patent owner could file for an SPC. Therefore, the SPC does not solve the possible relocation threat of innovative pharmaceutical companies. Moreover, this study provides strong evidence that the SPC has caused relocation of generic pharmaceutical companies. However, this study does not provide insights into the magnitude of generic relocation.

Finally, in this study no evidence is found for lower drug prices due to an extended patent life. This study concludes that the SPC probably does not substantially affect competition between innovative pharmaceutical companies. However, generic competition is delayed. Hence, the prices of medicinal products after patent expiration during the SPC are higher due to the SPC.

Many topics were touched upon due to the scale and complexity of pharmaceutical innovation and the pharmaceutical industry. The effects of the SPC regulation were assessed in this study, and it seems that most presumed effects were interpreted too specific and were not grounded. The broader interpretation in this study and the assessment of research productivity has lead to better understanding on how patent extension affects the pharmaceutical industry, including generic and innovative, and innovation.
9. Discussion
The aim of this study was to make an assessment of the rationales behind the SPC regulation. These rationales were derived from the content of the regulation (regulation (EC) 469/2009) and the explanatory memorandum (COM (90) 101 final – SYN 255) 1990) concerning the SPC. Interviews were conducted with key opinion leaders in the field of medicines and health policy to assess these rationales. The interviews with key opinion leaders, e.g. professors, pharmacologists and pharmaceutical sector specialists, provided state of art insights in the field of pharmaceuticals. In addition, the databases of RVO (Dutch Enterprise Agency) and SFK (Foundation for Pharmaceutical Statistics) were consulted to gain quantitative insights into the effects of the SPC. The results are discussed in the same order as the results chapter. Afterwards the strengths and weaknesses of this study are discussed.

9.1 Patent erosion and SPC statistics
The main rationale behind this regulation is that effective patent life (EPL) should be 15 years. This study has shown that the SPC has prolonged the EPL of eroded patents for medicinal products in the Netherlands. However, in half of the cases, when time-to-market is longer than 10 years, the eroded patent life beyond the 10-year boundary was not compensated. This means that the SPC is not adequate with regard to this rationale behind the SPC regulation.

Interviewees from this study and literature (BCG 2001, DiMasi et al. 2003, Paul et al. 2010, Morgan et al. 2011) suggest that creating a new medicinal product would take a decade. It was not possible to calculate an average R&D cycle time with the analysis of the Dutch SPC database, because market authorisation dates were not in the database. However, the Dutch SPC statistics has shown that the majority of SPCs are 48 months or longer. This indicates that most basic patents have eroded 9 years or longer. Hence, the analysis of the database has given evidence to the statements of the interviewees and the literature that cycle time is around 10 years.

This study provided new insights into SPC statistics in the Netherlands, i.e. increasing amount of granted SPCs. However, these results could not be compared to literature, because there is no substantial amount of peer-reviewed literature regarding SPC statistics in the EU or other specific European countries. De Pastors (1995), a civil servant at the French patent office, provided some statistics of the first two years of implementation. In addition, de Pastors have been posting SPC statistics on a niche blog, i.e. the spc blog.\textsuperscript{11} However, these statistics are not peer reviewed, and are not as detailed as the statistics in this study.

All published work of De Pastors show large differences between European countries. This means that a granted SPC in the Netherlands does not guarantee for a granted SPC elsewhere or vice versa. This indicates that the SPC is not a unified patent extension regulation as intended, regarding the completion of the single market in the European Union (Permanad 2006). Differences are caused by a variety of reasons, e.g. the basic patent, market authorisation, interpretation of the regulation. No generalised comments can be made about SPC statistics concerning the EU. However, other conclusion about the effects of patent extension can be made.

\textsuperscript{11} http://thespcblog.blogspot.nl/2013/06/spc-statistics-at-glance.html
9.2 Research productivity and innovation

It was stated in the SPC regulation that it would enhance innovation and increase the output of the innovative pharmaceutical sector. The SPC regulation has stated a mono dimensional link between patent erosion and innovation: patent erosion would lead to insufficient time to recoup the investments; this would be a disincentive for further investments; this disincentive would hamper innovation; therefore, prolongation of this effective patent life should solve this problem. In this study, the conceptual model of Paul et al. (2010) was assessed to get an understanding of this link between effective patent life on one hand and innovation and research productivity on the other.

9.2.1 Cost

This study could not indicate a relation between the SPC and the cost of R&D. Other studies have found that the cost of R&D has increased in the past decades (Light and Lexchin 2012, Fernald et al. 2013). This is in line with the answers of the interviewees in this study. Morgan and colleagues (2011) has concluded that a golden standard of the cost of R&D for one NCE cannot be made. In line with the literature, the interviewees in this study mentioned and debated this golden standard. Hence, this study did not provide new insights regarding this topic. Munos (2009) looked at 60 years of pharmaceutical innovation and concluded that the output of NCEs has effectively stayed the same. Hence, R&D productivity has decreased, if it is seen as a ratio between NCEs and R&D budget (Cohen 2005, Scannell et al. 2012, Fernald et al. 2013).

9.2.2 Cycle time

The results of this study indicate that the cycle time of drug development is increasing over time. Paul et al. (2010) have suggested many solutions to shorten cycle time, which would increase research productivity. However, this study does not provide evidence that the SPC has any effect on the length of the cycle time in R&D. The SPC only compensates for the time lost and is, therefore, only a salve on the wound. This study has shown that the SPC does not solve the problem of increasing cycle time. Moreover, as seen in the first paragraph of the results section, the SPC does not compensate all the time lost due to R&D. R&D cycle time longer than 10 years (DiMasi 2010) will lead to an EPL of the corresponding extended basic patent of less than 15 years. This is the case in almost 50% of all the extended patents. This means that the SPC, in this form, is insufficient in most cases to compensate for patent erosion. This means that the debate about patent erosion is not closed with the SPC.

9.2.3 Technical success

A reduction of the of the attrition rate, i.e. an increase of the technical success, would lead to an enhanced research productivity (Paul et al. 2010). However, there is no evidence from this study or other studies that the SPC or other (additional) patent extension regulations affect the technical success in the different stages of research and development. Therefore, pharmaceutical companies will continue to avoid unnecessary risks (Moors et al. 2014). Avoidance of unnecessary risks can be done, according to this study, by doing incremental innovation instead of radical innovation, i.e. improving existing drugs instead of developing completely new drugs.
9.2.4 Value
This study indicates the importance of the value of innovations. First, this study indicates a relation between therapeutic value and (un)met medical needs. The therapeutic value is relatively high if a new medicinal product would be a significant improvement compared to the existing products or treatments on the market, or if it would meet an unmet medical need.

Secondly however, this study has found no relation between economic and therapeutic value. The results of this research indicate that the economic value seems more important than the therapeutic value. Besides, the SPC only increases the economic value of medicinal products, since the SPC affects the EPL. In other words, the SPC only rewards economic high valuable medicinal products. For example, French (2005) has pointed out that 80% of Prozac sales in Europe over the last 10 years of effective patent protection were achieved in the 5 years covered by the SPC. Hence, the difference between economically attractive medicinal products and less attractive medicinal products has become bigger due to the SPC. The results of this study are in line with other literature of Moors et al. (2014) and suggest that the regulation of patent extension have skewed the incentives for innovation even more towards economically attractive innovations.

As illustration, the revenues of the innovative pharmaceutical companies have increased six times faster compared to the R&D budgets between 1995 and 2010 (Light and Lexchin 2012). Munos (2009) found that the output of the innovative industry has not changed. Hence, this would mean that the economic value of the output per NCE of the innovative pharmaceutical industry has increased. The increased number of granted SPCs in the Netherlands found in this study might indicate that patent extension is responsible for these increased revenues.

9.2.5 Work in progress
These previous discussed concepts of research productivity show that the SPC has provided an extra stimulus towards specific innovation, i.e. incremental, low(er) risk and economically valuable. These incremental innovations will lead to follow-on drugs. Cohen et al. (2006) has showed an increasing amount of ‘follow-on’ drugs between 1985 (48% follow-on drugs) and 2005 (62% follow-on drugs). During this period, between 1984 and 1993, patent extension regulations were implemented in the US (1984) in Japan (1988) and in the EU (1993). It is plausible that the SPC, other similar regulations and patents in general have been an important factor for this increasing trend of follow-on drugs.

Much literature has been written about research productivity of the pharmaceutical sector and how to improve this. As stated by Scannell and colleagues: “(...) the ratio of published cures to diagnoses [with regard to the decline in pharmaceutical R&D efficiency] is already too high” (2012), and so far no evidence has been found, including this research, that that patent extension could increase R&D productivity or innovation (Moors et al. 2014).

9.2.6 Vicious circle
The effects of the SPC on research productivity were assessed in this study. One finding has not yet been discussed, i.e. a finding of a possible vicious circle of increasing trial size (Scannell et al. 2012). Three interviewees (ID 1, 2, 6) have mentioned this plausible vicious circle in their interviews and elaborated that the SPC has probably strengthened this. This circle is probably the result of the skewed preference towards incremental innovations.
Literature (DiMasi et al. 2010, Morgan et al. 2011, Scannell et al. 2012) and the interviewees of this study have argued that the cycle time and R&D cost have increased in the last decades. It was stated by the interviewees that these bigger trials are needed to prove safety and efficacy. Hence, this vicious circle is especially the case for incremental innovations, i.e. follow-on drugs in existing (big) markets. Every new drug, including follow-on drugs, needs to complete all the stages of R&D and regulatory approval. However, if a drug is developed for an existing market, which has already several treatments, it was argued by the interviewees that bigger trials and tests were needed in order to show improved effectiveness and safety, also known as 'better than the Beatles' problem (Scannell et al. 2012). The data from these trials are the evidence that is needed in order to gain MA and, moreover, reimbursement. In addition, this study provides evidence that the SPC encourages these incremental innovations even more. This would lead to a vicious circle of increasing cycle time and increasing cost of drug development.

9.3 Effects of SPCs on relocation of pharmaceutical industry
The results of this study have suggested that the SPC does not remove the incentive for relocation. Other studies, which have looked at factors that influence location of pharmaceutical industries, did not suggest a link between patent extension and (re)location (Kumar 1996, Hanel 2006). These studies suggest that patent protection is important for large (pharmaceutical) companies to locate their R&D facilities. However, R&D is done during patent protection and not during SPC protection, since an SPC is granted after MA. Moreover, this study indicates that many other factors seem also important such as the size of the market, the country’s ability to provide necessary technological resources or distribution channels or the factors described in the results chapter 7.3.1. Therefore, a causal connection between patent extension and (re)location of innovative pharmaceutical industry is unlikely.

In addition, this study indicates that the SPC is an incentive for generic industry to relocate outside the European Union. The SPC extends the patent rights of the corresponding basic patent of, for example, medicinal product ‘A’, according to articles 4 and 5 of the SPC regulation (EC 469/2009). Therefore, generic companies in the EU are not allowed to start production, distribution or other commercial activities in a European country in which that SPC is in force, concerning medicinal product ‘A’. Hence, a EU-based generic company cannot start production, even though the basic patent rights are expired. Hence, there seems a causal connection between the SPC and relocation of European generic companies. However, no additional peer reviewed literature concerning this subject was found.

9.4 Competition and drug prices
This study has indicated that the patent cliff is delayed and that there is no evidence for lower drug prices due to a longer EPL, these results are in line with other literature (Andelin et al. 1981, Moors et al. 2014). In addition, as predicted in an old report that examined the relation between patent extension and pharmaceutical innovation (Andelin et al. 1981): “Competitive pressures on patented drugs from generically equivalent drugs will be delayed and in some cases prevented by patent-term extension.” Moreover, they concluded: “the prices of drugs whose patents are extended are likely to be higher during the extended period than they would
have been if patent protection had ended." (page 5) This is illustrated in figure 7 of the results section.

The patent cliff in this study was determined with an additional methodology. Most studies looked at the revenues of a blockbuster drug on a global level. This study has examined the price per DDD (daily defined dose) for a particular drug, defined with the ATC code. A specific ATC-code includes all different drugs with one specific active ingredient, regardless of the manufacturer. Hence, before patent expiry during a monopoly period with no generic competition, the total amount of DDD is represented by one medicinal product. After patent expiration this amount is represented by both the reference drug, i.e. original patented drug, and multiple generic versions. It was not possible to differentiate between the different manufacturers with the SFK database. Hence, analysis toward the amount of generic entry after patent could not be done.

Saha et al. (2006), who researched the effects of generic entry on drug prices, has found that generic competition is bigger, i.e. more generic entries after patent expiration, when the sales of the innovative drugs are higher during patent protection. Hence, they found that generic competition to be particularly intense for blockbuster drugs. These blockbuster drugs experience significantly more generic entrants, price erosion, and generic penetration than other drugs. This partially explains that not all the researched drugs (e.g. Mizolastine) in chapter 7.5.2 have experienced a steep so-called patent cliff like Nebivolol, Losartan and Levetiracetam.

The explanatory memorandum (COM (90) 101 final) did not state anything about this delay of the patent cliff. It only stated a possible positive effect of patent extension. It stated that drug prices could lower due to a longer effective patent life. This research and other literature (Moors et al. 2014) did not find evidence for this statement. There is, although, one finding by Permanand (2006) that could support this statement. The casus of the SPC implementation policy process was discussed in this book. Permanand has described that EFPIA needed to choose between lobbying against price controls and lobbying in favour of patent extension. EFPIA had chosen to lobby in favour of patent extension and they have succeeded (Permanand 2006 p. 101). However, this resulted that the European Commission have implemented Directive 89/105/EEC, i.e. a Directive “relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems”. This Directive has given the member states competence to implement regulations that could affect drug prices substantially on a national level (SFK 2012 p. 31).

9.6 Strengths and limitations

9.6.1 Scope of the study

The scope of this study was eventually demarcated to one pull mechanism, i.e. the Supplementary Protection Certificate. However, the pharmaceutical sector is a complex sector. This great complexity has caused a relatively wide scope. For example, the SPC uses a law, i.e. patent law, and one directive, i.e. the directive for market authorisation, to determine the length. In addition, there were numerous presumed effects of the SPC, which has widened the scope. Although, the jurisprudence and teleological interpretation are two very important aspects of the use of the SPC, these were not in the scope of this study. The outcomes due to the jurisprudence were incorporated, and some results could be explained with these outcomes. However, the complexity of the jurisprudence and the lack experience of the author have lead to
an exclusion of the jurisprudence itself. However, the exclusion of the development of the jurisprudence had no complications for the results of this study.

9.6.2 Quantitative analysis
This study examined the effects of the SPC regulation a national level. However, the SPC is a European regulation. The quantitative assessment of this study has gained insights into the implementation of the SPC regulation in the Netherlands. However, more generalised conclusions about the effects of this regulation in the European Union and similar regulations in other regions could be drawn. The combination with the SFK statistics gave additional valuable insights towards price developments and the effect of patent extension.

The dates of market authorisation were not in the SPC database. This is a limitation of this study. Without these dates exact time to market could not be determined, and specific quantitative analysis could not confirm or reject the statements made by the interviewees about increasing cycle time. The analysis of the SPCs provided an indication, however this analysis is not specific. Therefore, more research is needed, regarding the increasing cycle time of R&D in the pharmaceutical sector.

9.6.3 Interviewees
The interviewees were key opinion leaders in the pharmaceutical sector. All interviewees had a substantial amount of experience in the pharmaceutical sector. Hence, their knowledge and expertise was enormous. Another strength of this part of research was that the participants had different backgrounds, e.g. public and private; innovative and generic. Therefore, a biased conclusion was less likely. Only generalised conclusions were made if multiple interviewees made a particular statement and, moreover, if literature could confirm these statements.

9.6.4 Author/interviewer
A master student of the VU University in Amsterdam who had limited experience did this research. However, two very experience researchers supervised the author, one PhD student from the VU University and one PhD and senior policy advisor from the Dutch Ministry of Health, Welfare and Sport.

The author conducted the interviews. The curiosity of the author and the experience of the interviewees have lead to many deviations during the interviews. These deviations did not necessarily lead to better insights for this research. However, they provided extra information for the author to get an understanding of the pharmaceutical sector.

9.6.5 Qualitative analysis
Fourteen interviews were conducted. Three interviews were not recorded, but notes were taken during the interviews and summaries were made immediately after these interviews in order to capture as much data as possible. The other interviews were recorded, transcribed and summarised. Hence, it was very unlikely that crucial information for this study was missed during the coding phase for these eleven interviews. All interviewees have validated their summary. This also increased the reliability.

9.6.6 Combining qualitative and quantitative research
The combination of both quantitative and qualitative research was a strong aspect of this study. The quantitative data gave extra body to the statements that were made by the interviewees.
This combination gave extra validity to this research and made it possible to draw more generalised conclusions.
10. Recommendations
The aim of this study was to assess the rationale behind the SPC regulation. All six were discussed. This section will elaborate on some recommendations. First of all, Einstein’s opening statement already gave a lead towards the findings of this report. This report is critical towards the SPC and, in particular, towards its implications regarding R&D productivity and innovation. However, the foundation of the SPC, the patent system, seems crucial for innovation. It is hard to imagine how innovation will continue without such system, especially in the pharmaceutical sector where investment costs are extremely high compared to production costs.

However, patents and the SPC particularly stimulate innovation towards economic valuable medicinal products, because a return on investment is needed. Research show that market size, i.e. potential economic value, and investment in drug development is highly correlated (Kyle and McGahan 2012). Therefore, therapeutic valuable drugs with a low economic value are likely to be neglected, leaving pharmaceutical gaps (Kaplan et al. 2013). Hence, research is needed to find (other) mechanisms that stimulate innovation and the development of medicinal products for these neglected diseases.

Second and finally, no impact assessment has been done regarding the SPC: i.e. how large is the impact of the SPC on national health budgets; how many generic companies have relocated to countries outside the European Union and what is the effect of this relocation on labour and export; and has there been relocation of innovative pharmaceutical companies? This study gives evidence that the SPC has affected these aspects. However, additional quantitative research is needed.
References

Angell, M., (2004a) Excess in the pharmaceutical industry CMAJ 171 (12)


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(scanned pdf in possession of the author)


Dissel, J. van, Leufkens, B., Pieters, T., Evenblij, M., (2013) Het Geneesmiddel, De wonderlijke wereld achter
medicijnen Biowetenschappen en maatschappij kwartaal 4


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Appendix A: Interview design

Introduction
What are the major challenges that you/your company/your sector encounters?

Have these challenges been the same in the last decades, or is there a pattern in the challenges that you are facing? What type of challenges are these?

*If not mentioned in the challenges question:*
To what extend do you experience patent erosion in the pharmaceutical sector. In other words, is the effective patent life is decreasing?

Why is patent extension, by regulation, needed/vital to the industry, since evergreening or drug repurposing are also ways to increase protection for medicinal products?

SPC Content
Now I would like to talk about the SPC regulation, the regulation for patent extension in the EU. The explanatory memorandum (EM, toelichting op de nota) has stated several rationales and presumed effects why the SPC should come into force. I would like you to share your views on these reasons. It is possible that you are not able to comment or give answers to some points. It is okay to state: no comment.

The SPC EM states that there would be more innovation in pharmaceutical sector. What is the possible relation between patents, patent extension and the amount of innovation?

How could patent term extension increase research productivity, when we look at the different aspects of R&D productivity?

On which different aspects do pharmaceutical companies choose to conduct R&D?

Isn't it that a short patent life has a positive effect on the amount of innovation? You could assume that faster innovation is needed, because there is less time to make a profit out of your medicinal product? Therefore, a longer patent life has a negative effect? What are your thoughts?

Can you name barriers for innovation that you and your colleagues/competition experience?

Could you elaborate on the competition, between innovative companies and between innovative and generic companies, in the pharmaceutical business?

What is the effect of the patent term on competition in the pharmaceutical sector?

What are important factors for a pharmaceutical company to locate in a particular country?

What are, according to you, the possible effects of patent extension on drug prices?

Are there things, so far, you would like to add?
Concluding remarks
Are there things you like to add which we did not discuss so far?

And do you have any questions?

Do you have contact information of more interesting people who I can interview?

I would like to thank you for your time. We will have contact via email. Are you interested also to see the presentation of my report and are you interested in a copy of my report.
Appendix B Coding Scheme

Initial coding scheme
- Effective patent life

- Research productivity & innovation
  Work in progress
  Risks and success
  Value
  Cost of R&D
  Cycle time of R&D

- Relocation of innovative pharmaceutical companies

- Competition in the pharmaceutical sector

- Prices of medicinal products during patent/SPC protection
- Prices of medicinal products after patent/SPC expiration

- Interest of innovative pharmaceutical companies
- Interest of generic pharmaceutical companies

Final Coding Scheme, after open coding
- Effective patent life

- Research productivity & innovation
  Incremental innovation
  Radical innovation
  Work in progress
  Risks and success
  Economic Value
  Therapeutic Value
  Cost of R&D
  Cycle time of R&D

- Relocation of innovative pharmaceutical companies
- Relocation of generic pharmaceutical companies
- Business climate

- Competition between innovative pharmaceutical companies
- Competition between innovative and generic companies

- Prices of medicinal products during patent/SPC protection
- Prices of medicinal products after patent/SPC expiration

- Interest of innovative pharmaceutical companies
- Interest of generic pharmaceutical companies
### Appendix C SPC statistics

Table with all SPC ranked by the different status in May 2014.

<table>
<thead>
<tr>
<th>Status of SPC</th>
<th>Number of SPCs</th>
<th>Incorporated for further analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapsed, due to lapsed basic patent</td>
<td>26</td>
<td>No</td>
</tr>
<tr>
<td>Denied</td>
<td>101</td>
<td>No</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>57</td>
<td>No</td>
</tr>
<tr>
<td>Renounced</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Lapsed, not paid taxes</td>
<td>26</td>
<td>No</td>
</tr>
<tr>
<td>Submitted</td>
<td>58</td>
<td>No</td>
</tr>
<tr>
<td>Processed</td>
<td>27</td>
<td>No</td>
</tr>
<tr>
<td>Incomplete submission</td>
<td>34</td>
<td>No</td>
</tr>
<tr>
<td>Granted</td>
<td>225</td>
<td>Yes</td>
</tr>
<tr>
<td>In force</td>
<td>123</td>
<td>Yes</td>
</tr>
<tr>
<td>Lapsed, lawful term expired</td>
<td>334</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1021</td>
<td></td>
</tr>
</tbody>
</table>

Table with all the granted SPCs, i.e. 'Granted', 'In force' and 'Lapsed, lawful term expired', ranked by length in May 2014.

<table>
<thead>
<tr>
<th>Duration (months)</th>
<th>Granted</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0</td>
<td>1</td>
</tr>
<tr>
<td>0 - 9</td>
<td>43</td>
</tr>
<tr>
<td>10 - 19</td>
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<td>20 - 29</td>
<td>67</td>
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<td>30 - 39</td>
<td>67</td>
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<td>40 - 49</td>
<td>68</td>
</tr>
<tr>
<td>50 - 59</td>
<td>55</td>
</tr>
<tr>
<td>60+</td>
<td>319</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>682</td>
</tr>
</tbody>
</table>
Appendix D SPCs ranked to SPC application date

Table with all granted SPCs ranked to SPC application date in the Netherlands in up to May 2014.

<table>
<thead>
<tr>
<th>Year</th>
<th>SPC grants</th>
<th>SPC &lt;60</th>
<th>SPC 60+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>108</td>
<td>76</td>
<td>32</td>
</tr>
<tr>
<td>1994</td>
<td>19</td>
<td>12</td>
<td>7</td>
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<td>26</td>
<td>12</td>
<td>14</td>
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<td>1996</td>
<td>25</td>
<td>19</td>
<td>6</td>
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<td>1997</td>
<td>33</td>
<td>21</td>
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<td>7</td>
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<td>2003</td>
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<td>9</td>
<td>15</td>
</tr>
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<td>9</td>
</tr>
<tr>
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<td>17</td>
</tr>
<tr>
<td>2011</td>
<td>24</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>2012</td>
<td>22</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>2013</td>
<td>34</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>2014</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
Appendix E SPCs ranked to basic patent term

Table with all granted SPCs ranked to basic patent application date in the Netherlands up to May 2014.

<table>
<thead>
<tr>
<th>Year</th>
<th>SPCtotal</th>
<th>SPC&lt;60</th>
<th>SPC 60+</th>
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<tbody>
<tr>
<td>1973-1993</td>
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<td>0</td>
<td>3</td>
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<tr>
<td>1974-1994</td>
<td>6</td>
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<tr>
<td>1975-1995</td>
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<td>0</td>
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</tr>
<tr>
<td>1976-1996</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>1977-1997</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>1978-1998</td>
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<td>4</td>
<td>7</td>
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<td>1979-1999</td>
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<td>1980-2000</td>
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<td>12</td>
<td>8</td>
</tr>
<tr>
<td>1981-2001</td>
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<td>1982-2002</td>
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<td>5</td>
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<td>1983-2003</td>
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<td>13</td>
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<td>1984-2004</td>
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<td>1985-2005</td>
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<td>1986-2006</td>
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<td>1987-2007</td>
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<td>1988-2008</td>
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<td>1997-2017</td>
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<td>1998-2018</td>
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<td>1999-2019</td>
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<td>2000-2020</td>
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<td>2007-2027</td>
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</tbody>
</table>
Appendix F SPCs ranked to country of basic patent owner

All granted SPCs in the Netherlands ranked to the country of the basic patent owner up to May 2014.

<table>
<thead>
<tr>
<th>Granted SPCs to non-EU countries</th>
<th># SPCs</th>
<th>Granted SPCs to EU countries</th>
<th># SPCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU</td>
<td>5</td>
<td>BE</td>
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</tr>
<tr>
<td>BM</td>
<td>4</td>
<td>CH</td>
<td>65</td>
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<td>CA</td>
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<td>2</td>
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<td>IL</td>
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<td>DK</td>
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<td>JP</td>
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<td>ES</td>
<td>6</td>
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<td>KR</td>
<td>1</td>
<td>FI</td>
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<tr>
<td>MY</td>
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<td>FR</td>
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<td>PA</td>
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<tr>
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<tr>
<td>US</td>
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<td></td>
<td></td>
<td>IT</td>
<td>9</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>352</td>
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<td>330</td>
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<table>
<thead>
<tr>
<th># SPCs</th>
<th>Percentage</th>
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</thead>
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<td>352</td>
<td>51.6</td>
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<tr>
<td>330</td>
<td>48.4</td>
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<tr>
<td>682</td>
<td></td>
</tr>
</tbody>
</table>
Appendix G Development of standardised prices of medicinal product in the Netherlands

Standardised cost per DDD (%cDDD) of 11 medicinal products between 2005 and 2013. SPC expired in 2010 for all these medicinal products. Below are the two tables with the corresponding raw data.

<table>
<thead>
<tr>
<th>ATC code</th>
<th>Generic name (basic patent expiration)</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>C07AB12</td>
<td>Nebivolol (2009)</td>
<td>139.7</td>
<td>135.6</td>
<td>134.3</td>
<td>120.9</td>
<td>100.0</td>
<td>86.6</td>
<td>39.2</td>
<td>22.6</td>
<td>22.5</td>
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<tr>
<td>C08CA12</td>
<td>Barnidipine (2005)</td>
<td>100.0</td>
<td>100.0</td>
<td>99.8</td>
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Total reimbursed cost (RC) of the corresponding medicinal products. Numbers represent the total amount of reimbursed cost in the Netherlands in Euro.

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