



FACULTY OF LAW
University of Lund

Karin Hedberg

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Versus
Generic Competition

-In the Context of the New EU Pharmaceutical
Legislation

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Supervisor
Hans Henrik Lidgard

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Summary

Development of innovative drugs is a lengthy, risky and expensive enterprise, and the research-based pharmaceutical industry depends uniquely on intellectual property rights, e.g. patents and regulatory data protection to support its investments in drug development activities. After the expiry of intellectual property rights for original drugs, generic drugs may enter the market. A generic drug is a copy of an original drug, sold at a considerable price discount in comparison with the original drug. In the vast majority of cases, the entry on the market by generic drugs results in huge and rapid losses of market shares on behalf of the originator.

The EU pharmaceutical legislation has recently been revised through the 2001 Pharma Review. On one hand, recent legislative and regulatory developments on both the EU and national level threaten the value of pharmaceutical innovation in two distinct respects. Firstly, patent rights are being restricted through the inclusion of a Bolar provision in the EU, allowing generic competitors to conduct pre-patent-development work. Secondly, state governments increasingly introduce systems favouring the use of generics, in order to cut down their healthcare budgets. These factors contribute to making investments in pharmaceutical research and development even more hazardous from a risk return perspective. On the other hand, there is a possibility to obtain increased periods of market exclusivity for innovative drugs in the EU. Furthermore, under the new EU pharmaceutical legislation, original drugs, and thereby the research-based pharmaceutical industry, will benefit from an increased and harmonised period of regulatory data protection.

At first sight, it is hard to see how legislative measures actually affect the conflicting interests of research-based pharmaceutical companies on one hand and generic competitors on the other. In this thesis, changes introduced by the 2001 Pharma Review is scrutinised and compared to the earlier legislative situation. The intent is to elucidate as to what extent the new EU pharmaceutical legislation succeeds in striking a balance between pharmaceutical innovation and generic competition.

In the concluding part of this thesis, the main finding is that through the new EU pharmaceutical legislation, in connection with national practises promoting the use of generic drugs, the generic industry is favoured and therefore the incentives to engage in pharmaceutical research and development are found to be diminished.

Abbreviations

Amendment Directive	Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use
CPC	Community Patent Convention
ECJ	European Court of Justice
EFPIA	European Federation of Pharmaceutical Industries and Associations
E.I.P.R. Review	European Intellectual Property
EPC	European Patent Convention
IP	Intellectual Property
IPR	Intellectual Property Right
MCA	UK Medicines Control Agency
Medicinal Products Directive	Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
MPA	Swedish Medical Products Agency
OTC	Over-the-Counter
PBB	Swedish Pharmaceutical Benefits Board
R&D	Research and Development
SPC	Supplementary Protection Certificate
SPC Regulation	Council Regulation No 1768/92 concerning the creation of a supplementary protection certificate for medicinal products
TRIPs Agreement	1997 Agreement on Trade-Related Aspects of Intellectual Property Rights
WTO	World Trade Organisation

1. Introduction

1.1. Background

A generic pharmaceutical is a drug whose active substance already exists on the market when it is launched; it is a product equivalent to an original pharmaceutical product, the patent of which has expired.¹ A generic drug may be marketed either under a brand name or unbranded. In the latter case, it is identified by its internationally approved proprietary scientific name – the “generic” name. In most cases, a generic drug is produced and marketed under its generic name, e.g. omeprazole, as opposed to LOSEC, a brand name for the original drug produced by AstraZeneca.

Generics are cheaper to produce than the original drugs that they are based on. In certain respects, generic manufacturers can take advantage of the research and development (R&D) conducted by research-based companies, to create the original drug. As a result, generic drugs can be sold at much lower comparative prices, challenging the market share of established drugs.

The pharmaceutical industry is unique in having a clearly differentiated generic sector², the members of which await with eager anticipation the expiry of patent protection for innovative drugs. The size of the generic market differs widely in the EU Member States. Generics make up a relatively large part of the pharmaceutical market in Germany (41%), Sweden (39%), Denmark (22-40%), the UK (22%) and the Netherlands (12%). In Italy, Spain and Portugal, generics hardly count for 1% of the pharmaceutical market, compared to 3-4% in France.³

Those figures effectively underline the importance of generic medicines in today’s society, where governments and other healthcare providers continuously strive to achieve cost savings in pharmaceutical expenditure. All EU Member States have independent domestic systems and policies concerning national healthcare. The major part of drug costs in the EU is paid by drug reimbursement systems, where consumers and patients are reimbursed for their drug expenses by the state. Within the pricing and reimbursement systems, there are two important objectives. Firstly, a state strives to provide for superior standards of treatment for each individual patient. In order to achieve this, it is important to promote pharmaceutical research and development resulting in new, more effective drugs, and new improved ways of treatments. One incentive used to promote R&D is the

¹ I use the term “original”, “innovative”, “new” or “established” drug as referring to a new drug developed through a complete research and development process undertaken by a research-based pharmaceutical company. The term “generic” pharmaceutical product or “copy” drug is used to describe pharmaceutical drugs developed by a manufacturer of generics, not undertaking a full R&D process.

² Even though research-based pharmaceutical companies have to an increased extent started to engage in the development and manufacturing of generic drugs.

³ “Generic Medicines”, available at <<http://www.euractiv.com/Article?tcmuri=tcm:29-117497-16&type=LinksDossier>>, last visited on 4 February 2005.

granting of patents and other IP rights relating to innovative drugs, allowing research-based companies to recoup their investments in research and development. Secondly, governments are under a constant budget restraint, aiming to lower the costs for pharmaceutical expenditure, by providing for as cost-effective healthcare as possible. This is where generic drugs enter the scene, providing for cheaper copies of established drugs of which the patents have expired, thus enabling health care providers to save considerable amounts of money. In order to cut healthcare budgets, governments worldwide as well as in the EU have actively promoted the use of generic drugs. The increased use of generic pharmaceutical products is an important factor in improving the sustainability of health care financing for pharmaceuticals.

Naturally, governmental efforts to encourage the use of generics has been heavily criticised by the research-based industry as a direct attempt to undermine pharmaceutical innovation. It has been argued that reduced incentives to get involved in expensive R&D to discover new drugs, will deprive patients of much-needed breakthrough products in the future and may damage the research-based pharmaceutical industry as a whole.⁴ In return, the generics industry argue that cost-effective generic medicines save EU patients and healthcare systems over €13 billion each year, thus helping to ensure patient access to essential medicines and providing urgently needed budget headroom for the purchase of new and innovative treatments.⁵

On 30 April 2004, the day before the accession of ten new Member States⁶ to the European Union, four new pieces of legislation affecting the legal framework for pharmaceutical products in Europe (hereinafter referred to as the 2001 Pharma Review) were published in the Official Journal. The overall objectives of the new pharmaceutical legislation as outlined by the European Commission is to guarantee a high level of public health protection for EU citizens, to complete the internal market in pharmaceutical products, to meet the challenges of the EU enlargement and to rationalise and simplify the drug authorisation system as far as possible. The review is also designed to strengthen European competitiveness internationally in the pharmaceutical area, seeking to strike the right balance between innovation and generic competition. One explicit objective is to increase the availability of innovative medicinal products, while at the same time encouraging competition with generic products.⁷ All pharmaceutical companies that market products in the EU need to comply with the new legislation, which will be operational in late 2005.

⁴ Izmirlieva, M., *Regulatory Efforts to Promote the Use of Generics – Government Versus Big Pharma*, available at <http://www.bbriefings.com/pdf/15/pg031_r_izmirlieva.pdf>, last visited on 4 February 2005.

⁵ “About the EGA – Intro”, available at <<http://www.egagenerics.com/ega-intro.htm>>, last visited on 4 February 2005.

⁶ I refer to the ten states that entered the European Union in May 2004, namely Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia, as the new Member States.

⁷ Commissioner Erkki Liikanen, addressing the EP on 16 December 2003 before the plenary vote (SPEECH/03/615).

One of the major changes discussed in this thesis is a harmonised and increased period of regulatory data protection. Regulatory data protection is a relatively new intellectual property right, relating to documents submitted to a regulatory authority to obtain marketing authorisation for innovative drugs. Furthermore, the new legislation provides for a pro generics statutory provision, allowing generic competitors to start preparing for a commercial market launch while the original drug still is under patent protection. Those changes will be discussed from the perspective of pharmaceutical innovation versus generic competition, seeking to clarify whether the objective of striking a balance between those competing interests by the new legislation is likely to succeed.

The WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs), negotiated in the 1986-94 Uruguay Round and in force since 1 January 1995, introduced intellectual property rules into the multilateral trading system for the first time. It resulted in a substantial degree of harmonisation to intellectual property protection worldwide, and did so in the context of a system that, unlike the Paris Convention for the Protection of Industrial Property, has real powers of enforcement. The Agreement is tied to the WTO and therefore to trade matters. This fact gives TRIPs a substantial amount of authority. Failure to comply with the TRIPs Agreement can lead to trade retaliation by other countries. However, before such trade retaliation can occur, member countries are required to try to settle their disputes pursuant to the Dispute Settlement Understanding.⁸ Nevertheless, the prospect of a claim being brought, and the ultimate possibility of economic sanctions for failure to bring national laws into compliance, means that despite a very limited number of cases actually being brought, most national governments have tried very hard to bring their laws into line.⁹ For those reasons, and specifically since this thesis deals with the issue of intellectual property rights (IPR), the status of the TRIPs Agreement will be reviewed in each section of this inquiry.

1.2. Purpose and Delimitations

The purpose with this thesis is to elucidate as to what extent the new EU pharmaceutical legislation succeeds in striking a balance between pharmaceutical innovation and generic competition. The changes introduced by the 2001 Pharma Review will be discussed from a holistic perspective, trying to assess the imminent legislative situation for research-based pharmaceutical companies on one hand and generic manufacturers on the other, in the light of the importance of generic drugs to governments and national healthcare policies.

The thesis considers the institutions of patent protection, regulatory data protection and the mandatory procedure to obtain marketing authorisation

⁸ Derzko, N. M., *A Local and Comparative Analysis of the Experimental Use Exception – Is Harmonization Appropriate?*, in IDEA: The Journal of Law and Technology, 2003, at 1.

⁹ Brazell, L., *The Protection of Pharmaceuticals and Regulatory Data: EU Enlargement Update*, in E.I.P.R. 2002, 24(3), pages 155-161.

for a drug. The ongoing struggle between original drugs and generics is fought by all possible means, such as copyrights and trade secrets protection. However, only the above-mentioned aspects will be discussed in this essay. The different *procedures* available to obtain marketing authorisation will not be scrutinised, instead the focal point will be the factual requirements in this process. The issue of national pricing and reimbursement systems will only be briefly examined, by the example of the Swedish policy concerning generic drugs.

Due to the limited scope and the purpose of this thesis, I have chosen to exclude the US perspective, and therefore provisions under US law will be scrutinised only to a limited extent, even though most pharmaceutical companies have a genuine interest for both regimes.

1.3. Method and Material

The method used in this thesis is a traditional method for legal research, combining a descriptive and analytical study of the legal sources. The foundation is the Community pharmaceutical legislation, as provided in relevant Regulations and Directives. Furthermore, for reasons explained in the introductory part of this thesis, relevant provisions of the TRIPs Agreement will be highlighted in each subsection.

In order to give a perspicuous description of these controversial issues, I have used doctrinal texts, both articles and books. Since the focus is on the EU law aspect, I have made a survey of relevant leading cases from the European Court of Justice. When needed, I have used the case law from national courts of the Member States. EU law is very dynamic since it is a field of law under constant development. Due to this fact, in order to find material of immediate interest, I have also searched the internet, trying to find and refer to objective and reliable sources.

1.4. Outline

In the second chapter, the scope of patent protection in the EU is considered. Furthermore, the SPC legislation, providing for the possibility to obtain extended terms of market exclusivity for innovative drugs, is reviewed.

The third chapter surveys the necessary conditions needed to apply for a marketing authorisation, with the prime focus on criteria under the abridged procedure related to generic products. Moreover, the rules concerning regulatory data protection are explained to the reader. Both as regards abridged applications for marketing authorisations and regulatory data protection, the changes introduced by the 2001 Pharma Review will be discussed.

Chapter four concentrates on exceptions to the exclusive rights of a patent holder, in the form of so-called experimental use exceptions. The main question to be answered is what preparations a generic competitor can undertake before the patent expiry of the original product. In order to

highlight the similarities and differences in national patent laws, case law on the experimental use exception in four Member States, namely the UK, the Netherlands, Germany and France, will be compared. This discussion is continued in chapter five, where pro generic statutory provisions, so-called Bolar provisions, are deliberated. The new EU Bolar provision will also be considered.

In the sixth chapter, the Swedish pricing and reimbursement system is briefly examined, and specifically the system of mandatory generic substitution is surveyed.

The seventh chapter of this thesis contains an analysis, where I try to assess, drawing conclusions from the initiating descriptive chapters, how the new EU pharmaceutical legislation will affect the pharmaceutical industry in the enlarged Community, and if a fair balance between pharmaceutical innovation and generic competition has been reached.

2. Patent Exclusivity

Pharmaceutical research and development is a long-lasting, hazardous, and expensive business, and the research-based pharmaceutical industry depends on patent protection to recoup resources invested in innovative activities. In this chapter, the R&D process will be described and the importance of patents to the research-based pharmaceutical industry will be considered. Further, an overview of the scope of patent rights afforded to pharmaceuticals in the EU, as well as the possibility to obtain extended periods of market exclusivity for innovative drugs will be scrutinised.

2.1. The Development of a New Drug

The discovery of a new chemical compound in no way ensures that a commercial drug can be delivered to patients. This new compound needs to be developed into an effective pharmaceutical product.¹⁰

The R&D process is initiated by preclinical trials, where the discovered compound is optimised and examined by tests performed both *in vitro*¹¹ and *in vivo*¹² to evaluate the safety and toxicity of the compound. From the discovery of a possibly interesting chemical compound until the preclinical phase is completed, it takes on average six years. If the data from pre-clinical trials are favourable, the compound is qualified for the next step in the process, clinical trials. However, in a majority of cases, research on a compound is terminated at this time due to negative results. Only five in five thousand compounds that enter preclinical trials are qualified to go into clinical trials.¹³ Thus, the rate of success at this stage is 0,1%.

The process of clinical trials is divided into three phases. In phase I, a drug candidate is given to a small number of healthy volunteers. This phase takes approximately two years. In phase II, a ca one-year process, the drug is given to a small number of patients, suffering from the relevant disease, at various dosage levels and in different dosage forms, to examine its efficacy

¹⁰ For the purpose of this thesis, it has been problematic to establish the time aspect of the different phases in the R&D process. However, after comparison of a number of sources, I reached the conclusion that the figures provided by EFPIA (although this organisation represents the research-based industry) are an average value, and therefore their document will be referred to in this paragraph.

“The Making of New Medicines - Manufacturing, the Environment and the Pharmaceutical Industry”, at page 15, June 2001, available at <http://www.efpia.org/6_publ/document/makingmedicines.pdf>, last visited on 4 February 2005.

¹¹ Test tube testing.

¹² Testing in various animals.

¹³ “How New Drugs Move through the Development and Approval Process”, 11/1/2001, available at <<http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=4>>, last visited on 4 February 2005.

and to determine appropriate dosage profiles. In phase III, the drug is given to a large number of patients at multiple sites for quite a long time in order to confirm its efficacy and safety. Phase III studies typically include several hundred to several thousand people, and on average it takes one year of work.¹⁴ Out of five compounds that enter into clinical trials, only one is finally approved as a commercial drug.¹⁵ This means that the success rate at this stage is 20%. The reasons for failure might be e.g. that the compound in clinical trials proves to have a less biological effect in humans than anticipated from the results in pre-clinical testing, that the compound shows to have unacceptable side effects, or that the drug is too complicated or expensive to produce.¹⁶

When clinical trials are successfully completed, the company applies to a regulatory authority to obtain authorisation to manufacture and market the drug. The administrative procedure to obtain a marketing authorisation requires between two and three years, and once completed the producer can initiate marketing.¹⁷ To conclude this survey of the R&D process; from the discovery of an interesting chemical compound to the commercial market launch of a new drug, it takes on average between twelve and thirteen years.¹⁸

During the past two decades, development of pharmaceutical products has become more expensive and hazardous. The risks involved in drug development are obviously substantial since the rate of success is low. Furthermore, the enterprise of innovation is connected to large investments. Two recent studies of differing methodology estimate the average cost to develop a new drug at \$897 million and \$1.7 billion respectively. In May 2003, the average cost to develop a new medicinal product was estimated to \$897 million.¹⁹ According to this analysis, \$897 million represents the fully capitalized cost to develop a new drug, including studies conducted after receiving regulatory approval.²⁰ This study was based on an analysis of data covering 68 drugs from ten multinational pharmaceutical companies during the 1990s. According to the second study, presented in November 2003, when the costs of failed prospective drugs are included, the cost of

¹⁴ Hara, T., *Innovation in the Pharmaceutical Industry - The Progress of Drug Discovery and Development*, Cheltenham, Edward Elgar, 2003.

¹⁵ "How New Drugs Move through the Development and Approval Process".

¹⁶ Domeij, B., *Pharmaceutical Patents in Europe*, Stockholm, Norstedts Juridik, 2000, at page 20.

¹⁷ "The Making of New Medicines - Manufacturing, the Environment and the Pharmaceutical Industry".

¹⁸ "Comparing Facts: Value Added in Europe Innovative Medicine vs. Generic Copy", available at <http://www.efpia.org/3_press/FMLgenericvsinnov.pdf>, last visited on 4 February 2005.

¹⁹ "Total Cost to Develop a New Prescription Drug, Including Cost of Post-Approval Research, is \$897 Million", Press Release, 13 May 2003, available at <<http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29>>, last visited on 4 February 2005.

²⁰ Post-approval R&D costs are incurred by drug developers after receiving regulatory approval to market a new product. Such costs may be incurred to conduct studies assessing the long-term safety and effectiveness of the marketed drug in a broader patient population or specific patient subgroups, such as children or the elderly, testing the marketed drug in new indications, and development of new formulations.

discovering, developing and launching a new drug has risen by 55% over the last five years to nearly \$1.7 billion.²¹ This alleged increase was said to be a result from a drop in cumulative success rates from 14% to 8% and an increase in research, development and launch costs of nearly 50% for each of these steps.²²

By contrast to innovative pharmaceuticals, the development cost for a generic drug is approximately \$1 million and the total time for development and completion of administrative procedures is between two and three years.²³ Hence, generic pharmaceuticals are considerably less expensive to develop than original drugs, since the producers of generics do not incur the risks and costs associated with the R&D of innovative drugs. Rather the investments for a producer of generic drugs lies in fixed assets like machinery and plants adjusted to achieve cost competitive production, and costs incurred by marketing and sales. As a generic drug will never benefit from patent protection, and thus never be able to exclude competition from similar competing products, the return for manufacturers of generics is obtained by large sales volumes.

2.2. The Importance of Patents to the Research-Based Pharmaceutical Industry

Limited monopolies conferred by the state to those who develop or introduce certain aspects of technology have traditionally been justified on the basis that without such remuneration the development and spreading of new technology will not be encouraged. Patents have been the traditional such incentive and are clearly the key form of intellectual property in the pharmaceutical industry. The importance of patents to pharmaceutical innovation has been reported by economists in several cross industry studies. Two surveys conducted in the US concerned which factors are most important and necessary in appropriating the benefits from innovations.²⁴ These factors included the competitive advantages of being first in the market, superior sales and service efforts, secrecy and complexity of productions and product technology, as well as patents. In both studies, the results showed that representatives for the pharmaceutical industry placed

²¹ Gilbert, J., Henske, P., Singh, A., *Rebuilding Big Pharma's Business Model*, In Vivo – the Business and Medicine Report, 2003, Vol. 21, No. 10, available at <http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf>, last visited on 4 February 2005.

²² Ibid.

²³ “Comparing Facts: Value Added in Europe Innovative Medicine vs. Generic Copy”.

²⁴ Grabowski, H., *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, Duke University, July 2002, available at <<http://www.dklevine.com/archive/grabow-patents.pdf>>, last visited on 4 February 2005. He refers to Levin, R. D., et al., *Appropriating the Returns from Industrial Research and Development*, Brookings Papers on Economic Activity (1987): 783-820; Cohen, W., et al., *Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector*, Working Paper (Pittsburgh: Carnegie-Mellon University, 1997).

by far the highest importance on patents. Many other research-intensive industries, such as computers and semiconductors, attached greater weight on elements like lead-time and learning by doing efficiencies in production accruing to first movers. The findings of these studies are in accordance with an earlier study performed in the UK.²⁵ In this survey, managements for research-based pharmaceutical companies stated that on average 64% of the companies' most recent developed drugs would not have been developed if it had not been possible to obtain patent protection for the products in question. The corresponding reduction in development was only 8 % across all industries. Thus, patents are considered a prerequisite for a profitable business on behalf of positive return of investment in pharmaceutical R&D.

The explanation for why patents are so important to pharmaceutical companies follows directly from the characteristics of the pharmaceutical R&D process. As noted above, it takes several hundred million dollars to discover, develop, and gain regulatory approval for a new drug. In the absence of patent protection, generic competitors would be able to free ride on the innovator's investment and copy the original product for a small fraction of the originator's costs, since the duplication costs in pharmaceuticals are extremely low relative to the innovator's total costs.²⁶ Hence, the granting of patent rights is essential for an innovator to recoup costs invested in R&D by allowing him or her to exclude competition for a specific product for a fixed time period.

2.3. Patent Protection Under the TRIPs Agreement

The TRIPs Agreement defines a basic set of intellectual property rights that member countries of the WTO must provide for in their national intellectual property legislation. According to Article 27.1 of the TRIPs Agreement, patent protection must be available for both products and processes in almost all fields of technology. Article 28 enshrines that:

“1. A patent shall confer on its owner the following exclusive rights:

(a) where the subject matter of a patent is a product, to prevent third parties not having the owner's consent from the acts of: *making, using, offering for sale, selling, or importing* for these purposes that product;

²⁵ Grabowski, H., *Patents, Innovation and Access to New Pharmaceuticals*, Duke University, July 2002, available at <http://levine.sscnet.ucla.edu/archive/grabow-patents_innov.pdf>, last visited on 4 February 2005. He refers to: Taylor, C. T., Silberston, Z. A., *The Economic Impact of the Patent System*, (Cambridge, England: Cambridge University Press, 1973); Silberston, Z. A., *The Economic Importance of Patents* (London: The Common Law Institute of Intellectual Property, 1987); Mansfield, E., *Patents and Innovation: An Empirical Study*, 32 *Management Science* (1986) 175.

²⁶ Ibid.

(b)where the subject matter of a patent is a process, to prevent third parties not having the owner's consent from the act of *using* the process, and from the acts of: *using, offering for sale, selling, or importing* for these purposes at least the product obtained directly by that process.”

Article 33 establishes a minimum term of protection of twenty years, counting from the filing date of the patent application. In the EU, all Member States fulfil this prerequisite. The impact of this provision and the TRIPs Agreement on the whole, can be shown by the example of US legislation. Since 1861, the US government had granted patents terms for seventeen years, counting from the date of *issue*. This term was changed, in accordance with the TRIPs Agreement, and the new legislation provides for a patent term of twenty years from the application filing date.

2.4. Patent Protection in the EU

Patent protection in the EU is available either under the national patent systems of the Member States or under the European Patent Convention (EPC).²⁷ If a patent under the EPC is granted, competence is transferred to the designated Member States, where it affords the same level of legal protection as a national patent.²⁸ European patent applications are filed with the European Patent Office or with national patent offices in the contracting states. The term of patent protection in the EU is twenty years, starting from the patent application filing date.²⁹ If there would be two applications for the same or too similar inventions, the patent will be issued to the applicant who filed first. This is referred to as the first-to-file system.

To qualify for a patent, an invention has to be new, it must signify an inventive step and it must have industrial applicability.³⁰ A patent gives the patent holder an exclusive right to prevent other parties from *making, using, selling, and importing or stocking* the protected product for these purposes. In case of process patents, there is an exclusive right to *use* the process and to offer it for use. Furthermore, there is an indirect patent protection, granting the patent holder an exclusive right to products manufactured by the patented process. Once the patent expires, the subject of the patent comes into the public domain, which in the pharmaceutical area opens up for generic competition.³¹

²⁷ Convention on the Grant of European Patents (European Patent Convention) of 5 October 1973 as amended by the act revising Article 63 EPC of 17 December 1991 and by decisions of the Administrative Council of the European Patent Organisation of 21 December 1978, 13 December 1994, 20 October 1995, 5 December 1996 and 10 December 1998.

²⁸ EPC Article 64.1.

²⁹ EPC Article 63.1.

³⁰ EPC Article 52.1.

³¹ For a thorough survey of patentability and the patent system, I refer to Domeij's doctoral PhD dissertation, "Pharmaceutical Patents in Europe", which provides an excellent account of the matter.

In the case of pharmaceutical products, a patent can apply to e.g. a drug (product patent), a specific drug substance (substance patent), a method to produce the chemical ingredients for a drug (process patent) or to an encapsulation method or a special delivery system of a drug (formulation patent). Since patent protection for a pharmaceutical product is of vital importance, research based pharmaceutical companies practise “total product strategies” by seeking to obtain as many patents as possible during the development and marketing period, and to extend them for new uses of established products. The risk of infringing existing patents therefore arises in any drug development and clearly, research-based companies seek to exclude generic competition by enforcing patent rights. The risk of infringement arises particularly for manufacturers of generics because a generic drug is defined as being identical to an original product.³²

In the pharmaceutical industry, patents are typically applied for early in the R&D process, soon after initial indications from preclinical studies that a compound may have beneficial biological activity. The stage in the development programme at which a patent application is filed will vary somewhat from company to company. However, it will normally be at an early stage in the pre-clinical process. To decide when to apply for a patent is a difficult task. On one hand, there is a risk that competitors file patent applications for similar inventions. Under the first-to-file system, this would obviously entail fatal consequences. On the other hand, every day a company waits to apply for a patent entails an added sales profit of approximately \$1 million, counted on an averagely successful drug.³³ However, irrespective of how long a pharmaceutical company waits before applying for a patent, the application will still be made at a very early stage in the development process compared to other industries. Since the patent protection starts on the application date, a great deal of the patent term will pass during the remaining R&D process.

A significant loss in effective patent life³⁴ has thereby occurred by the time of market launch as it takes many years for a product to pass through the R&D process and the regulatory review. As stated above, a factoring together of various data concerning pharmaceuticals shows that discovering, developing and launching a new drug takes approximately twelve to thirteen years.³⁵ According to Domeij, on average between nine and eleven years elapse between the patent application date and the day when effective sales can begin. This leaves an effective patent term of between nine and eleven years.³⁶ Consequently, in the vast majority of cases, holders of pharmaceutical patents are unable to exploit their full patent term. The US and the EU both allow patent holders to recoup at least a portion of this lost

³² “Pharmaceutical Patents”, available at <<http://www.egagenerics.com/gen-phrmapatents.htm>>, last visited on 4 February 2005.

³³ Domeij, B., *Läkemedelspatent*, Stockholm, Jure, 1998, at page 1.

³⁴ I use the terms “effective patent life” or “effective patent term” as defining the time from the date of regulatory marketing approval to the date of patent expiration.

³⁵ “Comparing Facts: Value Added in Europe Innovative Medicine vs. Generic Copy”.

³⁶ Domeij, B., *Pharmaceutical Patents in Europe*, at page 267.

time of protection through patent term extension laws, and below the EU practise on the matter will be presented.³⁷

2.4.1. Extended Market Exclusivity - The SPC Regulation

In the late 1980s/early 1990s the innovative pharmaceutical industry in the EU experienced that the effective patent term had been eroded so much that it threatened the viability of innovative research and development. An important factor contributing to the erosion of the effective patent life was the more and more extensive demands for clinical trials from the competent authorities granting marketing authorisations. Furthermore, the national regulatory authorities faced severe backlogs and it could take as long as six years in some Member States³⁸ to obtain a marketing authorisation.³⁹ Moreover, the existence of patent term extension provisions in the US and Japan for some time had put, in the opinion of the European Commission, EU-based innovative pharmaceutical companies at a competitive disadvantage.⁴⁰

On June 18, 1992, the European Parliament enacted Regulation 1768/92 concerning the creation of a Supplementary Protection Certificate for medicinal products⁴¹ (hereinafter referred to as the SPC Regulation), with the express goal of compensating research-based pharmaceutical companies for the reduction of effective patent life caused by delays in the regulatory approval process. The SPC Regulation came into force in January 1993 in the Member States.

A Supplementary Protection Certificate is designed to provide for an increased period of market exclusivity for innovative medicinal products. The market exclusivity is achieved by denial to grant marketing authorisations to generic products during the term of the certificate. Article 2 (a) of the SPC Regulation gives the following definition of the *medicinal products* for which supplementary protection is obtainable:

“(a) [a] *medicinal product* means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;

³⁷ This possibility was introduced in the US, as part of the Hatch-Waxman Act in 1984 and in the EU in 1993.

³⁸ For example Spain, Portugal, Italy and Germany.

³⁹ “Why were Supplementary Protection Certificates Introduced?”, available at <http://www.ims-global.com/insight/news_story/news_story_000417c.htm>, last visited on 4 February 2005.

⁴⁰ von Morze, H., Hanna, P., *Critical and Practical Observations Regarding Pharmaceutical Patent Term Restoration in the European Communities (Part I)*, in Journal of the Patent and Trademark Society, 1995, at 479.

⁴¹ Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products, Official Journal L 182 , 02/07/1992 P. 0001 – 0005.

(b) *product* means the active ingredient or combination of active ingredients of a *medicinal product*.”

In this provision, a distinction is made between *medicinal product* and *product*. The latter term refers to the active substance of the drug to which the first term refers. *Medicinal products* are the category of products eligible for supplementary protection. However, the protection applies only to the *product*, i.e. the active substance.⁴² Any active substance (or combination of active substances) protected by a patent in a Member State and subject, prior to being placed on the market, to a marketing authorisation procedure, may be the subject of a certificate. Only one SPC will be granted for each substance or combination of substances.

2.4.1.1. The Extent of Protection Granted

An SPC is not an automatic right. The application has to be made in each Member State where a certificate is desired, within six months of having obtained the first marketing authorisation in that Member State, or within six months from patent grant, whichever is later. According to Article 13 of the SPC Regulation, the supplementary protection takes effect at the date of patent expiry, and lasts for a period equal to the period that elapsed between the patent application date and the date of the first marketing authorisation in the Community reduced by five years. The maximum term of SPC protection is five years and the total period of effective protection, afforded by patent- and SPC protection, is fifteen years from the first marketing approval in the EU.

The SPC period is the difference between the patent application date and the date of the first marketing approval in the Community, subtracting five years. If this sum is greater than five years the SPC period will be the maximum five-year term. If a patent was applied for five years or less before the first marketing approval then subsequently the term of supplementary protection is zero years.⁴³

When the SPC Regulation was drafted, it was first proposed that an SPC should have the same scope as a patent, i.e. include all medicinal use of the active substance. The Commission, however, opposed this and the result were the narrower protection restricted to the fields of use for which the marketing authorisation has been granted. Hence, an SPC is not a formal extension of the patent term; it only protects the active substance for which a marketing authorisation has been granted.⁴⁴ Other ingredients described

⁴² Domeij, B., *Pharmaceutical Patents in Europe*, at page 271.

⁴³ For example: if a patent application for a compound X was filed on January 1, 1990 and the first marketing approval in the Community was granted on January 1, 2003 you take thirteen years minus five years. The sum from this is eight years, and accordingly, the SPC will provide five years of extra market exclusivity for compound X.

⁴⁴ Mazer, E., H., *Supplementary Protection Certificates in the European Economic Community*, in *Food and Drug Law Journal*, 1993, at 571.

and claimed in the patent are not protected once the patent has expired. Therefore, a certificate cannot be said to provide full patent rights.

The Salt-Problem

An important question, in this thesis referred to as the *salt-problem*, is if a certificate can be granted only for the specific chemical form mentioned in the marketing authorisation, or if the protection may be broader. Drugs are often administered in combination with different salts, but the choice of salts *seldom* affects the therapeutic properties of a drug. If the certificate should protect only the particular salt form of the active substance mentioned in the marketing authorisation, whereas the patent protects the active substance as well as salts thereof, any competitor would be able (after patent expiry) to apply for and obtain marketing authorisation for a different salt of the same active ingredient, earlier protected by that patent.⁴⁵

This was one of the issues in *Proprietary medicinal products*⁴⁶, where the ECJ ruled that SPC protection is not necessarily limited to the form of the product approved in the marketing authorisation. Instead, where a patent protects a drug in the form referred to in the marketing authorisation, the SPC may cover that product in any of the forms enjoying patent protection. The Court found this interpretation necessary to protect the rights of the patent holder. If the SPC protection was limited to the approved form of the drug, a third party might frustrate the goals of the SPC legislation by making essentially the same product merely by using a different salt form. This judgement settled the *salt-problem* in relation to the SPC legislation. However, as will be shown later, the problem remains in relation to generic drugs and is a somewhat controversial issue in the pharmaceutical industry.

Concluding Remarks

- *On average, the R&D process to come up with a new drug takes twelve to thirteen years and costs at least \$897 million.*
- *Patents are considered a prerequisite for a profitable business on behalf of positive return of investment in pharmaceutical R&D.*
- *The patent term in the EU is twenty years from the patent application date. A patent gives the patent holder an exclusive right to prevent other parties from **making, using, selling, and importing** or **stocking** the protected product for these purposes.*
- *Supplementary Protection Certificates confer an extended period of market exclusivity for innovative drugs. The maximum period of supplementary protection is five years.*

⁴⁵ Domeij, B., *Pharmaceutical Patents in Europe*, at page 274.

⁴⁶ Case C-392/97 *Bundesgerichtshof – Germany Proprietary medicinal products - Supplementary protection certificate* [1999] ECR I-05553.

· The maximum term of market exclusivity from patent- and SPC-protection is fifteen years starting from the first marketing authorisation in the Community.

3. Regulatory Exclusivity

Before a medicinal product may be placed on the market, the company responsible for the product must obtain a marketing authorisation. In this chapter, this regulatory procedure, both as concerns new drugs and generic products, will be described. Moreover, the institution of regulatory data protection, an intellectual property right deriving from this procedure, is introduced and explained to the reader. Each subsection starts with the current legislative situation in the Community, and thereafter the changes introduced by the 2001 Pharma Review are highlighted.

3.1. Marketing Authorisation

Pharmaceutical products may only be placed on the market when a marketing authorisation has been issued by the competent regulatory authority of a Member State for its own territory (national authorisation), or when an authorisation has been granted by the Commission for the entire Community (Community authorisation). The procedural provisions for making an application for a Community authorisation are set out in Regulation (EEC) 2309/93⁴⁷. However, as stated in the introductory part of this thesis, the different *procedures* to obtain marketing authorisation will not be scrutinised. The focus will be on Directive 2001/83/EC⁴⁸ (hereinafter referred to as the Medicinal Products Directive) and the *practical requirements* to obtain a marketing authorisation.

The same levels of quality, safety and efficacy must be demonstrated by all pharmaceutical products and in all Member States. To obtain a marketing authorisation for a new pharmaceutical product an applicant is required to submit a complete and independent application, in accordance with Article 8 of the Medicinal Products Directive. Under this provision, a number of particulars and documents, i.e. the results from pharmaceutical tests, pre-clinical and clinical trials, must be filed together with the application.⁴⁹ Furthermore, in some Member States, namely Belgium, Germany, Luxembourg, Spain, Ireland, Italy, the Netherlands, Portugal and Sweden, the applicant is obliged to enclose a physical sample of the drug to which

⁴⁷ Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, Official Journal L 214 , 24/08/1993 P. 0001 – 0021.

⁴⁸ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Official Journal L 311, 28/11/2001 P. 0067 – 0128.

⁴⁹ The particulars and documents that are to accompany an independent application are listed in Annex I. The provisions are a codification of Directive 2001/83 as amended by Directive 2004/27 (see below), in order to provide an up to date overview.

the application refers.⁵⁰ However, samples do not need to be submitted together with the application in all those Member States, in some countries it is enough that the applicant provides a sample at the request of the competent authority. In Sweden, a sample of the finished drug is always to be submitted before the competent authority finally grants the marketing authorisation.

3.2. Abridged Application for Marketing Authorisation

When a certain period (six or ten years, see regulatory data protection below) has elapsed since the first marketing authorisation for a new drug was granted, a generic manufacturer may submit a so-called abridged application for marketing authorisation. Under this procedure, the second applicant is not required to repeat the pre-clinical and clinical trials already performed by the originator. For information concerning the safety and efficacy of the copy product, the regulatory authority is referred to the data established in the first application. The generic company only needs to prove the copy product equal to the original drug. This is done by less complicated and less time-consuming so-called bioequivalence studies. When making an abridged application for marketing authorisation, the second applicant is enabled to save the time and expenses necessary in order to gather the pharmaceutical, pre-clinical and clinical data. It also avoids, on public policy grounds, the repetition of tests on humans or animals where it is not absolutely necessary. Just as in the case of complete and independent applications, a second applicant needs to provide a physical sample of the generic drug in some Member States. This is the case in Italy, Luxembourg, Spain, Sweden and Portugal, where physical samples of generic drugs must be supplied *at the same time* as the submission of the application.⁵¹

The abridged procedure is laid down in Article 10.1.a of the Medicinal Products Directive. To be able to benefit from this procedure, the second applicant must show:

- “(i) either that the generic product is essentially similar to a product authorised in the Member State concerned by the application and that the holder of the marketing authorisation for the original medicinal product has *consented* to the pharmacological, toxicological and/or clinical references contained in the file on the original medicinal product being used for the purpose of examining the application in question;
- ii) or that the constituent or constituents of the medicinal product have a well-established medicinal use, with recognized efficacy and an

⁵⁰ Notice to Applicants Volume 2A Procedures for marketing authorisation, Chapter 7, General Information, December 2004.

⁵¹ Notice to Applicants Volume 2A Procedures for marketing authorisation, Chapter 7, General Information, December 2004.

acceptable level of safety, by means of a detailed scientific *bibliography*;

- (iii) or that the medicinal product is *essentially similar* to a product which has been authorised within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made.

Although there is no official terminology, it is common to refer to applications under paragraph (i) as *informed consent applications*, applications under paragraph (ii) as *bibliographic applications*, and those under paragraph (iii) as *abridged applications*. In the case of informed consent applications, the market authorisation holder has approved to the use of the original dossier and accordingly those applications raise few significant legal issues. Therefore, they will not be discussed further, except to note that such applications can be submitted only after the application on which they are based has been approved. The bibliographic route has been intended only to be of limited application. According to Cook, it has been laid down that the period required for establishing a well-established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.⁵² The bibliographic procedure will not be highlighted in this inquiry. In practice, it has been the true abridged application route provided by paragraph (iii), based on the notion of essential similarity that has provided the basis for the majority of generic authorisations.⁵³ In certain respects the scope of this provision is not entirely clear, and this have given rise to differences in interpretation accentuating the research-based/generic divide and which have only relatively recently started to be addressed.⁵⁴ Therefore, below the focus will be on abridged applications, in an attempt to clarify the term *essentially similar* enshrined in paragraph 10.1.a (iii).

3.2.1. The Definition of Essentially Similar

The Medicinal Products Directive does not define the prerequisite of *essentially similar*. The concept was considered by the European Court of Justice in *Generics*.⁵⁵ In this case generic manufacturers sought to rely on the abridged procedure. The main issue of the questions asked by the national court was the precise criteria that a pharmaceutical product must meet in order to satisfy the prerequisite of being *essentially similar* to an original product, and thereby benefit from approval under the abridged

⁵² Cook, T. M., *Regulatory Data Protection of Medicinal Products in Europe*, in Bio Science Law Review, 2003, available at <http://pharmalicensing.com/features/disp/1046957520_3e674dd06906d>, last visited on 4 February 2005.

⁵³ *Ibid.*

⁵⁴ *Ibid.*

⁵⁵ C-368/96 *The Queen v The Licensing Auth. established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex parte Generics (UK) Ltd., the Wellcome Found. Ltd. and Glaxo Operations UK Ltd. and Others*, [1998] ECR I-7967.

procedure. In particular, the English court asked by reference to which physical or other characteristics of the medicinal product in question this should be determined. The ECJ concluded that:

“... a medicinal product is *essentially similar* to an original medicinal product where it satisfies the criteria of having the *same qualitative and quantitative composition in terms of active principles*, of having the *same pharmaceutical form* and of being *bioequivalent*, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards *safety or efficacy*.”⁵⁶

In essence, the notion of essential similarity consists of three aspects; the products need to have the same composition in terms of *active principles*, the same *pharmaceutical form* and to be *bioequivalent* to the original product. Below I will go through these prerequisites in mentioned order, to some extent addressing conceivable problems arising from the interpretations as made by the ECJ.

In *Generics*, the Court did not explain the concept of *active principles*. The question then is whether the term is limited to the active ingredient or whether it should also cover the specific salts and esters⁵⁷ used by the originator. Again, we are faced with a *salt-problem*. As noted above, drugs are often administered in combination with different salts, but the choice of salts seldom affects their therapeutic properties. However, the advantages of salts and esters may become apparent after a number of years, and they *may* have an influence of the safety and efficacy profile of a product.⁵⁸

According to my opinion, this is an important question as one might find safety risks involved. If a generic product containing a salt not included in the original product is deemed *essentially similar* to the original product under Article 10.1.a (iii), there might arise a safety problem several years after the assessment. For example, the combination of chemicals in the generic product may show to have unexpected side effects. When defining the concept of *essentially similar* the Court states that a generic product is *essentially similar* to an original product

“[...] unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards *safety or efficacy*”.⁵⁹

The wording of the judgement seems insufficiently precise since the primary purpose of any rules concerning medicinal products is said to be the safeguarding of public health. Therefore, the ECJ should have been interested in clarifying the matter to the utmost possible extent.

The term *pharmaceutical form* was not defined in the *Generics* case. This was done several years later in *Novartis*⁶⁰ where the ECJ, basing itself on a list of reference terms in the European Pharmacopoeia⁶¹, laid down that the

⁵⁶ Paragraph 36 of the *Generics* judgement.

⁵⁷ An ester is a chemical substance derived from an acid and alcohol.

⁵⁸ Campolini, M., *Protection of Innovative Medicinal Products and Registration of Generic Products in the European Union: Is the Borderline Shifting? State of Play and the Proposed European Medicine Legislation*, in E.I.P.R., 2003, 25(2), pages 91-97.

⁵⁹ Paragraph 36 of the *Generics* judgement.

“[...] *pharmaceutical form* is defined as the combination of the form in which a pharmaceutical product is presented by the manufacturer and the form in which it is administered, including the physical form.”⁶²

The products concerned in *Novartis*, SANDIMMUN, NEORAL and SANGCYA were all products presented in the form of a solution to be mixed in a drink for administration to the patient. When mixed, these three products formed a macroemulsion, a microemulsion and nanodispersion respectively. Those products are all a chemically stable mix from a fat and a water solution. The difference between the products is in essence the size of the fat particles, where the nanodispersion has the smallest particles. According to the ECJ, this fact could provide information as to the form of administration, but did not preclude their being treated as having the same pharmaceutical form. The Court concluded that for the purpose of determining the *pharmaceutical form* of a medicine under 10.1.a (iii) the three products were to be treated as having the same pharmaceutical form, if the differences in the form of administration were not *significant in scientific terms*. Again, the European Court of Justice leaves a question vaguely answered with the wording of *significant in scientific terms*, necessarily leading to assessments being made on a case-by-case basis by regulatory authorities and ultimately national courts in the Member States. However, the prerequisite of *pharmaceutical form* seems to be interpreted widely.

For the last prerequisite of *bioequivalence* to be fulfilled, a generic drug must contain the same amount of an identical active ingredient and have the same clinical effect on the body as the original drug when administered in equal doses under equal conditions. Bioequivalence is demonstrated by trials measuring the bioavailability of two formulations of the same active ingredient. The bioavailability of an active substance is the fraction absorbed (both speed and amount) by the body by a given dosage form (capsule, tablet, injectable etc).⁶³ The purpose of a bioequivalence study is to show that the bioavailability of the formulations under investigation is equal. Based on that conclusion, one may subsequently claim that the therapeutic quality of the formulations at hand is identical. The latter means that both the beneficial and side effects are identical and hence the formulations are truly interchangeable. In *Novartis*, the ECJ expressly laid down that products cannot be regarded as *essentially similar* for the purposes of the application of Article 10.1.a (iii) where they are not *bioequivalent*. Due to the scientific exactness included in the concept, the

⁶⁰ C-106/01 *Novartis Pharmaceuticals UK Ltd v The Licensing Authority established by the Medicines Act 1968* [2004] ECR 00000.

⁶¹ As had earlier been suggested by Advocate General Ruiz-Jarabo Colomer in his opinion in *Generics*.

⁶² Paragraph 37 of the *Novartis* judgement.

⁶³ If a substance is injected directly in a vein, the bioavailability is 100%. If given in the form of a tablet, the bioavailability may be everything from 0% to 100%, depending on factors such as the chemical characteristic of the product, the influence of additives (i.e. talcum, magnesium oxide) and how the tablet in question is manufactured.

prerequisite of bioequivalence is clear and comprehensive, not generating any crucial considerations.

3.3. The New Rules Concerning Abridged Applications

Below the focus will be on Directive 2004/27,⁶⁴ (hereinafter referred to as the Amendment Directive) amending the Medicinal Products Directive. The latest date of implementation of this Directive in the Member States is 30 October 2005. References will also be made to the interpretation of the legislation as made by the Commission in the 2004 Notice to Applicants (NTA).⁶⁵ This document is not legally binding but is supposed to give guidance, taking into account the various developments at the ECJ level.

The new pharmaceutical legislation does not significantly alter the rules concerning the practical requirements for abridged applications. However, two new concepts concerning the abridged procedure are introduced. To benefit from the abridged procedure under the new legislation a generic product has to be identical to a *reference medicinal product*. In the earlier wording of Article 10.1.a (iii) of the Medicinal Products Directive, a generic product had to be *essentially similar* to:

“[a] medicinal product which has been authorised within the Community, in accordance with Community provisions in force [...]”

In for instance the *Generics case*, the ECJ translated this provision, and used the notion of *original medicinal product*. In the new text, the concept is clarified, and according to Article 10.2 (a) of the Amendment Directive, a *reference medicinal product* is a medicinal product developed by an innovator and authorised by the means of a full and independent marketing authorisation application. Thus, this means that the concept of *original medicinal product* is abandoned and replaced by the notion of *reference medicinal product*. This change is no direct legal importance; nevertheless, the definition is plain and comprehensive, which must be appreciated.

The other concept introduced by the Amendment Directive is the notion of *generic medicinal product*. This was done to clarify the requirements a copy product needs to meet in order to benefit from the abridged procedure. As noted in the aforementioned paragraph, according to the earlier wording of the Medicinal Products Directive, a generic product was required to be *essentially similar* to an original product. This expression was vague. Following interpretation by the ECJ, three conditions were recognised for the prerequisite of *essentially similar* to be met. In the new legislation, the concept of essentially similarity is exchanged for the notion of *generic medicinal product*.

⁶⁴Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, Official Journal L 136 , 30/04/2004 P. 0034 – 0057.

⁶⁵ Notice to Applicants Volume 2A Procedures for marketing authorisation, Chapter 1, Marketing Authorisation, February 2004.

In Article 10.2 (b) of the Amendment Directive, a *generic medicinal product* is formally defined as:

“[...]a medicinal product which has the same qualitative and quantitative composition in *active substances* and the same *pharmaceutical form* as the reference medicinal product, and whose *bioequivalence* with the *reference medicinal product* has been demonstrated by appropriate bioavailability studies.”

This definition replaces the existing concept of essential similarity but builds, as is clearly seen, on the existing interpretation of that concept from the judgement in *Generics*, updated in *Novartis*. Hence, in order to benefit from the abridged procedure, a generic product still will need to have the same qualitative and quantitative composition in terms of *active substances*, the same *pharmaceutical form* and to be *bioequivalent* to the innovative medicinal product in question. However, in the new Directive, two of the requirements are somewhat clarified, namely the concepts of *pharmaceutical form* and *active principles*.

According to Article 10.2 (b) of the Amendment Directive:

“The various immediate-release oral *pharmaceutical forms* shall be considered the same pharmaceutical form.”

This wording follows the interpretation made by the ECJ in *Novartis*, where the term was extensively interpreted. Furthermore, it is in accordance with the Commission’s interpretation of the concept as provided for in the 2004 Notice to Applicants, where the Commission states that the term must be understood broadly. Clearly, this means that various immediate-release oral forms are regarded as the same pharmaceutical form, and therefore generic drugs might be presented in a different immediate-release oral form compared to the reference product and still benefit from approval under the abridged procedure. However, from this it is not evident how to interpret the concept of immediate-release pharmaceutical form. As a main rule the concept refers to a formulation that dissolves immediately in the mouth, e.g. nitro-glycerine used to treat heart pain that is absorbed through the gums within about fifteen seconds. Nevertheless, sometimes the concept can be used to describe formulations where “gravel” from the drug falls down in the throat, giving an effect after approximately one minute. Therefore, the assessment whether two products have the same pharmaceutical form will have to be made by competent authorities on a case-by-case basis. It is likely that these assessments will be the subject of controversy in many cases, as an originator is most likely to argue that a copy product does not fulfil the requirements to be of the *same pharmaceutical form* as the original drug.

The term of *active principles* is spelled out and defined in Article 10.2 (b), where it is constituted that:

“The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same *active substance*, unless they differ significantly in properties with regard to safety and/or efficacy.”

Here it is of interest to note the changed wording, from active *principles* to active *substances*. According to Campolini, the term *substance* is more exact than that of *principle*.⁶⁶ However, in the 2004 NTA, the concepts of *active principle* and *active substance* are assimilated. The Commission states that in the context of Article 10.1.a (iii) the concept of same qualitative and quantitative composition of active principles must be understood broadly, and that the notion covers all products containing the same active substance and having the same properties with regard to safety and efficacy. Thus, the altered wording in itself does not entail any actual change. However, the fact that it is clearly expressed that different salts are to be regarded as the same active substance implies that the *salt-problem* is still inherent in the term *generic medicinal product*, and this might be a problem as concerns the safety of drugs approved under the abridged procedure.

To summarise the introduced changes related to the practical requirements under the abridged procedure, it is my opinion that the Amendment Directive cannot be said to entail any radical change to the requirements, but rather to establish the case law as laid down by the ECJ.

⁶⁶Campolini, M., *Protection of Innovative Medicinal Products and Registration of Generic Products in the European Union: Is the Borderline Shifting? State of Play and the Proposed European Medicine Legislation*, in E.I.P.R., 2003, 25(2), pages 91-97.

3.4. Regulatory Data Protection

Regulatory data protection is the intellectual property right granted to data submitted by a first applicant (i.e. data relating to an original drug) for revision by a regulatory authority granting marketing authorisations. As noted above, the data required in a full and independent application consists of a number of particulars and documents, i.e. the results from pharmaceutical tests, pre-clinical and clinical trials.⁶⁷ It is those results and the connected documents that are covered by the protection. Regulatory data protection (sometimes referred to as data exclusivity) means that during a period of six or ten years, starting from the first marketing approval in the EU, a regulatory authority cannot assess (and therefore cannot approve) an abridged application. It is not until the expiry of the data protection that authorities are allowed to refer to the information in the original dossier when assessing an abridged application.

As it is in general uneconomic for manufacturers of generics to generate their own independent data, the regulatory data protection effectively confers a *de facto* right in respect of a particular drug in favour of the first applicant.⁶⁸ Therefore, generic companies duplicate tests and clinical trials only under exceptional circumstances, as in the case when a generic company decides to make a specific development. In the vast majority of cases, generic producers simply await the expiry of the data protection period and then submit an abridged application in order to reduce their costs of copying.⁶⁹

Apart from patent protection, the protection of regulatory data is the most relevant form of intellectual property right for the pharmaceutical industry. In normal circumstances, where patent/SPC protection is effective, data protection does not play a role in protecting an innovative product from copy. As noted in the previous chapter, patents combined with SPC will provide for up to fifteen years of exclusivity from the first marketing authorisation in the Community, whereas the data protection period is currently limited to a maximum of ten years. For the innovative industry, regulatory data protection is nonetheless needed in a limited but important number of cases. These cases relate to circumstances where the effective length of patent/SPC protection is reduced owing to an exceptionally long development time or where the patent has been declared invalid.⁷⁰ Furthermore, in some cases, there may be no patent protection, or the patent protection may be weak. Ordinarily, that does not affect the position under regulatory data protection, which may therefore provide the sole effective

⁶⁷ The particulars and documents that are to accompany an independent application are listed in Annex I. The provisions are a codification of Directive 2001/83 as amended by Directive 2004/27 (see below), in order to provide an up to date overview.

⁶⁸ Cook, T., M., *The Protection of Regulatory Data in the Pharmaceutical and Other Sectors*, London, Sweet & Maxwell, 2000, page 2.

⁶⁹ Campolini, M., *Protection of Innovative Medicinal Products and Registration of Generic Products in the European Union: Is the Borderline Shifting? State of Play and the Proposed European Medicine Legislation*, in E.I.P.R., 2003, 25(2), pages 91-97.

⁷⁰ *Ibid.*

protection for the compound or for its use, enabling partial recovery of the research investment for the innovator.⁷¹

Again, we are faced with an intellectual property right that is limited in time. Generic competitors are not able to enter the market with their lower-priced copy products until the expiry of the regulatory data protection. To be more precise, generic competitors are not able to get their lower-priced copy products *approved* before the expiry of the data protection, and thus they are not able to enter the market. Repeatedly in this thesis, the time aspect arises that, with the considerable amounts of money involved, is of utmost importance in the area of pharmaceuticals.

3.4.1. Regulatory Data Protection under the TRIPs Agreement

At the time when TRIPs was under negotiation, there was considerable variation internationally in the protection awarded to regulatory data. As a result, the TRIPs Agreement leaves much unsaid, leaving much latitude for variations in its national implementation. However, Article 39.3 of the TRIPs Agreement, together with Article 39.1, sets certain minimum standards for the protection of regulatory data. It requires WTO members to protect test and clinical trial data submitted to regulatory authorities when applying for marketing authorisation against *unfair commercial use*. The term *unfair commercial use* sets the parameters for deciding when, and under what circumstances reliance by generic companies is fair or unfair. The term is not defined in the text, but the negotiating history of Article 39.3 clearly indicates that this concept means that the originator's data cannot be relied upon for the benefit of a generic competitor during the protection period.⁷² It seems to be generally accepted that the principal unfair commercial use of data occurs when one party uses the data of another party in order to obtain a marketing approval during the protection term. Such use is unfair because it allows the second party to take advantage of the investment of another. There is no minimum requirement in Article 39.3 as for how long regulatory data has to be protected.

3.4.2. Regulatory Data Protection in the EU

Since 1987, Community legislation has provided protection for the data filed in support of marketing authorisations for pharmaceuticals, and the regulatory data protection is currently enshrined in Article 10.1.a. (iii) of the Medicinal Products Directive. According to this provision, the period of data protection shall be six or ten years from the marketing authorisation application date. Ten years of protection is obligatory for so-called high

⁷¹Cook, T., M., *The Protection of Regulatory Data in the Pharmaceutical and Other Sectors*, at page 27.

⁷² "Position Paper, TRIPs Article 39.3 (Protection of Undisclosed Data), A Critical Issue for the Continued Development of Safe and Innovative Medicines for Patients", November 2000, available at <<http://www.efpia.org/4%5Fpos/legal/trips%2D39%2D3.pdf>>, last visited on 4 February 2005.

technology products (most biotechnology products) and for products authorised by the centralised procedure (e.g. new chemical entities). Member States however have the option of applying a ten-year period to all medicinal products and all the major European markets, namely France, Germany, Italy and the United Kingdom have chosen to do so.⁷³ The Member States who have opted for a six-year protection are currently at liberty not to apply this six-year period beyond the expiry of a patent protecting the drug. This means that a Member State allowing for a six-year data protection may have a rule stating that when the patent expires for a certain product, automatically the regulatory data protection ceases as well. The Member State in question thereby *links* the regulatory data protection to the patent status of the drug. This may have the result that if there is no patent protection available for a certain product, there is no possibility to benefit from regulatory data protection either. As noted above, it is in cases where patent protection is lacking, for whatever reason, that data protection is most valuable to the inventor. Therefore, this option is somewhat absurd. Moreover, as noted by Campolini, the compatibility of this option with TRIPs Article 39.3 is certainly debatable.⁷⁴ As noted above, the TRIPs Agreement requires member states to protect test and clinical trial data submitted to regulatory authorities when applying for marketing authorisation. If a country uses the policy of *patent linkage*, it cannot be said to fulfil this requirement, since in the absence of patent protection for a certain drug the product does not stand a chance to benefit from regulatory data protection.

3.5. The New Rules - A Harmonised Period of Regulatory Data Protection

One of the major revisions in the 2001 Pharma review is contained in Article 10.1 of the Amendment Directive, providing for a harmonised data protection period in compliance with the new so-called “8+2+1 formula”.⁷⁵ According to the new rules, original drugs will be entitled to eight years of *data exclusivity* and two years of *marketing exclusivity*. During the latter two years, generic companies will be allowed to engage in certain testing activities and to apply for marketing authorisation under the abridged procedure (see below about the Bolar provision). Abridged applications for

⁷³ Currently Belgium, France, Germany, Italy, Luxembourg, Netherlands, Sweden and the UK apply ten-year protection for all medicinal products, whereas Austria, Denmark, Finland, Ireland, Greece, Portugal and Spain apply six-year protection for medicinal products, other than those authorised through the centralised procedure for which ten-year protection applies. The data protection in the new Member States is uniformly six years.

⁷⁴ Campolini, M., *Protection of Innovative Medicinal Products and Registration of Generic Products in the European Union: Is the Borderline Shifting? State of Play and the Proposed European Medicine Legislation*, in E.I.P.R., 2003, 25(2), pages 91-97.

⁷⁵ For medicinal products authorised under the centralised procedure according to Regulation 2309/93, the same formula will be valid through Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Official Journal L 136, 30/04/2004 P. 0001 – 0033.

marketing authorisation can be filed, and approved, after eight years from the first approval of the reference product in the Community.

In the former “six-year” countries, originators will obtain a *de facto* increase of *data exclusivity* of two years, and an increase in *market exclusivity* of approximately two years, where an extra year of protection under the “+1” provision is not granted.⁷⁶

In the former “ten-year” countries, originators will lose two years of *data exclusivity*, and thereby approximately two years of *market exclusivity*, in cases where an extra year is not granted. If one additional year has been obtained under the “+1” provision, consequently only one year of market exclusivity will be lost.

The “+1” provision in the “8+2+1 formula” is a means for a product still under its data exclusivity period to get one extra year of protection. This extra year of protection will be granted, firstly, to data from trials supporting an approval for a *new indication* of a well-established substance, and secondly, when there are data from trials supporting the *switch* of a drug from Prescription-Only to over the Over-the-Counter status.

The first scenario under the “+1” provision, as noted in the aforementioned paragraph, is when there are clinical studies supporting approval of new indications for well-established substances. Such developments are often made by research-based companies, trying to extend the life cycle of a certain established product. When getting an approval for a new therapeutic indication, the original product is generally well established on the market, with a well-known brand name. Thus, an extra year of market exclusivity is an easy way to maximise the sales profits from a certain product for the originating company.

According to the fourth subparagraph of Article 10.1, one extra year will be granted:

“If during the first eight years from the original marketing authorisation, the marketing authorisation holder obtains an authorisation for one or more *new therapeutic indications* that, during the scientific evaluation prior to their authorisation, are held to bring a *significant clinical benefit* in comparison with existing therapies.”

To give an intelligible picture; All medicinal products are approved for a certain field of use, e.g. high blood pressure, depression, ingrown toenails etc. The *therapeutic indication* is the approved way of using a product. Let us assume that a product has been approved as a medicine to lower the blood pressure. The originator then conducts further research on the medicine, and documents an effect for treating migraine. If this new therapeutic indication is approved for marketing by a competent authority, accordingly one extra year of protection is granted. Unfortunately, there is no comprehensible explanation as to what the subordinate clause “are held to bring *significant clinical benefits* in comparison with existing therapies”

⁷⁶ When the time for completion of administrative procedures of marketing authorisation and pricing and reimbursement is appreciated to two years.

are meant to imply for the assessment. One might assume that a predictable new therapeutic indication, such as a headache medicine's effect for treating migraine, will not benefit from an extra year. Consequently, the question whether a certain new indication is held to bring a significant clinical benefit will have to be assessed by the competent authorities granting marketing authorisations on a case-by-case basis.

The second scenario under the “+1” provision is for so-called *switch data*, e.g. clinical or pre-clinical data supporting the change of a medicinal product from Prescription-Only to over the Over-the-Counter status. This case is clear-cut, since the change will have to be approved by a competent authority and there are existing rules constituting when such a change shall be approved.⁷⁷ Switching a product to OTC status is another way to maximise the profits deriving from a certain drug before market exclusivity ends, with the result of large rewards for the originator. This extra year of protection cannot be renewed in any of the two scenarios.

Importantly, the “8+2+1 formula” is not retroactive; the effect of the new data protection period will be limited to pharmaceutical products approved after the new pharmaceutical legislation becomes operational in 2005 and will therefore only affect abridged applications from 2014 at the earliest.

The harmonisation of the data protection period throughout the Community means that all new Member States, and about half of the old ones, will have to lengthen their data protection period from six to ten years. Furthermore, the option of linking the regulatory data protection to the patent status of a certain product is removed. This means that data protection will be available to all new drugs approved for marketing authorisation, and that even though a certain drug is not patent protected, it will be able to benefit from regulatory data protection. The harmonised, and in several Member States increased, period of data protection, evidently favours the research-based pharmaceutical companies, and thus can be said to promote innovation.

However, under the new rules, abridged applications for marketing authorisation can be filed, and approved, after eight years from the first approval of the reference product in the Community, and generic products can be marketed after ten or eleven years respectively. This brings about an important change, since under the current legislative situation, generic competitors must wait until the expiry of the data protection period to get an abridged application assessed. As noted earlier, the administrative procedures requires between two and three years. With the new legislation, generic manufacturers will thus be able to launch their products as soon as the data protection expires (unless, of course, there is still a valid patent).

⁷⁷ A Guideline on changing the classification for the supply of a medicinal product for human use, European Commission, September 29, 1998, available at <<http://pharmacos.eudra.org/F2/eudralex/vol-2/C/g1981003.pdf>>, last visited on 4 February 2005.

Concluding Remarks

- *All medicinal products must obtain a marketing authorisation before they may be commercially launched.*
- *For generic pharmaceutical products, there is a simplified procedure to obtain marketing authorisation, the abridged procedure. On the whole, the practical requirements for this procedure will be unchanged by the 2001 Pharma Review.*
- *The data concerning innovative products submitted to regulatory authorities for review enjoys a separate form of IPR, namely regulatory data protection. Currently, during the period of regulatory data protection, (six or ten years) abridged applications for marketing authorisation cannot be assessed or approved.*
- *Under the new pharmaceutical legislation, the period of data protection will be harmonised in accordance with the “8+2+1” formula. Abridged applications may be submitted and approved after eight years. This is in favour of the research-based industry and thereby pharmaceutical R&D.*

4. Limitations on Patent Exclusivity – Experimental Use Exceptions

All national patent laws contain exceptions to patent rights, with the content and scope of those exceptions varying widely. All European patent laws have a specific provision providing that so-called "experimental use" is not to be regarded as patent infringement. Those rules are of immense interest to producers of generic drugs, since they affect the possibility to conduct pre-patent-development work. This chapter aims at providing an overview over the scope of experimental use exceptions in the Member States, thereby clarifying what preparations a generic competitor currently can undertake before patent expiry.

4.1. The Experimental Use Exception

The patent system is intended to promote innovation and technical progress, and this being so, the obstruction of experiments would be counter-productive. Until very recently, pre-patent-expiry development work was not regulated at EU level and the various Member States have treated the issue in a diverse manner. Generally, patent laws recognise an exemption to the exclusive rights of the patent holder and allow non-consensual use of patented inventions for experimental or research purposes. This is referred to as the *experimental use exception*. In Europe, the experimental use exception arises from the draft Community Patent Convention (CPC)⁷⁸ from 1989, which although reflected in the national laws of most Member States, never formally has become European law. Article 27 of the CPC provides:

“The rights conferred by a Community patent shall not extend to:
[...] (b) acts done for *experimental purposes* relating to the *subject-matter* of the patented invention ...”

This provision has been incorporated into Article 9 of the Proposed Regulation on Community patent.⁷⁹ Most national European patent laws include an express exemption from patent infringement for experimental purposes relating to the subject matter of a patented invention. Currently, however, no harmonisation on Community level is operational, and therefore under the present legislative situation, it is entirely up to national legislation what is and what is not to be regarded as experimental use.

⁷⁸ 89/695/EEC: Agreement relating to Community patents - Done at Luxembourg on 15 December 1989, Official Journal L 401, 30/12/1989 p. 0001 - 0027.

⁷⁹ Proposal for a Council Regulation on the Community Patent - revised text (June 2003), <<http://register.consilium.eu.int/pdf/en/03/st10/st10404en03.pdf>>, 2004-12-05.

The experimental use exception has become of increasing importance in the pharmaceutical industry, partly due to the exacting demands that drugs, both original and generic, need to meet before a marketing authorisation is granted. This situation has led to a growing interest on the part of generic manufacturers to carry out necessary tests before patent expiry of the original drug. Necessary tests to benefit from the abridged procedure are, as noted earlier, bioequivalence studies. Producers of generic pharmaceuticals do not have a significant interest to conduct a complete R&D process; they only wish to perform bioequivalence studies during the patent term of the original product. If bioequivalence studies may be conducted during the patent term, the generic drug will not need to go through the administrative procedure to obtain a marketing authorisation after patent expiry. Thus, if pre-patent-development work can be conducted, generic manufacturers have the prospect to put their products on the market immediately upon patent expiry, (unless there is still patent protection for the original drug) saving between two and three years.

4.2. The TRIPs Agreement and Exceptions to Patent Rights

The TRIPs Agreement does not provide much guidance as to what exceptions to patent rights WTO member states should provide for in their national legislation. Article 30 of the TRIPs Agreement deals with the subject in very general terms, stating:

”Members may provide *limited* exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a *normal exploitation* of the patent and do not unreasonably prejudice the *legitimate* interests of the patent owner, taking account of the legitimate interests of third parties.”

The vague wording of Article 30 indicates how difficult it was for the negotiating parties to agree on the nature and extent of exceptions to patent rights. The provision leaves the WTO member states with considerable freedom to define the nature and extent of exceptions to the exclusive rights of a patent holder. Consequently, the WTO member states have not been able to harmonise the exceptions to patent rights under Article 30 which has led to divergent approaches and differing standards firstly, in state and regional instruments and secondly, in their interpretation by courts.

4.3. Preparations under the Experimental Use Exception in the EU

It has been stated that patent protection and regulatory data protection are the most important forms of intellectual property rights for pharmaceuticals. I have also mentioned that the two forms of protection will be separate from each other under the new pharmaceutical rules, since Article 10.1.a. (iii) is not linked to the patent status of the original product. In the EU, once the

period of data protection has expired, regulatory authorities will approve abridged applications for products with valid, unexpired patents. Hence, regulatory authorities do not take notice of patent rights; they deal exclusively with market authorisations and therefore regulatory data protection. However, conducting certain tests and acts needed in order to apply for a marketing authorisation might infringe the patent for the original product. In that case, the patent holder might intervene and claim that the generic manufacturer is guilty of patent infringement. Below, possible scenarios occurring in the normal preparation process for generic competitors will be observed and discussed; with an aim to appraise at what stage the preparations actually infringe the patent protecting the original drug.

4.3.1. Filing an Application For Marketing Authorisation

In most Member States, when filing an application for marketing authorisation, a generic manufacturer does not need to supply a sample of the drug. In those countries, subsequently the only particulars provided to the regulatory authority are documents - papers. It is an established rule that the *paper actions* implied by an application for marketing authorisation shall not be deemed to constitute patent infringement, e.g. offering for sale. This rule has been established by the Stockholm court of First Instance⁸⁰, and the same conclusion has been reached in English law.⁸¹ According to Cook, in no European country have *paper acts* been deemed to constitute infringement of a pharmaceutical patent.⁸² As earlier noted, a patent confers the rights on the patent holder to prevent others from *making, using, selling, or importing or stocking* the protected product for these purposes. An application cannot be a *use* of an invention, because an application for marketing authorisation does not contain the essential technical features of the invention as disclosed in the patent application. In the Member States that do require a sample of the drug along with the application, the situation is divergent. This will be discussed below. An application cannot be regarded as an *offer for sale* either, since there is no intention of inducing the regulatory authority to acquire physical copies of the medicinal product. Furthermore the requirement of marketing authorisation is statutory not voluntary.⁸³

In summary, as long as generic products are not being presented physically to an authority, an application for marketing authorisation can be supplied without being regarded as infringing the original patent.

⁸⁰ Stockholm City Court T 7-536-93 and T-7-737-94 of 15 June 1995.

⁸¹ *The Upjohn Company v T. Kerfoot & Co. Ltd*, Patents Court, [1998] FSR 1.

⁸² Domeij, B., *Pharmaceutical Patents in Europe*, at page 293 where he refers to Cook, T. M., Patent World February 1997, 38.

⁸³ *Ibid*, at pages 293-294.

4.3.2. Submission of Samples to a Regulatory Authority

In some Member States⁸⁴, namely Italy, Luxembourg, Spain, Sweden and Portugal, an applicant under the abridged procedure is required to enclose a physical specimen of the drug to which the application refers.⁸⁵ Thus, the submission of samples is not mandatory throughout the EU; this paragraph is only relevant to the abovementioned Member States.

When applying for a marketing authorisation in the countries referred to, the generic manufacturer consequently has to *make* a product, identical to the original one. The consensus view is that the submission of samples is a critical factor that creates patent infringement when the normal preparations are being made for the commercial market launch of a generic product.⁸⁶ This was laid down by the Stockholm court of First Instance, in the same cases referred to in the aforementioned paragraph.⁸⁷ The question has been touched upon, but not directly adjudicated, by the ECJ. In *Generics BV v Smith Kline & French Laboratories Ltd.*⁸⁸, the Court however ruled that it was not contrary to Community law for rules of national patent law to forbid other parties than the patent holder, during the term of a patent, to submit specimens of a patented drug to a regulatory authority.

Therefore, in a country requiring samples as part of an application, generic competitors must put off applying for marketing authorisation until the patent for the original drug has expired not to risk conducting patent infringement.

4.3.3. Conducting Bioequivalence Studies

Generally, most generic competitors wait until the data protection period has expired, and then applies for a marketing authorisation under the abridged procedure. Producers of generic pharmaceuticals do not have a significant interest in conducting a complete R&D process; this is far too expensive and time-consuming. The model in the generics industry is straightforward, to obtain an approval for a copy product under the abridged procedure by using a minimum of time and money. Therefore, it is clear that manufacturers of generic drugs only wish to perform bioequivalence studies during the patent term of the original product.

Most of the case law concerned with the experimental use exception has been developed in the pharmaceutical area. The principal question in these cases has been whether during the period of patent protection, clinical testing involving a patented product may be conducted without the consent of the patent holder. Where a substance is protected as a medicine for a

⁸⁴ See paragraph 3.2.

⁸⁵ Domeij, B., *Pharmaceutical Patents in Europe*, at page 294.

⁸⁶ *Ibid.*, at page 294 where he refers to Cook, T. M., *Patent World* February 1997, 38.

⁸⁷ Stockholm City Court T 7-536-93 and T-7-737-94 of 15 June 1995.

⁸⁸ Case C 316/95 *Generics BV v Smith Kline & French Laboratories Ltd.* [1997] ECR I-03929.

certain indication, one might divide the tests that can occur during the patent term into two different characters. The first type is tests with the aim of finding new indications for substances that have been patented only for one indication. Research based companies wish to carry out experiments in order to find new indications for patented substances. Hence, these tests are aimed at obtaining new *patents*. The second type of tests is studies done by generic competitors wishing to obtain an abridged marketing authorisation during the term of patent protection.⁸⁹ Only the latter situation concerns generic competition and will be discussed below.

The UK

One common denominator for the European case law seems to be that experiments aimed at providing information *about* a patented invention comes under the experimental use exception, whereas experiments conducted solely with the view to obtain regulatory approval are considered acts of infringement. This was established in the UK in *Monsanto Co v Stauffer* from 1985.⁹⁰ In this judgement, it was laid down that trials carried out to discover something unknown or to test a hypothesis, or to find out whether something that is known to work in specific conditions will work in different conditions, was regarded as falling within the scope of the experimental use exception. Trials carried out in order to demonstrate to a third party (e.g. a regulatory body) that a product works as its maker claims were however *not* regarded as acts done for experimental purposes, hence falling outside the exception.

The Netherlands

The interpretation made by Dutch courts seems to be equal to that in the UK. In *SmithKline and French Laboratories v Generics BV*⁹¹, the Dutch Supreme Court held that the importation and manufacture of a patented pharmaceutical and the conduct of clinical trials with such product for the purposes of obtaining regulatory approval must be considered as patent infringement.⁹²

Germany

While the UK and the Netherlands can be said to represent a middle course regarding the construction of the experimental use exception, the German interpretation is the most extensive and liberal in the Community. The landmark cases in German case law are *Clinical Trials I* and *Clinical Trials*

⁸⁹ “Patenting and the Research Exemption”, available at <http://www.ipr-helpdesk.org/documentos/docsPublicacion/pdf_xml/8_BP-Patenting-and-the-Research-Exemptio%5B0000003268_00%5D.pdf>, last visited on 4 February 2005.

⁹⁰ *Monsanto Co. v. Stauffer Chem. Co. & Another*, 1985 RPC 515 (Court. of App. - Civ. Div. 1985).

⁹¹ *SmithKline and French Laboratories v Generics BV* (1997) Dutch Supreme Court, September 29, 1997, BIE 1997/21.

⁹² L'Ecluse, P., Longeval, C., *The Bolar Clause in the New European Pharmaceutical Regulatory Package*, available at <<http://global.practicallaw.com/jsp/article.jsp?item=:5405699&tab=1>>, last visited on 4 February 2005.

II from 1995 and 1997 respectively.⁹³ In *Clinical Trials I*, the German Supreme court established that trials conducted with the aim of obtaining regulatory approval, but also with the aim of obtaining information about new indications of a patented active ingredient, were permitted under the experimental use exemption. According to this judgement, a collateral commercial purpose does not prevent experiments from being non-infringing. In the second decision, clinical tests were conducted with the aim of determining whether the generic product in question differed in a clinically relevant manner from the original product. The trials at hand served the purpose of obtaining the necessary data for regulatory approval. Again, the German Supreme court went for an extensive interpretation and stated that the clinical trials at issue did not constitute patent infringement because they had resulted in information about the patented ingredient's effectiveness. The court recalled that the only statutory requirement is that the tests are intended to yield knowledge about the subject matter of the patented invention, regardless of a possible commercial objective. In German law, as a result of those judgements, the crucial consideration is not whether the experiments are performed commercially but whether they amount, at least in part, to search for new knowledge. Clinical research with a patented pharmaceutical product is permissible as long as it takes place on a planned basis and for the purpose of gaining insights serving to dismiss uncertainties regarding the therapeutic effects or toxicity of substances. The fact of the experiments also being intended to serve as the basis for the grant of marketing authorisation does not prevent them from being permissible with reference to the experiment exception.

France

France seems to embrace the position of German case law. In *Wellcome v Parexel International and Flamel Technologies*⁹⁴, clinical trials carried out by Flamel were intended to compare different modes of administration of a patented product and find effective dosing regimes. In the opinion of the Paris District Court, it could not be argued that the trials were not performed for experimental purposes relating to the subject matter of the invention, notwithstanding the aim of further commercialisation. Furthermore, in *AJC Pharma Expanpharm v Servier*⁹⁵, the Paris Tribunal de Grande Instance ruled that bioequivalence trials are intrinsically linked to the registration process and to the generic approval for the purpose of which they were performed, and as such, they constitute acts of experimental use.⁹⁶

Sweden

The Swedish experimental use exception is contained in the Swedish Patents Act, section 3, which provides that non-commercial experiments related to the subject matter of a patented invention is lawful. If the

⁹³ *Clinical trials I*, Federal Supreme Court, July 11, 1995, RPC 1997, 623. *Clinical Trials II*, Federal Supreme Court, April 17, 1997, RPC 1998, 424.

⁹⁴ *Wellcome v Parexel International and Flamel Technologies* Paris District Court 6 March 1998.

⁹⁵ *AJC Pharma Expanpharm v Servier* TGI Paris, 12 October 2001.

⁹⁶ L'Ecluse, P., Longeval, C., *The Bolar Clause in the New European Pharmaceutical Regulatory Package*.

experiments are performed solely to comply with regulatory requirements of the drug administration or other regulatory requirements, the exemption does not apply and the acts are regarded as patent infringement. However, it should be noted that no case concerning the interpretation of the experiment exception has been adjudicated by any Swedish court and, therefore, there is no established national practice.⁹⁷

From the above the conclusion might be drawn that, generally, experimental use exceptions are aimed at enabling scientific research pending patent validity, and not at enabling acts having a commercial or regulatory purpose. Generally, under the current legal status in the Community, bioequivalence studies cannot be said to fall within the scope of the experimental use exception in the majority of the Member States. According to the German and French extensive interpretations, a collateral purpose can be deemed permitted, and bioequivalence trials can therefore be seen as non-infringing acts. However, this position is very liberal, and cannot be said to represent a consensus view.

Tests conducted with the aim of demonstrating that a generic drug is bioequivalent to a patented pharmaceutical are obviously inspired by a regulatory purpose – to be able to get a copy product approved under the abridged procedure while the original product is still traded under patent protection. If this is possible, a generic drug can be commercially launched immediately upon patent expiry. This is crucial, since two extra years of marketing can generate large sales profits for the generic company. Those profits will otherwise accrue to the company marketing the original drug. When a generic competitor performs bioequivalence studies, with clearly commercial intentions, those acts cannot be regarded as intended to search for new knowledge about the patented pharmaceutical. In most countries, bioequivalence studies do not come under the experimental use exception, since their finality is too remote from the reasons that induced the legislator to adopt an exception to the principle of patent infringement.⁹⁸ For bioequivalence studies conducted during the patent term without the consent of the patent holder to be lawful, there is obviously a need for special provisions. The issue of “pro-generic statutory provisions” (so-called Bolar provisions) will be explained and discussed in the forthcoming chapter, along with the WTO Panel decision in *EC v. Canada*, which concerned this type of exceptions.

⁹⁷ Jaenichen, H.R., Stolzenburg, F., *Patent Infringement by Clinical Trials in EPC Contracting States?*, available at <<http://www.vossiusandpartner.com/eng/publication/pub-epc.html>>, last visited on 4 February 2005.

⁹⁸ Véron, P., *Experimental use exemption for clinical trials: Europe vs. North America*, 12 December 2002, available at <<http://www.italy.les-europe.org/docs/veron.pdf>>, last visited on 4 February 2005.

Concluding Remarks

- *There are exceptions to the exclusive rights of a patent holder. So-called experimental use is not to be regarded as patent infringement.*
- *Currently, no harmonisation on Community level as regards experimental use is in force; the interpretation is nationally limited. This results in a legal uncertainty within the EU as to what pre-patent-development work is to be regarded as permissible.*
- *“Paper acts” have not been deemed to constitute patent infringement.*
- *Submission of samples to competent authorities is the critical factor that creates patent infringement when the normal preparations are being made for the commercial market launch of a generic product*
- *Generally, bioequivalence studies do not fall within the scope of experimental use exceptions, since these studies have a purely commercial or regulatory purpose, and thus cannot be said to search for new knowledge about the patented product.*

5. Limitations on Patent Exclusivity – Bolar Type Provisions

In the foregoing chapter, the concept of experimental use exceptions, as developed by different national case law, has been discussed. However, some legislative systems have clarified the issue of pre-patent-development work on behalf of generics producers further, by introducing pro generic statutory provisions, so called Bolar provisions. In this chapter, the issue of Bolar provisions and the introduction of a Bolar clause in the EU will be discussed.

5.1. Beyond Experimental Use Exceptions: Bolar Type Provisions

A Bolar provision (sometimes referred to as an early working provision) is a policy allowing generic manufacturers to prepare production and regulatory procedures before patent expiry of innovative drugs. Under those circumstances, generic medicines can be ready for sale as soon as the patent for the original product ends, rather than having to go through the preparatory process after the patent expiry. A Bolar provision typically allows a third party to undertake, without the authorisation of the patent holder, certain testing activities in respect of a patented product necessary for the purpose of obtaining regulatory approval for a copy product. Even though Bolar provisions are a common feature of patent law in many countries, such as Canada and the US, it has until recently not existed in the EU.

The term Bolar provision originates from the US case *Roche Products, Inc. v Bolar Pharmaceutical*⁹⁹ from 1984. In this judgement, the US Court of Appeals for the Federal Circuit held that the manufacture or use of a patented medicine before patent expiry for the purpose to generate test results for a marketing authorisation application constituted patent infringement. Immediately after (and to reverse) this decision, as part of the Hatch-Waxman Act¹⁰⁰, the so-called Bolar provision was introduced in US law.

The Hatch-Waxman Act was introduced in an attempt to strike a balance between the interests of the generic industry and the innovators' intellectual property rights. In exchange for allowing “Bolar-type infringements”, patent

⁹⁹ *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984).

¹⁰⁰ 1984 Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984); Law No. 27 of 1987, reprinted in Official Gazette, May 25, 1987, at 2. These statutes became effective January 1, 1988.

holders could apply for a patent term extension to compensate for the length of time it took to receive marketing authorisation (compare the SPC legislation in the EU). The Hatch-Waxman Act was an unprecedented attempt to achieve two seemingly contradictory objectives, namely, to make lower-costing generic copies of approved drugs more widely available and to assure that there were adequate incentives to invest in the development of new drugs. By the Hatch-Waxman Act, the Bolar provision, lowering the barrier to entry for generic firms, and patent term extensions for innovative drugs were introduced simultaneously. Clearly, this has not been the case in Community law, where the SPC legislation was introduced ten years ago.

5.2. The TRIPs Agreement and Bolar Type Provisions

As noted above, Article 30 of the TRIPs Agreement deals with exceptions to patent rights in vague terms. However, the consistency of Bolar-type provisions towards the TRIPs agreement was reviewed by a WTO Panel during Dispute Settlement proceedings initiated by the European Communities and their member States, *EC v Canada*, concerning patent protection of pharmaceutical products.¹⁰¹ This decision is interesting since the WTO's and the EC's attitudes towards Bolar provisions are effectively displayed. In the proceedings, the EC argues against the legality of Bolar provisions, whereas the Panel reaches the conclusion that Bolar provisions *per se* are seen as compatible with TRIPs.

5.2.1. The WTO Panel Decision EC v. Canada

In March 2000, Canada's experimental use exception became the subject of a decision by a WTO Panel pursuant to the organisation's dispute resolution process. Canada had introduced an equivalent provision to the US Bolar provision and also permitted pre-patent-expiry stockpiling of patented products in the six months leading up to the expiry of a patent.

Under Canadian patent legislation a third party was allowed to, without the consent of the patent holder, use a patented invention to:

- carry out experiments and tests required (proof of safety and bio-equivalency) to obtain marketing approval of the copy of an innovative medicine before the expiration of the relevant patent in order to ensure market access immediately following the patent expiry; (the Bolar provision)

- manufacture and stockpile patented products for a period of up to six months before patent expiry for sale after expiry. (the stockpiling provision)

¹⁰¹ *Canada – Patent Protection of Pharmaceutical Products*, Proceedings WT/DS114/R.

The European Communities desired the Panel to request Canada to bring its domestic legislation into conformity with its obligations under the TRIPS Agreement. The EC argued that the Bolar provision violated the patent holder's right to prevent third parties from making, using, offering for sale, selling, or importing the patented product without the patent holder's consent. Furthermore, the EC argued that Canada, by treating patent holders in the field of pharmaceutical inventions by virtue of these provisions less favourably than inventions in all other fields of technology, violated its obligations under Article 27.1 of the TRIPs Agreement requiring patents to be available and patent rights enjoyable without discrimination as to the field of technology.

Concerning the stockpiling provision, the European Communities argued that this provision had the result that Canada only provided for nineteen years and six months of the minimum patent protection as mandated by Articles 28.1 and 33 of the TRIPS Agreement, instead of the required term of twenty years from filing. This due to the fact that anybody in Canada was allowed to make, construct and use the invention during the last six months of the patent term without the authorisation of the patent holder.

The Panel found the Canadian Bolar provision to be in accordance with the TRIPs Agreement. The three requirements mentioned in Article 30 were found to be fulfilled by the provision. The exception was found *limited* because it applied only to conduct needed to comply with the needs of a regulatory approval process. The arguments submitted by the EC as to the *normal exploitation* of the patent were rejected, and the Panel found that the Bolar provision did not conflict with a normal exploitation of patents, within the meaning of the second condition of Article 30 of the TRIPS Agreement. Finally, the panel found that the interests of the patent holder as defined by the EC, notably the interest to impose a delay on generic producers for their market entry equivalent to the one suffered by the original drug producer due to the regulatory approval process, were not *legitimate* within the meaning of Article 30.

On the contrary, the stockpiling provision was found inconsistent with Canada's obligations under the TRIPs Agreement. The Panel held that it shortened the patent holder's rights to a not *limited* extent. In Article 28 of the TRIPs Agreement, the rights of the patent holder are defined not only as the exclusive right to sell the product, but also as the exclusive rights to make and use the product. The stockpiling exception was found to remove this protection entirely during the six last months of the patent term, and was therefore not considered as being *limited* in nature.¹⁰²

It is clear from the Panel decision that early working provisions are regarded as compatible with the TRIPs Agreement. The WTO clearly regards Bolar provisions as an admissible instrument to be used by governments in order to stimulate the competition between original drugs and generics. However, to allow manufacturing and stockpiling of a patented product before patent expiry without the patent holder's consent is to violate the exclusive rights

¹⁰²L'Ecluse, P., Longeval, C., *The Bolar Clause in the New European Pharmaceutical Regulatory Package*.

of patent holders and thereby a state's obligations under the TRIPS Agreement. This indicates that the exclusive rights conferred upon patent holders are still being safeguarded, and for the time being the acceptance of early working provisions are seen as a sufficient step.

5.3. The 2001 Pharma Review – Introducing a Bolar Provision in the EU

With the background of the arguments made by the EC in the WTO Panel Decision, where the EC explicitly questioned the legality of Bolar provisions, it is interesting to see the recent amendments to Community legislation. One of the most important changes to Community law is the introduction of a Bolar provision in the EU. This has been long awaited by pharmaceutical professionals representing the generic industry, advocating a more competitive patent legal framework in the Community. Furthermore, some of the new Member States wishing to maintain their healthcare budget at the lowest possible level have been in favour of the inclusion of an EU Bolar provision, since early working provisions unambiguously promote the development and use of generic products, thus cutting governmental costs for pharmaceuticals.¹⁰³ Moreover, since Bolar provisions have existed in the US and Japan for several years, the inclusion of an early working provision in the EU is intended to put the European pharmaceutical industry on an equal footing with competitors internationally. Enactment of the EU Bolar provision is also intended to keep the technical expertise and the investment money in R&D within the expanded Community and to avoid that scientific tests required to prepare an application are carried out outside the Community for purely legal reasons. It is hoped that it will actually stop the generic industry from resorting to out-of-EU testing and thereby make Europe more competitive.¹⁰⁴

Moreover, it has been argued that through the introduction by the SPC legislation but not a Bolar provision, the research-based industry obtained “double” benefits. If generic competitors must wait until after patent expiry to perform regulatory testing, the patent term for the original product is effectively extended for the duration of generic testing and regulatory approval. As noted above, in the US, patent term restoration and the Bolar provision was introduced simultaneously, whereas in the EU the legislator started by granting extended market protection to innovative products and after ten years introduced benefits for the generic industry.

The Bolar provision is enshrined in Article 10.6 of the Amendment Directive, providing that:

“conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 [to an abridged application] and the consequential practical requirements shall not be regarded as

¹⁰³ The national legislation of the Czech Republic, Hungary, Malta, Poland, Slovakia and Slovenia already included a Bolar clause.

¹⁰⁴ L'Ecluse, P., Longeval, C., *The Bolar Clause in the New European Pharmaceutical Regulatory Package*.

contrary to patent rights or to supplementary protection certificates for those medicinal products.”

This provision puts in place for the first time a harmonised, Community wide provision allowing the use of patented drugs for generic testing and development work in any Member State, without such early working being considered patent infringement. Consequently, this provision allows a generic company to perform the research and development needed to apply for a marketing authorisation under the abridged procedure before the patent has expired on the original product. Article 10.6 further enshrines that “the consequential practical requirements” shall not be regarded as contrary to patent rights of the original drug. To be able to apply for a marketing authorisation under the abridged procedure, the submission of samples is mandatory in some Member States. Thus, in my view, generic manufacturers will be able to manufacture a patented pharmaceutical prior to patent expiry. The manufacturing of samples must be seen as a “consequential practical requirement”, allowable under the new EU Bolar clause. If this would not be the case, the intent of the provision, to promote the development and use of generic products and to stop the generic industry from resorting to out-of-EU testing, would be opposed.

Accordingly, generic drugs will be available on the market immediately after the expiry of the originator products patent/SPC periods. This certainly brings about a change. Before this new legislation was introduced, generic products could well be imported into the Community shortly after patent expiry for the original product. However, before effective marketing of a generic product could commence, the administrative procedure needed to be completed. As noted earlier, on average, this procedure requires between two and three years.¹⁰⁵ Before the introduction of the Bolar provision, generic products could not be introduced on the common market until approximately two years after the patent expiry for the original product. The fact that generics will be able to hit the market immediately upon patent expiry will, in the vast majority of cases, involve huge losses in sales on behalf of the companies marketing original drugs. As stated by Domeij, a company makes a sales profit of approximately \$1 million per day from an averagely successful (original) drug.¹⁰⁶ Consequently, the financial loss for research-based companies will be considerable.

As illuminated in this chapter, the extent as to which pre-patent-development work has been permitted in the Community has been imprecise. This is due to the lack of harmonisation on Community level and the scope of experimental use exceptions being nationally limited. For generic competition, the ratification of the EU Bolar provision will without doubt put experimental use exceptions in a less highlighted position, thereby circumventing the problem with different national interpretations of exceptions to patent rights. After the implementation of the new pharmaceutical legislation, generic manufacturers will be able to rely on

¹⁰⁵ “The Making of New Medicines - Manufacturing, the Environment and the Pharmaceutical Industry”.

¹⁰⁶ Domeij, B., *Läkemedelspatent*, at page 1.

cohesive Community legislation. It is although worth to note that when implementing the provision into national law, national legislators will need to pay attention to the aim of the European legislator - to grant the same rights to generic manufacturers in the EU as they enjoy in i.e. the US. However, as always in the case of legislation through Directives, there is a danger of a diverging application from one Member State to another and the general wording of the Bolar clause will probably cause some problems in the near future. Therefore, it would be appropriate to further define its scope by for example guidelines.¹⁰⁷

Concluding Remarks

- *Bolar provisions are pro generic statutory provisions, allowing generic competitors to conduct pre-patent-development work to prepare a commercial market launch without the consent of the patent holder.*
- *Bolar provisions are seen as compatible with the TRIPs Agreement, whereas stockpiling provisions are not.*
- *By the 2001 Pharma Review, a Bolar provision has been introduced in the EU. This clarifies the situation as to what preparations are permitted on behalf of generic competitors, and circumvents the problem with the nationally limited experimental use exceptions.*
- *The inclusion of a Bolar clause favours the generic industry, and thereby the development and use of generic drugs are being promoted.*

¹⁰⁷L'Ecluse, P., Longeval, C., *The Bolar Clause in the New European Pharmaceutical Regulatory Package.*

6. A Swedish Perspective – The System of Generic Substitution

The granting of a marketing authorisation does not imply that the product at hand is automatically covered by the national healthcare system, thereby being subsidised by the state. To obtain reimbursement status, a drug must comply with requirements set forth in the different national pricing and reimbursement system. This chapter aims at providing an overview of the Swedish system of mandatory generic substitution, a policy adopted to stimulate a greater price competition on the pharmaceutical market and to reduce the government's expenditure on pharmaceutical products.

6.1. Introduction

All medicinal products require regulatory approval before they may be marketed. Under Swedish rules, the requirements to obtain marketing approval are equal to the requirements under Community law, as discussed earlier. However, as noted in the introduction to this chapter, obtaining marketing approval for a certain product is not synonymous with the drug being covered by social healthcare systems, thereby being subsidised by the state. Pricing and reimbursement systems are not regulated on an EU level; this is an issue for national governments and healthcare providers.

The completion of national pricing and reimbursement procedures is the last step for a pharmaceutical manufacturer on the way to commercial market launch. Therefore, I find it to be of interest briefly considering this procedure in Sweden, along with the practical requirements thereof.

Under Swedish rules, if a product is to be covered by the pharmaceutical benefits scheme, the company responsible for marketing the product must apply to the Pharmaceutical Benefits Board¹⁰⁸ (PBB), which decides whether the specific product is to be included in the benefits scheme. The decision is to be made in accordance with the New Pharmaceutical Benefits Act.¹⁰⁹ If the product is to be included in the system, the Board sets a fixed sales price for the product. The drug is then said to have reimbursement status. Concerning generic products, when this procedure has been completed, the Medical Products Agency¹¹⁰ (MPA) makes an assessment whether the product shall be covered by the generic substitution system. The Swedish system of mandatory generic substitution implies that a prescribed drug qualified for subsidy is exchanged for the cheapest (as deemed by the MPA) exchangeable, generic alternative available at the local pharmacy. In Sweden, there is a monopoly on retail sales of pharmaceuticals. Therefore,

¹⁰⁸ Läkemedelsförmånsnämnden.

¹⁰⁹ The New Pharmaceutical Benefits Act (2002:160).

¹¹⁰ Läkemedelsverket.

drugs can only be sold from a pharmacy and all pharmacies are part of one company, Apoteket AB, owned by the government.

6.2. The Pharmaceutical Benefits Scheme

In April 2002, the Swedish Parliament introduced a new law concerning pharmaceutical benefits¹¹¹, which became effective on 1 October 2002. In order to receive reimbursement status, the company responsible for marketing a product files an application with the Pharmaceutical Benefits Board, stipulating and motivating the preferred price for the product.¹¹² The PBB then makes the decision on the granting of reimbursement status for the particular drug. The product will only be included in the pharmaceutical benefit scheme if they fulfil the criteria set forth in §15 of the New Pharmaceutical Benefits Act. For a medicinal product to be reimbursed the cost for using the product should be reasonable and fair from a medical, humanitarian and social-economic perspective taking into account §2 of the Health and Medical Service Act.¹¹³ Furthermore the board is bound to consider whether there are any other available medicines or methods of treatment deemed considerably more suitable, observing §4 of the Medicinal Products Act.¹¹⁴ According to §11 of the new Pharmaceutical Benefits Act the Board may couple a decision with certain conditions, e.g. that the product shall be covered by the benefits scheme only for a certain field of use. This has been done for, e.g. XENICAL, a prescription drug used to help obese people lose weight, that received coverage only for certain patient groups. Furthermore, VIAGRA, a drug used to treat erection difficulties, has been denied coverage by the pharmaceutical benefits system whereas CRESTOR, a medicine for patients with high cholesterol containing the new entity rosuvastatin, is covered only for patients who have first tried products containing simvastatin.¹¹⁵

The pharmaceutical pricing in Sweden is free; a company may set its own price for a certain drug and disregard the opportunity of being covered by the pharmaceutical benefits scheme. However, for generic products, it is of importance to be regarded as interchangeable with original products, since it is as substitutes for original products they are making profits.

6.3. Generic Substitution

The right or the obligation conferred upon pharmacists to exchange a prescribed medicine (original or otherwise) to a lower-priced product having

¹¹¹ Bill 2001/02:63, the New Pharmaceutical Benefits Reform.

¹¹² The application shall be formulated in accordance with Pharmaceutical Benefits Board Regulation (LFNFS 2003:1) on Applications to and Decisions by the Pharmaceutical Benefits Board Pursuant to the Act (2002:160) on Pharmaceutical Benefits, etc.

¹¹³ The Health and Medical Service Act (1982:763).

¹¹⁴ The Medicinal Products Act (1992:859).

¹¹⁵ Hoffmann, M., *Drug Reform in Sweden, Major Changes for Patients, Doctors and Healthcare Managers*, available at <<http://www.hospital.be/menegem012004-4.html>>, last visited on 4 February 2005.

the same therapeutic effect is a tool increasingly used by Member States to achieve cost savings. The Swedish version of mandatory generic substitution entails that a pharmacist has to dispense the least expensive (as deemed by the MPA exchangeable) available pharmaceutical product unless the physician, for medical reasons, opposes the substitution or if the patient opposes such substitution. If the patient opposes substitution, he or she has to pay the difference in price.

6.3.1. The List of Substitutable Medicinal Products

When a certain product has received a fixed sales price through a decision by the PBB, and thereby is covered by the pharmaceutical benefits scheme, the Medical Products Agency automatically decides whether the product is to be regarded as interchangeable with any other product. The MPA provides a list over those products that are updated on a regular basis. The list is displayed at the website of MPA and distributed to the pharmacies.

For a pharmaceutical product to be regarded as interchangeable it has to meet the following requirements as specified by the MPA.¹¹⁶ The products must have the same qualitative and quantitative composition in terms of *active principle(s)*. However, according to the MPA the use of different salts might be accepted in some cases. As a main rule, the products must have the same *pharmaceutical form*. This is however not the case concerning capsules and tablets with a quick stomach and intestinal release, that might have a different pharmaceutical form and still be regarded as interchangeable. Furthermore, the products need to be packaged in equally sized *containers*, i.e. 100 capsules are exchangeable to 98 capsules, but 100 capsules are not exchangeable to 14 capsules.

A medicinal product might be somewhat dissimilar to the original product and still be regarded as exchangeable. Generally, it does not play a decisive role whether a product contains preservatives or not, which dyestuffs that are comprised in the product, if a product is perfumed or unscented or whether the medicine at hand is presented in a can or in a blister pack. Moreover, differences concerning the approved indication text might be seen as admissible, as long as no essential information, i.e. warnings, is missing.¹¹⁷

Before a decision regarding a certain drug is announced, both as regards the decisions by the PBB and the MPA, it is referred to the parties concerned for consideration. In the latter case this means that the company responsible for marketing the *generic* product, the company responsible for marketing the *original* product and the county council are informed for consideration. Within three weeks, the concerned parties are entitled to request the PBB or MPA to reassess the matter and the applicant of a requested change is entitled to deliberate the issue with the authority. If a decision is made against the will of a concerned party, an appeal against the decision can be made in a public administrative court.

¹¹⁶ “Kriterier för Utbytbarhet”, available at http://www.mpa.se/humanlakemedel/lakemedelformanen/LMF_utbytbarhet.shtml, last visited on 4 February 2005.

¹¹⁷ Ibid.

As a regulatory authority, the Medicinal Product Agency does not take notice of patent rights. The assessment whether a generic product is regarded as interchangeable is made as soon as a fixed sales price has been set by the PBB. This practise entails that a generic product can be on the list of substitutable medicinal products that is distributed to pharmacies and displayed on the MPA's website, a considerable time before the generic product will actually be commercially launched. This practise might possibly be seen as a first step on the way to enter the market for generic drugs and this issue will be considered in the forthcoming analysis.

The analysis contained in the following and last chapter of this thesis has the purpose to link the findings in the initial descriptive chapters together in a comprehensive discussion. Conclusions will be drawn concerning the time aspect in the pharmaceutical industry, governmental measures currently taken in respect of generic drugs, and regulatory measures and patent related measures taken on Community level in the 2001 Pharma Review.

Concluding Remarks

- The receipt of a marketing authorisation for a certain product does not entail that the product in question is covered by the national healthcare system. In Sweden, the PBB decides whether a certain product shall be reimbursed by the State.*
- The MPA subsequently decides whether a generic drug is to be deemed interchangeable with an original pharmaceutical product.*
- In its capacity as a regulatory authority, the MPA does not take notice of patent rights. Therefore, a generic drug might be placed on the list of substitutable medicinal products before it is commercially launched.*

7. Concluding Analysis

To make the concluding part of this thesis clear and comprehensible, this chapter is divided into three main subtitles, in which recent developments on Community level concerning pharmaceutical products are discussed. Firstly, governmental measures taken in relation to generic drugs are reviewed. Secondly, regulatory measures are highlighted, i.e. the regulatory data protection and the abridged procedure for marketing authorisation. Thirdly, measures taken in respect of patent rights are considered and evaluated. In conclusion, the 2001 Pharma Review and its possible consequences for the pharmaceutical industry will be considered.

7.1. Time is Money

Throughout this thesis, one aspect constantly reoccurs, the time aspect. The discussion is consistently focused on what steps actors on the pharmaceutical market can undertake, but most importantly *when* they can take action. This is regulated by time limited intellectual property rights as well as by regulatory rules, discussed in the descriptive parts of this thesis.

The reason for the time aspect being vital is that in the pharmaceutical area, time literally is money. After patent expiry for an original drug, the profit goes down drastically, primarily due to generic competition. It is during the period of market exclusivity, provided by patent/SPC or regulatory data protection, innovative companies actually reap the harvest of their investments into R&D. This makes the time of market exclusivity crucial. Thus, for the research-based pharmaceutical industry, intellectual property rights, securing a certain time of market exclusivity, are a prerequisite for a profitable business on behalf of positive return of investment. For this reason, research-based companies struggle hard to extend their time of market exclusivity, whereas generic competitors wish to minimise the said period in order to be able to enter the market immediately upon patent expiry, gaining market shares by competition with means of price pressure.

7.2. Governmental Measures

During the past two decades, nations have been faced with the difficult task of providing IPR, sufficient to promote investment into new drug development, while at the same time promoting the use of generics. It is indeed a complex task to strike a balance between those competing interests. Governments and other healthcare providers worldwide are in trouble with their healthcare budgets, and attempt to stem the growth in pharmaceutical expenditure. Nevertheless, governments also strain to provide for superior standards of treatments, and thus pharmaceutical R&D must be encouraged, to ensure that new, more effective drugs and improved ways of treatment

reach the market. The introduction and active promotion of generic drugs as a cheaper alternative to original drugs is one of the most favoured cost-containment methods, and accordingly the markets of generics are growing fast.

From the generic side of the pharmaceutical industry it is argued that cost-savings achieved from use of generic drugs provides headroom in national healthcare budgets for the purchase of new and innovative treatments.¹¹⁸ This argument does not fully convince me. If a government succeeds in cutting their healthcare budget with the help of generic drugs, it could be presumed that the saved money is urgently needed elsewhere in the state budget, such as in public expenses for education or infrastructure. For example, the governmental subsidy for pharmaceutical R&D in Sweden has remained constant over the last ten years.¹¹⁹ This fact indicates that even though the Swedish healthcare system relies increasingly on the use of generic drugs, the saved funds are not invested in pharmaceutical innovation. This might have the result that savings and efficiency gains from using generic drugs will be considerable only in a short-term perspective. Investment into R&D to develop new innovative drugs is the same investment that might lead to future drugs being able to treat diseases that are incurable today. Without investment into those drugs, the society risks making a huge efficiency loss as regard the accessibility of superior methods of treatment.

7.2.1. The Swedish System of Generic Substitution

The Swedish policy concerning the use of generic products surveyed in the previous chapter, serves as an example to illustrate how a state may promote the generic drugs to achieve cost-containment. The Swedish system of mandatory generic substitution clearly demonstrates a growing tendency to favour generic drugs, by Swedish policy-makers. The system as such has to be deemed appropriate and justified. However, the national practise with the list of substitutable products might be seen as disadvantageous from the perspective of research-based companies.

In their capacity as regulatory authorities, the Pharmaceutical Benefits Board and the Medicinal Products Agency act independently of the patent status of an original drug. The assessment whether a generic drug is to be regarded as interchangeable is done *ex officio* when a certain drug has obtained reimbursement status. Under those circumstances, a generic product might be placed on the list of substitutable products before the patent expiry for the original product in question. This list is distributed to pharmacies and published on the MPA website, displaying the sales price and launch date. This practise clearly assists generics manufacturers to advertise their products to pharmacies, which are the only retailers for prescription drugs in Sweden, i.e. the only potential customers. By the list of

¹¹⁸ "About the EGA – Introduction", available at <<http://www.egagenerics.com/ega-intro.htm>> , last visited on 4 February 2005.

¹¹⁹ "Oro bland lundaforskare för låga anslag", Sydnytt den 3 februari, 2005, available at <<http://www.svt.se/malmo/sydnytt/>> , last visited on 4 February 2005.

substitutable products, pharmacies are informed which exchangeable products that are imminent to enter the market, as well as their fixed sales price and the date of commercial launch. In my view, this fact must certainly affect purchaser's decisions on what products to order and at what time to place certain orders.

The focus in this thesis has not been the practical procedures of pricing and reimbursement systems. By referring to the Swedish system, I merely want to make a remark that generic products are *directly* favoured by e.g. systems of generic substitution. This conclusion is in no way ambiguous or speculative. My concern is the MPA's practise related to the list of substitutable medicinal products, which I see as part of *indirect* governmental generic promotion. Certainly, the promotion of generic drugs as a method cost-containment is rational. There is however a risk that governments act inconsiderately, in order to achieve immediate economic savings. This might lead to the implementation of *disguised* measures favouring one side or the other, in the absence of virtue by official law, which entails concerns connected to the legal certainty on behalf of the actors on the pharmaceutical market. In my view, the practise with the list of substitutable products might be seen as such a *disguised* measure.

7.3. Regulatory Measures

Seeking to strike a balance between pharmaceutical innovation and generic competition, the Community legislator used the harmonised, and in most Member States increased, period of data protection to conciliate the research-based pharmaceutical industry. The abridged procedure for marketing authorisation is largely unaltered.

7.3.1. Regulatory Data Protection

Under the old rules, abridged applications could be assessed and approved after six or ten years respectively. As noted earlier, the *practical* requirements concerning the abridged procedure are not significantly altered by the new rules. It is the point at which applications under the abridged procedure can be submitted and approved that is altered, as a direct consequence of the "8+2+1 formula".¹²⁰

These calculations have to be put in relation to the EU enlargement. The ten new Member States, and about half of the old ones, practised six years of data protection. Therefore, in the majority of countries, there will be an increased period of protection, and the market with harmonised protection is expanded. Regulatory data protection applies only to innovative drugs, and therefore the research-based industry benefits from those changes, except in the cases of the former "ten-year" countries where two years are lost.

¹²⁰ The "8" in this formula refers to the period of data exclusivity, whereas the "+2" and "+1" provisions refer to a time of market exclusivity for the innovator. During the last two or three years, abridged applications may be submitted, assessed and approved.

However, as noted earlier, a discussion concerning regulatory data protection isolated from patents is only relevant in a limited number of cases.¹²¹ In the vast majority of cases, the patent/SPC protection extends further in time than the regulatory data protection.¹²² Therefore, since the majority of new drugs benefit from patent protection, the change concerning data protection can be said to be of minor importance in the context of pharmaceutical innovation versus generic competition.

Moreover, the extension of regulatory data protection must be seen as directly connected to the inclusion of the EU Bolar provision. In an attempt to conciliate the research-based industry, that firmly opposed the inclusion of an early-working provision, the legislator endeavoured to reach a more balanced approach by offering an increased period of data protection. Specifically, the research-based industry is granted one extra year, the “+1” provision, in some cases. The case relating to new therapeutic indications is vaguely expressed and thereby the actual impact of this provision is difficult to predict. The wording of *significant clinical benefit in comparison with existing therapies* is ambiguous. Subsequently, it remains to be seen under which criterions this extra year of protection can actually be obtained, and from these concrete cases in question, a conclusion might be drawn as how advantageous this provision really is to innovative companies.

The new Bolar provision and the “+2” provision combined signifies that generic competitors will be able to conduct “early working” two years before the expiry of whichever IPR (patent or data protection) that expires the latest. Consequently, the “8+2+1” formula is designed to comply with the Bolar provision.

7.3.2. Abridged Applications – the Safety Concerns

The primary purpose of any legislation concerning medicinal products is said to be to safeguard public health. The abridged procedure for marketing authorisation is one issue in the new EU pharmaceutical legislation where I am of the opinion that the legislator has disregarded this prime objective. In Article 10.2 (b), it is stated that, as a main rule, different salts of an active substance shall be considered the same active substance. Next, the legislator makes a reservation against situations where the different salts differ significantly concerning *safety and efficacy*. I do not concur with this wording; there should be no such main rule. First and foremost, the assessment of a generic medicinal product ought to be done with reference to safety aspects. Different salts *might* affect the safety profile of a certain drug, and this might show after several years. Therefore, I argue that the wording of this provision is inadequate; that the safety aspect is neglected, and therefore the wording clearly contradicts the EU policy on

¹²¹ As noted in paragraph 3.4, this concerns cases where there is no patent protection, or the patent protection is weak, where the length of patent/SPC protection is reduced due to an exceptionally long development time, or where a patent has been declared invalid.

¹²² Patent/SPC provides for a maximum of fifteen years from the first marketing authorisation in the Community, whereas the maximum period of regulatory data protection under the new rules is eleven years.

pharmaceutical products, as declared by the European Commission.¹²³ Furthermore, when legislating by the means of Directives, it is of utmost importance to provide a clear-cut text, considering the risk of misimplementation in the different Member States.

7.4. Patent Related Measures

The most striking change introduced by the 2001 Pharma Review is without doubt the introduction of the EU Bolar provision. Below the uncertainties under the current practise with experimental use exceptions will be discussed, as well as the implications for the pharmaceutical industry from the Bolar clause.

7.4.1. Problems Connected to Experimental Use Exceptions

Experimental use exceptions are nationally limited. Because of the varying national case law in the Community, there has been a great legal uncertainty as to the true position of permitted preparatory acts. This legal uncertainty has led producers of generic medicines to carry out their product development and related testing in non-EU countries while patents still pending in the EU, trying to avoid the delays that would have occurred if they had waited for the expiration of patents in the Member States before beginning testing.¹²⁴ In addition, the first wave of manufacturing of generics has largely been carried out outside the Community.¹²⁵ For example, the national legislation of the Czech Republic, Hungary, Malta, Poland, Slovakia and Slovenia included Bolar provisions. As a result, those countries, together with i.e. the US and Canada, have been popular locations for generic development work.¹²⁶

When the required trials had been completed, either in a Member State with a broadly construed exception, or outside the Community, a generic producer has been able to make use of the data obtained even in Member States where the conduct of the experiments at hand would have been deemed an infringement. This is due to the fact that, as soon as the data protection has elapsed, it is possible for a regulatory authority to approve an application under the abridged procedure, without taking notice of patent rights. Nevertheless, in countries requiring physical samples this has not been possible, since the submission of samples has been deemed to create patent infringement. In those countries, generic competitors have been

¹²³ As expressed e.g. in (4) of the preamble to Directive 2001/83.

¹²⁴ L'Ecluse, P., Longeval, C., *The Bolar Clause in the New European Pharmaceutical Regulatory Package*, available at <<http://global.practicallaw.com/jsp/article.jsp?item=:5405699&tab=1>>, last visited on 4 February 2005.

¹²⁵ "Generic Medicines", available at <<http://www.euractiv.com/Article?tcaturi=tcm:29-117497-16&type=LinksDossier.>>, last visited on 4 February 2005.

¹²⁶ L'Ecluse, P., Longeval, C., *The Bolar Clause in the New European Pharmaceutical Regulatory Package*, see fn. 124.

forced to wait to apply for marketing authorisation until after patent expiry for the original drug.

A narrow construction of the experimental use exception in certain Member States has not prevented generic testing from being carried out, because there has always been some country or region where patents have not been applied for, or where the exception has been broadly construed, or where Bolar provisions exist. Thus, a restrictive construction of the experimental use exception only has had the result that the generic research has been conducted in a specifically chosen country, or outside the Community.

In my opinion, according to the different national case law, generally, bioequivalence studies have not been covered by the experimental use exception. Even though there has been an extensive interpretation of the exception in for instance Germany and France, this construction has not been regarded as a common rule. It has however been suggested in the doctrine that the SPC legislation was intended to allow pre-patent-development work. Christiansen is of the opinion that since supplementary protection does not provide full patent rights, generic testing during the term of the Supplementary Protection Certificate is allowed, under the condition that the experimental use exception is interpreted broadly.¹²⁷ Therefore, he argues, the SPC legislation seemed on its face to achieve the same goals in one action that the Hatch-Waxman Act did in two.¹²⁸ He argues that, instead of allowing for both patent term extension and pre-patent-development work, the SPC legislation allows generic competitors to conduct clinical trials following patent term expiration but before SPC expiration. This is an interesting thought. However, I do not share his opinion. Firstly, in the majority of the Member States, the experimental use exception has not been interpreted to cover clinical trials during the patent term. Secondly, an SPC protects the active substance of a certain drug, thus excluding the possibility to conduct clinical trials on the protected substance. Thirdly, in the WTO Panel decision, the European Communities argue explicitly against the legality of Bolar provisions, thus showing that the SPC legislation was in no way intended to provide for a pre-patent-development work in the EU.

7.4.2. The New EU Bolar Provision

Against this background, it is suitable to discuss the changes implied by the inclusion of the EU Bolar provision. This provision circumvents the problems connected to experimental use exceptions, providing a cohesive and harmonised approach to pre-patent-development work throughout the Community. Under the new legislation, generic manufactures will be able to conduct bioequivalence studies during the patent term for the original product, without the patent holder's consent. Furthermore, the submission of physical samples will no longer be seen as patent infringement. Therefore,

¹²⁷ Christiansen, W.T., *Patent Term Extension of Pharmaceuticals in Japan: So You Say You Want to Rush that Generic Drug to Market in Japan....Good Luck!*, in *Pacific Rim Law and Policy Journal*, 1997, at 613.

¹²⁸ By the Hatch-Waxman Act, the US introduced patent term restoration provisions and a Bolar provision simultaneously.

under the new rules there will be no difference between countries that do require samples and countries that do not.

The new Bolar provision will probably stop generic manufacturers from resorting to out-of-EU testing, thereby strengthening the EU's competitiveness internationally. It is however likely that the new Member States with a Bolar provision already in place, will continue to be preferred locations for generic development, since they have a well-established tradition of generic development. The inclusion of the Bolar provision makes the EU pharmaceutical legislation more alike the US situation. This strengthens the EU-based industry's competitiveness internationally since players on the pharmaceutical market will be able to rely on cohesive legislation, and generic competitors will be able to conduct pre-patent-development work. The benefits for generic competitors introduced by the 2001 Pharma Review will thereby lead to an increased competition on the drug market. The presence of competition threatens inefficiencies and cuts out over profits, and this leads to a more efficient and faster moving market. In the end, this efficiency should benefit end consumers, since lower priced drugs will be available sooner on the market.

In the aspect of pharmaceutical innovation versus generic competition, it is evident that the Bolar provision favours the generic industry. Generic drugs will be able to hit the market immediately upon patent expiry, which is approximately two years earlier than under the previous rules. This will cause research-based companies huge losses in sales, due to the restriction of their time of market exclusivity.

7.5. Pharmaceutical Innovation versus Generic Competition in the 2001 Pharma Review

As an overall reflection, the 2001 Pharma Review favours the generic pharmaceutical industry. Furthermore, cost-containment pressures on governments and other healthcare providers has led to increased adoption of generic substitution in many Member States, boosting volume and value for the generic industry. While the generic industry is being promoted, accordingly the incentives to engage in R&D to develop new drugs are being diminished.

Investments in generic development have become increasingly beneficial due to the favourable legislative environment surrounding the generic industry, as considered in this thesis. This has led to a situation where research-based companies themselves start to engage in the generics industry. Thus, the traditional line between research-based pharmaceutical companies and generic manufacturers is fading, as companies on both sides of the industry divide has come to realise the advantage of having a mixed business.

At an initial stage, the promotion of generic drugs will presumably lead to a decline in investments into pharmaceutical innovation. At this stage, state

governments and end consumers will benefit from the boost in generics. Generics contribute to an increased competition on the pharmaceutical market, threatening inefficiencies and a reduction in over-profits that innovative drugs have earlier been subject to. The presence of generic drugs thereby leads to meaner, leaner and faster moving market. However, it is important to note that the one-sided promotion of generic drugs cannot be indefinite in time, because of the risks of hampering pharmaceutical innovation. If that would be the vision of the future, the reduced incentives to get involved in pharmaceutical R&D to discover new drugs will deprive patients of much needed break-through drugs in the future.

Annex I

This text is an informal codification of Directive 2001/83/EC as amended by Directive 2004/277EC. This in order to make the requirements for an independent application for marketing authorisation comprehensible to the reader. Note that only the versions as published in the Official Journal of the European Community are binding.

Article 8

[...]

3. The application shall be accompanied by the following particulars and documents [...]:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference for the relevant chemical name.

(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

(d) Description of the manufacturing method.

(e) Therapeutic indications, contra-indications and adverse reactions.

(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.

(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment.

(h) Description of the control methods employed by the manufacturer.

- (i) Results of:
- pharmaceutical (physico-chemical, biological or microbiological) tests,
 - pre-clinical (toxicological and pharmacological) tests,
 - clinical trials.
- (ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.
- (ib) A statement as to the effect that clinical trials carried out outside the European Union meets the ethical requirements of Directive 2001/20/EC.
- (j) A summary, in accordance with Article 11, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in Article 54, and of the immediate packaging of the medicinal product, containing the details provided for in Article 55, together with a package leaflet in accordance with Article 59.
- (k) A document showing that the manufacturer is authorised in his own country to produce medicinal products.
- (l) Copies of any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21. Copies of the package leaflet proposed in accordance with Article 59 or approved by the competent authorities of the Member State in accordance with Article 61. Details of any decision to refuse authorization, whether in the Community or in a third country, and the reasons for such a decision.

This information shall be updated on a regular basis.

(m) A copy of any designation of the medicinal product as an orphan medicinal product under Regulation (EC) no 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, accompanied by a copy of the relevant Agency opinion.

(n) Proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of a any adverse reaction suspected of occurring either in the Community or in a third country.

The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials

referred to in point (i) of the first subparagraph shall be accompanied by detailed summaries in accordance with Article 12.

An abridged application for marketing authorisation shall contain all the above documents and particulars; except for the ones provided for in point (i), i.e. the results of pharmaceutical tests, pre-clinical tests and clinical trials. (Authors remark)

Bibliography

LITERATURE

- Cook, T., M. *The Protection of Regulatory Data in the Pharmaceutical and Other Sectors*, London, Sweet & Maxwell, 2000.
- Domeij, B. *Läkemedelspatent*, Stockholm, Jure, 1998.
- Domeij, B. *Pharmaceutical Patents in Europe*, Stockholm, Norstedts Juridik, 2000.
- Hara, T. *Innovation in the Pharmaceutical Industry - The Progress of Drug Discovery and Development*, Cheltenham, Edward Elgar, 2003.

ARTICLES

- Brazell, L. *The Protection of Pharmaceuticals and Regulatory Data: EU Enlargement Update*, in E.I.P.R. 2002, 24(3), pages 155-161.
- Campolini, M. *Protection of Innovative Medicinal Products and Registration of Generic Products in the European Union: Is the Borderline Shifting? State of Play and the Proposed European Medicine Legislation*, in E.I.P.R., 2003, 25(2), pages 91-97.
- Christiansen, W.T. *Patent Term Extension of Pharmaceuticals in Japan: So You Say You Want to Rush that Generic Drug to Market in Japan.... Good Luck!*, in Pacific Rim Law and Policy Journal, 1997, at 613.
- Cook, T. M *Regulatory Data Protection of Medicinal Products in Europe*, in Bio Science Law Review, 2003, available at http://pharmalicensing.com/features/disp/1046957520_3e674dd06906d, last visited on 4 February 2005.

- Derzko, N. M. *A Local and Comparative Analysis of the Experimental Use Exception – Is Harmonization Appropriate?*, in *IDEA: The Journal of Law and Technology*, 2003, at 1.
- Gilbert, J.
Henske, P.
Singh, A. *Rebuilding Big Pharma's Business Model*, In *Vivo – the Business and Medicine Report*, 2003, Vol. 21, No. 10, available at <http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf>, last visited on 4 February 2005.
- Grabowski, H. *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, Duke University, July 2002, available at <<http://www.dklevine.com/archive/grabow-patents.pdf>>, last visited on 4 February 2005.
- Grabowski, H. *Patents, Innovation and Access to New Pharmaceuticals*, Duke University, July 2002, available at <http://levine.sscnet.ucla.edu/archive/grabow-patents_innov.pdf>, last visited on 4 February 2005.
- Hoffmann, M. *Drug Reform in Sweden, Major Changes for Patients, Doctors and Healthcare Managers*, available at <<http://www.hospital.be/menegem012004-4.html>>, last visited on 4 February 2005.
- Izmirlieva, M. *Regulatory Efforts to Promote the Use of Generics – Government Versus Big Pharma*, available at <http://www.bbriefings.com/pdf/15/pg031_r_izmirlieva.pdf>, last visited on 4 February 2005.
- Jaenichen, H.R.
Stolzenburg, F. *Patent Infringement by Clinical Trials in EPC Contracting States?*, available at <<http://www.vossiusandpartner.com/eng/publication/pub-epc.html>>, last visited on 4 February 2005.

- L'Ecluse, P.
Longeval, C. *The Bolar clause in the new European pharmaceutical regulatory package*, available at <<http://global.practicallaw.com/jsp/article.jsp?item=:5405699&tab=1>>, last visited on 4 February 2005.
- Mazer, E., H. *Supplementary Protection Certificates in the European Economic Community*, in *Food and Drug Law Journal*, 1993, at 571.
- Véron, P. *Experimental use exemption for clinical trials: Europe vs. North America*, 12 December 2002, available at <<http://www.italy.les-europe.org/docs/veron.pdf>>, last visited on 4 February 2005.
- von Morze, H.
Hanna, P. *Critical and Practical Observations Regarding Pharmaceutical Patent Term Restoration in the European Communities (Part I)*, in *Journal of the Patent and Trademark Society*, 1995, at 479.

ELECTRONIC SOURCES

Euractiv,

“Generic Medicines”, available at <<http://www.euractiv.com/Article?tcmuri=tcm:29-117497-16&type=LinksDossier>>, last visited on 4 February 2005.

European Generic Medicines Association

“Pharmaceutical Patents”, available at <<http://www.egagenerics.com/gen-phrmapatents.htm>>, last visited on 4 February 2005.

“About the EGA – Intro”, available at <<http://www.egagenerics.com/ega-intro.htm>>, last visited on 4 February 2005.

IMS Health

“Why were Supplementary Protection Certificates Introduced?”, available at <http://www.ims-global.com/insight/news_story/news_story_000417c.htm>, last visited on 4 February 2005.

IPR Helpdesk,

“Patenting and the Research Exemption”,
available at

<http://www.ipr-helpdesk.org/documentos/docsPublicacion/pdf_xml/8_BP-Patenting-and-the-Research-Exemptio%5B0000003268_00%5D.pdf>, last visited on 4 February 2005.

Medical Products Agency

“Kriterier för Utbytbarhet”, available at

<http://www.mpa.se/humanlakemedel/lakemedelformanen/LMF_utbytbarhet.shtml>, last visited on 4 February 2005.

SVT

”Oro bland lundaforskare för låga anslag”, Sydnytt den 3 februari, 2005,

available at <<http://www.svt.se/malmo/sydnytt/>>, last visited on 4 February 2005.

The European Federation of Pharmaceutical Industries and Associations

“The Making of New Medicines - Manufacturing, the Environment and the Pharmaceutical Industry”, June 2001, available at

<http://www.efpia.org/6_publ/document/makingmedicines.pdf>, last visited on 4 February 2005.

“Comparing Facts: Value Added in Europe Innovative Medicine vs. Generic Copy”, available at

<http://www.efpia.org/3_press/FMLgenericvsinnov.pdf>, last visited on 4 February 2005.

“Position Paper, TRIPs Article 39.3 (Protection of Undisclosed Data), A Critical Issue for the Continued Development of Safe and Innovative Medicines for Patients”, November 2000, available at

<http://www.efpia.org/4_pos/legal/trips%2D39%2D3.pdf>, last visited on 4 February 2005.

Tufts Center for the Study of Drug Development,

“How New Drugs Move through the Development and Approval Process”, 1 November 2001, available at

<<http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=4>>, last visited on 4 February 2005.

“Total Cost to Develop a New Prescription Drug, Including Cost of Post-Approval Research, is \$897 Million”, Press Release, 13 May 2003, available at

<<http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29>>, last visited on 4 February 2005.

LEGISLATIVE MATERIAL

Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products, Official Journal L 182 , 02/07/1992 P. 0001 – 0005.

Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, Official Journal L 214 , 24/08/1993 P. 0001 – 0021.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Official Journal L 136 , 30/04/2004 P. 0001 – 0033.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Official Journal L 311, 28/11/2001 P. 0067 – 0128.

Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, Official Journal L 136, 30/04/2004 P. 0034 – 0057.

89/695/EEC: Agreement relating to Community patents - Done at Luxembourg on 15 December 1989, Official Journal L 401, 30/12/1989 p. 0001 - 0027.

Convention on The Grant of European Patents (European Patent Convention) of 5 October 1973 as amended by the act revising Article 63 EPC of 17 December 1991 and by decisions of the Administrative Council of the European Patent Organisation of 21 December 1978, 13 December 1994, 20 October 1995, 5 December 1996 and 10 December 1998.

Proposal for a Council Regulation on the Community Patent - revised text (June 2003).

1984 Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984); Law No. 27 of 1987, reprinted in Official Gazette, May 25, 1987, at 2.

The New Pharmaceutical Benefits Reform, Bill 2001/02:63.

Pharmaceutical Benefits Board Regulation (LFNFS 2003:1) on Applications to and Decisions by the Pharmaceutical Benefits Board Pursuant to the Act (2002:160) on Pharmaceutical Benefits, etc.

The New Pharmaceutical Benefits Act (2002:160).

The Health and Medical Service Act (1982:763).

The Medicinal Products Act (1992:859).

GUIDELINES AND NOTICE TO APPLICANTS

A Guideline on changing the classification for the supply of a medicinal product for human use, European Commission, September 29, 1998, available at <<http://pharmacos.eudra.org/F2/eudralex/vol-2/C/g1981003.pdf>>, last visited on 27 January 2005.

Notice to Applicants Volume 2A Procedures for marketing authorisation, Chapter 1, Marketing Authorisation, February 2004.

Notice to Applicants Volume 2A Procedures for marketing authorisation, Chapter 7, General Information, December 2004.

SPEECH

SPEECH/03/615, Commissioner Erkki Liikanen, addressing the EP on 16 December 2003 before the plenary vote.

Table of Cases

THE EUROPEAN COURT OF JUSTICE

- C-106/01 *Novartis Pharmaceuticals UK Ltd v The Licensing Authority established by the Medicines Act 1968* [2004] ECR 00000.
- C-392/97 *Bundesgerichtshof – Germany Proprietary medicinal products - Supplementary protection certificate*, [1999] ECR I-05553.
- C-368/96 *The Queen v The Licensing Auth. established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex parte Generics (UK) Ltd., the Wellcome Found. Ltd. and Glaxo Operations UK Ltd. and Others*, [1998] ECR I-7967.
- Case C 316/95 *Generics BV v Smith Kline & French Laboratories Ltd.* [1997] ECR I-03929.

GERMANY

- Clinical trials I*, Federal Supreme Court, July 11, 1995, RPC 1997, 623.
Clinical Trials II, Federal Supreme Court, April 17, 1997, RPC 1998, 424.

FRANCE

- AJC Pharma Expanpharm v Servier*, TGI Paris, 12 October 2001.
Wellcome v Parexel International and Flamel Technologies, District Court of Paris 6 March 1998.

SWEDEN

- Stockholm City Court T 7-536-93 and T-7-737-94 of 15 June 1995.

THE NETHERLANDS

- SmithKline and French Laboratories v Generics BV*, (1997) Dutch Supreme Court, September 29, 1997, BIE 1997/21.

THE UNITED KINGDOM

Monsanto Co. v. Stauffer Chem. Co. & Another, 1985 RPC 515 (Court. of App. - Civ. Div. 1985).

The Upjohn Company v T. Kerfoot & Co. Ltd, Patents Court [1998] FSR 1.

THE UNITED STATES

Roche Products, Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed. Cir. 1984).

WTO

Canada – Patent Protection of Pharmaceutical Products, Proceedings WT/DS114/R.