

Monica Donghi

Patent Strategy in Pharmaceutical Industry: Are additional patents valuable?



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Preface

This thesis is the result of research and analysis of the patent portfolio regarding two commercially successful drugs of significant importance for public health. The investigation has sought to analyse the various motivations which are behind such patent portfolio as well as its potential value.

The research culminating in this thesis was carried out as part of the LL.M. Program at the Munich Intellectual Property Law Center (MIPLC). It has been generously supported by Dr. Heinz Hammann and Dr. Ulrich Kebekus of the Boehringer Ingelheim group's patent department, who provided access to some crucial data and also took time to make very helpful comments, for which I am very grateful.

I wish to thank my classmates and friends at the MIPLC LL.M. Program, for inspiring and supporting me, in particular Hyewon. Most importantly, I would like to thank my family. This dissertation would not have been possible without their support.

Munich in January 2014

Monica Donghi

Abstract

Lifecycle management is used by companies attempting to maximize the value of their product portfolio and it is often referred to by generic drug manufacturers as “evergreening”. Lifecycle management arises in response to the increasing generic competition and to the constantly growing expenses necessary to develop new drugs. Between the various strategies being pursued this thesis analyses and evaluates two of them, namely product improvements and product line extensions. In particular, an evaluation of the patents that follow the basic one and that accompany the development of a drug from research to market is attempted.

Two “blockbuster” drugs, Taxotere and Xalatan, were randomly chosen to carry out such analysis. The patent portfolio of the originator companies is outlined and some important patents for each area of research (e.g. formulations, combinations, delivery devices) are shortly described. Moreover, the patent filing trends for the two drugs, both in regard of the originator and in regard of other competing companies (amongst these also the generics) are schematically shown.

The evaluation of the patent portfolio indicates in both case studies that the follow-on patents did not stop profit erosion after expiry of the basic patent. Various obstacles and drawbacks may be identified. In particular, many patent applications were withdrawn or did not result in a granted patent. Granted patents that covered valuable improvements of the characteristics of the two drugs, such for example a better formulation in the case of Taxotere, could not be maintained in some European countries and in the U.S. These follow-on patents tend to be weaker than the basic one and more difficult to defend for the originator, which appears to be due to a concomitant increase in knowledge as research moves forward, enhancing the basis of prior art to be considered.

Abstract

Stronger patents are necessary to protect research that aims to improve a market drug. Such research is criticized by many and seen as deviating resources from the discovery of NCEs, nonetheless a benefit for the public arises in many cases from it. Innovation derives also from small incremental steps.

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Acronyms and Abbreviations

AGCM	Autorità Garante della Concorrenza e del Mercato
ANDA	Abbreviated New Drug Application
Art.	Article
CDK inhibitor	Cyclin dependent kinase inhibitor
CI	Clinical Investigation
C.F.R.	Code of Federal Regulation
CJEU	Court of Justice of the European Union
D.C.	District Court
DCP	Decentralized Procedure
EC	European Community
ECJ	European Court of Justice
EMA	European Medicines Agency
EFPIA	European Federation of Pharmaceutical Industries and Associations
EPC	European Patent Convention
EPO	European Patent Office
FDA	Food and Drug Administration
FDLI	Food and Drug Law Institute
Fed. Cir.	Federal Circuit
Ger.	Germany
HIV	Human Immunodeficiency Virus
ICA	Italian Competition Authority
IP	Intellectual Property
It.	Italy
MRP	Mutual Recognition Procedure
NCE	New Chemical Entity
NDA	New Drug Application
NHS	National Health System
O.J.	Official Journal
PGF_{2α}	Prostaglandin F2 alpha
SPC	Supplementary Protection Certificate
R.	Rule
R&D	Research and Development
TRIPs	Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, THE LEGAL TEXTS: THE RESULTS OF THE URUGUAY ROUND OF MULTILATERAL TRADE NEGOTIATIONS 320 (1999), 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994)
UK	United Kingdom

Acronyms and Abbreviations

U.S.	United States of America
U.S.C.	United States Code
USPTO	United States Patent and Trademark Office

I. Introduction

In 2011, the world pharmaceutical market was worth an estimated 614.6 billion € at ex-factory prizes. The European share of this market is estimated to be around 26.8% (or 157.3 billion €), with an annual market growth of ca. 2.6% for the five major European markets.¹ The world's fastest growing markets are the Brazilian and Chinese markets with an estimated growth of more than 20%.²

In Europe, the researching pharmaceutical industry (constituting the so-called “originator companies”) is the leading high technology industry in terms of investment in research and development. An estimated 27.8 billion € has been invested in the year 2010 (a year of global economic downturn) into research directed towards new chemical and biological entities (drugs) and their development to bring forth new innovative cures for diseases.³ This figure has more than doubled in the past ten years, and is over ten times more than the figure in 1980. The cost of pharmaceutical research has been increasing dramatically over the years for several reasons.⁴ First, with the increasing knowledge acquired through the various genome projects, science has become much more complex. Not only have become known much more potential targets to be addressed by a drug to treat a given disease, but also much more is known about potential collateral targets which need to be avoided in order not to cause undesired side reactions.⁵ As a further consequence of the increased knowledge, also

1 European Federation of Pharmaceutical Industries and Associations (hereinafter ‘EFPIA’): The Pharmaceutical Industry in Figures, 2012 Edition, found at: http://www.efpia.eu/sites/www.efpia.eu/files/EFPIA_Figures_2012_Final-20120622-003-EN-v1.pdf (last visited Aug 2, 2012).

2 *Id.* at 4.

3 *Id.* at 9.

4 *Id.*

5 G. Emilien, M. Ponchon, C. Caldas, O. Isacson and J.-M. Maloteaux, *5 Impact of genomics on drug discovery and clinical medicine*, 93 QJM. Int. J. Med. 391, 394 (2000).

regulatory obligations in preparation of the data package to obtain market approval become more and more stringent. This results in ever larger and lengthier clinical trials and an enhanced rate of failure.⁶ The increased regulatory obligations have consequently reduced the period of time where the originator companies have market exclusivity and the number of drugs which arrive to the market.⁷ This situation has led the pharmaceutical industry to pay more attention to the patent portfolio and to invest into research connected with already marketed products (such as development of combination therapies).

The climate in which the pharmaceutical industry operates can be characterized as lacking acceptance of the business model and critical regarding the value it creates for society. The critics deny any fair analysis of achievements of commercial pharmaceutical research and focus on failures – disregarding the industries commitment to supply the market with safe and efficacious drugs.

This thesis will start by giving a short overview on the different phases of pharmaceutical drug research and a summary of the European Medicines Agency (EMA) regulations which deal with the approval of new and generic drugs. Next, this thesis will seek to describe different kinds of subject matter (e.g. salts, formulations, combinations, delivery devices) pursued by the patent protection. These patents that accompany the development of a drug from research to market are referred to as follow on patents and are often considered by generic companies as “evergreening”.

In particular, it will compare the originators’ patent portfolio built to protect drugs for two selected pharmaceuticals. It will attempt to analyse the various motivations which are behind such patent portfolio, whether follow up patents are of value and if not the reasons leading to this conclusion. This thesis will also highlight challenges that

6 Jack W. Scannell, Alex Blanckley, Helen Boldon, Brian Warrington, *Diagnosing the decline in pharmaceutical R&D efficiency*, 11 Nat. Rev. Drug Disc. 191, 193 (2012).

7 Ronald D. Fitzmartin, *The challenge of global electronic submission standards in the biopharmaceutical industry*, 32 Drug Inf. J. 745 (1998).

this current patent strategy could encounter in the future especially as far as competition law is concerned.

II. Background

A. Pharmaceutical Industry – The Development of a New Drug.

The development of a new drug currently takes an estimated 10-12 years, but this time has risen significantly over the past 40 years (by the end of the 1960's it took only around 8 years)⁸. The increase in development time is linked to several determining factors, namely the increased regulatory requirements, resulting for example in the need for a higher number of participants in clinical trials and longer trials.⁹ An additional factor is the nature of the diseases under study, where a shift towards the treatment of certain chronic conditions can be observed. Since treatment in such cases is over a prolonged period of time (or even lifelong), the duration of the clinical trials necessarily extends to be able to forecast (or in the best case to exclude) side-effects during a chronic therapy.¹⁰ High failure rates of clinical trials have been bringing the current estimated average cost of researching and developing a new drug to about 1 billion €. ¹¹ Since the chance of a chemical entity becoming a marketable drug is about 1 in 10000 and for every successful project there might be at least 9 unsuccessful projects (investigational drugs)¹² which however also need to be financed, it is evident that a launched medicine needs to generate a continuous and substantial revenue to finance the development of fu-

8 M. Dickson, J.P. Gagnon, *The Cost of New Drug Discovery and Development*, <http://www.discoverymedicine.com/Michael-Dickson/2009/06/20/the-cost-of-new-drug-discovery-and-development/> (last visited Jul 30, 2012).

9 *Id.*

10 *Id.*

11 EFPIA *supra* note 1 at 6.

12 Tudor I. Oprea, Current trends in lead discovery: *Are we looking for the appropriate properties?* 16 *J. Comp. Mol. Des.* 325, (2002).

ture drugs. Or as Jacob LJ put it in very clear words: “The few winners must pay for all the losers.”¹³

Such investments are however nearly entirely borne by the originator companies from their own resources which makes it clear that a significant and sustained income needs to be generated to be able to maintain a position in this research intensive area of industry. To facilitate the understanding of the aforementioned research process, the following illustrative scheme should be considered:

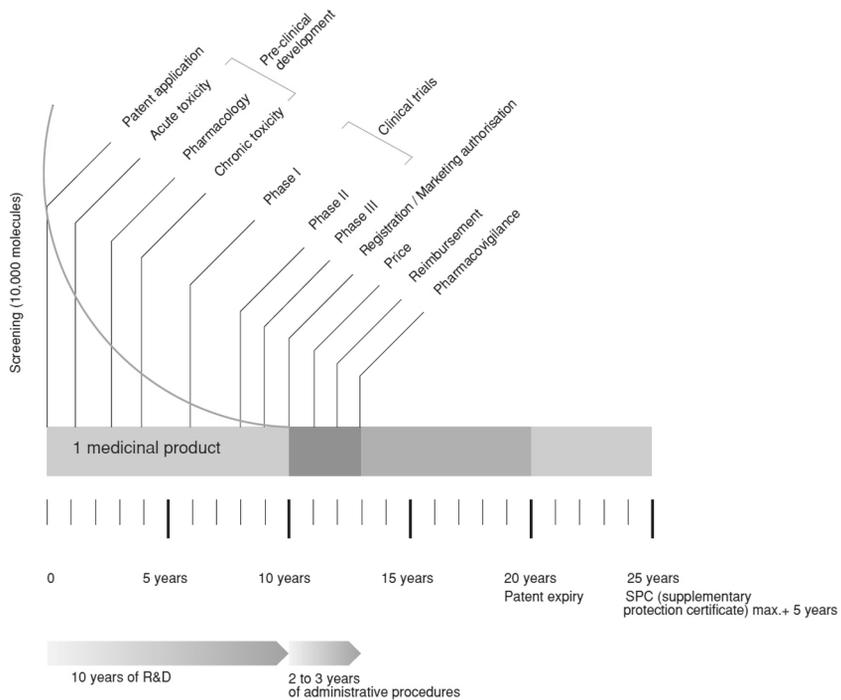


Figure 1: Phases of the Research and Development Process¹⁴

13 Sir R. Jacob, *Patents and Pharmaceuticals – a speech given on 28th November 2008 at the presentation of the Directorate-General of Competition’s Preliminary Report of the Pharma-sector inquiry*, found at <http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/jacob.pdf>, at 4, lines 21-22 (last visited Aug 2, 2012).

14 EFPIA *supra* note 1 at 7.

II. Background

The different stages of the process exhibited in figure 1 show the registration of a patent application regarding certain chemical entities at a time 0 and the market authorization at ca. 10 years. At this point it should not be left out of sight, that the filing of a patent application is preceded by a time of basic research directed towards the identification of a suitable biological target for a given disease followed by the identification and first round of optimization of chemical compounds which are suitable for the purpose (e.g. inhibiting a metabolism, a viral action, bacterial growth etc.). This time may conservatively be estimated to range from 1 to 3 years, depending on the complexity and the novelty of the biological target.¹⁵ During the phase of preclinical development, several of such optimization cycles are usually being run through until candidate compounds which are suitable for Phase I clinical trials are available. While the expenditures of the Preclinical Phase may already be significant (depending on the disease models available, some viral diseases can for example only be studied in primates), the clinical phases do exceed them several times. As part of the preclinical development of a drug candidate, toxicology and safety studies as well as studies regarding suitable pharmaceutical formulations and the stability are being carried out. Many compounds fail already in this stage, as they might have a desirable activity profile, but turn out to be also toxic. While an early understanding of the interactions with other drugs is desirable, such studies are oftentimes not being carried out before the completion of Phase I clinical trials.¹⁶

B. New Drug Approval Regulations

The European system offers three routes for the authorisation of medicinal products, the so-called centralized procedure¹⁷ using the

15 Authors own experience from drug research in various pharmaceutical companies.

16 EMA, *Guideline on the Investigation of Drug Interaction*, (Apr. 22, 2010) http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090112.pdf, at 7 (last visited Aug 2, 2012).

17 Regulation (EC) 726/2004, 2004, O.J. (L 136) 1.

EMA, the mutual recognition procedure¹⁸ and the decentralized one.¹⁹ The decentralized procedure (DCP) for medicinal products, which have not been authorized before in any member state, allows for the marketing authorisation application to be submitted simultaneously in several Member States, one of which acts as the reference member state and coordinates the process. At the end of this procedure national marketing authorisations are granted in all the Member States involved. If the medicinal product has already been granted a marketing authorisation in one of the EC member states, then the mutual recognition procedure (MRP) is used.²⁰

Article 3 and the Annex of the Regulation²¹ define the types of products which fall within the scope, in particular article 3(1) and the Annex define the medicinal products for which the centralized procedure is mandatory.²²

C. Generic Drugs Approval.

As far as generics are concerned, pre-clinical tests and clinical trials are not necessary if it has been demonstrated that the generic product has “the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product²³, and whose bioequivalence with the reference medicinal

18 Regulation (EC) 764/2008, 2008, O.J. (L 218) 21.

19 Directive (EC) 2004/27, 2004, O.J. (L 136) 34.

20 EMA, *EMA procedural advice for users of the centralised procedure for generic/hybrid applications*, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004018.pdf (last visited March 5, 2012).

21 *Supra* note 17.

22 *Supra* note 17, Art. 3(1) and Annex.

23 Art. 10(1) and Art. 10(2)(a) of Council Directive (EC) 2004/27/EC of 31 March 2004, OJ L 136, 34, 39 (2004): “Reference medicinal product shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8”, and “which is or has been authorised under Article 6 for not less than eight years [Data exclusivity 8+2 market exclusivity +1 for new indication] in a Member State or in the Community”.

II. Background

product has been demonstrated by appropriate bioavailability studies.”²⁴

In the case where the results of the appropriate pre-clinical tests or clinical trials shall be provided,²⁵ studies and trials required for applying for a MA in a Member State do not constitute patent infringement under the so-called “Bolar exemption”.²⁶ However, the exact scope of the exemption is unclear and left to interpretation by the national Courts.²⁷ Up to April 2009, “the aim to harmonize the laws of the different EU countries regarding the treatment of the acts performed in order to gain the data necessary to obtain a market authorization has been reached only in part.”²⁸

24 *Id.* Art. 10(2)(b).

25 *Id.* Art. 10(3): “In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.”

26 *Id.* Art. 10(6): “Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.”

27 Stéphanie Michiels, Béatrice Holtz, *Patent exemption for clinical trials: current status of the Bolar-type provisions in Europe*, Life Sci. IP Rev. 68, (2008).

28 See *Brief report on the so called “Bolar” Exemption* Annex of Union of European practitioners in intellectual property – Biotechnology Commission, Newsletter, (May 1, 2009), found at <http://www.union-ip.org/union/WebObjects/union.woa#vieweditmember>, (last visited Sept. 1, 2012).

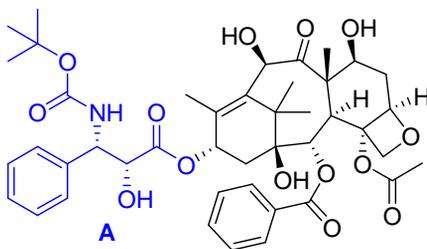
III. Case Studies-Facts

This section will discuss patent strategies that companies undertake in the course of developing a drug. This study will be conducted by highlighting the patent portfolio of two randomly selected successful drugs whose basic patent protection has been expired: Taxotere® and Xalatan®.²⁹

A. Taxotere

1. General

Docetaxel (brand name Taxotere) is an “anti-mitotic agent” (Formula 1) the administration of which causes the “inability of cells to divide”.³⁰



Formula 1

-
- 29 The trademarks are property of their respective owners and are used throughout the remainder of the thesis without the symbol ®.
- 30 A. Sulkes, J. Smyth, C. Sessa, L.Y. Dirix, J.B Vermorken, S. Kaye, J. Wanders, H. Franklin, N. LeBail, J. Verweij, *Docetaxel (Taxotere), in advance gastric cancer: results of a phase II clinical trial*, 70 British Journal of Cancer 380, (1994).

treatment of various types of cancer, including breast, ovarian and non-small cell lung cancer.³⁴

2. Patent Portfolio

a) Process

The synthetic procedure, disclosed in the basic patent family, while allowing for the production of larger amounts of docetaxel was however still far from being optimal since it involved an unselective reaction step with a consequent substantial loss of product. A company, which has to produce material for the various clinical studies and for a possible launch, therefore needs to address this issue as can be seen by the large number of successive patents in this area. E.g. EP 0336841 A1³⁵ disclosed an optimized synthesis which is no longer based on a late-stage reaction with poor selectivity, but introduces the synthetic fragment (A) (side-chain: Formula 1) as complete building block. Hence, any difficult reaction step potentially involving a loss of material is carried out before the valuable core (baccatin III) (B, Formula 2) extracted from the natural source is brought into play. This improved process found by the Rhone-Poulenc group demonstrates therefore a significant advantage, both from the technical (less difficult) and the economic (less material loss) point of view.

Successive patents³⁶ in the period from 1989 to 1994 deal with several alternative preparations of the fragment (A). Moreover, research was also directed towards the improvement of joining the two

34 O. Esposito, M. Bonfill, E. Moyano, M. Onrubia, M.H. Mirjalili, R.M. Cusidó, J. Palazón, *Biotechnological Production of Taxol and Related Taxoids: Current State and Prospects*, 9 Anti-Cancer Agents in Medicinal Chemistry 109, 110, (2009).

35 Filed in October 1989, French priority: FR 8804513, (06 April 1988).

36 WO 91/13066, WO 93/04038, WO 93/17997, WO 94/07847, WO 94/22813 and WO 94/24103.

fragments (A) and (B) together and 6 further patent families³⁷ originated from this work.

A final process patent discloses the stable crystal form (docetaxel trihydrate) which is necessary to allow for a storage stable form to be delivered to the patient (WO 96/01815).³⁸ Docetaxel trihydrate is actually the form which is packaged into the vials which are marketed.³⁹

Hence, process research contributed to the patent portfolio around docetaxel with 14 patent families as listed by their international applications.

b) Formulation

Another problem to be dealt with after the discovery of a potential drug during preclinical and clinical studies and also after marketing is the identification of a suitable formulation. Safety problems or simply the desire to identify a more user friendly dosage form can drive research in this area. In the case of docetaxel patents from 1990 to about 1999 regard certain aspects of injectable dosage forms. Taxane products have low water solubility and traditionally for clinical use taxane formulations were obtained by addition of ethanol and a surfactant.⁴⁰ This formulation could cause “manifestations of alcohol poisoning during treatment”.⁴¹

The FR 9108527 patent family addressed the ethanol issue and disclosed novel stable injectable taxane compositions with low ethanol

37 WO 93/01179, WO 93/18210, WO 94/07876, WO 94/07877, WO 94/07879 and WO 94/10169.

38 The corresponding EP 0770070 filed in 1995 will expire in 2015, the corresponding US 6022985 was filed in 1997 but can be followed only until its issue date in 2000.

39 L. Zaska, M.A. Perrin, C. Daigebonne, O. Guillou, *Docetaxel (Taxotere® Trihydrate) Forms: Crystal Structure Determination from XRPD & XRSCD data*, 443-444 Mat. Sci. Forum 411, (2004).

40 John Zhikong He, *Docetaxel*, IP Front Line, <http://www.ipfrontline.com/depts/article.aspx?id=24725&deptid=5> (last visited March 11, 2012).

41 Reported in US 5,714,512.

content. Marketing authorisation in the major markets was obtained for this new formulation (single vial). Patents of this family will expire in Europe,⁴² Canada⁴³ and Australia in July 2012, while expiry in the U.S.,⁴⁴ where a paediatric extension was granted, will be in January 2013.⁴⁵

The successive patent family EP 0671912 B1 protects a formulation in a twin compartment system which solves the problem of gelling observed upon dilution of the previously known composition. The date of expiry of these patents is in November 2013 except in the U.S. equivalent where paediatric extension was granted until May 2014.⁴⁶ No opposition has been filed against this patent, which it is still in force. However, this formulation compared to the challenged single vial composition appears less practical.

c) Combination Therapy

Between 1993 and 2009 research activities had also been directed towards the identification of combination therapies (see figure 2).

However, clinical studies of product combinations can be quite complex due to potential drug interaction.⁴⁷

About 10 patent applications regarding combination therapies with further anticancer agents and antibiotics have been filed.⁴⁸ For example, patent application WO 03/097164 A1⁴⁹ covers the use of doc-

42 EP 0593601 B1 and EP 0593656 B1.

43 CA 2102777 and CA 2102778.

44 US 5,698,582, US 5,714,512 and US 5,750,561.

45 See Zhikong He *supra* note 40.

46 See Zhikong He *supra* note 40.

47 Jan I. Drayer, James P. Burns, *From Discovery to Market: The Development of Pharmaceuticals*, in BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY, 251, 280-282, (Manfred E. Wolff ed., 1995).

48 WO 94/10995, WO 96/22101, EP 0827745, EP 1093811, EP 1295597, WO 03/097164, WO 2004/037258, EP 1537871, FR 2887454, WO 2010/067027, EP 1169059 B1.

49 Filed on 15 May 2003.

etaxel in combination with doxorubicin and cyclophosphamide (further anticancer agents) in adjuvant therapy of breast and ovarian cancer. The application was restricted to breast cancer during proceedings because of lack of support for the treatment of ovarian cancer and then refused on ground of obviousness. The applicant appealed the decision.⁵⁰ This combination has been approved either by FDA and EMA and it is the current primary treatment for breast cancer.⁵¹

The binary combination of docetaxel and cyclophosphamide is covered by EP 0827745 B1.

Another application WO 02/076484⁵² regards the combination of Taxotere and the CDK-inhibitor flavopiridol. Clinical trials for such combinations are ongoing or being evaluated.

Of these patents 3 have been revoked,⁵³ 3 were not granted and 1 is under appeal.

d) New Uses

In addition, new uses for docetaxel have been identified: the treatment of parasitic diseases (as covered by WO 95/01790) and the treatment of hepatoma (WO 01/15675). Further research which accompanied the already marketed drug was directed towards the identification of biological markers allowing for the prediction of docetaxel response, resistance or sensitivity (WO 00/39590, WO 2006/062811 and WO 2009/140304). Hence, these patents are more related to diagnostic

50 Appeal T 1902/09 ongoing. See EPO register: document of July 24, 2012 found at <https://register.epo.org/espacenet/application?number=EP03738122&lng=en&tab=doclist> (last visited Aug. 28, 2012).

51 John Crown, Michael O'Leary, Wei-Song Ooi, Docetaxel and Paclitaxel in the Treatment of Breast Cancer: A Review of Clinical Experience, 9 (suppl. 2) *The Oncologist* 24, 30, (2004).

52 Filed in March 2002.

53 E.g. EP 0827745 B1: binary combination (docetaxel/cyclophosphamide), or EP 1169059 B1 (docetaxel/ Rhumab HER2) revoked by the BundesPatentGericht (BPatG) [Federal Patent Court]: BPatG Mar. 1, 2011, BECK-RECHTSPRECHUNG (BeckRS), 14402, 2011 (Ger.).

procedures and allow for better determination of the target patient population.

e) Derivatives

The research around docetaxel did not diminish the efforts in basic research to find new innovative drugs. Attempts to improve various aspects (for example the anti-tumoural activity) of docetaxel resulted in nine patent families dealing with novel derivatives of taxoids.⁵⁴ This research work successfully led to the marketing of Jevtana (cabazitaxel), approved in the U.S. in June 2010. Cabazitaxel was first disclosed in the patent WO 96/30335 (oral formulation WO 00/41482). Despite attempts to switch to the new therapy, docetaxel is still part of the widely used first line therapy. Cabazitaxel currently finds more use in retreatment of patients previously treated with a docetaxel-containing regime.⁵⁵ For some types of cancer there is currently no data (no studies done) at hand which proves an added benefit of cabazitaxel over docetaxel, while for others it has been demonstrated that the life time is significantly improved for cases of refractory cancer.⁵⁶

3. Use of Procedural Provisions: Supplementary Protection Certificates (SPCs)/Patent Term Extension

In Europe, Supplementary Protection Certificates can be requested from the national patent offices under Regulation (EC) 496/2009

54 WO 92/09589, WO 93/23389, WO 94/08984, WO 94/11547, WO 94/20484, WO 95/01969, WO 95/11247, WO 96/03395 and WO 97/23473.

55 Institute for Quality and Efficiency in Health Care, IQWiG Reports – Commission No. A11-24 Cabazitaxel – Benefit assessment according to § 35a Social Code Book V, (Jan. 12, 2012), found at https://www.iqwig.de/download/A11-24_Extract_Cabazitaxel_Benefit_assessment_35a_Social_Code_Book_V.pdf, (last visited Sept. 11, 2012).

56 *Id.*

which codifies Council Regulation (EEC) 1768/92.⁵⁷ The SPC had been introduced for the purpose of allowing originator pharmaceutical companies to benefit of a maximum market exclusivity of 15 years from marketing authorisation, whereby the certificate may have duration up to 5 years.⁵⁸ Both Regulations foresaw transitional periods.^{59, 60}

The keystone of the patent protection for docetaxel in Europe is EP 0253738 which has been filed in July 1987. Said patent was to expire after a patent term of 20 years in July 2007. Market approval for docetaxel in Europe was obtained only in November 1995,⁶¹ after more than eight years of research to determine safety and efficacy of the drug in various clinical trials, which were necessary to fulfil the regulatory obligations. To facilitate the recovery of the high cost of R&D the originator company could avail itself of the application for an SPC. Further protection of docetaxel until November 2010 was obtained in 9 EU Member States, while in Switzerland the extension was granted until December 2011.⁶² The rights conferred by the SPC did however

57 Regulation (EC) 469/2009, 2009 O.J. (L 152) 1 supersedes Council Regulation (EEC) 1768/92, 1992, O.J. (L 182) 1.

58 SPCs must be requested within 6 months after a valid authorization to place a medicinal product on the market has been granted in accordance with the Directive 2001/83/EC, see Council Regulation (EEC) 469/2009, Articles 7(1) and 3(b), 2009 O.J. (L 152) 1, 2-3.

59 Council Regulation (EEC) 1768/92, Article 19, 1992, O.J. (L152) 1, 6: it was stipulated that for products which had received marketing authorisation after 01 January 1985 the 6 month period would start from the date the Regulation entered into force. Initially, only 4 exceptions were foreseen: for Belgium and Italy, the first marketing authorisation might have been received as early as 01 January 1982; for Denmark and Germany, not earlier than 01 January 1988. Exceptions were later also applied for three countries of the European Economic Area established in 1994 which at that point in time were not members of the European Union: Austria, Finland and Norway. The former two countries have since then joined the European Union (1. January 1995), the latter has remained a European Free Trade Association (EFTA)-state within the European Economic Area. For Austria, the 1982 limit date is relevant, for Norway and Finland 1988 is the limit date.

60 For provisions regarding transitional periods relating to the enlargement of the community see Regulation (EC) 469/2009, Article 20, 2009 O.J. (L 152).

61 *Supra* note 32.

62 EPO registry.

not stop the Israeli generic pharmaceuticals company Teva Pharma to request (*via* its Dutch subsidiary) and obtain market authorization for docetaxel from the French authorities. Presuming an imminent infringement of its rights, Sanofi-Aventis filed a lawsuit against Teva Pharma with the *Tribunal de Grande Instance de Paris*.⁶³ The court however, following French case law, ruled in favour of the defendant and decided that the request for a market authorization does not constitute an infringement. According to the court a market authorization requested by and granted to the defendant does not automatically allow to assume that a generic product will actually be marketed prior to the expiry of the claimant's rights.^{64, 65} Permission for paediatric studies targeting nasopharyngeal carcinoma was granted by the EMA in May 2008.⁶⁶ Results of the studies are not yet in the public domain.

A similar patent term extension is available also in the U.S.⁶⁷ The basic patent US 4,814,470 was due to expire in July 2007 and the marketing approval of Taxotere was obtained in 1996. Therefore, the requirements of extension of the patent term were met and an extension of 1035 days was granted.⁶⁸ A further paediatric exclusivity⁶⁹ (6

63 *Aventis v. Teva*: Tribunal de Grande Instance de Paris, Mar. 17, 2011, http://kluwerpatentblog.com/files/2010/12/2010-08-19_TGI_Paris_Aventis_Teva_translation.pdf (last visited Feb. 9, 2012).

64 Pierre Véron, *Submission of a tender: imminent infringement?*, Wolters Kluwer Patent Blog, (Dec. 8, 2010) <http://kluwerpatentblog.com/2010/12/08/submission-of-a-tender-imminent-infringement/> (last visited Feb. 9, 2012).

65 Simon Klopschinski, *Arzneimittelrechtliche Genehmigungsverfahren, staatliche Preisfestsetzung und Kostenerstattung für Arzneimittel im Lichte des Patentschutzes – Rechtsprechungsübersicht Belgien, Deutschland, Frankreich und Österreich*, GRURInt. 993, 1000, (2011).

66 EMA, EMA decision of 16 May 2008 on the application for agreement of a Paediatric Investigation Plan for Docetaxel, Taxotere (EMEA-000029-PIP01-07) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended, found at http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500005480.pdf, (last visited Aug. 3, 2012).

67 35 U.S.C. § 156: Extension of patent term.

68 See Image File Wrapper at the Public Patent Application Information Retrieval (PublicPAIR) of the USPTO.

69 21 U.S.C § 355A: Pediatric studies of drugs.

months) for the treatment of solid tumours extended the patent protection of Taxotere to November 2010.⁷⁰

4. Conclusion

In its patent strategy Sanofi-Aventis focused mainly on three innovation tracks: formulations, combinations and process. Use of SPCs was also important to prolong in Europe and in the U.S. the life of the patent application that first disclosed docetaxel.

The patent filing trends for docetaxel (figure 2) show a first increment of filing activity in 1996 after launch followed by a second surge in 2002 and a third one in 2006. However, around 280 entities contributed actually to such filing whose distribution is shown in figure 3.⁷¹ Of particular note is the large number of individual and academic inventors in the case of docetaxel, which is likely due to the particular interest cancer research attracts both in terms of public grants and in terms of public visibility. However, just contributing to total patent numbers, most of these patents appear to be neither a real challenge for the position of the originator, nor are they of particular commercial interest. There seem to be only a few cases, where, in the phase after marketing had started, Aventis secured patents through collaboration with university partners.⁷²

As already mentioned, a substantial number of patents (75%) is directed towards the research fields of formulation, combination and process (figure 2). However, only a limited amount of these has been submitted by the originator company. In the formulation track for example, although the number of patent families is very high, only three patent families belong to the originator company after 1996 (launch year). Other two companies, Forest Laboratories (14 patents) and

70 See Zhikong He *supra* note 40.

71 The data forming the basis for the graphic display of the patent filing trends has been kindly provided by the Patent Department of Boehringer Ingelheim GmbH.

72 For example WO 02/070498 has been obtained by collaboration with a group at the State University of New York.

Nitto Denko Corp. (7), were very active in this area. The same trend can be seen in the field of drug combinations, the number of active entities was quite high and in addition to Sanofi-Aventis other competitors companies showed great interest. For example, Pfizer filed eight patent families, Roche Holding AG five, while Sanofi-Aventis accounted for six families. Finally, as process research is concerned, the two top companies in terms of filing numbers in addition to Sanofi-Aventis are the two generic manufacturers Dr Reddy's Laboratories and Shanghai Parling Pharma-Techco.

Additionally, a number of patent applications (3%) have been directed both by the originator as well as by external research to alternative compounds, i.e. derivatives of the taxan core with great resemblance of the marketed drug.

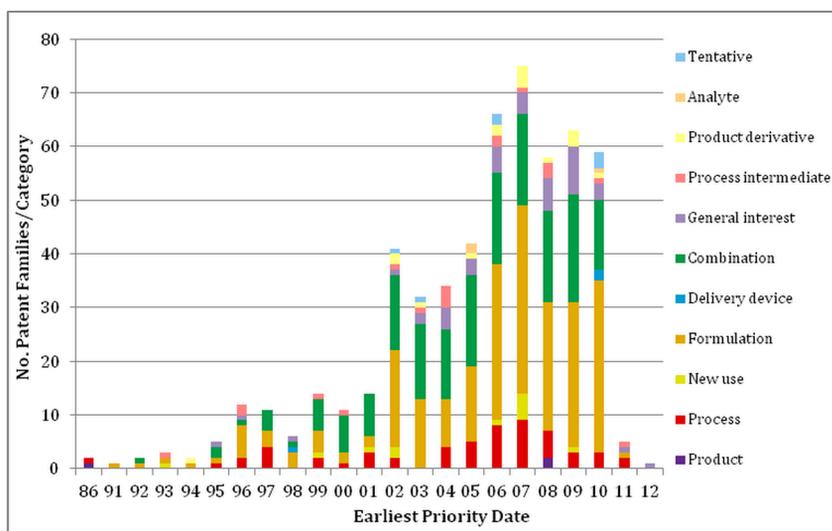


Figure 2: Patent filing trends: docetaxel⁷³

⁷³ *Supra* note 71.

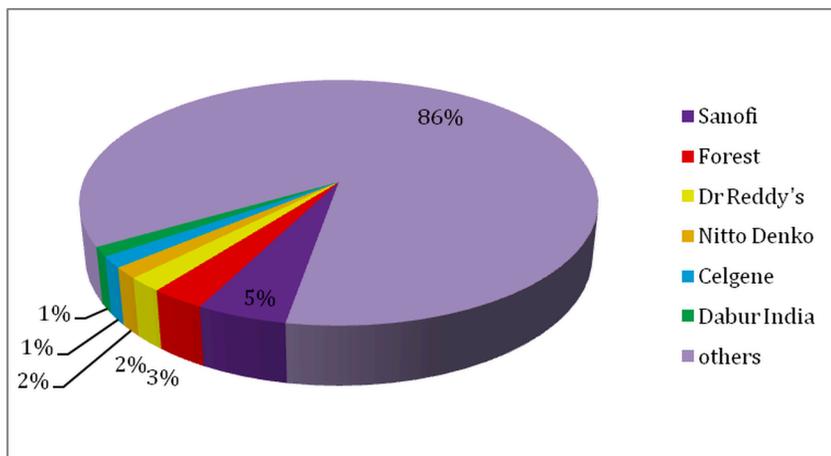
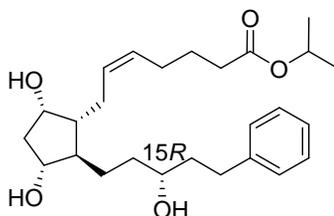


Figure 3: Top patent applicants for docetaxel (474 patents)⁷⁴

B. Xalatan

1. General

Latanoprost (trade name Xalatan: Formula 3) is an ophthalmic solution used to treat glaucoma and ocular hypertension by reducing elevated intraocular pressure.



Formula 3

74 *Id.*

The compound has been originally disclosed in EP 0364417 B1⁷⁵ belonging to Kabi-Pharmacia. The drug was launched in 1996 in the U.S. and in Europe⁷⁶. The patent protection for the basic compound expired in March 2011.

During previous research at Columbia University⁷⁷ it had been found that prostaglandine PGF_{2 α} and its iso-propyl ester could lower the intraocular pressure in patients with open-angle glaucoma. However, these compounds had low therapeutic value due to the poor cornea permeability and their side effects (e.g. ocular irritation, conjunctival hyperemia). Further studies at Kabi Pharmacia addressed these issues. Variation in the structure of PGF_{2 α} allowed achieving the desired effects. Furthermore, a more efficacious compound was obtained by separating the 15*R*-epimer (Formula 3). The ester prodrug is hydrolyzed on the cornea and the parent acid is active as a selective prostaglandin F-receptor agonist and reduces the intraocular pressure preventing further optic nerve damage and preserving remaining vision.⁷⁸

2. Patent Portfolio

a) Process

The initial method of synthesis covered by the basic patent family (EP 0569046 resp. WO 90/02553) was based on the final separation of the two epimers at C15 (Formula 3) resulting therefore in a tedious procedure and in low yield taking in account the fact that only the 15*R*-epimer is desired. Further studies were therefore directed to solve the

75 Filed in September 1989 and invoking a Swedish application priority: SE 8803110 and SE 8803855.

76 E.g. Marketing Authorisation in Sweden 18 July 1996: see European Patent Register, Legal status: EP 0364417, <https://register.epo.org/espacenet/application?number=EP89850294&Ing=en&tab=legal>, (last visited Aug. 3, 2012).

77 U.S. 4,599,353.

78 Information about Xalatan were taken from Sajiv K. Nair, Kevin E. Henegar, Modern Drug Synthesis 329-330 (Jie Jack Li, Douglas S. Johnson eds., 1st ed. 2010).

issues to obtain latanoprost in good yield, large amount and desired purity. The patent family EP 0544899 claims the process for the preparation of the 15*R*-epimer (latanoprost), based on a selective reduction of a key intermediate⁷⁹ and the various intermediates of the synthesis. This patent expired in June 2012. An earlier patent family EP 0495069 was also directed to solve the same issue. However, it covers only an advanced intermediate and the selective reduction is more tedious being based on the use of protecting groups.⁸⁰ The last patent of the originator company (US 6,689,901, filed in June 2002) covers instead the selective preparation of the other (15*S*) epimer. This could be the result of a failed process strategy.

b) Formulation

It appears that no particular research interest had been directed to the identification of specific formulations with improved characteristics. As the standard therapy using latanoprost involves a topical application directly to the target organ (eye), seemingly no particular difficulties needed to be overcome. Only one patent has been obtained by Pfizer with respect to a different dosage form, EP 1471890 B1. This patent claims an intraoral dosage in form of a disintegrating tablet with the effect that the drug is taken up via the oral mucosa of the treated subject. It must be noted however, that this patent is neither directed specifically to latanoprost, nor does this appear to the skilled artisan the most straightforward way of administering the drug, which has to act on the eye.

79 EP 0544899 B1 claims 1 and 2: reduction of the α,β -unsaturated enone key intermediate.

80 EP 0495069 B1: claim 1.

c) Combination Therapy

The earliest claimed combination therapy of latanoprost is the one which combines the drug with a tyrosinase inhibitor as claimed in EP 0977575 B1. The specific reason behind this combination is the avoidance of a known side effect of latanoprost which very often leads to an increased pigmentation of the eye.⁸¹

One of the more important patent applications in this field appears to have been WO 02/38158 A1. This application dealt with a combination of timolol and latanoprost, which is the basis for a marketed composition named Xalacom®. During the European proceedings however, Pharmacia had not been able to establish novelty over a published experimental clinical report⁸² and the application finally was abandoned.⁸³

Further combinations for which patent applications had been filed or for which patents have been granted are those with other drugs known in the field of glaucoma treatment.

As such, a series of applications has been directed to combining latanoprost with inhibitors of Cyclooxygenase-2. WO 02/05815 claims a combination of the blockbuster celecoxib (trade name Celebrex®) with latanoprost. The application entered the European phase and later was withdrawn.⁸⁴ WO 2005/021004 makes the same claim but did not enter the regional phases. WO 2005/099691 again claims and exemplifies the combination, but results withdrawn after entry into the European phase.

A claimed combination of latanoprost with Pfizer's antihypertensive (diuretic) eplerenone (trade name Inspra®) resulted in the grant of US 7,015,210.

81 See EP 0977575 B1, description lines 8-22.

82 M. Diestelhorst, Brigitta Almegård, *Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma*, 236 Graefe's Archive for Clinical and Experimental Ophthalmology 577, (1998).

83 EPO register.

84 *Id.*

Pfizer's ongoing research on glaucoma led to the discovery of new active compounds. Some patents covering such compounds also include claims to combinations with Xalatan.⁸⁵ Further patent applications were directed to combinations involving carbonic anhydrase inhibitors which are also used as treatments for glaucoma and ocular hypertension. None of these⁸⁶ however, progressed to a granted patent as they all result to be withdrawn in the European phase.

d) New Uses

With respect to new uses identified by the originator it appears that no substantial amount of research had been dedicated to it. The only application in this field is WO 95/11003 which is directed to a method of using latanoprost and its analogues for increasing the pigmentation of tissues and especially hair. However, this is not the fruit of dedicated studies into identifying further purposes for the compound at hand, but a known side-effect of the drug.^{87, 88} Though the application entered the European phase, it results as withdrawn as novelty was objected.⁸⁹

e) Delivery Devices

Two applications were directed to methods of treatment using a special applicator for the drug latanoprost.⁹⁰ The applicator is in form of an aerosol discharger and dispenses an effective amount of the drug directly to the eye. While certainly giving the product a competitive

85 E.g. WO 2006/048750 A2, EP 1893609 B1, WO 2006/134481 A1.

86 WO 2004/014352, WO 2008/075155.

87 Upon the topical use in the eye, the eyelids darken as well as does the iris colour due to increase in pigmentation.

88 M.A. Johnstone, *Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost*, 124 Am. J. Ophthalmol. 544, (1997).

89 See procedural documents available via EPO register.

90 Published as WO 2004/028420 A1 and WO 2004/028421 A1.

edge with respect to ease of application, this method of administering the drug to the eye would not have created any market entry barrier as there is a sufficient number of generic ways to do so. In any case, these applications have not been pursued and are deemed withdrawn.⁹¹

f) Packaged Product

In 2005, Pharmacia & Upjohn filed two patent applications⁹² in the United States exclusively which are directed to a special method of packaging latanoprost into plastic vials, as well as to the plastic vials filled with the drug *per se*. It appears, that there existed a need to stabilise the packaged drug and that the company had identified a solution for this. However, both applications were objected to by the USPTO under the aspect of unity of invention⁹³ and the company by that time must have had decided not to pursue the issue any further, as both patent applications result abandoned by mid-2008.

A further patent application has been filed with respect to the packaging of a combination of the drugs timolol and latanoprost, which is sold under the trade name Xalacom.⁹⁴ Also this application has been refused due to lack of unity and was then abandoned.⁹⁵

3. Use of Procedural Provisions

a) Divisional of Basic Patent

The basic patent EP 0364417 B1 gave rise to 9 divisional applications filed between 1993 and 2003 which are directed to more specific embodiments comprised in the parent application. In particular, EP

91 *Supra* note 89.

92 Published as US 2005/0049311 A1 and US 2005/0287325 A1.

93 See USPTO *supra* note 68.

94 Published as US 2005/0048122 A1.

95 See USPTO *supra* note 68.

1225168 B1 filed in 2002 covers various prodrugs including Xalatan. This patent was revoked by the EPO in 2011 and fell under the scrutiny of the Italian competition authority (ICA)⁹⁶. Pfizer appealed the decision of the EPO. In the course of the procedure Pfizer filed a new main request and further auxiliary requests. With regard to the new main request, the opponents to the patent withdrew their opposition. In May 2012 the Board of Appeal remitted the case to the first instance with the order to maintain the patent on the basis of the main request as presently on file.⁹⁷ Instead of being directed to latanoprost and its ester analogues, the patent now claims the use of Xalatan in specific amounts for a specific indication.⁹⁸

b) Supplementary Protection

The basic patent protection for latanoprost in Europe is derived from EP 0364417 which has been filed in September 1989. Said patent was to expire after a patent term of 20 years in September 2009. The regulatory obligations to be able to commercialize latanoprost had been fulfilled within seven years after filing and thus first marketing approval for Xalatan could be obtained in Sweden on 18 July 1996⁹⁹ and subsequently in other EU countries. Based on the SPC regulation, extension of the patent term up to 15 years after the first MA could be requested nationally.¹⁰⁰ Further protection of latanoprost was thus obtained in various EU Member States and gave additional coverage until July 2011.¹⁰¹ In addition, Pfizer in early 2011 was able to request

96 Autorità Garante della Concorrenza e del Mercato (AGCM) (Italian Competition Authority), Jan. 30, 2012 Bollettino 5 (XXII-2) (It.).

97 T 2402/10 available in the EPO register under the number of the patent in suit.

98 EPO register, set of claims of 9.3.2012.

99 See European Patent Register *supra* note 76.

100 Council Regulation 469/2009, 2009 O.J. (L 152) 1.

101 In Switzerland as non-EU country until September 2011, based on the Swiss MA.

additional coverage under the regime of paediatric extension.¹⁰² This was granted and brought the overall protection to 17 January 2012. For unknown reasons, no supplementary protection had been requested in Italy, where the patent term was due to expire in September 2009, 20 years after the patent application had been filed.

In the United States latanoprost was covered by the patent US 5,296,504 which had been filed in December 1992 and expired in March 2011. Patent term extension could not be requested because FDA approval was obtained in June 1996 and therefore the remaining patent term exceeded 14 years.¹⁰³

4. Conclusion

In the case of Latanoprost prolongation of patent protection was obtained through supplementary protection certificates and paediatric extension.

A substantial number of patents (93%) have been filed after the launch of the product in 1996 which were mainly (71% of these) directed to formulation, processes and delivery devices as can be seen from figure 4.¹⁰⁴ However, of these only few have been filed by the originator company. Of the reported patent families only 13 belong to Pfizer or its predecessors and the last application attributable to the originator dates to 2003.

A significant number of the patents directed to processes have been filed by Johnson Matthey (15%), a company specialized in catalyst and process development. Their patent filing activity started in 2001,

102 Council Regulation 1901/2006, Article 36, 2006 O.J. (L 378) 1, 12: according to the Regulation (EC) on medicinal products for paediatric use additional 6 month protection period may be obtained, when the holder of a patent or a supplementary protection certificate files study results in paediatric patient populations with the respective authorities.

103 35 U.S.C. § 156 (c)(3).

104 The graphics reports the number of families for priority date. If a specific patent refers to more indications, it has been counted for each category.

about five years after the launch of Xalatan when its success was presumably already evident. Regarding the patents directed to delivery devices, figure 4 shows that they were filed mainly from 2007 onward. However, various companies are active in this area and amongst them the more prolific is QLT Inc., a biotechnology company whose research is focussed on innovative ocular products.

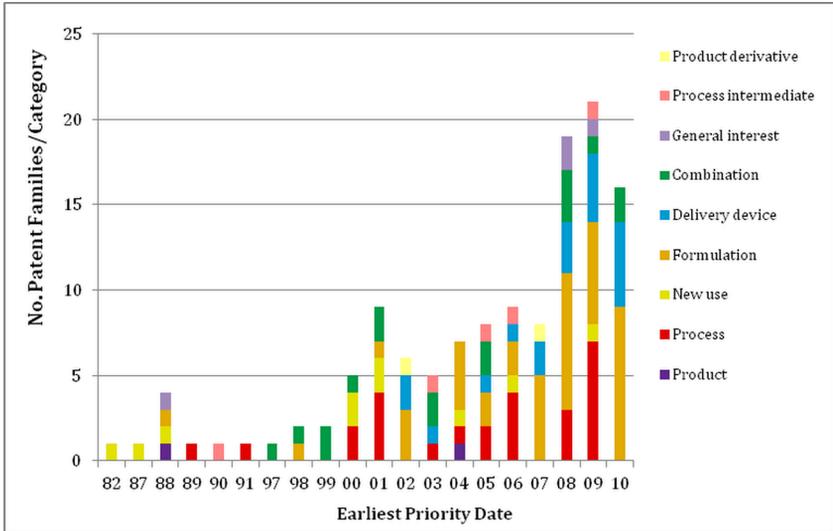


Figure 4: Patent filing trends: latanoprost¹⁰⁵

105 *Supra* note 73.

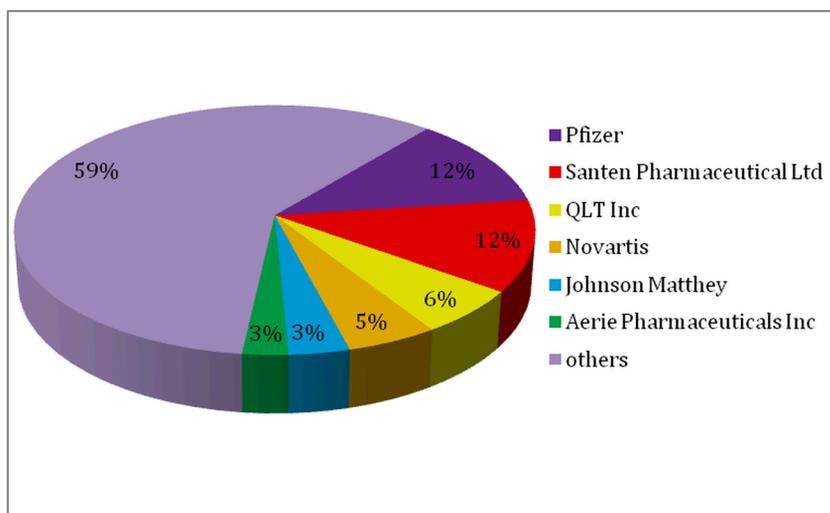


Figure 5: Top patent applicants for latanoprost (118 patents)¹⁰⁶

The third most prolific area of research covers formulations. This area is dominated by Santen Pharmaceutical (25%) which moreover is the major competitor of Pfizer (2.3%) (figure 5), as far as latanoprost is concerned, and which in 2011 announced the positive outcome of Phase II studies for Catioprost®. Catioprost is a preservative-free formulation of latanoprost with reduced side-effects and thus regarded as next generation glaucoma treatment.¹⁰⁷

¹⁰⁶ *Id.*

¹⁰⁷ Press release Novagali Pharma, Catioprost Phase II positive results (Sept. 8, 2011).

IV. Discussion

A. Lifecycle Management: Criticism and Supports

It has been reported that “[o]ver the next few years, patent exclusivity will expire for drugs with combined annual sales of \$140 billion.”¹⁰⁸ With increasing generic competition and constantly growing expenses for developing new chemical entities (NCEs) into successful drugs, drug companies are forced to maximise the value of their product portfolio. To deal with this challenge, active lifecycle management represents a response and comprises the efforts of improving return from R&D investments.¹⁰⁹ Various strategies are being pursued and among these figure product improvements and product line extensions.¹¹⁰

Members of the generic industry argue that “[...] such practices are anticompetitive and result in higher cost of healthcare to the patient and government bodies [...]”.¹¹¹ The strategies employed are often-times pejoratively called “evergreening” strategies.^{112, 113, 114} This negative connotation stems from the impression, that the originator drug companies have the ability to obtain multiple patents on a drug which in turn leads to an effective extension of the patent term. Such

108 Angelo DePalma, *Patent expiration: Innovate or die*, Eyeforpharma, Feb. 3, 2011, available at <http://social.eyeforpharma.com/>.

109 John Fraher, *Life-Cycle Management: The Link to Drug Delivery*, 2 *Drug Deliv. Tech.* 158, (2002).

110 Leighton Howard, *Use of patents in drug lifecycle management*, 4 *J. generic medicines* 230, 236, (2007).

111 *Id.*

112 Kate S. Gaudry, *Evergreening: a common practice to protect new drugs*, 29 *Nat. Biotechnol.* 876, (2011).

113 C. Scott Hemphill, Bhaven N. Sampat, *Evergreening, patent challenges, and effective market life in pharmaceuticals*, 31 *J Health Econ.* 327, (2012).

114 Gaurav Dwivedi, Sharanabasava Hallihosur, Latha Rangan, *Evergreening: A deceptive device in patent rights*, 32 *Technology in Society* 324, (2010).

strategy is seen as impeding entry of generic drugs to the market. In this context, one cannot fail to observe that the term “evergreening”¹¹⁵ in itself is entirely incorrect and inappropriate as it implies that the same invention is repeatedly protected. However, the patents obtained are generally different from one another and are directed to various aspects. The patenting strategies employed generally conform to the letter of the law. GlaxoSmithKline took publicly position on this issue. The innovator company argues that no evidence has ever been produced that those practices coined “evergreening” have an impact on patients or markets.¹¹⁶ Furthermore, GlaxoSmithKline pointed out three key issues. First, improvement patents are available only if they meet the normal requirements of patentability. Second, it is disputed “that improvements subject to later patents are not medically important and should not be encouraged.” The patent system provides an incentive to improve products and “the importance of such improvements is assessed by the market and clinical demand.” Third, there is no motivation why patented improvements should delay generic competition, because the patent systems allow and foster competition.¹¹⁷

The generic industry holds against the point of view that in their opinion a multitude of low-quality patents is granted which to be revoked and worked around binds a considerable amount of resources and of money.¹¹⁸ The same issue of quality of late secondary patents was also considered by the EU Commission in its recent sector inquiry.¹¹⁹ The Commission recognized the importance of subsequent

115 *Id.*

116 GlaxoSmithKline Briefings, *Evergreening*, (March, 2007), found at <http://www.gsk.com/policies/GSK-and-evergreening.pdf>. (last visited, July 25, 2012).

117 *Id.*

118 See Howard *supra* note 110.

119 Research Paper in Law Cahiers juridiques, Nicoleta Tuominen, Patenting Strategies of the EU Pharmaceutical Industry Crossroad between Patent Law and Competition Policy No 1 (2011), at 16.

improvements made to the initial invention.¹²⁰ They agreed that such contributions, if inventive, merit patent protection but they call for a closer scrutiny of patent applications.¹²¹

Patents that try to protect improvements of a drug incorrectly are deemed to prolong the life of the basic patent. First, they do not impede the commercialization of the drug, whose patent is expired. Second, everyone is free to invest into research and identify (incremental as well as substantial) improvements to existing inventions by building on the existing knowledge. The only advantage the originator initially has over a competitor is the know-how generated on the way to the first patent and finally the marketed drug. However, this know-how came at a price (the investment into research) to the originator company, this price being generally orders of magnitude higher than the one paid for later increments. As some authors observed the use of the clinical know-how gained can lead to cheaper and faster development of novel applications, offering a benefit for both industry and patients.¹²²

Given the continuous advances in science and the consequent gain of knowledge the inventive step disclosed in some of these applications is smaller than in a pioneering patent. Notwithstanding the fact that such patents are considered weaker and of low quality, an inventive step may oftentimes be identified. The gain from such incremental improvement is to the benefit of all. If no protection would be available for these improvements identified during the lifecycle management and if all researching industry would focus only on providing “blockbuster” drugs, which then however would not be refined into the best possible formulation or made with the most economic process, then it may be expected, that due to reduced revenue less drugs

120 European Commission, *Communication from the Commission – Executive Summary of the Pharmaceutical Sector Inquiry Report*, (July 8, 2011) at ¶1323, http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf, (last visited Aug. 1, 2012).

121 *Id.* at ¶1324.

122 Christian Sternitzke, *Knowledge sources, patent protection, and commercialization of pharmaceutical innovations*, 39 *Research Policy* 810, 812, (2010).

will reach the market in the end, and fewer medical needs will be addressed.

B. Further Filing Strategy: Commercial Value

Further research to improve properties of a drug and to address unmet needs benefit not only the industry but also the public. Such research needs incentives but it is debatable whether the strategy of further filing is of any value in this context. The further filing connected with a blockbuster drug might present various problems also on the side of the originator. Such problems can be highlighted through the analysis of the case studies reported in this work. First, innovation tracks such as formulation, combination, new uses and process have many shortcomings for the originator; second, the patent strategy pursued by an originator in a dominant position can fall under scrutiny of competition law.¹²³

It is also important to underline that such strategy *per se* does not preclude competition but on the contrary can foster it both in regard of innovation (as this work will try to evidence) and of price. On this point it has been shown in the past that 80% of the new entrants to an existing class (follow-on drugs) were launched in the U.S. with a price discount and the discount rate was on average 26%.¹²⁴

Furthermore, inventions whose patent have expired can be marketed by a generic competitor, since improvement patents are narrower in scope.¹²⁵

123 E.g. Xalatan: see AGCM *supra* note 96.

124 Joseph A. DiMasi, Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22 *Pharmacoeconomics* 1, 12 (2004).

125 See GlaxoSmithKline *supra* note 116.

1. Innovation Tracks

a) Formulations

A new formulation may bring an added benefit to patients, for example when providing a reduced dosage frequency, improved uptake of the drug into the body (and thus reduced dosage amount) or when it is possible to switch from an injectable dosage form to an oral dosage form.¹²⁶ In the U.S. new formulations comprising a previously approved drug have the potential to obtain further three years of market exclusivity based on the so-called Clinical Investigation (CI) Exclusivity which may be requested with a supplemental application.^{127, 128} This gives the possibility to the originator company to delay generic entrance, if the supplemental application is filed close to the end of the lifetime of the chemical entity's patent and if a switch to the new formulation is made. Such provision, on the other hand, is not available in Europe, where a new formulation will be of added value to a company only if the market will support the switch from old to new. This is likely to occur only if there is a real added benefit. As such may be mentioned formulations improving the dosing regimen which have an established positive impact on patient compliance.^{129, 130} The additional investment made into research towards providing such added benefit needs and deserves an incentive such as additional market exclusivity through patent protection or regulatory measures.

126 Patrick J. Crowley, Luigi G. Martini, *Formulation design: new drugs from old*, 1 Drug Discovery Today: Therapeutic Strategies 537, (2004).

127 21 C.F.R. § 314.70 (g) and 21 C.F.R. § 314.108 (b)(5)(ii).

128 To support CI Exclusivity the sponsored clinical trials must be new, essential to approval, sponsored by the applicant and not just a mere bioavailability study.

129 W. Kruse, W. Eggert-Kruse, J. Rampmaier, B. Runnebaum, E. Weber, *Dosage frequency and drug-compliance behaviour – a comparative study on compliance with a medication to be taken twice or four times daily*, 41 Eur. J. Clin. Pharm. 589, (1991).

130 Ami J. Claxton, Joyce Cramer, Courtney Pierce, *A systematic review of the associations between dose regimens and medication compliance*, 23 Clin. Ther. 1296, (2001).

With respect to patent protection some considerations must be made. Competitors finding themselves in the position to need to work around such improvement patents covering a marketed drug product tend to challenge these.¹³¹ It has been argued that such challenging could also reflect a low quality of the application or patent granted.¹³² The most direct challenge is directed at failure to fulfil the non-obviousness requirement.¹³³ In the case of docetaxel the FR 9108527 patent family has the capacity to procure between two to three years of additional exclusivity.¹³⁴ However, it was challenged several times in various jurisdictions. In the UK, EP 0593656 B1 was revoked by the Patents Court¹³⁵ and as a consequence, Aventis initiated a centralised limitation procedure^{136, 137} with the EPO (07 January 2009) which led to the reissue of this patent as EP 0593656 B3. The reissued patent covers a single specific formulation for Docetaxel. Nonetheless, this patent got invalidated in Germany¹³⁸ and Sweden.¹³⁹

US and Canadian equivalents were challenged in October 2007 by Hospira and successively by Apotex.^{140, 141} Sanofi-Aventis responded

131 See Zhikong He *supra* note 40.

132 See Sector Inquiry *supra* note 120 at ¶1313.

133 Dan-Feng Mei, Josephine Liu, Michael A. Davitz, *Formulation Patents and Dermatology and Obviousness*, 3 *Pharmaceutics* 914, 917, (2011).

134 Patents of the FR 9108527 patent family which covers a formulation with low ethanol content and for which marketing authorisation was obtained were to expire in Europe in 2012 and in the U.S in January 2013.

135 HC 08 C01493, UK Pat. J. 6227, September 24, 2008, and UK Pat. J. 6239, December 17, 2008.

136 EPC 2000 Art. 105a.

137 Designed to avoid litigations over validity and to enhance legal certainty, useful for example if relevant prior art is found after grant. For more details see Derk Visser, *The annotated European patent convention*, at 241, (17th ed., 2009).

138 BPatG June 15, 2010, BeckRS, 24071, 2010 (Ger.): The BPatG held obvious the exchange of surfactant against another known surfactant with fewer side effects.

139 Sweden: February 10, 2011 (source: Patent- och registreringsverket, Svensk Patent-databas).

140 The two generic companies filed an ANDA based on paragraph IV certifications [21 U.S.C. § 355 (j)(2)(A)(vii)] against four US patents.

141 The Thomson Corporation, News & Highlights from week 39, *Curr. Pat. Gaz.*, Sept. 26 2008.

by filing infringement actions^{142, 143} and the two cases were consolidated for the trial. Apotex and Hospira contended that the patents in suit were invalid, since the technology was not new and the formulations would have been obvious. In September 2009 the Delaware District Court ruled in favour of the defendants,¹⁴⁴ and the Court of Appeals for the Federal Circuit affirmed this finding.¹⁴⁵ Claim 5¹⁴⁶ of US 5,750,561 and claim 7¹⁴⁷ of US 5,714,512 were held obvious. The Court refused to impose additional limitations to the claims as suggested by Sanofi because the company had initially agreed on their interpretation.¹⁴⁸ In claim 5 the use of an exclusive wording (“less than”) instead of an inclusive wording (describing an exact range) rendered it vulnerable to interpretation in a way which excluded completely the features which are supposed to be present, albeit in a minimal amount and reduced it to nothing else than just a perfusion *per*

142 For two of the equivalents in both Canada (CA 2102777 and CA 2102778) and the U.S. (US 5,714,512 and US 5,750,561). In the U.S. *Aventis Pharma SA v. Hospira Inc.* Civil Action (CA) No. 1:07-CV-00721-GMS (D. C. Delaware Sept. 11 2007).

143 *Aventis Pharma SA v. Apotex Inc.* CA No. 1:08-CV-00496-GMS (D.C. Delaware Aug. 27, 2008).

144 *Aventis Pharma SA v. Hospira Inc. and Apotex Inc.*, 743 F. Supp. 2d 305, 2010 U.S. Dist. LEXIS 101442 (D. C. Delaware Sept. 27, 2010): the validity of some claims was denied due to obviousness and indefiniteness; those claims actually infringed were unenforceable due to inequitable conduct on the part of the plaintiff.

145 *Aventis Pharma v Hospira Inc.*, 2011 F.3d 1018 (Fed. Cir. Apr. 2012).

146 Claim 5 reads: “A perfusion, which contains approximately 1 mg/ml or less of compound of formula as defined in claim 1, and which contains less than 35 ml/l of ethanol and less than 35 ml/l of polysorbate, wherein said perfusion is capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith.”

147 Claims 1, 6 and 7 read: “1. A composition comprising a compound of the formula (I) in which Ar is unsubstituted phenyl, R⁷ is phenyl or t.butoxy, R⁶ is hydrogen, R⁵ is acetyloxy or hydroxy, R³ and R⁴ taken together form an oxo radical, R¹ is hydroxy and R² is hydrogen, said composition being dissolved in a surfactant selected from polysorbate, polyoxyethylated vegetable oil, and polyethoxylated castor oil, said composition being essentially free or free of ethanol.

6. The composition of claim 1, wherein R⁵ is hydroxy and R⁷ is t.butoxy.

7. The composition of claim 6, wherein said surfactant is polysorbate.”

148 See *Aventis supra* note 144 at § II.A.

se, which then was held obvious.¹⁴⁹ In Claim 7 of US 5,714,512 the term “essentially free of ethanol” was interpreted by all parties involved as “not comprising more than 5% of ethanol”.¹⁵⁰ Not being specifically directed to perfusions got then interpreted to the effect that it also comprises “stock solutions”. A specific stock solution fulfilling the requirements was already disclosed in US 4,814,470¹⁵¹ and therefore the range was regarded as being anticipated.¹⁵² Additionally, the Court affirmed the finding of inequitable conduct¹⁵³ and held that neither of the two patents at issue was enforceable at all.^{154, 155}

Another point to be made regarding this innovation track is that such formulation patents do not stop other companies to work in the same field in an attempt to find alternatives or even improvements and to patent around them as demonstrated by both the Taxotere and the Xalatan case. As far as Taxotere is concerned formulation research was actually one of the most prolific fields of patenting which attracted a number of competing companies trying to solve the main issue of solubility. In the case of Xalatan, patent filing on formulations was carried out not only by the originator but mainly by Santen Pharmaceutical (Novagali). Their research led to the discovery of Catio-

149 No basis can be found in the patent’s claims, the specification or in the prosecution history suggesting that the claimed perfusion must satisfy certain safety or efficacy standards: See *Aventis supra* note 145 at § II.A.

150 *Id.* at § II.B.

151 Col. 10: composition example.

152 See *Aventis supra* note 145 at § II.B. The Court actually holds the claim obvious, but interestingly then argues with anticipation.

153 At the time of filing *Aventis* had not disclosed all prior art known to it and material to the subject-matter claimed. The test for inequitable conduct requires that the information which is withheld from the Patent Office is material to the determination of patentability, for example such prior art which, if known to the Patent Office, would prevent the grant of the patent (“doctrine of unclean hands”): see Kevin Mack, *Reforming Inequitable Conduct to Improve Patent Quality: Cleansing Unclean Hands*, 21 *Berkeley Tech. L. J.* 147, 152-153, (2006).

154 See *Aventis supra* note 145 at § II.C.

155 Eddy D. Ventose, *Federal Circuit clarifies patent unenforceable for inequitable conduct*, 7 *J. Intell. Prop. L. & Pract.* 551, (2012).

prost.¹⁵⁶ Catioprost is a preservative-free formulation of latanoprost which deals with the corneal toxicity side effect caused by the presence of an antimicrobial agent in the formulation.^{157,158} Clinical studies on this new drug are still ongoing. Another example of such situation is the commercial successful reformulation of methylphenidate used for the treatment of attention deficit hyperactivity disorder. Alza (Johnson & Johnson) developed the drug Concerta, which is a once a day drug and replaced Ritalin three times a day drug which had to be taken by children at school.¹⁵⁹ Ritalin is marketed by Novartis.

It must be concluded therefore, that patent filings in the field of drug formulations do not preclude competition on innovation. As long as there is need and room for improvement there will be competing research done in this area and this will inevitably lead to a bouquet of patents stemming from various companies. Moreover, competing formulations of a given drug might each try to achieve a market share. A substantial market share may however only be expected, if a formulation shows a competitive edge over other formulations. Due to the substantial head start in research which the originator company has over its competitors in many cases one of the best formulations may stem from him. This however, does not exclude that later on another company may come up with a significantly improved formula-

156 For Phase II studies results see Dahlia Ismail, Mourad Amrane, Jean S. Garrigue, Ronald Buggage, *A phase II, randomized study evaluating the safety and efficacy of Catioprost® compared to Travatan Z® in subjects with glaucoma and ocular surface disease*, 89 *Acta Ophthalmol.* 188, (2011).

157 Philippe Daull, Ronald Buggage, Grégory Lambert, Marie O. Faure, Janet Serle, Rong F. Wang, Jean S. Garrigue, *A Comparative Study of a Preservative-Free Latanoprost Cationic Emulsion (Catioprost®) and a BAK-Preserved Latanoprost Solution in Animal Models*, *J. Ocul. Pharm. Ther.*, (online ahead of print: June 6, 2012).

158 This issue was already addressed by the use of less aggressive preservative in Travatan Z as compared to Travatan (by Alcon): see Christophe Baudouin, Luisa Riancho, Jean-Michel Warnet, Françoise Brignole, *In vitro Studies of Antiglaucomatous Prostaglandin Analogues: Travoprost with and without Benzalkonium Chloride and Preserved Latanoprost*, 48 *Invest. Ophthalmol. Vis. Sci.* 4123, (2007). Travatan however shows other side effects over Xalatan.

159 Edd Fleming, Philip Ma, *Drug life-cycle technologies*, 1 *Nat. Rev. Drug Discov.* 751, (2002).

tion, as in the case of Xalatan or Concerta. Moreover, the finding of a new formulation does not preclude the offering by a generic company of the older version; the choice is left to the market.

However, to have better chances to sustain an invalidity attack and therefore to be more valuable, patents protecting formulations might need to be drafted as specific as possible. This is due to the fact that the pharmaceutical compound itself represents part of the prior art and that issues surrounding the administration of the specific compound could be common to a variety of drugs and therefore may be solved by analogy.¹⁶⁰ This is not always the case but such reasoning may form the basis of a non-obviousness challenging. This view is supported by the fact that nearly 40% of the challenges to formulation patents are successful, as compared to only 23% in the case of patents on active pharmaceutical ingredients.^{161, 162} Hence, formulation patents are significantly weaker than basic patents and cannot be regarded as the best option to avoid profit erosion.

160 *McNeil-PPC v Perrigo Company*, 485 F.3d 1157 (Fed. Cir. Apr. 2008). Perrigo claimed that McNeil's Patent US 5,817,340 was invalid for obviousness. The patent disclosed an impermeable coating to mask the bitter taste of a certain active ingredient. The court found that all of the relevant limitations, i.e. using a coating for taste masking of drugs were known in the prior art, even though not for the specific compound in object. Moreover, under *KSR*, a skilled artisan would have been motivated to combine the teachings to mask the bitter taste of the active ingredient and make the drug more marketable.

161 Steven C. Carlson, Willy Chang, "Obviously" a challenge: *Patent survival statistics*, 5 *Ind. Biotechnol.* 172, (2009).

162 The European Commission's sector inquiry found that, in the period 2000 to 2007, originator companies engaged in nearly 700 cases of patent litigation with generic companies concerning the sample of products investigated. 54% of the cases were initiated by the originator company. Secondary patents accounted for 64% of all litigated patents while primary patents made up the remaining 36%. Of all cases where a final judgment was taken (149) generic companies won 62%: see European sector inquiry *supra* note 120 at ¶¶ 610, 611, 628 and summary on p. 238.

b) Combinations

Combination therapies can not only facilitate the treatment compliance of patients but also can result in an improved therapeutic effect (synergism). In particular, “chemotherapy drugs are most effective when given in combination”.¹⁶³ The use of drugs with different mechanisms of action can decrease the insurgence of resistant cancer cells which will not respond anymore to the therapy. Moreover, in this way often intolerable side effects can be diminished by using lower doses.¹⁶⁴ The same is true for other diseases. Research in this field is therefore desirable and of public interest.

As far as the patents that protect such research are concerned, some drawbacks must be mentioned. First prior art can be difficult to overcome. For example, patent coverage for the combination of timolol and latanoprost (successfully marketed as Xalacom) could not be obtained as novelty over a published experimental clinical report could not be established.¹⁶⁵ Upon expiry of the patent on latanoprost also the combination lost exclusivity.

Moreover, in a large number of cases the non obviousness requirement appears to be the more challenging obstacle of these patents. The fact that the single drugs are published prior art can result in an obvious benefit deriving by their combination and therefore patents to such combinations are subject to refusal of grant or vulnerability for invalidity claims. In some cases even the combinations may have had a prior use. For example the Sanofi-Aventis patent on the triple combination¹⁶⁶ (WO 03/097164) was refused on grounds of obviousness.¹⁶⁷ During the proceedings in the European Phase of this appli-

163 The Merck Manual Home Health Handbook, *Combination Cancer therapy*, <http://www.merckmanuals.com/home/sec15/ch182/ch182h.html> (last visited on March 11, 2012).

164 *Id.*

165 See Diestelhorst *supra* note 82.

166 Docetaxel/Doxorubicin/Cyclophosphamide.

167 Decision of the examining division on application EP 03 738 122 (06 March 2009), retrieved from European Patent Register.

cation, the examining division held that the prior art actually disclosed the claimed combination and that the only difference was the patient population targeted (first line treatment vs. adjuvant treatment). Based on the prior art, it was argued, that the selection of the new patient population would be made with a reasonable expectation of success (certainty of success not being required), otherwise also no investment into clinical studies would be made. Moreover, there was no indication in the art that such a therapy would fail, but the skilled artisan would rather reckon with a nearly 50% chance of success. Therefore, the use of the known therapeutic combination in a new patient population was regarded as obvious to the skilled person. Sanofi-Aventis appealed this decision.¹⁶⁸ The corresponding US application (US 20040146494) was abandoned.¹⁶⁹ In the meantime a number of producers have obtained MA for generic docetaxel (e.g. Teva, Mylan, Accord, Hospira) in Europe¹⁷⁰ and U.S.¹⁷¹ Their summary of product characteristics included as proposed indication the claimed triple combination and in general all possible combinations.¹⁷²

A second weakness of combination patents could be the off-label use and the difficulty to prevail in infringement actions (especially if the combination is not delivered via a single pill). In the case of docetaxel, for example, due to the fact that the three drugs are not being comprised in a single formulation, the doctors¹⁷³ could still use any commercially available version of the drug in the combination treatment, especially, since a variety of combination therapies are poten-

168 T1902/09, ongoing (16 July 2009).

169 See USPTO *supra* note 68.

170 EMA assessment reports for generic docetaxel.

171 Center for Drug Evaluation and Research Summary Review for Regulatory Action, NDA# 22234, 04 March 2011.

172 As part of an application for a marketing authorisation, a summary of the product characteristics including therapeutic indications and dosages must be submitted. These information need to be reflected also in the package leaflet accompanying the drug.

173 Under many jurisdictions, the prescription by a physician to an individual of a given drug for a given indication is exempt from patent protection: see Ulrich Storz, *Biopatent Law: Patent Strategies and Patent Management* 25-41 (Ulrich Storz, 1st ed. 2012), at 40.

tially possible and it will be difficult to determine, to what extent infringement (if found at all) may have occurred if the patent (WO 03/097164) would be granted. Traditionally, case law concerning certain combinations or specific use in patient groups¹⁷⁴ has found against infringement, if the package leaflet did not explicitly refer to the patented therapeutic indication (e.g. drug combination or patient group) or dosage.¹⁷⁵ Therefore, it appears that the generic companies' ability to provide very limited summary of product characteristics documents (and thereby relatively restricted package leaflets; "carving out"¹⁷⁶) might significantly limit the value of combination claims. However, a recent judgment from the Court of Appeal of England and Wales indicates that to establish infringement it may be sufficient to show that the defendant (the potential infringer) knew or ought to have known that some of the end users would make the modifications necessary to bring the product within the scope of the claims.¹⁷⁷ Transferring the decision to a combination of drugs, it may be enough that a generics company supplies a drug which may be combined with further drugs and that the generics company should have known that some of the end users actually will combine it. As the end users are exempt from finding infringement (basis: the patient taking a drug

174 WO 03/097164 actually comprises a combination of both: use of a drug combination in a certain patient group.

175 See for example Landgericht Düsseldorf [Regional Court] Feb. 24, 2004, GEWERBLICHER RECHTSSCHUTZ UND URHEBERRECHT [GRUR, hereinafter 'GRUR'] 193, 2004 (Ger.): Claim 1 of the patent was directed to a combination of ribavirin and interferon to be used in hepatitis C patients having a viral load of more than 2 million copies of the virus per millilitre of serum. The defendant was selling ribavirin capsules with a package leaflet referring to a combination of ribavirin with interferon, however without specifying the patient group. The court concluded that there was no infringement.

176 Terry Mahn, *Protecting New Investments in Old Drugs*, Issue 2 FDLI Update Magazine 38 (2009), available at <http://www.fr.com> (last visited Sept. 11, 2012).

177 KCI Licensing v. Smith & Nephew, (2010) England and Wales High Court (EWHC) 1487 (Pat).

combination is making a private, non-commercial use), the supplying company will be potentially be an indirect infringer.¹⁷⁸

An advantage in patenting drug combinations is the possibility to obtain a SPC. With respect to this topic the Court of Justice of the European Union (CJEU) has recently handed down two judgements which clarify how EU countries should apply SPCs to combination products.^{179, 180} These judgements address a number of unclear points in the SPC regulation. The first point regards the question in what way Article 3(a) of the Regulation¹⁸¹ may be interpreted with respect to a patent, claiming only one active ingredient from a combination of active ingredients in an authorised drug and whether such patent can be used to obtain an SPC for that drug. The court decided that “Article 3(a) [...] must be interpreted as precluding [...] from granting a supplementary protection certificate relating to active ingredients which are not specified in the wording of the claims [...]”.¹⁸² An SPC for a combination of two compounds A and B may therefore only be granted, if the literal claim wording recites specifically a combination of both. A second point addressed by the CJEU was whether an SPC could be issued for a combination of two active ingredients, if the marketed product comprises more active ingredients than just these two. This regards an interpretation of Article 3(b) of the same Regulation and the Court decided positively on this issue, stating “that provision does not preclude [...] from granting a supplementary protection certificate for a combination of two active ingredients, corresponding to that specified in the wording of the claims of the basic

178 Ravi Srinivasan & Chris Milton, *EPO second medical use claims: The skinny SmPC loophole*, Managing IP Magazine Supplement Life Science IP Focus (9th ed. 2011) available at <http://www.managingip.com/IssueArticle/2918674/Supplements/EP-O-second-medical-use-claims-The-skinny-SmPC-loophole.html?supplementListId=83781>, (last visited Sept 7, 2012).

179 ECJ, C-322/10, *Medeva BV v. Comptroller General of Patents, Designs and Trade Marks*, November 24, 2011.

180 ECJ, C-422/10, *Georgetown University, University of Rochester, Loyola University of Chicago v. Comptroller General of Patents, Designs and Trade Marks*, November 24, 2011.

181 *Supra* note 57.

182 See *Medeva supra* note 179 at 28.

patent relied on where the medicinal product for which the marketing authorisation is submitted in support of the application for a special protection certificate contains not only that combination of the two active ingredients but also other active ingredients".^{183, 184}

In view of the above rulings, it may be expected that SPCs granted on combinations which have not been explicitly mentioned in the claims will be affected and that national courts will invalidate them.¹⁸⁵ This is confirmed by the fact that first courts have already stayed preliminary injunctions previously granted under SPCs for combination drugs, where the patent the SPC was based upon does not fulfil the criteria set out by the CJEU with respect to Article 3(a) of the Regulation.¹⁸⁶

In light of the disadvantages mentioned and also of the clarification made by the CJEU regarding SPC, patents and patents applications protecting or seeking to protect such research might be of limited economic value. As emanates from the present case studies patents and applications covering combinations rarely provide additional instruments that could avoid profit erosion after the expiry of the basic patent. Nonetheless, there have been success stories. An example is Symbicort® (Asthma treatment), a combination of budesonide and formoterol. This drug combination of AstraZeneca with annual sales in 2010 of 2.7 billion dollar replaced the blockbuster Pulmicort®

183 *Id.* at 42.

184 See Georgetown University *supra* note 180 at 35.

185 Ulrich M. Gassner, *Supplementary protection certificates for combination products: new combinatorics?*, 7 J. Intell. Prop. L. & Pract. 52, 60, (2012).

186 *Novartis v. Mylan*, Tribunale Ordinario di Roma Sezione Nona, R.G. 68881/2011, November 25, 2011 found in the blog Anna Pezzoli, SPC protection for combination products: future scenarios, (Feb. 2012), <http://www.eupatent.com/spc-protection-for-combination-products-future-scenarios/> (last visited Aug. 9, 2012). A preliminary injunction granted by that Court on November 11, 2011 based on an SPC Novartis holds for its drug combination Co-Tareg (Valsartan and hydrochlorothiazide) was stayed after Mylan appealed this decision on grounds of the CJEU decision cited under ref. 179.

(budesonide) ensuring high revenue for at least further 3 years after budesonide patent expiry.¹⁸⁷

c) Process

The sector inquiry of the European Commission looked in detail at patent strategies of originator companies. Amongst the additional (secondary) patents covering a multitude of aspects of the drug compound figure also those related to processes of manufacture.¹⁸⁸ In the view of the originator companies these “[p]rocess patents are not the biggest block but can put generics off if a superior chemistry job is done.”¹⁸⁹ In some cases, it is the chemistry itself which may stop a generics company to develop a process to a drug, for example when it does not possess the specific know-how to handle certain synthetic steps which are notoriously dangerous on large scale.¹⁹⁰

However, the possibility to invent around is still the main weakness of process patents. For example, in the case of Taxotere although the compound marketed is the trihydrate salt, for which a preparation process is protected by the originator at least in Europe until 2015, profit erosion after expiry of the basic patent could not be avoided. Process patents extend to the direct product made by the claimed process,^{191, 192} but if a generic company will be able to make the product

187 Annual Report and Form 20-F Information, AstraZeneca, Therapy Area Review Respiratory & Inflammation 67, (2010).

188 OECD Policy Roundtables, “Roundtable on Generic Pharmaceuticals 2009” DAF/COMP(2009)39, October 5, 2010 at 147.

189 *Id.*

190 Cases are known, where the originator company had outsourced the synthesis of a drug to a specialised fine chemicals supplier, who can handle certain particular chemistry steps and from where, after expiry of the process patents, also the generic drug company sources its supplies. Two of these cases are the antibiotic minocycline and the angina treatment isosorbide mononitrate. The first compound requires a unique raw material, while the second synthesis involves a potentially explosive reaction step, see: Michael McCoy, *Generic Drugs*, 80 Chem. Eng. News 23, (2002).

191 See EPC Art. 64(2).

192 Bengt Domeij, *Pharmaceutical Patents in Europe*, at 287 (2000).

(in this case docetaxel trihydrate) using a different process than they can still market it.¹⁹³

The view of the originator company expressed above is easily understandable if one considers that a synthetic process for a drug has to be cost effective in order to allow for a profit margin. If the originator company has done an excellent job to identify the most favourable synthetic route, and if such route is still protected by a patent on the process once the patent on the compound itself is no longer available, then this may pose a difficulty to a generic company which is not to be underestimated. If the generics company does not succeed to come up with an alternative process (which in turn it will of course attempt to protect by a own process patent to protect its investments¹⁹⁴) allowing it to produce at a cost which is low enough for successful market entry, then the secondary protection has fulfilled its purpose.

Concluding, it must be stressed, that process patents do not come at zero cost to the originator company, and that a considerable amount of resources is put generally into the development of an industrial large-scale synthesis.¹⁹⁵ For example in the case of Taxotere, while the uninvolved bystander looking (with hindsight) at the methods *per se* might consider them to be standard chemistry taken from literature, it was at the time not obvious, that such chemistry could work on such a highly complex molecule without causing damage to it. Based on the data of the drugs analysed however, the possibility to patent around diminishes greatly the efficacy of a process patent to keep generics companies out of the market. Given the multitude of synthetic strategies which may be chosen to synthesise a given molecule, patents on processes are amongst those most easily circumvented. As mentioned above, the key parameter to keep in sight is cost-effectiveness.¹⁹⁶

193 *Id* at 331.

194 See Howard *supra* note 110 at 232.

195 Kim B. Clark, Steven C. Wheelwright, *Managing New Product and Process Development: Text and Cases*, 845-847 (1st ed. 1993).

196 Other factors to be considered involve regulatory and safety obligations.

d) New Uses

“[T]he pharmacologist and Nobel laureate James Black said, [that] the most fruitful basis for the discovery of a new drug is to start with an old drug.”¹⁹⁷ Pharmacokinetics and safety profiles are known and often approved by regulatory agencies for human use. This factor renders therefore the evaluation of the newly identified use in phase II clinical trials more rapid. It has been reported that in light of the fact that these studies typically last two years and cost \$17 million, the drug companies can “bypass almost 40% of the overall cost of bringing a drug to market”.¹⁹⁸ The repurposing or repositioning of drugs continues to attract increasing interest. Various known drugs are currently explored in clinical and animal testing for new indications.¹⁹⁹ By 2007, 24 previously approved active ingredients had been already repositioned.²⁰⁰

Patent protection of new indications is available in most jurisdictions. In EU such possibility exists since 1985 when the Enlarged Board of Appeal of the EPO granted to Eisai a patent (in the so-called Swiss-type claim form) for a second pharmaceutical use of a known compound.^{201, 202} Furthermore, the new European Patent Convention 2000 (EPC 2000), explicitly allows second-use claims.²⁰³ In practice, the possibility of the originator company to extend patent protection on a compound by means of a second medical use claim might be restricted. The fact that third parties can file applications for second

197 Curtis R. Chong, David J. Sullivan Jr., *New Uses for old Drugs*, 448 *Nature* 645, 645 (2007).

198 *Id.*

199 B. M. Padhy, Y. K. Gupta, *Drug repositioning: Re-investigating existing drugs for new therapeutic indications*, 57 *J. Postgrad. Med.* 153, (2011).

200 See Chong *supra* note 197.

201 Brian Whitehead, Stuart Jackson, Richard Kempner, *Managing generic competition and patent strategies in the pharmaceutical industry*, 3 *J. Intell. Prop. L. & Pract.* 226, 229 (2008).

202 G 5/83, OJ EPO, 64, 1985.

203 Art. 54 (5) EPC 2000.

medical uses induces pharmaceutical companies to disclose every conceivable medical use in the original patent.²⁰⁴

The scope of such patents is also limited to the specific new use. Originator companies might at maximum stop a generic competitor from promoting his version of a drug for the new use for example by advertisements or statements on the package insert or the package itself. In addition, they cannot prevent medical practitioners from prescribing for the patented new use a generic product which is already on the market for an earlier indication.^{205, 206} Hence, the main drawback of such patents is the off label use. Moreover, infringement by a generic company providing the drug but not actively marketing it for the new indication might be difficult to prove.

In Europe on the other hand, if approval for the new indication is obtained within 8 years from 1st MA and significant clinical benefits are shown one additional year of marketing exclusivity can be obtained.^{207, 208} The second applicant is not allowed to market drugs with labels for old indications during the protection period. This might provide a further incentive to invest into such research.

With respect to the two drugs studied in this thesis no major work has been done in this field by the originator. In the case of Xalatan investigation into new uses include a method of treatment of multiple sclerosis²⁰⁹, inner ear diseases²¹⁰ and in general further eye diseases. However, this work has been pursued by other companies. As far as Taxotere is concerned a patent was granted on its use for hepatoma but Sanofi-Aventis did not sustain this patent in the long run. Only a few patents have been filed in addition by other companies. On the other hand the clinical use of docetaxel already covers a broad range

204 See Whitehead *supra* note 201, at 230.

205 Philip W. Grubb, *Patents for Chemicals, Pharmaceuticals and Biotechnology* 220-222 (5th ed. 2010).

206 See Storz *supra* note 173.

207 Directive 2004/27 EC, art 10 (1), (2),(4), 2004, O.J. (L136) 34.

208 This provision is not retroactive but available only to MA after October 2005.

209 University of Sheffield, US 20020004525.

210 Synphora AB, WO 02/56890.

of cancer indications and may render obvious new chemotherapeutic uses.

Concluding, it may be remarked that the left-open possibility to invent around, the off label use and the possible difficulty to overcome the inventive step requirement render these patents of lesser commercial value and they do seem neither an effective strategy to support further investment in research nor an impediment to competition. On the other side, the additional one year market exclusivity that can be obtained in Europe by developing a drug with a new medical indication seems more effective. Profit erosion can indeed be postponed for one year.

e) Delivery Devices

The research on delivery systems aims to provide “[...] the right amount of drug to the right part of the body, at the right time and for the requisite period.”²¹¹ A delivery system different from the standard route of administration could increase patient convenience and compliance, optimise effects and reduce side effects. The delivery device might be a crucial component of the delivery system and research effort has to be placed on its development: for example, the device needs to be patient-friendly, robust and capable of a reliable release. An example is the delivery of drugs to the lungs by inhalation.²¹² In the case of Xalatan research on various applicators such as aerosol dischargers²¹³ or a punctual plug²¹⁴ aimed to address delivery of the effective amount of the drug directly to the eye.

The main drawback of patents that protect this research is the ease with which they can be circumvented. Secondly, such research and

211 See Crowley *supra* note 126, at 539.

212 N. R. Labiris, M. B. Dolovich, *Pulmonary drug delivery. Part II: The role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications*, 56 Br. J. Clin. Pharm. 600, (2003).

213 WO 2004/028421.

214 WO 2007/115259.

the patents connected to it stem very often by more specialized companies as shown in the Xalatan case study. As already mentioned,²¹⁵ QLT inc. was one of the more prolific players regarding patent filing in this field of research. QLT's patent application (WO 2007/115259) on nasolacrimal drainage system implants has been granted in U.S. and Japan while it is still pending in Europe. Phase II clinical studies of this device showed promising results.²¹⁶

Patents that cover such delivery devices can only further protect the use of the concerned drug in connection with the patented system and do not create any market entry barrier. They do not impede the administration to the patient of generic version of the traditional drug or the use of other versions belonging not to the originator company. The economic success of such delivery device is more dependent from the marketing strategy.

2. Xalatan SPC Request: a Case for Competition Law?

The patent protection (EP 0364417) for Xalatan based on obtained SPCs was due to end in July 2011. This however was not the case in Italy where the expiry date was still September 2009 and generic companies could enter the Italian market already on that date. To maintain its market position also in Italy, Pfizer in 2002 (13 years after the parent patent) filed a divisional patent application of the basic patent (EP 1225168). The patent on the divisional application granted²¹⁷ in January 2009 was then validated only in Italy. Successively, an SPC based on the divisional patent could be requested. This conduct fell under scrutiny of the Italian competition authority which

215 See section II B 2 f) of this thesis.

216 Press release, QLT inc., QLT shows positive 4 week efficacy in phase II study for glaucoma using latanoprost punctual plug delivery system, (Aug. 29, 2011).

217 EP 1225168 was revoked in October 2010 because new findings were added.

defined it as a complex strategy to avoid generic entrance.^{218, 219} According to the authorities such strategy allowed to artificially prolong Xalatan's protection in Italy from September 2009 to July 2011 and moreover, due to an additional paediatric extension in various European countries including Italy, to January 2012.

The conduct of Pfizer was strongly criticised by the Italian Competition Authority (ICA). The ICA sustained that this situation determined a climate of legal uncertainty with respect to the possibility of commercializing equivalent drugs based on latanoprost. This uncertainty was further increased by numerous warnings sent to the generic companies concerning an administrative and civil dispute in case of commercialization of the corresponding generic before July 2011.²²⁰ This behaviour was said to have delayed by seven months the commercialization of generics (Ratiopharm applied later due to this legal uncertainty) causing a big economic loss to the Italian State health system (NHS). On the other hand this delay for Pfizer meant a profit of approximately 17 million Euro (ICA calculation). In a press release the ICA stated: "Thanks to its strategy, Pfizer managed to: 1) increase the effective market entry costs for the manufacturers of generic drugs; 2) delay the market entry of Xalatan-equivalent specialty drugs by at least 7 months; 3) maintain the *de facto* exclusive commercialization of medicines based on latanoprost even after patent coverage had expired; 4) cause an estimated 14 million Euro in lost savings by the NHS. These elements led the Authority to classify the sanctioned competitive violation as very serious."²²¹

The Italian authorities objected also to the request of paediatric extension stating that glaucoma is a disease which typically affects old

218 See AGCM *supra* note 96.

219 Michele Giannino, *Patents: Beware of competition law! Relying on patents to extend protection for medicines may be anticompetitive*, 7 J. Intell. Prop. L. & Pract. 391, (2012).

220 Press release, AGCM, Drugs: Pfizer sanctioned with 10.6 million Euro fine for abuse of a dominant position (Jan. 17, 2012).

221 *Id.*

people and therefore this request was also an action with the only purpose to extend patent protection.²²²

The ICA relied on the General Court's judgment in AstraZeneca²²³ and argued that such use of administrative procedures by a dominant company is outside the competition on the merit. However, some authors comment that Pfizer behaviour is "[...] nothing more than attempt to rely on the patent and SPC system to protect its innovative glaucoma treatment across the European Union for the maximum period allowed by the legislation."²²⁴ Such legislation is intended to foster innovation and if the available measures of protection are arbitrarily reduced by competition law incentives to develop new drugs will be reduced.²²⁵ This argument was also raised in the AstraZeneca case but the then Competition Commissioner Neelie Kroes commented "[m]isleading regulators to gain longer protection acts as a disincentive to innovate and is a serious infringement of EU competition rules."²²⁶ While this statement was objected as being without support²²⁷ it might be remarked that innovation cycles might be prolonged.

Pfizer appealed the decision and interestingly the Italian administrative court overruled in its entirety the findings of abuse of a dom-

222 See AGCM *supra* 96 at ¶ 214.

223 European General Court, T-321/05, AstraZeneca v Commission, July 1, 2010, E.C.R. II-02805.

224 Christopher Stothers, Marco Ramondino, *Aftermath of AstraZeneca and the Pharmaceutical Sector Inquiry: The Big Chill?*, 12 Eur. Comp. L. Rev. 591, 594 (2011).

225 *Id.*

226 Press release, IP/05/737, (Jun.15, 2005).

227 Johanna Müller-Graff, Filipe Fischmann, *Der Fall AstraZeneca: "Tool boxes" im Arzneimittelsektor – wer hat die besseren Werkzeuge und welche sind erlaubt? Zum Urteil des Gerichts der Europäischen Union vom 1. Juli 2010, Rs. T-321/05*, 792 GRUR Int 1, (2010) at 10.

inant position.^{228, 229} The court found that, by relying on the provisions of the EPC and the SPC regulation, Pfizer had been using legal measures available to it and not carried out procedural abuses or misrepresentations. In particular, the court stated that the ICA, by finding the divisional application abusive with the intent to exclude generic companies, had not considered that the divisional had been filed seven years before the supposed generic market entry.²³⁰ The Court also commented that the ICA seemed to have based its decision on the revocation of the divisional patent by the EPO ignoring that such revocation could be appealed and it was not final.²³¹ The Court's decision may still be appealed.²³²

With its actions (the divisional patent application and the SPC request based on the divisional) Pfizer tried to remedy a former mistake and as a consequence to obtain more protection in Italy. Such strategy used instruments allowed by patent law²³³ and by the SPC regulation²³⁴. From a commercial point of view this behaviour is legitimate, and the Italian administrative court held that it has also legal bases.

Nonetheless, the AstraZeneca case and the Pfizer case should warn dominant companies that, by making use of the patent and/or regulatory system to delay generic entry and to avoid profit erosion, they

228 Pfizer v AGCM, Tribunale Amministrativo Regionale [Regional Administrative Court] per il Lazio Sezione Prima, 07467/2012 REG.PROV.COLL., Sept. 4, 2012 available at http://www.giustizia-amministrativa.it/DocumentiGA/Roma/Sezione%201/2011/201109968/Provvedimenti/201207467_01.XML (last visited Sept. 12, 2012).

229 For a summary of the decision in English see Micaela Modiano, *Italian u-turn on latanoprost abuse of dominant position dispute*, The SPC blog, (Sept 7, 2012) available at <http://thespcblogger.blogspot.de/2012/09/italian-u-turn-on-latanoprost-a-buse-of.html> (last visited Sept. 11, 2012).

230 See Pfizer *supra* note 228 at 58.

231 *Id* at 61.

232 See Modiano *supra* note 229.

233 R. 25(1) EPC 1973: Filing of divisional application was possible for any pending application. The rule has since been amended introducing a time limit for filing divisional applications (R. 36 EPC 2000).

234 The SPC regulation does not draw any distinction between parent and divisional patent, see Stothers *supra* note 224.

might fall under scrutiny of competition law and incur a fine. The use of certain ways of action permitted by other branches of law²³⁵ does not preclude the application of competition law.^{236, 237}

Finally, a comment needs to be made regarding the objection on Xalatan paediatric studies.²³⁸ Although the percentage of children who need such drug is low (around 1%) it is duty of the health system to guarantee that a safe drug is available to them. The scope of paediatric extension is to give an incentive to companies to provide such drugs, therefore the ICA point of view cannot be shared and Pfizer's use of paediatric extension should have not been penalized.

C. Patent Strategy and Innovation

The main criticisms on pharmaceutical R&D are directed to the reduced number of NCEs approved by the FDA and the EMA and to the reduced number of new breakthrough drugs compared to "me-too drugs" (follow-on drugs). Nonetheless, drugs based on new biological mechanisms continue to be discovered (e.g. Isentress the first HIV-integrase inhibitor introduced by Merck in 2007).²³⁹ The reasons for the apparent reduction of NCEs are various.²⁴⁰ However, these are not within the scope of the present study.

235 E.g. AstraZeneca deregistered a Marketing Authorisation, which *per se* is not forbidden by the regulations guiding the pharmaceutical market.

236 See AstraZeneca *supra* note 223 at ¶677.

237 Josef Drexl, *Astra Zeneca and the EU Sector Inquiry: when do patent filings violate competition law?*, Max Planck Institute for Intellectual Property and Competition Law Research Paper No. 12-02, 21 (2012).

238 Vanessa Peden, Imti Choonara, Brian Gennery, Hilary Done, Recruiting Children to a Clinical Trial, 4 Paed. Perinat. Drug Ther. 75, (2000): "In children, one can only study those children who are to undergo a clinical procedure and may benefit from a medicine."

239 John E. Calfee, White Paper on Pharmaceutical Market Competition Issues, June 2, 2008, available at <http://62.102.106.100/content/default.asp?PageID=559&DoCID=4894> (last visited Aug. 3, 2012).

240 See Chapter I of this thesis.

Innovation may be regarded as the creation of an improved product. Based on this understanding, the question arises whether improvements made on existing drugs can be disqualified. The TRIPS agreement states “[...] patents shall be available for any inventions,[...], in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. [...] without discrimination as to [...] the field of technology [...]”.²⁴¹ Technical advance in most cases proceeds incrementally and innovators are able to obtain patents on improvements. Such improvements in the pharmaceutical field may be of considerable practical significance to patients and other customers. It has been stated that “[s]ignificant incremental innovation to existing pharmaceutical products has been occurring in the form of supplementary approvals for new dosages, formulations, and indications. These innovations account for a substantial share of drug utilisation and associated economic and medical benefits. Productivity trends for research and development based on counts of new molecular entities alone have therefore overlooked an important source of innovation in pharmaceuticals.”²⁴² As already mentioned, also the EU Commission in its recent sector inquiry recognized the importance of subsequent improvements made to the initial invention.²⁴³

For example, patents on drugs combinations are very often criticized with respect to their inventive step. They are often seen by various interest groups as deviating resources from original research dedicated to identifying treatments for unmet medical conditions. However, advances made in the field of the so-called combination therapies are in many therapeutic areas indispensable (e.g. viral diseases or cancer) as already mentioned earlier.²⁴⁴ Combination therapies can have superior effect compared to the single components. In

241 Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), Art. 27, Apr. 15, 1994.

242 Ernst R. Berndt, Iain M. Cockburn, Karen A. Grepin, *The impact of Incremental Innovation in Biopharmaceutical*, 24 *Pharmacoeconomics* 69, (2006).

243 See sector inquiry *supra* note 120.

244 See section IV A 4 of this thesis.

the case of Latanoprost, research into drug combinations has been carried out, as no drug modulating the intraocular pressure was able alone to address the needs of the complete (and growing) patient population. While achieving an average reduction in eye internal pressure of about 30% by treatment with Latanoprost results to be sufficient in the majority of the patients, there is however a significant patient subpopulation, where this reduction of ocular hypertension still does not lead to a curative effect. Xalacom (Latanoprost plus Timolol) allows reducing further the intraocular pressure in patients where Xalatan alone has an insufficient effect.²⁴⁵ This demonstrates that research carried out in this area is of interest to the public and thus patents are important to incentivise investment in such research. On the other hand, patent law should guarantee that only for demonstrated new increments companies will receive exclusivity. Patent protection on Xalacom could not be obtained because the originator company had been publishing more than 2 years before the priority date the results of a clinical study demonstrating exactly the unexpected over-additive (synergistic) effect.^{246, 247}

Research in formulation attracts similar criticisms. The new and improved composition aimed for in the case of docetaxel tried to overcome a safety issue. As the drug in its original formulation is dosed intravenously in a solution with a fairly high content of ethanol, in some cases the occurrence of alcohol intoxication during infusion was observed.²⁴⁸ These events were particularly pronounced in patients with a history of alcohol dependence.²⁴⁹ The identification of a low-alcohol formulation could provide the patient benefit needed and remediate the problem noticed and therefore, cannot be seen as a de-

245 William C. Stewart, *Combination Therapy: Is the Whole Greater?*, Rev. Ophthalmol., Jun. 15 2005.

246 See Diestelhorst *supra* note 82.

247 This demonstrates the importance of an effective internal review process prior to external publication to hold back important research results until a patent application has been filed.

248 *Supra* note 41.

249 Anonymous, *Docetaxel: Alcoholic intoxication due to alcohol excipient: case report*, Reactions Weekly 13, Issue 1375 (Oct. 9, 2011).

viation of resources. This improved composition was subsequently patented, investigated in clinical trials and market authorisation was obtained. However, the patent family protecting this improvement got under fire by generic drug providers and in the end got revoked or was held unenforceable. In this context, it is important to note, that the revocation due to obviousness was mainly caused by the drafting of the patent application and especially its claims which on one hand did not take sufficient account of pre-existing own patents and on the other hand left room for interpretation.²⁵⁰ In summary, the originator had basically failed to protect his new invention by not delimiting it sufficiently clear from the prior art.

In addition, competition is fostered because further innovation is open to anyone. For example with respect to Xalatan first, several follow-on drugs based on prostaglandine derivatives have been developed by various companies (e.g Saflutan, Travatan, Lumigan); and second, further studies on improved formulations attempting to address side effects were sponsored mainly by competitors, as already mentioned.²⁵¹

D. Summary: Taxotere v Xalatan

A comparison of the originator filing activity concerning the two drugs Taxotere and Xalatan can be made. Successive to the filing of their respective basic patent, activity in the different areas of research was correlated to the studies necessary for their commercialization: in particular formulations, process and drug combinations in the case of Taxotere and formulations, process and delivery devices in the case of Xalatan.

In the case of Taxotere, the originator company's filing activity continued up to the expiry date of the basic patent (2011). In its later phase it was mainly directed to the finding of more practicable for-

250 See Aventis *supra* note 145.

251 See section IV B 1 a) of this thesis.

mulations improving patient comfort and moreover to the discovery of new combinations which could give better therapy results both in term of reduced side effects and patient response. Instead, in the case of Xalatan filing activity was observable during the first 15 years, ending however completely in 2003. The activity following the drug's launch from 1996 to 2003 was directed mainly to the discovery of new delivery devices to improve application of the drug and to new combinations. Another difference is the number of patent applications directed to the identification of alternative compounds resembling the structure of Taxotere (i.e. derivatives of the taxan core) while in the Xalatan case, such research does account for a more limited number of applications. This may be attributed to the different disease targeted. Since cancer cells may become resistant to a drug, there is a great need to identify alternative compounds.

In both cases there is strong indication that the filing of patents successive to the basic patent was not of any help in prolonging exclusivity after the end of the due protection. Most of the patent applications concerning new combinations of either Xalatan or Taxotere were not granted, leaving the commercialization of some important combinations open also to competitors and generic companies. Taxotere formulation patents were mostly attacked on grounds of invalidity due to obviousness and subsequently restricted and/or revoked. Patent applications regarding delivery devices for Xalatan were equally largely unsuccessful, as ocular delivery devices were known in the art, and no specific effects deriving from or influence on the use of Xalatan in such devices could be demonstrated.

Patents in the area of derivatives may be regarded as not having any influence on the marketed drug, neither during the monopoly time, nor at the later stage. Such patents may however be of significant value when the need arises to identify an improved version or a follow-on drug. In fact, this has happened in the Taxotere case, where upon expiry of the patent protection for docetaxel, the drug Jevtana²⁵² has been introduced into the market by Sanofi. In 2011, sales of Jevtana

252 See this thesis at § III A 2 f).

increased by 135.4% reaching 188 million.²⁵³ However, as this drug is currently used as a second line treatment after Docetaxel it “is not expected to become a blockbuster with sales on par with [...] Taxotere”.²⁵⁴

In both the presented case studies the used strategy did not help to avoid profit erosion after the generic market entrance. Concerning Taxotere it was announced: “As expected, sales of Taxotere® declined significantly (-67.5% to €150 million) in the fourth quarter, reflecting generic erosion in the U.S. (sales down 90.4% to €14 million) and Western Europe (sales decreased 84.2% to €23 million). Full year 2011 sales of Taxotere® were €922 million, down 57.0%.”²⁵⁵

With respect to the second example analyzed in this thesis it appears that after commercialization of follow-on drugs although market shares declined²⁵⁶ sales were maintained at high level²⁵⁷ probably due to the growth of the patient base. However, with the generic entrance in 2011 sales decreased by two thirds.²⁵⁸ The data for the two brand drugs relying on the latanoprost patent, Xalatan itself and Xalacom (latanoprost/timolol), indicates a decline of sales in the U.S. by two thirds to US \$ 159 million in the first nine months of 2011. During the same period in Europe where SPC protection ended in January 2012 10% reduction of the sales was observed.²⁵⁹ It has also been reported that in the near future the glaucoma therapeutics market will be dominated by generic drugs. New me-too drugs or product extension will likely not be able to capture a significant market share if they offer a safety and efficacy profile only slightly better than the mar-

253 Press release, Sanofi, 2011 Results Benefit from Genzyme Acquisition Net Sales and Business EPS1 up 9.2% in Q4 (Feb. 8, 2012), at 3.

254 Jessica Merrill, *2010 Drug Launches: A Year of Firsts Offers Hope for a Rebound*, 11 *The Pink Sheet*, Jan. 3, 2011, at 3.

255 *Supra* note 253.

256 Jeff Viksjo, *Pharmaceutical Treatments in Ophthalmology*, 1 *Healthcare Observer* 2, 3 (2009).

257 Anonymous, *News & highlights from week 40*, 12 *Curr. Pat. Gaz.* 1, (2009).

258 Anonymous, *Latanoprost SPC ends in top EU markets*, *Generics bulletin*, Jan. 13, 2012, at 24.

259 *Supra* note 258.

keted drugs. This situation could change only by the development of drugs with novel mechanism of action targeting the cause of the disease.²⁶⁰

E. Conclusion and Suggestions

A common theme in both case studies is that subsequent patent applications by the respective originator companies failed to adequately protect further advances (too early publication of own results and patent drafting). More care needs to be taken in regards of existing prior art. As already mentioned the invention must be more clearly delimited and the claims should be more specific to have a better chance to overcome obviousness requirements and to sustain an invalidity attack. Very important is also an effective document clearance inside the company to avoid novelty problems caused by pre-publication as in the case of Xalatan.

In addition in the case of research on combination patents that aim to protect these results would be more useful and valuable if the combination could be administered in a single formulation. In this way the problem of off label use could be avoided.

Finally, because these secondary patents are often a weak strategy to cover investment in research a possible additional incentive could be a longer time of marketing exclusivity for a demonstrated clinical benefit as the additional year for a new use available in Europe.

260 Anonymous, *Patent expiries to hit glaucoma drug market growth until 2018*, The Pharma Letter, Sept. 18, 2011.

V. Final Remarks

The purpose of this work was to highlight a few points concerning lifecycle management which is very often considered an issue and sometimes labelled as “evergreening”.²⁶¹ First, critics of this business model argue that secondary patents prolong the monopoly the originator holds on a drug at a cost for society.²⁶² In both the cases at present analysed this could not be confirmed. Also in cases of examples where secondary patents led to commercial success, like the protection of Symbicort (Asthma treatment: combination of budesonide/formoterol), it needs to be stressed that such a patent does not constitute a unilateral advantage for the originator company.²⁶³ This is for two reasons: first, society has the choice between the classical and the improved treatment and second, any third party, desiring to provide the original drug not anymore covered by a patent, is free to offer it to the market and to compete with the originator or others.

The second argument voiced against lifecycle management is that the originator companies put their efforts only on maintaining exclusivity on old blockbusters and not invest in NCEs. However, this argument fails to acknowledge that a successful product has to generate revenue for a multitude of unsuccessful projects.²⁶⁴ In this context it has also been remarked: “A study by the U.S. Federal Trade Commission indicates that brand-name companies currently file more patents to protect market exclusivity of their products. However, a few companies are using these frivolous patenting [strategies] to ob-

261 John R. Thomas, *Patent “Evergreening”: Issues in Innovation and Competition*, Congressional Research Service, (Nov. 13, 2009): this article highlights the debate on lifecycle management.

262 Kristof Roox, Julia Pike, Andrew Brown, Stefan Becker, *Patent-related Barriers to Market Entry for Generic Medicines in the European Union*, 12 (Kristof Roox ed., 2008): publication of the European Generic Medicines Association.

263 See AstraZeneca *supra* note 187.

264 See Jacob *supra* note 13.

tain market exclusivity to such an extent that these strategies may be referred to as abuse.”^{265, 266} While there are surely exceptions, one needs to keep in mind that also small increments might constitute innovation, and address so far unmet needs as was demonstrated throughout this thesis.

Another criticism raised is that the further filing increases costs as these might cover essential aspects of the marketed product such as a specific formulation or manufacturing process, for which substitutes need to be developed. However, this argumentation falls short of its target.²⁶⁷ Emphasis should be placed on the research and development cost. The development cost of a new drug is very high, the development of a new use still has a considerable cost also if reduced (due the clinical trials needed to prove efficacy), while on the other hand the costs of simply reproducing the drug is very low.²⁶⁸

On the other side, it must be conceded that if such granted secondary patents are of low quality this creates additional strain on resources. This cannot be considered a specific issue of secondary patents in the field of pharmaceuticals but in principle regards all patents also if data reported might sustain such arguments.²⁶⁹

As has been shown by performing the two case studies it oftentimes is a major problem to overcome own prior art and secondary patents are more vulnerable due to the increased knowledge in the public do-

265 V. N. Bhat, *The Challenges of the new EU Pharmaceutical legislation Pharmaceuticals Policy and Law*, Volume 6, 109-122 (J. L. Valverde, P. Wassenberg eds., 1st ed. 2005) at 118.

266 The “frivolous” patents mentioned in this context refer for example to pill boxes or computerized dispensing systems for specific drugs.

267 If a drug product could only be protected *via* the coverage of its active ingredient, any investment into the identification of an efficient process of production or a “patient-friendly” formulation could be considered to be without return and therefore not worth making. If on the other hand such an investment is made but not incentivised or protected, then the use of the results of such research would constitute a form of “free-riding”, which may not be considered to be a competition on the merits.

268 See Bhat *supra* note 265.

269 See sector inquiry *supra* note 120.

main. Therefore, more care is needed in drafting such patents. In addition, they might not be the best way to incentivise research on improvements of existing drugs. Other instruments like an additional market exclusivity period for a proven real benefit might be an option.²⁷⁰

The two case studies demonstrate that the originator companies concentrate their filing activities mostly during the premarketing period when there is not yet any guarantee of an impending commercial success, in some cases not even of a successful passing of the clinical trials. The spread of the patents over a period of many years also reflects the fact that the basic patent must be filed as early as possible when not all the research has been already done. The patent filing after the successful marketing of the drug derives from a multitude of entities of which the originator is only one. In addition, the large number of patents applications withdrawn by the originator company or not granted, demonstrate that the patent system works to effectively filter the applications, as desired by the Commission in its Pharmaceutical Sector Inquiry.²⁷¹

In summary, it is believed, that the case studies do not indicate the presence of “evergreening” strategies, but reflect the normal course pharmaceutical research is taking, where one step follows the other, and investment into a certain aspect or another is done according to the needs of the project until it arrives at the stage of marketing authorisation. While this filing strategy may be partially attributed to an interest in not losing a market position gained, at the same time the research done is a benefit to the public and may not be meaningfully carried out at an earlier point in time. In stating this however, it must not be neglected that sometimes the strategies used stretch the limits of competition on the merit.

270 A similar conclusion has been reached in: Manfred E. Wolff, *Drug Discovery Market Exclusivity After KSR: The Challenge to Pharmaceutical Scientists and the US Congress*, 100 J. Pharm. Sci. 3044, 3052-3053 (2011).

271 See sector inquiry *supra* note 120.

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