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.

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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 Court[135] 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 Germany[138] 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 s*upra* note 40.
132 See Sector Inquiry s*upra* 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 Patentdatabas).
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 5[146] of US 5,750,561 and claim 7[147] 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, R^7 is phenyl or t.butoxy, R^6 is hydrogen, R^5 is acetyloxy or hydroxy, R^3 and R^4 taken together form an oxo radical, R^1 is hydroxy and R^2 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 R^5 is hydroxy and R^7 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 4,814,470[151] and therefore the range was regarded as being anticipated.[152] Additionally, the Court affirmed the finding of inequitable conduct[153] 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 lateron 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 combination[166] (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 Europe[170] 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 doctors[173] 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 groups[174] 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 Regulation[181] 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/EPO-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 then 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 investments[194]) 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]

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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 sclerosis[209], inner ear diseases[210] 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

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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 dischargers[213] or a punctual plug[214] 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

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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 granted[217] 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.