V. IMPLICATIONS OF THE PATENTABILITY REQUIREMENTS ON INNOVATION AND COMPETITION IN THE PHARMACEUTICAL INDUSTRY

The patent system grants the right to exclude others from practicing the claimed invention. However, it does not convey the freedom to operate the invention.[970] The question of the freedom to operate mainly concerns whether one can practice in a certain area without infringing a patent held by another party.[971] It is quite possible for overlapping patents to be held by different parties leaving no single party with the freedom to operate.[972] If practicing the invention infringes another's patent, one patentee may consider avoiding another's patent, while trying to obtain a license from him, or invalidating his patent.[973] Sometimes designing-around the other patent is originally impossible, such as in the case of practicing a combination of active ingredients, one ingredient of which is covered by a valid patent; or in the case where it is very hard to separate one polymorph, since it is easily included even in trace amounts in the process of manufacturing the basic substance.

Chapter IV argued that there is a gradual relaxation of patentability requirement for selection invention in EPO practices and the case laws of Germany, the U.S., the U.K., and Korea. The lowered thresholds of patentability have a significant impact on competition. In particular, as the scope and length of patents defines what competitors may do, this chapter will examine the scope and length of second generation patents in this context.

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970 *Miller/Evans*, 2010, 2-5; *See e.g.* 35 United States Code ("35 U.S.C.") § 154 (2010) "the right to exclude others from making, using, offering for sale, or selling […] or importing the invention".

971 *Miller/Evans*, 2010, 6.

972 *Miller/Evans*, 2010, 6.

973 *Miller/Evans*, 2010, 4.

A. Concerns about lowered patentability

Firstly, patent offices are gate keepers of patent quality. Once the patent offices fail to fulfil their duties, the quality of patents issued deteriorates. One result of low quality patents is patent litigation war that is waged by the companies that can afford the cost of litigation and that try to obtain patent-based property rights on existing technologies.[974]

1. General concerns about lowered patentability

a) Superfluous second generation patents

The radical increase in patent applications and patents on second generation inventions was discussed in chapter III.B.5. To explain some impacts of these increases, the lesson from the "wild card patent term extension" is noted here. It was the key recommendation of a white paper prepared by the Infectious Diseases Society of America (IDSA) to incentivize the pharmaceutical companies to research into anti-infectious agents as supplementary intellectual property protection.[975] The IDSA recommended a balance between the special efforts needed to bring more medications to patients and the concerns about the social costs of those efforts.

A so-called, "wild card" patent term extension is a kind of transferable patent term extension concept. A company which successfully develops and acquires marketing approval for a certain antibiotic could extend the market exclusivity period of "another" FDA-approved drug for 2 years.[976] As is clear from the term "wild card" itself, the company may choose any other approved drug in its portfolio for which to apply for patent term extension. A study reported that this kind of patent extension as the compensation for treating multi-drug-resistant *pseudomonas aeruginosa* would be cost-neutral for 10 years after approval of the new antibiotics and would save society around $4.6 billion for 20 years after approval.[977]

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974 *Jaffe/Lerner*, 2004, 74.
975 *IDSA*, 2004, 24.
976 *IDSA*, 2004, 24.
977 *Spellberg, et al.*, 35 Infection 167, 170 (2007).

However, this proposal has been highly controversial and its proposed inclusion in the Project Bioshield II Act of 2005[978] was ultimately rejected. One of the bases for rejection was that this kind of newly created patent right would not only be inefficient, but would also create tens of billions of dollars in annual patent taxes[979] on other common diseases.[980] Critics also argued that this is very unfair for those patients who must pay an extra patent tax on the particular drug which is chosen for extension.[981] This is mainly because the patent term extension on the blockbuster drug would provide a tremendous income by transferring the cost to the patients, which would in turn be an extra burden to the health insurers. This would also be anticompetitive, because only the companies that already have a patent whose extension was exceptionally lucrative would contend for the reward[982] and because the generic companies would have to wait another two years to launch their products onto the market.

Similar conditions can be observed in the thriving area of second generation patents. By obtaining second generation inventions, the move of market exclusivity to these types of patents[983] could work like a patent term extension. Namely, the patients would have to pay an extra patent tax, which means higher exclusivity prices on the product covered by the selection patents; this would be a burden on society and on health insurers. The generic company would have to wait years longer, and the selection patents would follow the lucrative patents. More important, unlike the wild card patent term extension, society would not acquire something such as new antibiotics in the case of second generation patents. There is hardly any reason not to grant a patent to an invention that meets patentability requirements, but the social costs should be taken into consideration. If this is a consequence of lowering patentability requirements, the patent system could help to fix the problem.[984]

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978 Project Bioshield II Act of 2005. S. 975, 109th Congress (2005–2006).

979 Patent tax means the pharmaceutical patent rent appropriation upon consumers and insurers through higher prices during the period of marketing exclusivity.

980 *Outterson/Samora/Keller-Cuda*, 7 Lancet Infect. Dis. 559, 561-62 (2007).

981 *Power*, 12 Clin. Microbiol. Infec. 25, 32 (1998); *Nathan/Goldberg*, 4 Nat. Rev. Drug Discov. 887, 888-89 (2005); *Outterson/Samora/Keller-Cuda*, 7 Lancet Infect. Dis. 559, 562 (2007).

982 *Nathan/Goldberg*, 4 Nat. Rev. Drug Discov. 887, 889 (2005).

983 See subsection V.D.3.c).

984 See subsection VI.E.

b) Increased patent exclusivities and amplified uncertainties thereof

Along with the lowered novelty requirement, the lenient obviousness requirement more than any other has resulted in increased number of marginal patents, which could constrain the freedom to operate basic inventions.[985] The relaxed enablement requirement[986] would bring broader patent scopes.[987] Thus, the lower the patentability requirement becomes, the more patent applications (with a broader scope of patents) would be filed, the less attention would be paid to patent examinations considering the limited amount of resources and time in the patent offices, which would in turn lead to poorer quality of patents.[988] Lemley argues, regarding the low standard of patent examination ("Rational Ignorance"), that it would be socially efficient to ignore the low standard itself, since i) the majority of patents would have small economic importance and cost little to grant despite being invalid, and ii) only a fraction of all patents carrying heavy importance would be dealt with in the judicial system, which is expensive but still more efficient because of the small numbers that would be litigated.[989]

However, since it would be easier to obtain patents thanks to lower patentability requirements, the incentives to file marginal patent applications would increase and would complete this vicious circle.[990] For example, a single search for the keyword "esomeprazole" in the patent database of EPO as of December 20, 2013, showed 347 patent applications filed by many applicants, including AstraZeneca.[991] If the patent applications mentioning different terms of esomeprazole, such as its chemical name, are also taken into account, the number increases. In addition, this number includes only the second generation patent applications for esomeprazole, not those for

985 *Thomas*, 52 Am. U. L. Rev. 771, 773 (2003) ("A lenient view of nonobviousness is ordinarily seen as inventor-friendly and propatent. But this trend allows the patenting of marginal inventions, increasing the possibility that primary inventors will have to share the rewards of their pioneering inventions with follow-on inventors of improvements.").

986 This was not observed in the selection patents.

987 *Burk/Lemley*, 89 Va. L. Rev. 1575, 1953-54 (2003) (This is because if the invention is not enabled by the patent specification, the permissible breadth of a patent would be narrowed.).

988 *Friebel et al.,* 2006, 36; *Jaffe/Lerner*, 2004, 175-76.

989 *Lemley*, 95 Nw. U. L. Rev. 1495 (2001).

990 *Jaffe/Lerner*, 2004, 174-76.

991 Espacenet, available at: http://worldwide.espacenet.com. (Last accessed on December 20, 2013).

omeprazole. Moreover, the difficulty of appealing to a court should not be overlooked simply because of the cost of litigation, which pre-empts opportunities for many people to obtain judicial review. In other words, Lemley's rational ignorance argument can be applied to the case when most applicants can afford the costs of litigation. Furthermore, the poor quality of issued patents would result in overly broad patent claims and patent thickets.[992] These all, in turn, would force society to pay the increased exclusivity tax.[993]

Even the companies that could afford the litigation costs would still face the difficulty of accessing their positions because of rationally ignored low patentability standards. Using omeprazole as an example, in Europe, in 1994, AstraZeneca filed a patent application for a salt of an enantiomer, Nexium®, which the EPO granted a patent in 2000, with the following claim 1:

> "The magnesium salt of [S-enantiomer of omeprazole, i.e. Nexium®]."[994]

Following opposition by Ratiopharm in 2001, the EPO finally revoked the patent for this enantiomer in 2007.[995] But the story did not end there. AstraZeneca thereafter filed a divisional application of the patent application in 2000,[996] for which the EPO granted a patent in 2009 with the following claim 1:

> "The use of a magnesium salt of [S-enantiomer of omeprazole, i.e. Nexium ®] with an optical purity of ≥ 99.8% enantiomeric excess (e.e.) for the manufacture of a medicament for the inhibition of gastric acid secretion."[997] [Underline added]

However, oppositions was filed first by Hexal AG and then by others, and the patent was revoked in August 2011. [998] AstraZeneca immediately ap-

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992 *Ann*, 2009, 363.

993 *Kefauver*, 1966, 3 (noting "[e]very day in our lives monopoly takes its toll").

994 European Patent No EP0652872B1.

995 European Patent Register of European Patent No EP0652872 B1, available at: https://register.epo.org/ espacenet/regviewer (Last accessed on December 20, 2013).

996 This is one of the reasons the EPO limited the duration during when an applicant can file divisional applications under Rule 36.

997 European Patent No EP1020461B1, available at: https://register.epo.org/espacenet/regviewer (Last accessed on December 20, 2013).

998 European Patent Register of European Patent No EP1020461B1, with the record of 33 notices of oppositions.

pealed to the decision based on the suspicion of partiality, but it was rejected in November 2012.[999]

The situation in the United States is somewhat different. AstraZeneca settled with the first Paragraph IV[1000] filer Ranbaxy Pharmaceuticals in 2008, with Teva Pharmaceuticals in 2010, with Dr. Reddy's Laboratories in 2011 [1001], with Sandoz and Sun Pharm in 2011, and with Lupin Limited in 2012. [1002] While the ANDA filers conceded that all patents at issue were valid and enforceable, AstraZeneca granted licenses to these ANDA filers to allow them to enter the US American market in 2014.[1003] Meanwhile, AstraZeneca has either received a Paragraph IV notice letter from, or commenced a patent infringement action against four other companies.[1004]

Nexium® was launched in the European market in 2000 and in the American market in 2010,[1005] although the generic version of Nexium® will be available in some European countries when the 10-year data exclusivity has run out[1006] and in the American market in 2014 after the expiration of the patent. One may wonder why the long settlement history is enumerated here. Three reasons: Firstly, neither the validity of the omeprazole, nor the validity of the enantiomer of omeprazole (esomeprazole), nor even the validity of the magnesium salt of the esomeprazole, but the validity of certain purity of the same salt in esomeprazole entailed this long history. Secondly, even without resorting to harsh arguments and reports on the dubious effective-

999 *AstraZeneca/Hexal et al*., T 1760/11 (2012).

1000 Code of Federal Regulations Title 21, § 314.94(a)(12)(i)(A)(4): "[...]the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, [...]that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the abbreviated application is submitted. The applicant shall entitle such a certification 'Paragraph IV Certification.'".

1001 *AstraZeneca*, AstraZeneca Annual Report 2010, 186.

1002 *AstraZeneca*, AstraZeneca Annual Report 2011, 185.

1003 *AstraZeneca*, AstraZeneca Annual Report 2010, 186; *AstraZeneca*, AstraZeneca Annual Report 2011, 185.

1004 *AstraZeneca*, AstraZeneca Annual Report 2011, 185.

1005 *AstraZeneca*, AstraZeneca Annual Review 2000, 7.

1006 For example, http://www.shop-apotheke.com/arzneimittel/6456801/esomeprazol-ratiopharm-40mg-hartkapseln.htm?know=search%3Aesomeprazole~. (Last accessed on December 20, 2013).

ness of S-omeprazole over omeprazole,[1007] both the results of revocation for the patent covering a magnesium salt of esomeprazole in Europe and the tedious list of settlement with generic manufacturers in the United States, have established little if any improved effect of esomeprazole over omeprazole. Last but not least, even if the patent were ultimately invalidated, AstraZeneca have successfully delayed the launch of generic versions by competitors for many years.

The practice of granting a patent mistakenly or easily to a less significantly advanced invention, in turn, would cause substantial expense for society, because a technology that was already in the public domain could become private property.[1008] More important, the uncertainties created by overlapping patent claims and the uncertainties about the validity of patents due to the poor quality of examination would be major problems for players in the industry.[1009]

c) Encouraged waste of resources

Furthermore, the expensive process of obtaining a patent results in the waste of resources and money. In addition, almost every single step incurs cost. Consequently, the increased number of patents and of patent applications themselves threatens industry as well as society. Firstly, search costs should be mentioned. A large number of second generation patents must be searched and analyzed to determine whether there is room for further research or whether a generic version will infringe any of them. In addition to the innovative companies that secured the basic patents, other competitors, both other innovative companies and generic manufacturers, have actively filed patent applications surrounding the basic invention, either to gain a better position in licensing or to secure more tactical means after the expiration of the basic patent. Indeed, an empirical study found three-quarters of patents connected to high-cost drugs were owned by companies other than the drug's

1007 *E.g., Angell*, 2004, 78-79 (reporting trials which compared not likely equivalent doses but higher doses of Nexium® with Prilosec®, and two of the four trials showed Nexium® had marginal improvement); *Harris*, The Wall Street Journal, June 6, 2002.

1008 *Merges*, 76 Cal. L. R. 803, 876 (1988).

1009 *Jaffe/Lerner*, 2004, 174-76.

originator.[1010] The study further reported that non-original companies are investing substantial resources in second generation inventions related to blockbuster drugs.[1011] Even in the U.S., where the Orange book, a list of patents that covers a launched medicine, is available, simply looking at the list is insufficient,[1012] and those who wish to launch their own products without risk or with reduced risks need to spend a great deal of time and effort in conducting their own analyses. This response by the companies to the high number and low quality of patent application filings makes the situation worse for the industry, simply by adding more confusion, uncertainty and cost to the development process.[1013]

There are also costs involved in obtaining a patent, after filing a patent application. In the U.S., as long ago as 2001, it was reported to cost about $10,000 to $30,000 in filing fees, attorneys' fees, and other expenses to prepare a patent application.[1014] The increased number of patent rights on trivial improvements owing to lowered patentability requirements would result in blocking patent technology or increasing transaction costs without offsetting advantages in innovation.[1015] Considering the territoriality principle of patent protection,[1016] cost would be multiplied by the number of countries in which an applicant would seek a patent.

This problem is compounded by the fact that pharmaceutical companies will resort to creative litigation tactics, especially in securing evergreening patents.[1017] Based on these secured patents, companies not only try to bring the reformulated drugs to the market through regulatory approvals, but also turn to litigation to stifle competition based on those patent rights. Naturally, this adds to the cost incurred by generic companies in challenging or circumventing low-quality improvement patents.[1018] It is always easier and less costly to prevent patent applications from being patented than it is to invalidate the patents. Increasing numbers of challenges have been brought against patents covering products with revenues below $100 million as well

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1010 *Christie, et al*, 8 PLoS Med 1, 4 (2013) (further reporting that a multitude of players seek monopoly control over innovations to blockbuster drugs).
1011 *Christie, et al*, 8 PLoS Med 1, 4-6 (2013).
1012 *Christie, et al*, 8 PLoS Med 1, 4 (2013).
1013 *Howard*, 4 J. Generic Med 231, 235-36 (2007).
1014 *Lemley*, 95 Nw. U. L. Rev. 1495, 1498 (2001).
1015 *Landes/Posner*, 2003, 319.
1016 *Doi*, 26 Fordham Int'l L.J. 377 (2002).
1017 *Eisenberg,* 13 Mich. Telecomm. Tech. L. Rev. 345, 348-49 (2007).
1018 *Howard*, 4 J. Generic Med 231, 235-36 (2007).

as those covering the blockbusters with annual sales in excess of $1 billion.[1019] Long and tedious battles over dozens of patents on one drug force not only patent holders but also challengers to waste valuable resources.[1020] Yet, once again, this cost applies only to those who can afford to carry on the costly litigation procedure. The situation is worse in the United States than in other countries, since defending against patent infringement suits is particularly expensive there.[1021] In addition, the American civil procedure makes it easy for claimants to sue, basically because attorneys can charge contingency fees, and because there is no duty to reimburse the attorney fees of the winning party. Thus, right holders incur little financial risk at the time of filing a patent infringement suit.[1022]

d) Hindrance of pharmaceutical innovation

At the end of the day, all of the activities discussed above certainly distract the pharmaceutical companies from their genuine task of "providing the society with new medicines."[1023] Considering that when the number of NMEs increases, mortality and health problems decline, [1024] the problems caused by lowered patentability could hinder real pharmaceutical innovation and threaten our health. Some scholars have even argued that more than 90% of the "countering" drugs to recent challenges were likely to be reformulations or second generation products, at best marginal improvements over present-day pharmaceuticals, as compared with all other product introduction. [1025] Launch of these new forms of (older) drugs does not help to increase human longevity.[1026] Indeed, second generation patents have little to do with the drugs' medical use. Rai also argued that there were drugs that provided little or even no therapeutic advantage over existing drugs as follows:

1019 *Grabowski/Kyle*, 28 Manage. Decis. Econ. 491, 495-496 (2007).
1020 See subsection V.A.1.c).
1021 *Jaffe/Lerner*, 2004, 68.
1022 *Ann*, 2009, 363-64.
1023 *Herper*, Forbes, February 5, 2002.
1024 *Cockburn*, 2006, 2-3.
1025 *Higgins/Graham*, 326 Science 370, 370 (2009).
1026 *Lichtenberg*, 5 Int. J. Health Care Fi. 47, 70 (2005) ("Launches of (older) drugs that are not NCEs - any of which may already have been on the market -do not increase longevity. […] increasing the ratio of non-NCE to NCE launches reduces the fraction of people consuming NCEs, which in turn reduces longevity.).

> "The cost-effectiveness of me-too drugs, particularly in the [well established categories], is questionable. Although the me-too drug may prove more effective than the innovator drug for a certain population of patients, this marginal benefit is likely to be small."[1027]

Here, she meant "me-too drugs"[1028] as drugs addressing the same illness while managing to do so without infringing innovator patents,[1029] such as cimetidine (Tagamet®), ranitidine (Zantac®), or famotidine in the category of H2-receptor antagonist.[1030] These me-too drugs, however, at least can play some roles in curbing prices through limitation of the scope of exclusivity enjoyed by any given patented drug[1031] can function to generate another patient population which can be better treated by them,[1032] or can provide the patients with more choices. Contrary even to these me-too drugs, the therapeutic advantage would be harder to expect from the products (e.g. Esomeprazole) covered by second generation patents (e.g. S-enantiomer of omeprazole), which arguably contains the same active ingredient as Omeprazole. New versions (e.g. isomer) of basic drugs can often eliminate or mitigate their side effects, which were present in the old version of the drugs.[1033] However, it is debatable whether these incremental therapeutic advantages, can justify these new monopoly costs to the patients.[1034]

Apart from the effectiveness of second generation products, basic patentees greatly increased the spending attributable to line extensions as set out above, short-term priorities encouraged marginal inventions that provided more reliable returns on investment at the expense of major changes,[1035] and the market became flooded with products that did not provide significant clinical improvement over older medications.[1036] These factors result in more imitative research and fewer actual breakthroughs and drugs.[1037] This

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1027 *Rai*, Ill. L. Rev. 173, 205-06 (2001).
1028 See subsection II.D.2.
1029 *Rai*, Ill. L. Rev. 173, 201 (2001).
1030 H2-receptor antagonists are used in the treatment of dyspepsia or peptic ulcer disease.
1031 *Rai*, Ill. L. Rev. 173, 206 (2001).
1032 For example, the prototypical H2-blocker, Cimetidine has serious drug interactions with other drugs, but famotidine does not have serious interactions, which allows the patients to be less careful to take multiple medications.
1033 *Glasgow*, 41 IDEA 227, 251 (2001).
1034 *Glasgow*, 41 IDEA 227, 251 (2001).
1035 *Munos*, 8 Nat. Rev. Drug Discov. 959, 966 (2009).
1036 *NIHCM*, 2002, 18-19.
1037 *Munos*, 8 Nat. Rev. Drug Discov. 959, 966 (2009).

becomes a greater problem in conjunction with the lowered patentability of second generation patents. Merges and Nelson note that where incentives for improvement are increased, incentives for innovative inventions are decreased.[1038] Hunt also contends that, if protection were extended to more obvious inventions, there would be an additional social cost of monopolies and also additional losses, if firms redirect their research toward less risky projects.[1039] In addition, crucially, the uncertainty created by overlapping patent claims and the questionable validity of patents due to the poorer quality of examination with the increased number of patent applications will undermine incentives to invest even in new technology and will stifle innovation.[1040] Consequently, considering the limited resources of most companies and the effort required for second generation inventions, granting selection inventions may siphon off resources that can be exploited to research the new medical entities that society has found in short supply. Some scholars have also warned that there will be a clear risk of diverting a significant proportion of investment from more innovative research and from areas particularly in need of therapeutic breakthroughs.[1041] Therefore, the lowered patentability criteria on second generation inventions can actually hamper meaningful innovation in the pharmaceutical industry. Most importantly, the inordinate delay for marginal benefits disadvantages patients in need of new medicines.[1042]

2. Concerns about the novelty requirements

The problem faced by selection inventions concerns the most fundamental patentability requirement, novelty.

a) Language dependent prior art disclosure problem

As discussed in chapter IV.A.4., the amount of disclosure is more dependent upon the language of the claim than upon the disclosure perceived by the

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1038 *Merges/Nelson*, 90 Colum. L. Rev. 839, 873-78 (1990).
1039 *Hunt*, 1999, 11.
1040 *Jaffe/Lerner*, 2004, 174-76.
1041 *Pifferi/Perucca*, 20 Eur. J. Drug Metab. Ph. 15, 24 (1995).
1042 *Beary*, 339 Lancet 495 (1992).

person skilled in the art. In particular, the distinction between the disclosure of generic formulae and that of individual substances in prior art seems to have taken root within EPO case law in assessing novelty.[1043] In T181/82, the BOA stressed that there was a strict distinction between the "purely intellectual content" of the definitions and their "information content in the sense of a specific teaching with regard to technical action."[1044] In other words, the novelty of the selection invention was judged differently when the prior art disclosed the invention in a generic term rather than an individualized form.

However, it is very difficult to understand the absurd conclusion that the same expressions in scientific language, such as "$C_{1\text{-}4}$ alkyl" and "alkyl with less than five carbon atoms" disclose different radicals in legal language.[1045] According to the BOA, "$C_{1\text{-}4}$ alkyl" discloses only C_1 alkyl i.e. methyl, while the latter phrase discloses nothing, because this expression does not disclose any individual alkyl group. This method of interpretation does not appear to be performed through the eyes of a person skilled in the art, who cannot differentiate between these expressions. In addition, the assessment of novelty becomes dependent on the draft of the claim. For example, the applicant would need to draft depending upon whether he wants to destroy all prior art or whether he wants to leave room for another application to other parties or even to himself. For an applicant to achieve a "defensive patent application" or a "defensive publication," he must disclose every possible element other than the efficiency of disclosure. For example, according to the BOA, to disclose "$C_{1\text{-}4}$ alkyl," one must disclose methyl as a C_1 alkyl; ethyl as a C_2 alkyl; n-propyl and isopropyl as C_3 alkyls; and n-butyl, isobutyl, *sec*-butyl, and *tert*-butyl as C_4 alkyls. But if he wants to keep some for further application, the applicant would disclose only "$C_{1\text{-}4}$ alkyl" or even "alkyl with less than five carbon atoms." He would still be able to enforce the patent against the third party if he used it, since the claim would cover all eight alkyls in any case. The situation would be different if a third party patented it. This photographic approach to assessing novelty is problematic.

1043 *See* EPO Examination Guidelines G-VII, Annex 3.1.(iv) (noting that if the selected group has not been specifically disclosed in the prior art, it would have been the question of lacking of novelty rather than obviousness.).

1044 *Ciba-Geigy/Spiro compounds,* T 181/82, OJ EPO 1984, 401, 411.

1045 *Grubb/Thomsen*, 2010, 235.

b) Rendering inventive step requirement meaningless

Novelty examination is a separate test to determine patentability[1046] and is not the first step in examining obviousness. However, by lowering the bar for novelty, the courts appear to fail to sufficiently distinguish between the test of novelty from that of obviousness. In particular, the *Escitalopram* Courts in major jurisdictions made significant efforts to evaluate "the difficulty of the separation of citalopram" in order to assess novelty, after admitting that it was apparent that a racemate of a chemical compound like citalopram had equal amounts of two enantiomers. In the end, the courts found that difficult separation did not lead to Escitalopram being anticipated. This could be interpreted as rendering novelty dependent on the "difficulty" or amount of effort and time involved in obtaining a claimed compound, whose structure was described in the prior art based on the common knowledge of a person skilled in the art.

The level of enablement of the prior art reference is determined to assess novelty. [1047] This could be one of the reasons why the determination of novelty has become more relative and, to some extent, similar to that of obviousness. In the United States, for example, *prima facie* obviousness established based on the prior art disclosure of racemates and *de facto* disclosure of the enantiomer itself was rebutted based on no reasonable expectation of success and the difficulty of separation.[1048] It is indeed difficult to differentiate how difficult it will be for a skilled person to obtain the claimed invention within the context of anticipation depending on whether there was any expectation of success in separating within the context of non-obviousness. Once it is determined that the claimed invention was not easy to obtain from the prior art disclosure, the inventive step of the invention could also be established to some extent. This in turn suggests that the courts may not clearly distinguish between the novelty and the non-obviousness requirements, which is contrary to what the BGH has postulated in Germany.[1049]

Indeed, the BOA addressed a distinction between novelty and the inventive step of selection inventions to the arguments that deciding selection

1046 *BGH/Olanzapine*, IIC 2009, 596, 599.
1047 *See* subsection IV.A.3.
1048 *See Sweet*, 24 Berkeley Tech. L.J. 129, 142 (2009); *See also Forest Labs., Inc. v. Ivax Pharms., Inc.,* 501 F.3d, 1263, 1269 (Fed. Cir. 2007*)*; See subsection IV.B. 3.b).
1049 *BGH/Olanzapine,* IIC 2009, 596, 599.

novelty was identical or closely similar to that used to determine obviousness as follows:[1050]

> "[T]he Respondent sought to convince the Board that the legally correct approach for deciding selection novelty was identical or closely similar to that employed in determining obviousness. In particular, he put forward the proposition that in cases of overlapping ranges of compounds, a claim to a narrower range as compared with a broader prior art range was always selectively novel if it could be demonstrated that the narrow range was inventive over the broader range. […] Whereas it is undoubtedly true that there can be no selection novelty in a range of overlap where the choice of moving into that overlapping range from the prior art one is obvious, it doesn't either as a matter of law or as a matter of logic follow that the converse is true, namely that if a choice of a narrower range is inventive, then there must of necessity be selective novelty in it. For the above reasons, the Respondent's argument in this respect cannot be accepted."[1051]

Simply put, the Board admitted that if the selection from the prior art is obvious, then there is no novelty in the selection thereof. As the Board further noted, it is not always true; if the selection is inventive, then there is the novelty of selection. However, and importantly, the contrapositive of the first sentence is also undoubtedly true.[1052] If there is novelty in the selection in a range of overlap, then the choice of moving into the overlapping range from the prior art one is not obvious. Therefore, even borrowing the Board's own words, the same test is repeated in both steps, or both steps are determined by a single test for the assessment of patentability. In the end, can it be said that the test for novelty is placed in the broader context of the test for "inventive step"?[1053]

Furthermore, to assess inventiveness, more information is often required in addition to the teaching from the prior art disclosure. Given that that information seems to be close enough, such as the difficulty of separation, the additional information could already be used to destroy novelty. Thus, again it appears that, to some extent, the examination of patentability is *de facto* reduced to the examination of novelty, thereby making the test of obviousness redundant.

1050 *AKZO/Bleaching activators*, T 133/92, 1994.
1051 *AKZO/Bleaching activators*, T 133/92, 1994, point 2.1.4.
1052 *Peterson*, 1974, 9-10 (explaining when a statement is true, a contrapositive of the sentence is also true).
1053 *See e.g., Tilmann*, IIC 2010, 149, 158-59.

c) Potential concerns of "direct and unambiguous" disclosure requirement

According to the case law in selection inventions, the courts require that the prior art disclose the selection inventions "directly and unambiguously." [1054] However, there are further areas in which the rules for disclosure play a role. Firstly, the disclosure of priority application(s) matters to the validity of priority claiming compared with the disclosure of application claiming the priority. Secondly, the content of the application, in terms of the disclosure of patent specification matters to the sufficiency of the disclosure regarding the scope of the claim. Thirdly, the disclosure of the originally filed content of the patent application matters in whether it supports the amended claims. It is especially important that the species is not disclosed by the genus patent but falls within the scope of the same genus patent. Fourthly, when a patentee limits the scope of the patent, the disclosure of the granted patent specification matters to the scope of the limited patent.

Therefore, it will be interesting to see whether the courts will uniformly apply this concept of disclosure in terms of novelty to other areas of disclosure, and, if not, to what extent they will do so individually.

B. Implications considering the breadth of selection patents

A selection invention is generally chosen from the available broader prior art and directed to a specific species or a subgroup thereof which falls within the scope of the prior wider genus. As the other side of the coin, this kind of invention can be an overlap invention, as the result of which the later selection patent invention can be practiced only by licenses from the prior patentee, since the patent claiming general class will protect each member of the class, even though it is not considered a disclosure of those specific members.[1055] This is one of the cases where such claims may reach beyond the

1054 *See e.g. Tilmann*, IIC 2010, 149, 159; *See also Bublak/Coehn,* GRUR 2009, 382, 389.

1055 *Robinson*, IIC 1972, 139, 143; *Nastelski*, IIC 1972, 267, 293-94 (describing "product protection is simultaneously granted for every individual member of this group irrespective of whether or not such member has been specially designated in the group formula.").

scope that even the patentee had in fact invented in three circumstances.[1056] Needless to say, this phenomenon will often be observed according to the increased number of second generation inventions based on the lowered patentability requirements thereof. For this reason, the scope of second generation patents will be analyzed first, after which the impact of lowered patentability will be examined.

1. Scope of the protection

Even though the breadth of a patent is a more abstract concept than its length, the allowable breadth of claims is determined by examiners and upheld by the judiciary,[1057] and the "doctrine of equivalents" and "reverse doctrine of equivalents" are adopted by the courts.[1058]

The scope of the claim is a matter of quantity, and the clarity of the claim is a matter of quality. The claims are interpreted with the help of description and drawings.[1059] If there is another definition in the description, this definition is decisive in determining the scope of the patent.[1060] Thus, it is the function of the claims to define clearly and with precision the monopoly claimed, so that others may acknowledge the exact boundaries of the area within which they will be trespassers.[1061] In the EPO, the extent to which the breadth of the claims should be allowed is considered under Art. 83 EPC and Art. 84 EPC second sentence. Although Art. 83 EPC is directed to the

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1056 *Lemley*, 75 Tex. L. Rev. 989 (1997) (The other two cases are the case where the doctrine of equivalents can be applied; and the case when patent claims may reach new and unanticipated inventions made after the patent issues, but which fall within the literal language of the claims.).

1057 *Scotchmer*, 5 J. Econ. Perspect. 29, 30 (1991).

1058 *Friebel et al.,* 2006, 22.

1059 *See e.g.,* EPC Art. 69 and the Protocol on the Interpretation of Article 69 EPC, 35 U.S.C. § 113.

1060 *See e.g.*, *BGH/Bierklärmittel (Beer Fining Agent)*, GRUR 1984, 425, 426 (holding that if the definitions used in the patent specification differed from those in the literature in the field, the definitions in the specification prevailed for the interpretation of the patent); *see also, Electric & Musical Industries Ltd v. Lissen Ltd* [1939] R.P.C. 23, 57 (holding "[i]f the claims have a plain meaning in themselves, then advantage cannot be taken of the language used in the body of the specification to make them mean something different.").

1061 *Electric & Musical Industries Ltd v. Lissen Ltd* [1939] R.P.C. 23, 39; *See* e.g., EPC Art. 84, 35 U.S.C. § 112, second sentence.

disclosure of the invention, the underlying purpose thereof is the same as Art. 84 EPC, namely, to secure the grant of the proper breadth of patent exclusivity that can be justified by the technical contribution to the art.[1062] This reflects quite well the so-called "reward theory" of the patent system, which could be the most common justification. Regarding the claim construction, in the *Catnic* case, the British court tempered its previous way of interpreting claims, the "literal approach"[1063] to the "purposive construction."[1064] And the scope of patent is not generally limited to the version that the inventor invented, but could cover the subsequently modified versions as long as each falls within the scope.[1065]

Beyond the literal scope of claims, courts may consider an equivalent of certain elements in the claims, the so-called doctrine of equivalents. The application of the doctrine of equivalents in each jurisdiction is quite diverse. Notably, it is argued that there is no general doctrine of equivalents in ***British*** courts,[1066] which instead have used the so-called "pith and marrow" approach that is a similar principle.[1067] This means that the use of the pith and marrow of the invention, i.e. its important parts, is an infringement even though there are insubstantial differences between the allegedly infringing embodiment and the patent claim. There was a case in which the court applied its pith and marrow doctrine to the product claim.[1068] Similar to the terfenadine cases below, the issue was whether the prodrug infringed the metabolite patent. An acetone adduct (Hetacillin) of another medication (Ampicillin) was immediately hydrolyzed in the body to the medication (Ampicillin), and hetacillin in itself did not have an antibiotic effect. The Court held that the accused product infringed the patent, because it was a

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1062 *Exxon/Fuel oils*, T 409/91, OJ EPO 653, 661-62 (1994) point 3.5.

1063 *Electric & Musical Industries Ltd v. Lissen Ltd* [1939] R.P.C. 23, 39 (expressly noting that there was nothing like infringement of the equity of a patent).

1064 *Catnic Components Limited and another v. Hill & Smith Limited* [1982] R.P.C. 183, 243 (holding "[a] patent specification should be given a purposive construction rather than a purely literal one […]").

1065 *Kitch*, 20 J. Law Econ. 265, 268-69 (1977) (further noting this feature of the patent system is important to the drug industry, just as a new use invention to a known drug, e.g. secondary therapeutic indications.).

1066 *See e.g.*, *Occlutech GmbH v. AGA Medical Corp* [2010] EWCA Civ 702, paras 23; *see also Kirin-Amgen Inc v. Hoechst Marion Roussel Limited*, [2004] UKHL 46 (Lord Hoffman asserted again there was no doctrine of equivalents in UK).

1067 *Kirin-Amgen Inc v. Hoechst Marion Roussel Limited*, [2004] UKHL 46, paras 36-37.

1068 *Beecham Group v. Bristol Laboratories Ltd.* [1978] RPC 153.

temporarily disguised or altered form of the medication.[1069] A similar line of analysis is found in German jurisprudence, such as whether the allegedly infringing embodiment achieves the same function, or whether a person skilled in the art could replace the changed features while expecting the same effect.[1070]

In Germany, the following conditions must be met to find patent infringement: (i) Whether the modified embodiment solves the problem underlying the invention by means which have objectively the same technical effect, (ii) whether a person skilled in the art by means of his specialist knowledge is able to identify the modified means as having the same effect, (iii) whether the considerations that the person skilled in the art applies are drawn from the technical teaching of the patent claim (so that the person skilled in the art takes the modified embodiment into account as the equivalent solution in question), and (iv) whether the modified embodiment is anticipated or made obvious by the state of the art (the so-called "Formstein objection").[1071] Even though prosecution history estoppel,[1072] which requires an extensive research on the file wrapper, is not accepted, one may raise the Formstein defence that the allegedly infringing embodiment argued to be an equivalent would not be patentable over the prior art, either because it is known from the prior art, or because it is obvious in view of the prior art.[1073] This is obviously because the allegedly infringing product within the scope of the patent is not patentable over the prior art, and the patent claiming

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1069 *Beecham Group v. Bristol Laboratories Ltd.* [1978] RPC 153, 192 (noting "[t]he mere temporary cloaking or masking of a product does not in general suffice to avoid infringement of letters patent whose specification claims that product.").

1070 *See e.g.*, *BGH/Schneidermesser I (Cutting blade I),* GRUR 2002, 515, 517; *see also Catnic Components Limited and another v. Hill & Smith Limited* [1982] R.P.C. 183, 243; *see also Kirin-Amgen Inc v. Hoechst Marion Roussel Limited*, [2004] UKHL 46, paras 41-42, 75; *cf.*, *Occlutech GmbH v. AGA Medical Corp* [2010] EWCA Civ 702, para 28 (even though the decision is denying general existence of doctrine of equivalents in UK, it found German approach is lacking one question which is applied by the UK court, i.e. "[w]ould the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim").

1071 *BGH/Schneidermesser I (Cutting blade I)*, GRUR 2002, 515, 517; *BGH/Formstein*, GRUR 1986, 803, 805-06.

1072 *See infra* 1077 -1078 and accompanying texts.

1073 *BGH/Formstein*, GRUR 1986, 803, 805-06.

infringement also has a reason for invalidity. In other words, this is to prevent something in the prior art from being taken away from the public.

In the United States, this doctrine originated more than a century ago.[1074] Hand J noted that the purpose of this doctrine was to temper unsparing logic and to prevent an infringer from stealing the benefit of the invention.[1075] This was acknowledged by the Supreme Court in the *Graver Tank* case, where it held that to find the infringement under this doctrine, the alleged embodiment had to perform substantially the same function in substantially the same way to obtain the same result.[1076] In *Warner Jenkinson v. Hilton Davis*, while upholding this doctrine, the Supreme Court also noted that "prosecution history estoppel"[1077] was available as a defence to infringement, unless the amendment's purpose was not related to patentability. [1078] The following additional exceptions to prosecution history estoppel were provided in the *Festo* case: i) The equivalent might have been unforeseeable at the time of the application, ii) the rational underlying the amendment might bear no more than a tangential relation to the equivalent in question, or iii) there might have been other reasons.[1079]

In Korea, the Supreme Court recognized a five-step test of the doctrine of equivalents: When an element of an invention is substituted in an accused device, the substituting element of the accused device is equivalent to the substituted element of the patented invention, if i) the problem solving principles are the same in the patented invention and the accused device, ii) the substituting element of the accused device provides substantially the same operational effects as the substituted element of the patented invention, iii) the substitution is obvious to one having ordinary skill in the art, iv) the

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1074 *Graver Tank & Mfg. Co. v. Linde Air Products Co*., 339 U.S. 605, 608 (1950) (noting "[o]riginating almost a century ago in the case of Winans v. Denmead, 15 How. 330, 14 L.Ed. 717, it has been consistently applied by this Court and the lower federal courts, and continues today ready and available for utilization when the proper circumstances for its application arise.").

1075 *Royal Typewriter Co. v. Remington Rand, Inc*., 168 F.2d 691, 692 (2nd Cir. 1948).

1076 *Graver Tank & Mfg. Co. v. Linde Air Products Co*., 339 U.S. 605, 608 (1950).

1077 A patentee who had made narrowing amendments to the application in order to meet the patentability requirements, may not invoke the doctrine of equivalent to recapture the scope of his claims which he already surrendered.

1078 *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co*., 520 U.S. 17, 40-21 (1997).

1079 *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd*., 535 U.S. 722, 740-41 (2002).

accused device was not known or could not have been easily conceived from known technologies by a person skilled in the art at the time of filing the application for the patent, and v) there are no special circumstances such as intentional exclusion of the substituting element of the accused device from the claimed scope during the prosecution of the patent.[1080]

2. Scope of selection patents

a) Species selection patents

It is well established that a species selection patent falls within the scope of the previous genus patent,[1081] although there was an exceptional decision in Italy. [1082] In that case, a Markush type claim covered some 10 million compounds, and the active substance in Cimetidine was not explicitly mentioned in the patent specification.[1083] The Supreme Court of Italy held that a pharmacologically active substance, such as Cimetidine, which could be determined from a patented formula only through further complex research and experiments, was not eligible for the protection of the patent, because it was not clearly and completely described in the patent document.[1084] However, this decision was an exception.

b) Optical isomers

In Europe

In *Ranbaxy v. Warner-Lambert*, the issue was whether the claim[1085] was limited only to racemates or also covered enantiomers. [1086] Ranbaxy tried to argue that the claim must be limited to the racemates. It argued that since the patentee would have known that one enantiomer was ineffective, there

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1080 *Korean Supreme Court/Bayer Aktiengesellschaft v. Union Quimico Famaceutica*, S.A, 97Hu2200, Jul. 28, 2000, para 2.
1081 *See e.g., Domeij*, 2000, 317.
1082 *Corte di Cassazione/Cimetidin*, GRUR Int 1991, 497.
1083 *Corte di Cassazione/Cimetidin*, GRUR Int 1991, 497.
1084 *Corte di Cassazione/Cimetidin*, GRUR Int 1991, 497, 498-99.
1085 *See supra* 603 .
1086 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876.

was no reason to claim this ineffective enantiomer. Thus, he could not have intended to claim the other single enantiomer either.[1087] It further argued that if the patentee wished to, he could have done so easily by claiming one type of enantiomer explicitly. Therefore, the patent covered only the racemate.[1088] However, Jacob LJ reiterated the point in the *Kirin-Amgen* case[1089] regarding the purposive claim construction that the claim construction was an exercise in discerning what the person skilled in the art would have understood the claim to mean, not an exercise in over-meticulous semantic analysis.[1090] Jacob LJ dismissed this argument on the basis that, since the purpose of the claim was to "demarcate" the invention, there was no rational basis for assuming that the patentee would have intended to exclude the pure enantiomer, which he would have known was the substance that really mattered.[1091] Ranbaxy further argued that, according to convention, the structural formula shown in the patent could represent either a particular enantiomer or a racemate, but not both.[1092] This argument also failed, since this convention needed to be proved as a matter of fact, but the judge in the first instance had made no such finding.[1093] Accordingly, in the context of the patents, claim 1 was construed as covering *both* the racemate and either of the enantiomers.

Neuberger LJ further explained why the patent covered the enantiomers. He noted that although the racemate was the racemic mixture which would have been regarded as a different substance from either of the two enantiomers of which it was composed, it was a 50/50 mixture of the two enantiomers.[1094] He further noted as follows:

> "[W]here a racemate is administered as a drug, one enantiomer is likely to have all, or the great majority, of the biological activity, and that activity will be either unaffected or reduced by the presence of the other enantiomer. The fact that the racemate in the present case has the claimed pharmaceutical effect shows that it is no exception. This demonstrates that the sole or mainly effective enantiomer maintains its character and (at least to a substantial extent) its effectiveness,

1087 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 18.
1088 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 18.
1089 *Kirin-Amgen Inc v. Hoechst Marion Roussel Limited*, [2004] UKHL 46, paras 32-35.
1090 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 7.
1091 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 19.
1092 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 23.
1093 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 24.
1094 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, paras 44-45.

> notwithstanding that it is administered as part of a racemic mixture. Accordingly, it appears to me that it is wrong to conclude that a racemate, and in particular the racemate in this case, cannot be regarded as a mixture of the two enantiomers. […] "A+B" can be regarded both as a single entity, namely (A +B), and as a mixture of two entities, namely A and B."[1095]

Even though the patent claiming an enantiomer was held invalid because of the lack of novelty based on the fact that the prior art disclosed the method for producing the enantiomer,[1096] this Court clearly noted that one enantiomer was responsible for the efficacy of the racemate thereof, and a racemate was the mixture of two enantiomers. Even though Neuberger LJ noted that this construction was dependent upon the facts and on the context,[1097] a claim on a racemate can be construed so that it also covers the enantiomers.

To the contrary, the scope of a claim over an enantiomer does not extend to the old racemate, as Jacob LJ noted "such would be an absurd construction given the fact that the patent acknowledges that [the racemate] is old, having been disclosed in [the previous patent]."[1098]

In the United States

In *Pfizer v. Ranbaxy*, as it did before the British court, Ranbaxy argued that the structural formula I was limited to racemates.[1099] The specification of patent disclosed as follows: "The compounds of structural formula I above possess two asymmetric carbon centers … [which] gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans-form of the compounds of formula I above." Based on this intrinsic evidence, even though the claim 1 presented the formula of racemate, the Federal Circuit held that the patentee disclaimed the R-cis- and S-cis-isomers out of four isomers.[1100] The Federal Circuit further noted that the terms "racemate" or "racemic mixture" did not appear in the patent

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1095 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, paras 45-46.
1096 See *supra* 605 -606 and accompanying texts.
1097 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 47.
1098 *Generics (UK) v. Daiichi Pharmaceutical* [2009] EWCA Civ 646, para6; see also *Generics (UK) v. Daiichi Pharmaceutical* [2008] EWHC 2413 (Pat), para 317.
1099 *Pfizer, Inc. v. Ranbaxy Laboratories Ltd*., 457 F.3d 1284, 1288-89 (Fed. Cir. 2006).
1100 *Pfizer, Inc. v. Ranbaxy Laboratories Ltd*., 457 F.3d 1284, 1289 (Fed. Cir. 2006).

specification. Thus, there was no intrinsic evidence that limited claim 1 to trans-racemates, as opposed to an R-trans enantiomer, an S-trans enantiomer or any mixture thereof.[1101] Moreover, against Ranbaxy's contention that the examples did describe reaction sequences that produced racemates, the Federal Circuit held that "restricting claim 1 on this basis would improperly import limitation from the specification into the claims, which should be avoided unless the patentee clearly intends for the claims and the embodiments in the specification to be strictly coextensive**."**[1102] Accordingly, the Court held that the claim was correctly construed to include enantiomers and that the Ranbaxy's product infringed the patent.

c) Metabolite

In the United Kingdom

Section 64 of UK Patents Act provides a person with a personal right to continue an act if he or she was performing effective and serious preparations to carry out an act that would have been an infringement if the patent were in force, before the priority date.[1103] In *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* case, Merrell Dow argued that the existence of Section 62 showed that the Parliament recognized the effect of the new 1977 Act that people might find themselves unable to go on doing what they or someone else had done before. The House of Lords, however, held that this argument may produce results that seem contrary to common sense and, furthermore, that this provision had no application to the case, since no defendants were marketing terfenadine before the priority date of the acid metabolite patent.[1104] On the other hand, the Court solved the difficulty that the exclusivity of the parent drug could have been extended by the metabolite patent by holding that the patent was invalid because of the lack of novelty.[1105]

1101 *Pfizer, Inc. v. Ranbaxy Laboratories Ltd*., 457 F.3d 1284, 1289 (Fed. Cir. 2006).
1102 *Pfizer, Inc. v. Ranbaxy Laboratories Ltd*., 457 F.3d 1284, 1290 (Fed. Cir. 2006).
1103 UK Patents Act 1977, Section 64.
1104 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, paras 19-20.
1105 See *supra* 663 -666 and accompanying texts.

In Germany

The Munich Higher Regional Court held that the patent of metabolite was not infringed if, according to the expired patent, a pharmaceutically active ingredient could be made and used which was converted in the body to a substance protected under a new patent.[1106] The Court's holding was based on the facts that the defendant did not sell, market, or keep for the file the metabolite and that the terfenadine produced and marketed by the defendant was exactly the same compound protected by the plaintiff's patent that had expired. [1107] The Court held that, if the patent was expired, and the inventor was rewarded enough, the teaching of a patent must have been applicable.[1108] It further stated that, if scientific knowledge (in this case, active metabolite) has suddenly made the manufacturing of the old medication into "a purposive manufacture of medication," this way of interpreting the concept of manufacture was not in line with the patent protection.[1109]

In the United States

In the same terfenadine case, the District Court held that the patent on the metabolite was valid. However, it was not infringed because the scope of the patent to the metabolite was limited to the synthetic version of the metabolite.[1110] This approach seems to be difficult to reconcile with "contributory infringement."[1111]

In other cases, however, the Federal Circuit stated that a person might infringe a claim directed to a metabolite when the parent drug was administered to the person, since it would be metabolized to the claimed inven-

1106 *OLG München/Terfenadine*, GRUR, 1994, 746 (Because of the bifurcate system in Germany, this Court could not nullify the patent).
1107 *Vossius/Vossius/Vossius,* GRUR 1994, 472, 474, 476 (also noting that the defendant did not suggest another use either).
1108 *Vossius/Vossius/Vossius,* GRUR 1994, 472, 476.
1109 *Vossius/Vossius/Vossius,* GRUR 1994, 472, 476.
1110 *Marion Merrell Dow Inc. v. Baker Norton Pharmaceuticals, Inc*., 948 F.Supp. 1050, 1055-56 (S.D.Fla.,1996), appeal dismissed, 152 F.3d 941 (Fed. Cir. 1998).
1111 *Grubb/Thomsen*, 2010, 253.

tion.[1112] In *Zenith Laboratories, Inc. v. Bristol-Myers Squibb,* however, owing to the absence of evidence, the Federal Circuit reversed the District Court's decision holding that the patent had been infringed,[1113] the Federal Circuit stated that a compound as a form before the ingestion would fall within the scope of a compound claim to the metabolite.[1114] In a later case, Federal Circuit restated that it recognized this possibility of infringement of a patent claim directed to metabolite by taking medication, while holding a claim directed to the "bare" metabolite was anticipated by a prior art which disclosed administration of the parent drug.[1115] In other words, Rader J stated that one might obtain a patent on the synthetic version of something that was already in the public, unless it was an unrestricted product claim.[1116]

d) Polymorphs

The *SmithKlein Beecham v. Apotex* case involved the claim construction of one crystalline form of a known substance. In the late 1970s, a British company, Ferrosan, invented and acquired a patent over a compound known as paroxetine, which was licensed to SmithKline. Ferrosan eventually developed a process to produce the crystalline hydrochloride salt of paroxetine, or paroxetine hydrochloride ("PHC").[1117] In 1985, a chemist at SmithKline discovered a new crystalline form of PHC hemihydrates. These compounds were different from the PHC anhydrate which was Ferrosan's original form, because they comprised of PHC crystals with one bound water molecule for every two PHC molecules so that the compounds were more stable and easily

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1112 *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1421-22 (Fed. Cir. 1994) (holding infringement may occur if the administered product is converted in vivo into the claimed product); *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997) ("the right to exclude may arise from the fact that when administered, [parent drug] metabolizes into another product, [metabolite], which [patentee] has claimed).

1113 *Zenith Lab. Inc. v. Bristol-Myers Squibb Co*., 1992 WL 340761 (D.N.J.1992) (holding the use of a compound which would converted to the metabolite by a patient who took the parent drug was an infringing use).

1114 *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1422 (Fed. Cir. 1994).

1115 *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1380 (Fed. Cir. 2003).

1116 *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1380-81 (Fed. Cir. 2003).

1117 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1334 (Fed. Cir. 2005).

packaged.[1118] In this case, while construing claim 1 - "crystalline paroxetine hydrochloride hemihydrates" ("crystalline PHC") - to cover crystalline PHC *without further limitation, i.e. in any amount*, the Federal Circuit held that the Apotex's product would infringe this claim 1, based on the factual finding that Apotex's PHC anhydrate tablets would contain "trace amounts" of PHC hemihydrates.[1119] In this case, the claim was invalidated based on the inherent anticipation doctrine.[1120] The Federal Circuit acknowledged the District Court's concern that the above claim construction could result in "a considerable extension in the effective patent term of paroxetine, because it might become difficult or even impossible to manufacture the pure anhydrous form after the Ferrosan patent expired."[1121]

3. Analysis and conclusion

Genus patents are generally strong, because one can usually apply for a patent not only on the core structure molecules but also their analogues.[1122] Further, the patents are difficult to design around, which can make the patent holders wealthy.[1123] The difficulty of inventing around is not only technological but also a consequence of the product loyalty of both patients and doctors.[1124] This is clear in species invention, i.e. species invention falls within the scope of the genus patent. Thus, if a species selection patent holder is different from the patentee of the basic patent in force, the former cannot exploit his invention without licensing the basic patent (the so-called "blocking effect"). If the species selection patent is owned by the patentee of the basic invention, it could increase the possibility of extension of exclusive rights (the so-called "evergreening effect"). This is notable when one considers that the entire scope of a patent, in general, should be in the public domain once the patent has lapsed.[1125]

1118 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1334 (Fed. Cir. 2005).
1119 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1340-42 (Fed. Cir. 2005).
1120 *See supra* 660 -662 and accompanying texts.
1121 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1342 (Fed. Cir. 2005).
1122 *See supra* 109 and accompanying texts: One single claim can claim millions of different but analogous compounds.
1123 *von Hippel*, 1988, 53; *Landes/Posner*, 2003, 313.
1124 *Landes/Posner*, 2003, 313-14.
1125 *Grubb/Thomsen*, 2010, 335.

For the optical isomers, with the same issue, the British court held that the claim covered both the racemate and the enantiomers, while the American court held that the claim covered only the enantiomers. This case was special because the claim was drafted to show the structure in three dimensions. However, in general, the claim on the racemate would not cover the enantiomer; otherwise the enantiomer would not have been patented, and the scope of the enantiomer, of course, would not extend to the racemate.

In contrast to other jurisdictions, where it was held that selling a parent drug would not infringe the metabolite patent, the United States Federal Circuit repeatedly held that it "would" or "may" infringe the metabolite patent and that, when administered, it could metabolize into the claimed invention. One must wait for the development of case law on metabolites in the United States. Based on the decided cases, however, if a patent on the metabolite is granted, the scope should be restricted to the synthesized version.

The patent on a crystalline form was invalidated in the United States owing to inherent anticipation. However, the Court held that, if the crystalline form was included even in a trace amount, it could have infringed the patent on the crystalline form. One can imagine that, during the course of the production of a basic product, this kind of crystalline form would be co-produced and a patent infringement could be found, at least in the United States.

Of course, the lowered novelty or inventive step requirements have little to do with the scope of these patents. The relaxed sufficiency requirement would result in the broader scope of patent; however, it was not observed in the case law regarding the selection inventions. Nevertheless, the implication could be seen from a different angle, i.e. whether they could affect the entry of generic versions of the product covered by the basic patent, which will be discussed in chapter V.D.2.a).

C. Implications considering the length of selection patents

The term of a patent is the maximum period during which it can be maintained and enforced. It is normally expressed in the number of years from the filing date of the patent application, although it can be extended through the patent term extension. The exclusivity can also be prolonged based on the grant of selection patents on the specific characteristics of the basic compounds. This becomes more important if the substance of the selection

patents (e.g., enantiomer) can be eligible for the issuance of a patent term extension which provides further exclusivity.[1126]

1. Patent term and patent term extension

The "statutory" patent term is generally 20 years from filing in major jurisdictions.[1127] However, the race to the door of the patent office shortens the real time in which the inventor can enjoy the exclusivity.[1128] The "effective" patent term, which can be defined as the length of the period for which a product is marketed with the benefit of enforceable patent protection, is shorter. The effective patent terms for pharmaceuticals, probably the patent terms after the marketing approval, were reported to average between nine and eleven years,[1129] which is a bitter pill to the drug companies, because their long R&D periods encroach on their time of exclusivity.[1130]

Thus, the patent term extension can be applied for and granted to compensate the term which was subject to the regulatory approvals for the pharmaceuticals and agrochemicals. As a benefit in return for these patent term extensions, for example, the Hatch-Waxman Amendments in the United States insulates generic manufacturers from patent infringement actions during the term of the patent on the reference drug to obtain regulatory approval of their generic versions.[1131] Before the Hatch-Waxman act, it was considered a patent infringement if a generic company began the regulatory approval process before the patent term on the reference drug expired.[1132] A Supplementary Protection Certificate (herein after "SPC") in Europe is a kind of interface between the patent system and the regulatory system, since granting SPC protection relies on holding both a patent and a marketing authorization for a highly regulated product, such as a medication. These

1126 *BGH/Escitalopram,* GRUR 2010, 123, 131.
1127 The U.S. did not adopt this 20 years patent term until 1994, when it amended the patent law to comply with the TRIPS Agreement. *See* 35 U.S.C. § 15 (C)(1).
1128 *Landes/Posner*, 2003, 302.
1129 *Grabowski/Vernon*, 10 Suppl 2 Pharmacoeconomics, 110 (1996).
1130 See subsection III.A.1.b).
1131 *Coggio/Cerrito*, 52 Food & Drug L.J. 345, 346 (1997).
1132 *Eidson*, 82 Wash. U. L. Rev. 1169, 1169 (2004).

provisions are intended to encourage research and accelerate the release of new medications to the public.[1133]

a) In Europe

Different countries in Europe independently introduced corresponding legislation to the Hatch-Waxman Act in the United States in the early 1990s.[1134] Thus, the discrepancy of legislation, especially different extension periods of patent terms, resulted in the promulgation of Regulation 1768/92 in January, 1993. According to the Regulation creating the Supplementary Protection Certificate ("SPC") for pharmaceuticals,[1135] a patent term can be extended for the period equal to the time between the grant of the first marketing authorization in the European Community and the patent filing date, and reduced by five years, up to a maximum duration of five years.[1136] Since SPCs are national rights, a patentee should apply the SPCs in each member state within six months of either the date of the patent grant or the date of the marketing authorization, whichever is later.[1137] The marketing approval may be obtained from the regulatory authority of each country or centrally from the European Medicines Agency. Only one SPC can be granted to one patentee for a single product for the basic patent,[1138] even if the basic patent covers more than one marketed product,[1139] or more than

1133 *Coggio/Cerrito*, 52 Food & Drug L.J. 345, 346 (1997); *contra*, *Engelberg*, 39 IDEA 389, 419-25 (1999) (arguing special extensions of patent terms on pharmaceutical inventions were unnecessary).

1134 *Domeij*, 2000, 267.

1135 Council Regulation (EEC) 1768/92 of 18 June 1992 concerning the Creation of a Supplementary Protection Certificate for Medicinal Products, which was codified under Regulation (EC) No 469/2009 of the European Parliament and of the Council ("Council Regulation 469/2009") that had various amendments but no substantive changes.

1136 Council Regulation 469/2009, Art. 13.

1137 Council Regulation 469/2009, Art. 7.

1138 Case C-181/95, *Biogen v. Smithklein Beecham* [1997] ECR I-357, para 28 (holding if a product was protected by a number of basic patents in force, which might belong to a number of patent holders, each of those patents might be designated for the purpose of the procedure for the grant of a certificate, however, under article 3(c) of the Regulation, only one certificate might be granted for each basic patent).

1139 Council Regulation 469/2009, Art. 3(d).

one substance.[1140] If the patentee has more than one patent on the same product, no more than one certificate may be granted.[1141] The scope of protection extends only to the product covered by the marketing authorization and for the use of the product as a medicinal product that has been authorized before the expiration of the certificate.[1142]

Medicinal products are the category of products which are eligible for the SPC, and the product refers to the active ingredient, which receives the exclusivity right. In other words, the SPC is granted to the active ingredient of the medicinal product. Article 1 of the Council Regulation 469/2009 defines "medicinal product" as "any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals." It defines "product" as "the active ingredient or combination of active ingredients of a medicinal product." However, "the active ingredient" in Art. 1(b) is not defined in the Regulation. In this regard, the BGH stated that, through the definitions of a product and a medicinal product above, "the active ingredient" could be indirectly described as a component of the product, which was presented for treating or preventing human disease.[1143]

b) In the United States

According to the Hatch-Waxman Act, the patent term can be extended for a period corresponding to half of the clinical testing time of an investigative new drug (IND), plus all approval time of the new drug application (NDA), up to a maximum of five years, if the maximum patent term does not exceed 14 years from the NDA approval date and if any such IND or NDA time period to the grant of the patent is not taken into account.[1144] Only one patent can be extended in connection with the first NDA approval, i.e. first per-

1140 Council Regulation 469/2009, Art. 3(c).
1141 Regulation (EC) No 1610/96 of the European Parliament and of the Council of 23 July 1996 concerning the Creation of a Supplementary Protection Certificate for Plant Protection products ("Council Regulation 1610/96") Art. 3. Para 2 and Recital 17.
1142 Council Regulation 469/2009, Art. 4; *Brückner/von Czettritz*, 2011, Art. 4 Rdn 32.
1143 *BGH/Doxorubicin-Sulfate*, GRUR 2009, 41, 41.
1144 35 U.S.C. § 156 (c).

mitted commercial marketing or use of the product,[1145] and a patent cannot be extended more than once, though it covers more than one FDA approved products.[1146] This can thus be summarized as "one patent extension per patent, one patent extension per product, and one product per patent extension."[1147] The scope of protection is limited to the "approved product" for any approved use.[1148] Thus, only the scope covering the product is extended.

The product as an objective of the patent term extension means a drug product or any medical device subject to regulation under the FDA Act, and the drug product means the active ingredient of a new drug, including any salt or ester of the active ingredient.[1149]

Under the Hatch-Waxman Act, if the paragraph IV ANDA applicant successfully challenges the patent validity, he is offered 180 days of exclusivity, which prevents other generic makers from entering the market.[1150] The 180 day exclusivity holder will gain a large profit by pricing just below the reference drug without concern about competition from any other generics. However, in Europe, where no such 180 day exclusivity exists, once the first validity challenger is successful, other generics will benefit from the invalidation, and the first challenger will not easily recover the litigation cost.

c) In Korea

The term of the patent concerning drugs can be extended by a period of up to five years, during which the patented invention cannot be practiced, because an approval under other Acts is required to work a patented invention, and it takes an extended period to complete the efficacy or safety tests that are necessary to obtain such approval, and these are prescribed by Presidential Decree.[1151]

1145 35 U.S.C. § 156 (a)(5).
1146 35 U.S.C. § 156 (a)(2); *Merck v. Kessler*, 80 F.3d 1543, 1547 (Fed. Cir. 1996).
1147 *Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, No., 96-1718-c H/G, 2001 U.S. Dist. LEXIS 5753, 26 (S.D. Ind. 2001).
1148 35 U.S.C. § 156 (b)(1); *Merck v. Kessler*, 80 F.3d 1543, 1547 (Fed. Cir. 1996) (holding that the restoration period of the patent did not extend to all products protected by the patent but only to the product on which the extension was based).
1149 35 U.S.C. § 156 (f)(2).
1150 21 U.S.C. § 355(j)(5)(B)(iv).
1151 Korean Patent Act Art. 89.

In contrast to the other jurisdictions, more than one patent can be extended for one approval of the product. However, the same patent cannot be extended even if it covers more than one product approved by the regulatory authority. The scope of the patent term extension is also limited solely to the approved product for the approved use.

2. Patent term extension on selection patents

The issue with regard to a patent term extension on a selection patent is whether the subject matter of the patent can be the subject of the patent term extension as a separate product from the products covered by their basic patents.

a) Species selection patents

Although the scope of a species selection patent can be overlapped with that of the genus patent, since the active ingredient covered by the species selection patent will be different from that of the genus patent, the patent term extension will be granted to the species patent. Consequently, if the patentee of the species selection patent is the same as the genus patentee, he can enjoy much longer exclusivity. However, if the basic patentee would have developed the compound covered in the basic patent without securing a species patent, he can enjoy only the 20 years from the filing date of the genus patent.

b) Optical isomers

In Germany

While distinguishing from the *Doxorubicin-sulfate* case, the BGH held that a marketing authorization for a medicinal product containing racemate as an active ingredient did not present a bar to granting an SPC for a medicinal product that contained an enantiomer as an active substance, and that was also the subject matter of both a later marketing authorization and of its own

patent.[1152] In the *Doxorubicin-sulfate* case, even if the applicant argued that doxorubicin-sulfate had improved potency, better pharmacological effect and reduced side effects in comparison to doxorubicin-hydrochloride, the BGH dismissed the case and held that a previous SPC granted for doxorubicin-hydrochloride opposed the grant of an SPC of doxorubicin-sulfate, because the active compound was still the same as doxorubicin.[1153]

In the United Kingdom

The Appeal Court in *Generics (UK) v. Daiichi Pharmaceutical* also held that the previously granted SPC on a racemic compound (Ofloxacin) did not hinder granting an SPC for the enantiomer (Levofloxacin). [1154] The Court further held that this was because, while successive SPCs for mere variants of an active substance were not allowed, levofloxacin was not a minor variant but a novel and inventive improvement owing to its own distinctive activity, bioavailability, and toxicity.[1155] In Justice Jacob's words, "[o]nly a curmudgeon would say there was no invention there."[1156]

In the United States

The question whether enantiomers can have "first commercial marketing or use status" for the purpose of patent term extension was answered in *Ortho-McNeil Pharmaceutical v. Lupin Pharms*. [1157] The Federal Circuit upheld the District Court's decision that, regardless of its existence as a component (even the active component) of the previously approved and marketed ofloxacin, levofloxacin was the first permitted commercial marketing or use of this drug.[1158] In this case, the Federal Circuit also affirmed that the FDA and the USPTO practices were in accordance with *Glaxo v. Quigg*, in which the Court held that "product," as used in § 156(a), was "the active ingredient

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1152 *BGH/Escitalopram,* GRUR 2010, 123, 131; *see also BPatG/Escitalopram II,* 29.03.2011- 3 Ni 22/10 (a dismissed another challenge of nullity action against the granting of SPC based on the argument that escitalopram had no substantially different or improved pharmaceutical effect over the racemate citalopram).

1153 *BGH/Doxorubicin-Sulfate*, GRUR 2009, 41.

1154 *Generics (UK) v. Daiichi Pharmaceutical* [2009] EWCA Civ 646.

1155 *Generics (UK) v. Daiichi Pharmaceutical* [2009] EWCA Civ 646, para 68.

1156 *Generics (UK) v. Daiichi Pharmaceutical* [2009] EWCA Civ 646, para 45.

1157 *Ortho-McNeil Pharmaceutical v. Lupin Pharms.*, 603 F.3d 1377 (Fed. Cir. 2010).

1158 *Ortho-McNeil Pharmaceutical v. Lupin Pharms.*, 603 F.3d 1377, 1381 (Fed. Cir. 2010).

present in the product," not the biologically "active moiety." The Court also extended the term of the patent on a new ester of an acid, even though salts of the same acid had previously been approved.[1159] In order to clarify the availability of a patent term extension, the cases relevant to the salts are discussed.

In *Glaxo v. Quigg*, in which Glaxo sought an extension for its patent covering cefuroxime axetil, an ester of its biologically active moiety, cefuroxime, the Federal Circuit held that the "active ingredient of a new drug" in § 156 meant the "actual active ingredient in the product" as opposed to the "active moiety of the active ingredient", and affirmed the patent term extension on cefuroxime axetil over the previously marketed product including two salts of cefuroxime.[1160] However, about 15 years after the *Glaxo* case, Pfizer, which had a marketing approval for and sold amlodipine besylate salt, sued Dr Reddy's Lab, which sold amlodipine maleate salt, based on a patent whose term was extended.[1161] In *Pfizer Inc. v. Dr. Reddy's Laboratories,* the CAFC held that the patent term extension applied not only to the particular salt of molecule being used in marketing approval but also to all salts and esters of molecule covered by the patent.[1162] While reasoning that the "statute foresaw variation in the salt or ester of an active ingredient, and guarded against the very loophole now urged"[1163], the Federal Circuit held that the "product" was the active moiety, which seems to be different from the ruling in the *Glaxo* case.[1164] In *PhotoCure v. Kappos*, the Federal Circuit distinguished this case from the *Pfizer* case: "The issue in *Pfizer* was whether infringement of an extended patent on the drug amlodipine was avoided by

1159 *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990).
1160 *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990).
1161 *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd*., 359 F.3d 1361 (Fed. Cir. 2004).
1162 *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd*., 359 F.3d 1361, 1365-67 (Fed. Cir. 2004) (quoting also Title 21 Code of Federal Regulation - Food and Drugs ("21 C.F.R.") § 60.3(b)(10): "[h]uman drug product means the active ingredient of a new drug or human biologic product […], including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient).
1163 *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd*., 359 F.3d 1361, 1366 (Fed. Cir. 2004).
1164 *See also Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd*., 359 F.3d 1361, 1367 (Fed. Cir. 2004) (In his dissent, however, Meyer Chief J stated the patent term extension should be limited to the specific product which was the subject of FDA approval, since the product which was eligible for a patent term must have been subject to a regulatory review period before its commercial marketing or use, which was neither amlodipine, nor amlodipine maleate, but amlodipine besylate).

changing the salt." [1165] The Federal Circuit further noted that "*Pfizer* did not hold that extension is not available when an existing product is substantively changed in a way that produces a new and separately patentable product having improved properties and requiring full FDA approval."[1166] According to *PhotoCure*, therefore, separate patentability alone could justify finding a drug product distinct from a previously approved product for the purpose of § 156.[1167]

c) Polymorphs

In the case of *Laboratoires Servier v. Apotex*, after the first and basic patent for the active substance (perindopril) expired in 2003 with the effective extension by an SPC, if the second patent on the crystalline form of the active substance is valid, the exclusivity would be extended to 2020.[1168] Thus, the polymorph seems to be regarded as a different active ingredient from the basic product.

d) Metabolite

There seems to be no case law regarding the patent term extension on a metabolite. However, based on the above discussed cases, once the metabolite is patented, it will likely be able to enjoy the patent term extension as well.

3. Analysis and conclusion

For the optical isomers, the BGH distinguished the ofloxacin case from the doxorubicin-sulfate case by holding that, because the active compound of doxorubicin-hydrochloride and the doxorubicin-sulfate were the same as doxorubicin, the previously granted SPC opposed the grant of an SPC for the doxorubicin-sulfate. However, it is difficult to understand the reasoning

1165 *PhotoCure v. Kappos*, 603 F.3d 1372, 1376 (Fed. Cir. 2010).
1166 *PhotoCure v. Kappos*, 603 F.3d 1372, 1376 (Fed. Cir. 2010).
1167 *PhotoCure v. Kappos*, 603 F.3d 1372, 1376 (Fed. Cir. 2010).
1168 *Laboratoires Servier v. Apotex*, [2008] EWHC Civ 445, paras 4 and 9.

behind distinguishing the levofloxacin case from the doxorubicin case, because the active ingredient in citalopram is also the one enantiomer, i.e. escitalopram. It is equally hard to understand the reasoning of the ofloxacin case in the British court. The Court held that levofloxacin was patentable, thus, a different SPC should be granted after the SPC on the ofloxacin. Similarly, in the United States, even if the product covered by the second generation invention shares "an active moiety" with the previously approved drug, the applicants could obtain the patent term extensions as long as "the active ingredients" of the products are different.

In general, for other second generation inventions, as long as it could acquire a patent, the SPC would be granted on top of the SPC on the product covered by the basic patent.

Lowered patentability requirements on second generation inventions and the SPC

The scope of the patent extension covers the derivatives, such as salts and esters, which are protected by the basic patent, thereby preventing the third party preparing salts other than the basic patentee's substance and devaluing its SPC protection.[1169] However, if these derivatives are subject to patents specifically covering them, another SPC or patent term extension for derivatives of the substance can be granted.[1170] This could lead the basic patentee to work more on the trivial modifications of an active moiety, which was subject to the authorization of previous products. The phenomenon could be accelerated, because the patentability requirements on the second generation inventions have been lowered, and more derivatives may be patented. Namely, the lowered patentability requirement will allow more patents on the

1169 Council Regulation 1610/96, points 13 ("[w]hereas the certificate confers the same rights as those conferred by the basic patent; whereas, consequently, where the basic patent covers an active substance and its various derivatives (salts and esters), the certificate confers the same protection.") and 17 of preamble ("[w]hereas the detailed rules in recitals 12, 13 and 14 and in Articles 3 (2), 4, 8 (1) (c) and 17 (2) of this Regulation are also valid, mutatis mutandis, for the interpretation in particular of recital 9 and Articles 3, 4, 8 (1) (c) and 17 of Council Regulation (EEC) No 1768/92").

1170 Council Regulation 1610/96, points 14 ("[w]hereas the issue of a certificate for a product consisting of an active substance does not prejudice the issue of other certificates for derivatives (salts and esters) of the substance, provided that the derivatives are the subject of patents specifically covering them.") and 17 of preamble; *PhotoCure v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010).

second generation inventions, which in turn will result not only in longer exclusivity, but also in more incentives to working on second generation inventions than breakthrough innovations.

Patent term extension system and pharmaceutical innovation

The patent term extension system apparently encourages R&D more on the second generation inventions than on the NMEs.[1171] This is especially true for the medications whose safety testing and/or the toxicity testing takes longer than others. For example, for medicines that treat chronic diseases, Alzheimer's disease, or cancers, the maximum cap of five years of extension risk discourages companies from pursuing research in these medicinal fields.[1172] As discussed in chapter III.B.2.c), one of the reasons for the drought of new medications was the movement of focus to complex disorders such as these chronic diseases.

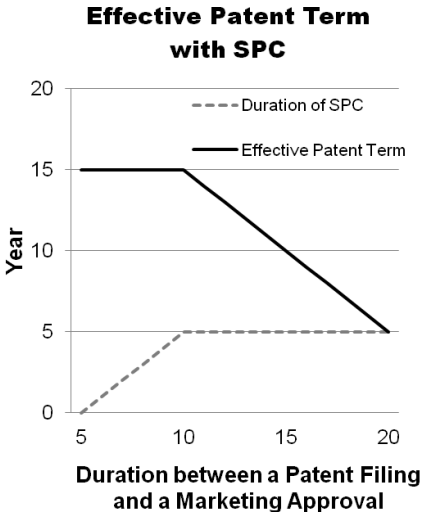
The condition of the SPC in Europe can be more serious, because the calculation system of the SPC is much more favourable to the secondary products than the NMEs. Under the SPC regulation, as seen in Figure 9, the maximum effective patent term protection of the product that succeeded in launching its product from five to ten years after the patent application date is not affected by actual durations. Thus, the medications that need more than ten years to reach the market from the patent filing date can never enjoy fifteen years of effective patent term.[1173]

1171 *See also* subsection VI.D.2.a)(1).

1172 *Domeij*, 2000, 282.

1173 This is different from the Korean patent term extension system which considers the whole period of clinical trials and of regulatory approvals or from the U.S. patent term extension system which considers the 1/2 of clinical trials and whole period of regulatory approvals.

Figure 9: Effective patent term with the compensation of SPC in Europe[1174]



By contrast, the medications that would take between five and ten years from the patent application date to acquire a market approval will enjoy the maximum effective patent term. Obviously, the gap between the patent application date and the market approval date should be much shorter for second generation products and could well be less than ten years. When the basic and second generation patentees are the same, the patentee could even have leeway to control the timing of the market launch up to ten years after the patent application date on the second generation invention. Given that the companies try hard to extend their exclusivities on products protected by their basic patents, this would increase the risk that the patentees who can enjoy the secondary SPC protections may try to use the leeway to bring their products to market later than the moment when society could have earlier access to those products.[1175] These can certainly be among the motivations for the pharmaceutical industries to focus more on second generation patents and products than NMEs.

1174 This figure is prepared by the author.

1175 Of course, this would be the case when they can make no gap from the basic patent's exclusivity.

D. Implications on the competition in the pharmaceutical industry

1. Introduction

According to Schumpeter, the existence of monopoly power spurs innovations by allowing the firm with the monopoly to appropriate the surplus generated by such innovations.[1176] He further argues that the old monopoly would eventually be challenged and replaced by the newer one by introducing the concept "Creative Destruction": A process through which the economic structures are revolutionized from within, by opening up new markets that will destroy the old one, and repeating this incessantly.[1177] In addition, as other commentators have noted, the arrival of new knowledge renders the old obsolete,[1178] and an inventor's descendants can actually become the instruments of his destruction.[1179] If there is no competition in the market, however, a patentee who holds an intellectual property right ("IPR") will also have little incentive to reinvest in further innovation,[1180] since this company could already control the market and impose monopoly prices.[1181]

According to Arrow, the incentive to innovate can exist even in perfect competition, and, by charging the royalty to a competitive industry, the inventor can receive a return equal to the monopoly profits. He therefore argues that the incentive of innovation is greater under competitive condition than under monopolistic conditions.[1182] If perfect competition exists in the market, exploitation cannot be confused with the pursuit of profits.[1183] If there is no intellectual property ("IP") protection, however, patentees will be concerned that competitors in the market will easily copy the product.[1184] Ex-

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1176 *Schumpeter*, 1942, 134-175 (holding that the firms with monopoly power are the main engines of innovation).

1177 *Schumpeter*, 1942, 137-138 ("[der] Prozess, … der unaufhörflich die Wirtschafts struktur *von innen heraus* revolutioniert, unaufhörflich die alte Struktur zerstört und unaufhörlich eine neue schafft.").

1178 *Belenzon*, 2006, 2.

1179 *Gallini/Scotchmer,* 2002, 65.

1180 *Kamien/Schwartz*, 1982, 190-91 (noting that IPR holders would do so because his reward from innovation is smaller than the total social benefit).

1181 *Drexl*, 2007, 18.

1182 *Arrow*, 1962, 619-22.

1183 *Seißer*, 2008, 2.

1184 *Drexl*, 2007, 18; *Kamien/Schwartz*, 1982, 190 (noting perfect competition corresponds to zero year of patent life, thus there is no reward from innovation, followed by no innovation.).

amples can be easily observed in history. For example, the price of penicillin, which was not patented, and the price of streptomycin, which was licensed on an unrestricted basis, dropped dramatically as the result of the rapid increase in demand during and after World War II and by the competition among many new suppliers.[1185] Therefore, the new "wonder drugs" were found to be unprofitable.[1186] Furthermore, this could make the companies hesitate to or not invest in R&D.[1187]

Competitive pressure could further result in socially wasteful over-investment in R&D or induce defensive investment by those who try to strengthen their bargaining position in the field.[1188] In addition, "more competition" may also involve social costs, such as duplication of entry costs, inefficient production, multiplied investments in the same products, and the like.[1189] In reality, competition is never perfect, and the market can be distorted by many factors, such as government regulation, central planning, monopolistic structures, and so on.[1190] Moreover, considering the limitation of an IPR's life (especially a patent), since the companies cannot enjoy their monopoly position perpetually, companies must reinvest to find another source of income. Furthermore, even if the innovation occurs at a slower pace than is socially optimal, the innovation occurs under monopoly.[1191] During the limited period of their monopoly rights, both IP laws and competition laws should be combined to promote dynamic competition.[1192]

Regarding the situation concerning second generation inventions, Merges and Nelson argue that, since there would be uncertainty, namely, that different technologies would be developed from the common basic innovation by different approaches from different parties, it would be better to let a

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1185 *Comanor*, 31 Economia, 372, 373 (1964) (noting "[t]he price of a standard form of penicillin dropped from $20 for 100,000 units in 1943 to 41 cents in 1950."); *Steele*, 5 J. Law Econ. 131, 138, fn24 (1962) (e.g. noting "[f]or the ten-year period 1951-1960 the bulk price of streptomycin dropped from $3.24 to $0.36 for ten grams"); *Temin*, 10 Bell J. Econ. 429, 436 (1979).

1186 *Scherer*, 2007, 11.

1187 *Drexl*, 2007, 18; *Kamien/Schwartz*, 1982, 190 (noting perfect competition corresponds to zero year of patent life, thus there is no reward from innovation, followed by no innovation.).

1188 *Cockburn*, 2006, 21-22, 25.

1189 *Denicolò*, 44 J. Ind. Econ. 249, 263 (1996).

1190 *Seißer*, 2008, 2.

1191 *Kamien/Schwartz*, 1982, 190-91.

1192 *Drexl*, 2007, 18.

variety of minds try.[1193] This provides economic support for improvement patents.[1194] Since, under the monopoly situation, the patent holder or some licensees can be expected to develop only some of the improvements further, many potential improvements might be underdeveloped or even ignored.[1195] Landes and Posner also mention, however, that it might be more efficient to leave the improvements to the original inventors at a slower speed and at a lower cost.[1196] In the end, the answer to the question of whether it would be better to have many improvements, depends on whether and how much these kinds of improvement inventions are needed.

Pharmaceutical companies can face antitrust challenges, because there is a thin line between their aggressive approach in this sector and anti-competitive behaviour.[1197] Some have argued that evergreening tactics and life cycle management based on second generation patents have caused delayed market access not only for the generic companies but also for the patients.[1198] For example, it was reported that the generic entry to the market was delayed, on average, seven months after patent expiration, with the range from zero to more than fifty months.[1199] According to the European Commission, tactics employed to respond to generic entry includes patenting activities of originators; contacts, disputes and litigation between originator and generic companies;opposition procedures and appeals before patent offices; patent settlements and other agreements between originator and generic companies; interventions of originator companies before national authorities deciding on marketing authorization, pricing and reimbursement of generic products; promotional activities; and second generation products.[1200] Other than interventions in national authority decisions, all of these

1193 *Merges/Nelson*, 90 Colum. L. Rev. 839, 873-74 (1990); *see also von Hippel*, 1988, 3-5 (showing generally different sources of innovations according to the field of industries and manufacturer was the sources of innovation in chemical industries, e.g. engineering plastics and plastics additives.).

1194 *Landes/Posner*, 2003, 190, 318-319 (also noting a quasi-Darwinian process, which is "a process almost of trial and error in which the market selects from among diverse approaches whose relative promise cannot be assessed in advance").

1195 *Merges/Nelson*, 90 Colum. L. Rev. 839, 873-74 (1990).

1196 *Landes/Posner*, 2003, 190, 322.

1197 *Safir*, 50 Food & Drug L. J. 335, 335 (1995).

1198 *See e.g.*, *Rathod*, 7 J. Generic Medicines 227, 227 (2010).

1199 *DG Competition*, 2009, 70-71.

1200 *DG Competition*, 2009, 16.

tactics are deployed in patenting. Even promotional activities can focus on second generation products covered by second generation patents.

On the one hand, the pharmaceutical industry was certainly "ingenious in finding ways to extend patents on its bestselling drugs," such as marketing a new combination of two old drugs.[1201] Gaudry insists that filing as many patents as possible with regard to the product would not only increase the total scope of patent protection but also achieve apparently competing purposes.[1202] On the other hand, it is theoretically possible that the generic companies would practice at least the basic patent once the patent expires. In addition, as EU pharmaceutical law clearly specifies, the development, application, and registration of a generic version are allowed before the expiration of the patent covering the product.[1203] In the following section, therefore, the substantive roles of second generation patents in the competition in generic markets will be analyzed.

2. Quasi-obstacles of generics market entry

a) Scope of second generation patents

There have been concerns that second generation patents could be used to extend the patent protection of basic products unjustifiably.[1204] Some have argued that second generation inventions would significantly impair generic competition but provide modest therapeutic gains for a small subset of the patient population, and thus government intervention must be made to prevent the losses from impaired competition while allowing access to the reformulation for those patients who really value it.[1205] Some also call these strategies "patent walls", which can be built where the innovator acquires patents on the variety of inventions related to the basic invention, but which

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1201 *Angell*, 342 New Eng. J. Med. 1902 (2000) (providing Vytorin (a combination of Ezetimibe and Simvastatin claimed in U.S. patent No. 5,846,966) as an example); *see also Glasgow*, 41 IDEA 227, 250-51 (2001).

1202 *Gaudry*, 29 Nature Biotech. 876, 877 (2011).

1203 Art. 10. 6 of Council Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use, as amended ("Council Directive 2001/83/EC).

1204 *Grubb/Thomsen*, 2010, 249; *Rathod*, 7 J. Generic Medicines 227, 227 (2010).

1205 *Shadowen/Leffler/Lukens*, IIC 2011, 698, 700.

exist less for the value than to protect the central innovations.[1206] However, second generation patents do not always prevent generics from entering the market, if generic manufacturers want to sell the older version covered by the basic patent after its expiration.

Although a *species selection invention* certainly infringes the basic patent, the exploitation of a basic patent after its expiration will not infringe the selection invention, since the scope of the species patent could not cover the older product. Thus, generic versions of the product covered by the basic patent would be sold soon after its expiration. Although the *Atorvastatin* decision held that the patent covers both racemates and *the enantiomers*,[1207] the decision seemed to be based on a claim drafting issue. More importantly, if the racemate infringes the enantiomer patent, the patent on the enantiomer must be invalidated according to the "infringement test" so that marketing the racemate will not infringe the enantiomer patent. For the *metabolite patent*, as the Munich Higher Regional Court held, exploitation of the parent drug does not infringe the metabolite patent, since the metabolite was not marketed. One may still worry about the contributory or inducement infringement. In addition, the Federal Circuit in the United States has continued to hold that it "would" or "may" infringe the metabolite patent and that, when administered, it could be metabolized into the claimed invention. One may need to await the further development of case law on metabolites in the United States. However, as we have seen from the House of Lords' decision, to find infringement would prevent someone from doing what he had already done before the filing date. Thus, even if a patent claiming a synthesized version of metabolite is granted, its scope should not be extended to the metabolite naturally made by the body.

For a *polymorph*, the concern can be justified. As the Federal Circuit held, if it is difficult or even impossible to manufacture one pure form of polymorph after the basic patent expires – e.g., in the course of manufacturing the basic product, the polymorph form could be synthesized together – a considerable extension in the effective patent term of basic invention will be concerned.[1208] However, if the probability of co-production is high, there

1206 *Hopenhayn/Mitchell*, 32 RAND J. Econ. 152, 163 (2001).
1207 See subsection V.B.2.b).
1208 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1342 (Fed. Cir. 2005).

will also be higher probabilities that the polymorph patent will be found invalid as inherent anticipation.[1209]

Therefore, there could be real concerns, such as species selection invention or the polymorph. However, contrary to the conventional perception, it could be said that there are fewer cases of the exploitation of a basic patent to be found than those infringing second generation patents.

b) Length of second generation patents

Apart from the patent term extension system's inherent problems,[1210] the patent term of second generation patents matters to the extent that their scope can prevent the generics' entry onto the market.

c) Delayed filing of second generation patent applications

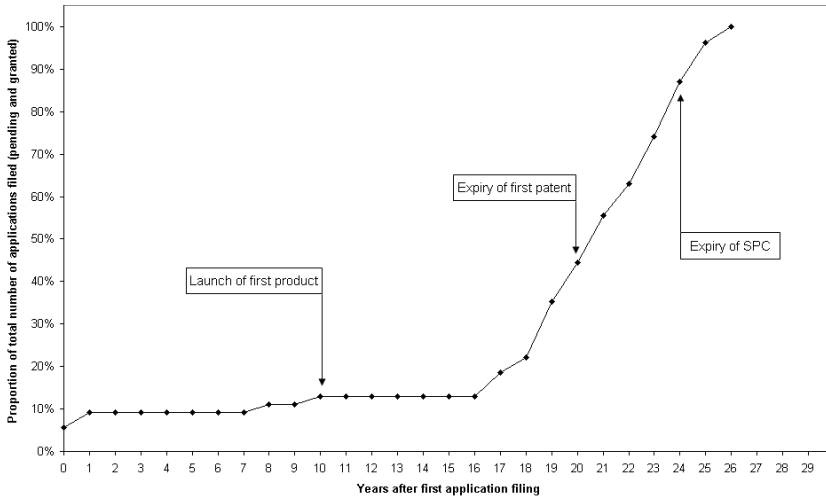
While presenting Figure 10, the European Commission argued that the second generation patents were filed at the very end of a patent term of basic invention.[1211]

1209 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1342-46 (Fed. Cir. 2005).

1210 See *supra* 1172 -1175 and accompanying texts.

1211 *DG Competition*, 2009, 176-77.

Figure 10: Post-launch patent portfolio for one of the top ten INNs by total sales (2000 – 2007)[1212]



Of course, the timing of second generation patenting is crucial. The later they are filed (but are granted before the primary patent expiration), the longer they can help to extend exclusivity in certain circumstances. However, this argument fails in two crucial respects in this field. First, the later the companies file patent applications, the more likely they will face prior arts and the less likely they will be issued as patents. Secondly, since the innovative companies are not the only ones that can file second generation patent applications, they cannot safely sit and wait to enjoy longer exclusivity with the help of second generation patents. Thus, the patentee of a basic patent cannot wait to file the patent applications until the expiration of the term of the basic patent.

The following issues are more burdensome to the generic manufacturers.

1212 *DG Competition*, 2009, 176-77.

3. Real obstacles to generics' market entry

a) Automatic thirty-month stay and new list up in the Orange Book in the United States

A patent linkage system refers to the practice of linking marketing approval or pricing/reimbursement status of generic drugs to the status of patents on the reference products. The American Orange Book is such a system. A new medication is usually relevant to more than one patent, and each patent listed in the Orange Book will likely have different patent expiration dates. One of the most significant problems with this system is the difficulty of evaluating the validity of patents claimed as being related to the reference products,[1213] because validity can finally be confirmed only by the courts.

When a New Drug Application ("NDA") is filed with the US FDA, the NDA applicant must submit a list of all patents that cover the drug regarding which a claim of infringement could be asserted.[1214] The FDA publishes the list of these patents with their expiration dates in the Orange Book[1215] to give notice to potential ANDA applicants that such patents may hinder them from introducing their generic versions. The generic manufacturers can prepare to launch their products after the analysis of patents listed in the Orange Book. However, the sudden announcement of a new patent grant covering the product will deter and prolong the generics' market entry, as occurred in the *In re Buspiron Patent Litigation* case.

Bristol-Myers obtained a patent for the compound buspirone in 1980, obtained marketing approval in 1986, and sold it on the market.[1216] On November 21, 2000, less than one day before the basic patent was set to expire, Bristol-Myers obtained a patent claiming one of the metabolites of buspirone.[1217] Around eleven hours before the original patent expired, Bris-

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1213 *Gaudry*, 29 Nature Biotech. 876, 876 (2011).

1214 21 U.S.C. § 355(b)(1)(G); 21 C.F.R. § 314.53.

1215 Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (Last accessed on December 20, 2013).

1216 *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 340, 345 (S.D.N.Y., 2002). It was sold under the Trademark "Buspar".

1217 U.S. Patent No. 6.150,365 (November 21, 2000, under the title of "Anxiety method", in original claim as filed the use of buspirone as a prodrug of the metabolite was also claimed); *In re Buspirone Patent Litigation*, 185 F.Supp.2d 340, 350 (S.D.N.Y., 2002); *Langreth/Murphy*, Forbes, Apr. 2, 2001.

tol-Myers hand-delivered copies of the metabolite patent to the FDA and applied to have it listed in the Orange Book[1218] as covering buspirone.[1219] The listing with the FDA triggered an automatic forty-five day period during which Bristol-Myers could bring patent infringement suits against generic competitors, who intended to market generic versions.[1220] Bristol-Myers filed suits for patent infringement against competitors within this forty-five day period, which in turn triggered an automatic stay of the FDA's approval of generic versions for up to the earlier of thirty months or until the relevant patent disputes were decided.[1221] One of the generic companies had already manufactured and was ready to ship its product at 12:00 am on November 22, 2000.[1222] The District Court held that the claim of the later patent did not cover uses of buspirone itself.[1223] In a different case, the Supreme Court reversed the Federal Circuit's decision[1224] and found that the patent delisting provision[1225] provided a mechanism for a generic company to challenge the accuracy of the use code in association with an Orange Book listed patent.[1226]

1218 Listing in the Orange Book is important mainly because when the generic company submit an ANDA, it is required to address each patent listed in the Orange Book that claims the drug. According to 21 USC § 355(j)(2)(A)(vii), an ANDA applicant must address for each patent listed i) that such patent has not been filed (paragraph I filing), ii) that such patent has expired (paragraph II filing), iii) the date on which the patent will expire (paragraph III filing), or iv) that such patent is invalid or will not be infringed by manufacture, use, or sale of the new drug for which the application is submitted.

1219 *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 340, 350 (S.D.N.Y., 2002).

1220 *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 340, 343 (S.D.N.Y., 2002).

1221 *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 340, 343 (S.D.N.Y., 2002); 21 U.S.C. § 355(j)(4)(B)(iii).

1222 *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323, 1327 (Fed. Cir. 2001), *cert denied* (holding neither the patent laws nor the Hatch-Waxman amendments permitted a private right of action to delist a patent from the Orange Book).

1223 *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 340, 363 (S.D.N.Y., 2002).

1224 *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd*., 601 F.3d 1359 (Fed. Cir. 2010).

1225 21 U.S.C. § 355(j)(5)(C)(ii)(I).

1226 *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1688 (U.S. 2012) (holding "[t]he statutory counterclaim we have considered enables courts to resolve patent disputes so that the FDA can fulfill its statutory duty to approve generic drugs that do not infringe patent rights. The text and context of the provision demonstrate that a generic company can employ the counterclaim to challenge a brand's overbroad use code.").

However, the NDA filers can have *thirty months exclusivity* without having to prove anything to anybody. Thus, the minimum of thirty months' delay in the generic entry certainly harmed not only the generics' businesses but also the public's access to the medication at substantially lower prices. Certainly, such a sudden delay must have damaged the generic companies' legal and economic expectations. Some commentators even argued that a reference drug patent holder could keep filing second generation patents for the same basic drug product with the FDA to receive almost unlimited consecutive thirty month stays, since a generic drug manufacturer had few ways to remove the listing until a Supreme Court decision in 2012.[1227] Second generation patents play pivotal roles in enabling these kinds of activities, and the impact will be expected in other countries[1228] that adopt similar patent linkage systems.

b) Pendency of patent applications: Uncertainty

(1) Pendency of patent applications

"*How on earth can this invention be patented?!*" was the question which the author was asked by a researcher about the Pfizer's patent application on the salts of amlodipine,[1229] which ultimately was invalidated. From her question, one may notice two important points. Firstly, she lacked the legal knowledge required to avoid confusing a patent with a patent application, which is often the case for researchers. Secondly, her scientific instinct was correct; thus, she could not understand how that kind of invention could be patented. However, considering that the application was granted by the USPTO and invalidated by the Federal Circuit, no one could have guaranteed whether the application would be granted or rejected.

1227 *Mahn*, 54 Food & Drug L.J. 245, 250-52 (1999) (noting that the examples of such patents were specially coated tablets, new formulations, crystalline forms of the same active ingredient, and variations on the drug delivery technologies; and that broadening the scope of patents which could be listed in the Orange Book, advantages accrued to NDA holders).

1228 Other examples are PMNOC proceeding in Canada, Administrative Action in Portugal and Mexico, similar system in Singapore, Patent certification processes in Australia, Indonesia, HK, and Italy.

1229 U.S. Patent No. 4,876,303 (November 7, 1989, under the title of "Pharmaceutically Acceptable Salts").

The pendency of a patent application, especially one filed by a major player in the pharmaceutical industry such as Pfizer,[1230] can cause researchers or companies to spend time searching and analyzing before they dive into a new field of research. That is to say, the uncertainty and insecurity about the patent ownership for competitors created by the patent pendency play important roles.[1231] Unlike the United States, where the patent office examines the invention regardless of whether the applicant has requested an examination or not, many other jurisdictions, such as Germany,[1232] the United Kingdom,[1233] and Korea[1234] require the applicant to request the substantive examination to proceed with the patent application. Thus, in these jurisdictions, the pendency of a patent application can be even longer and depend upon the decision each applicant makes. In addition, these uncertainties in the pharmaceutical industry can increase given the already increased number of second generation patents derived from the lowered patentability requirements for second generation inventions.

(2) Filing of divisional applications

The number of pending applications can be effectively increased by the filing of continuation applications in the United States or divisional applications.

Divisional applications

An applicant can file a divisional application with respect to subject-matter that does not extend beyond the content of the earlier application as filed.[1235] The date of filing of a divisional application would be that of the earlier, parent application,[1236] as a result of which the period of protection is the same as the parent's. Typically, a patent applicant files a divisional application after the communication from a patent office that an application

1230 She probably was not that much surprised if the application was filed by a small nameless company.
1231 *Somaya*, 38 J. Manage. 1084, 1100 (2012); *Henkel/Jell*, 2009, 1-2.
1232 GPA, Art. 4.
1233 U.K. Patent Act, Art. 18 (Substantive examination and grant or refusal of patent).
1234 Korean Patent Act, Art. 59 (Request for examination of a patent application).
1235 *See e.g.*, EPC Art. 76 (1).
1236 *See e.g.*, EPC Art. 76 (2).

covers more than a single general inventive concept.[1237] However, a patentee can also file a divisional application without a patent office's requirement. Voluntary divisional applications have been exploited to ward off a rejection, which has increased the incidence of double patenting.[1238] As the European Commission clearly pointed out, voluntary divisional patent application was a legitimate way of splitting an (initial) parent application, and could not extend the content of the original application nor the protection period.[1239]

Arguable abuse of procedural possibility

The possible problem appears to reside in the increase number of pending patent applications. This could also extend the examination period, as the examination of divisional applications continues even after the parent application's withdrawal or revocation, which, under certain conditions, could add to legal uncertainty for generic companies.[1240] This is particularly troublesome, since divisional applications are often filed at a late stage in the parent application, even though the late filing can arise from a change in the applicant's interests to another subject matter disclosed in the parent patent application.[1241]

In *Napp Pharmaceuticals v. Ratiopharm*, where there were "no less than nine divisional stemming from the original application,"[1242] Jacob LJ pointed out that, since each divisional application would stand or fall on its own merits, and each application could enforce its own right, the clutch of divisionals was likely to make it more difficult for the third parties to assess the position.[1243] He even noted that it was questionable whether this voluntary aspect of the divisional system should continue to be permitted.[1244]

Another interesting case involving divisional application was *Ratiopharm v. Pfizer* in Italy in 2012, where Pfizer was sanctioned with a more than 10 million Euro fine for alleged abuses of the patent system in violation of Art. 102 of the Treaty on the Functioning of the European Union

1237 *See e.g.*, EPC Art. 82.
1238 *Germinario*, IIC 2011, 387, 387.
1239 *DG Competition*, 2009, 201.
1240 *DG Competition*, 2009, 201.
1241 *Günzel*, GRUR Int 2008, 644, 644-65.
1242 *Napp Pharmaceuticals v. Ratiopharm* [2009] EWCA Civ 252.
1243 *Napp Pharmaceuticals v. Ratiopharm* [2009] EWCA Civ 252, paras 11-12.
1244 *Napp Pharmaceuticals v. Ratiopharm* [2009] EWCA Civ 252, para 12; *cf.* EPC Rule 36(1) (introducing the time limit for voluntary filing a divisional application).

("TFEU"),[1245] which was later annulled.[1246] In this case, Pfizer filed applications in 1997 for SPCs in all European countries except Italy. Thus, it was expected that the patent term would expire in July 2001 for other countries and in September 2009 in Italy.[1247] Pfizer filed a divisional application of the parent patent before the EPO in 2002, which was granted in 2009 and which was translated and validated only in Italy in June 2009,[1248] but was revoked in October 2010.[1249] Based on this divisional application, Pfizer applied for and received an SPC in Italy in July 2011,[1250] although it was also withdrawn according to the revocation of the patent.[1251] The Competition Authority found that Pfizer abused its dominant position by blocking or delaying market access to generics based on these activities. This case was different from the *AstraZeneca* decision of the CJEU, where the conduct in question was the submission of misleading information to the patent offices, not the use of the patent regime as such.[1252] Later, the decision was annulled by the Court, mainly because the Competition Authority failed to prove "a clear exclusionary intent based on a *quid pluris* as opposed to the mere summation of behaviours regarded as legitimate according to the administrative and judicial system."[1253] However, seeking a divisional application can be regarded as an abuse of procedure under certain circumstances, at least by competition authorities.

1245 *Ratiopharm v. Pfizer*, Italian Competition Authority, p23194, Jan 11, 2012.

1246 *Pfizer v. Italian Competition Authority et al.*, Regional Administrative Court for Latium, Case No. 07467/2012, Sept. 3, 2012.

1247 *Ratiopharm v. Pfizer*, Italian Competition Authority, p23194, Jan 11, 2012, para 73.

1248 *Ratiopharm v. Pfizer*, Italian Competition Authority, p23194, Jan 11, 2012, paras 79-81.

1249 *Ratiopharm v. Pfizer*, Italian Competition Authority, p23194, Jan 11, 2012, para 96.

1250 *Ratiopharm v. Pfizer,* Italian Competition Authority, p23194, Jan 11, 2012, para 81.

1251 *Ratiopharm v. Pfizer,* Italian Competition Authority, p23194, Jan 11, 2012, para 96.

1252 Case C-457/10, *AstraZeneca AB v. European Commission,* 2012.

1253 *Pfizer v. Italian Competition Authority et al.*, Regional Administrative Court for Latium, Case N. 07467/2012, Sept. 3, 2012., para 4.1. (appealed to the Italian Council of State (Italy's highest administrative court).

An attempt to adjust this phenomenon by the USPTO

In 2007, the USPTO proposed two regulations that would limit the chances of filing further patent applications. Specifically, an applicant would be permitted to file only two continuation applications and one request for continued examination per application family.[1254] These rules were challenged, and the District Court held that the rules were void because they substantively altered the existing law.[1255] On appeal, the Federal Circuit held that the rules were procedural in nature and within the scope of the USPTO's rulemaking authority.[1256] The challengers filed a petition for rehearing *en banc*, which was granted.[1257] Ultimately, however, the USPTO announced that it would rescind the proposed rules due to vehement opposition from patent applicants, who felt that the rules unduly restricted their capacity to protect their IPs.[1258]

Rule 36 EPC

This problem was also acknowledged by the BOA,[1259] especially in a case where the application under the appeal was the third one in a sequence A1, A2, and A3 of divisional applications, each divided from its predecessor and stemming from a root (originating) application A0.[1260] Based on the Art. 76(1) and Rule 25 of EPC 1973 related to the divisional application, the BOA held that sequences of divisional applications each containing the same broad disclosures of the original patent application with unamended description could be pending for up to twenty years. The BOA could not see any proper reason to impose an additional requirement.[1261] However, the BOA found this practice unsatisfactory and noted that, "It appears that what applicants consider a legitimate exploitation of the procedural possibilities

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1254 *Tafas v. Dudas*, 541 F.Supp.2d 805 (E.D.Va.,2008).
1255 *Tafas v. Dudas*, 541 F.Supp.2d 805, 817 (E.D.Va.,2008).
1256 *Tafas v. Doll*, 559 F.3d 1345, 1364-65 (Fed. Cir. 2009).
1257 *Tafas v. Doll*, 328 Fed.Appx. 658 (Fed. Cir. 2009).
1258 USPTO, USPTO Press Release #09-21 (Oct. 8, 2009), available at: http://www.uspto.gov/news/09_21.jsp
(Last accessed on December 20, 2013).
1259 *Astropower/Divisional*, G1/05 (2007); *Seiko/Sequences of Divisionals*, G1/06 (2007) (since similar sets of questions had been referred to the EBA and two proceedings were consolidated, "G1/05" is only referred).
1260 *Seiko/Sequences of Divisionals*, G1/06 (2007).
1261 *Astropower/Divisional*, G1/05 (2007), paras 13.3- 13.5.

afforded by the EPC, others consider an abuse in relation to the law as they think it ought to be rather than as it is."[1262]

The BOA considered this an issue of legal security for third parties, and recommended that the legislator consider this issue while mentioning some administrative measures.[1263] As Teschemacher points out, "the lesson should be clear, i.e. the more speedily examining divisions deal with divisional applications, the less the possibilities for abuse are."[1264] These views seemed to be reflected in Rule 36 of EPC 2000 in shortening the time span for filing a divisional application, namely, all divisionals must be filed within 24 months from either the issuance of the first communication from the examining division or the issuance of a lack of unity objection. [1265] Considering the still increasing numbers of divisionals and the continuing complaints of the users, above Rule 36 is de facto abandoned,[1266] however, a new Rule 38(4) EPC is instead provided with effect from April 1, 2014, i.e. imposing additional fee for second (or subsequent) generation divisional applications.

The legal uncertainty and difficulty of assessing the third parties' positions through the pendency of patent applications are certainly the cause of anxiety. This phenomenon could be amplified by the increased number of second generation patent applications and patents.

1262 *Astropower/Divisional*, G1/05 (2007), para 13.5.

1263 *Astropower/Divisional*, G1/05 (2007), para 13.5 (further mentioning administrative measures, such as giving priority to the examination of divisional applications and bundling and speedily deciding co-pending divisional, in order to minimize the possibility for applicants to keep the subject-matter alive).

1264 *Teschemacher*, IIC 2007, 703, 706.

1265 EPC 2000 Rule 36 [European divisional applications]
"(1) The applicant may file a divisional application relating to any pending earlier European patent application, provided that: (a) the divisional application is filed before the expiry of a time limit of twenty-four months from the Examining Division's first communication in respect of the earliest application for which a communication has been issued, or (b) the divisional application is filed before the expiry of a time limit of twenty-four months from any communication in which the Examining Division has objected that the earlier application does not meet the requirements of Article 82, provided it was raising that specific objection for the first time.".

1266 EPC 2000 Rule 38(4) EPC
"(4) The Rules relating to Fees may provide for an additional fee as part of the filing fee in the case of a divisional application filed in respect of any earlier application which is itself a divisional application."

c) Active movement of the market to new products

In general, once a patent on a product expires, consumers can choose to buy the products at a price lowered by the competition.[1267] Reformulation of products hardly hampers competition in most other markets, since consumers who decide whether the "improved product" deserves a higher price can simply buy a competing product instead.[1268] In the pharmaceutical market, however, the consumers choosing the product (physicians) do not have to pay for it, and those who have to pay for it, the patients or insures, do not choose it.[1269] Even though spending on direct-to-consumer advertisement has been reported as continuing to increase,[1270] the main interaction in this market is between the health care funder and the pharmaceutical industry.[1271] These circumstances may lead this market to suffer from a significant market failure,[1272] especially on new products based on second generation patents.

Efforts to move the market to products covered by second generation patents

In the late 1960s, Kefauver argued that the pharmaceutical industry had made a huge expenditure on marketing and promoting drugs, which was reflected

1267 *Scherer/Ross*, 1990, 624.
1268 *Shadowen/Leffler/Lukens*, IIC 2011, 698, 700.
1269 See subsection III.A.2.b); *see also McGuire/Drummond/Rutten*, 2004, 130-31 (noting "The clinician, acting as the agent for the patient, does not bear full, if any, financial responsibility for the purchase and may be affected by promotional activities of the companies."); *Shadowen/Leffler/Lukens*, IIC 2011, 698, 700; *Kefauver*, 1966, 29 (also noting this peculiar market structure is the reason the drug industry is particularly susceptible to monopoly control).
1270 *Donohue/Cevasco/Rosenthal*, 357 New Eng. J. Med. 673, 677-80 (2007); *Gilbody/Wilson/Watt*, 14 Quality & Safety in Health Care 246, 246 (2005); *United States General Accountability Office*, 2008, 1.
1271 *McGuire/Drummond/Rutten*, 2004, 131.
1272 *Shadowen/Leffler/Lukens*, IIC 2011, 698, 700.

in turn in the prices thereof.[1273] This argument continues to be made.[1274] For example, companies spend money on aggressive promotion of new versions of old drugs before the date of the basic patent expires.[1275] The drug makers typically bring a newly named drug for the same condition at the end of the basic patent's market exclusivity and then launch a huge promotional campaign to convert users to the new drug.[1276] One commentator argues that the pharmaceutical industry is famous for its superior ability to inform physicians about the results of clinical trials.[1277] When the physicians are persuaded to switch their patients to the new versions, such conversion efforts could protect the drug maker from market share erosion after the date of generic entry. [1278] This in turn will result in substantially elevated costs, both directly through their own relatively high prices and indirectly by reducing access to generics.[1279]

Example of Nexium®

One of the most telling stories is the case of AstraZeneca's "purple pill." After its glittering success with racemic Omeprazole (Prilosec®) and shortly before the patent on Omeprazole was about to expire, the company commenced a massive and unprecedented advertising campaign to persuade patients and doctors to move from Prilosec® to Nexium®.[1280] To promote this switch, AstraZeneca priced Nexium® a bit lower than Prilosec®, gave discounts, distributed free samples to doctors, and even offered coupons in newspapers, all of which cost the company half a billion dollars in 2001

1273 *Kefauver*, 1966, 68-97.

1274 *United States General Accounting Office*, 2002, 3 (reporting "[p]harmaceutical companies spend more on research and development initiatives than on all drug promotional activities, including [direct-to-consumer] advertising."); *Gagnon/Lexchin*, 5 PLOS Med. 29, 32 (2008) (Based on the estimate derived from a research comparing the data from two market research companies, namely, IMS and CAM, *Gagnon* and *Lexchin* argued that "it appears that pharmaceutical companies spend almost twice as much on promotion as they do on R&D", which was contrary to the industry's claim).

1275 *NIHCM*, 2002, 18; *Angell*, 2004, 77; *Harris*, The Wall Street Journal, June 6, 2002; *Hall*, The New York Times, March 11, 2001.

1276 Because of the high loyalty of patients and doctors (see subsection III.A.2.c)), fiercer promotional activity is required to convert.

1277 *See e.g., Privitera,* 68 Epilepsy Res. 52, 56 (2006).

1278 *NIHCM*, 2002, 4, 18.

1279 *NIHCM*, 2002, 4.

1280 *Angell*, 2004, 77; *Harris*, The Wall Street Journal, June 6, 2002.

alone.[1281] Again, AstraZeneca basically cut Prilosec® in half, though not without difficulty. The only important question was whether the new drug would be better than the old. The truth is that the new version is little better or even different.[1282]

This is also a good example of a phenomenon called "chiral-switch," which is often observed in chiral drugs that are already approved as a mixture of optical isomers that have been reevaluated, redeveloped and launched later as a single enantiomer.[1283] This is the line extension of established clinically effective and commercially profitable drugs, which provides a strategy to extend the profitable life of drugs, may result in extended patent protection, and may give an advantage against generic competition.[1284] Obviously, whether one may get a patent on the enantiomer will substantially affect profitability.[1285] It is axiomatic that AstraZeneca would not have invested in switching to S-omeprazole without patent protection. Based on the litigation and settlements in the United States and the appeals in Europe, the generic version of Nexium® seems to be available in some European countries after the ten-year regulatory exclusivity[1286] and will be available in 2014 in the American market at the earliest after the patent expires.[1287] Even if the patent were ultimately invalidated, thanks to the lowered patentability requirements and the patents granted as the result thereof, AstraZeneca suc-

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1281 *Angell*, 2004, 77-78; *Harris*, The Wall Street Journal, June 6, 2002.

1282 *Harris*, The Wall Street Journal, June 6, 2002.

1283 *Agranat/Caner*, 4 Drug Discov. Today 313, 313 (1999); *Caldwell*, 16 Hum. Psychopharm. S67, S69-S70 (2001); *Tucker*, 355 Lancet 1085, 1085 (2000); *cf. Pifferi/Perucca*, 20 Eur. J. Drug Metab. Ph. 15, 24 (1995) (arguing these 'chiral switch' can be justified not only in terms of technological innovation and marketing appeal but also, in terms of sound scientific motivations. Otherwise, they warned there would be a clear risk to divert a significant proportion of investment from more innovative research and from areas which are in particular need of therapeutic breakthroughs.).

1284 *Tucker*, 355 Lancet 1085, 1085 (2000); *Hutt/Valentová*, 50 Acta Facultatis Pharmaceuticae Universitatis Comenianae 7, 15 (2003); *BGH/Escitalopram*, GRUR 2010, 123, 126.

1285 *Hutt/Valentová*, 50 Acta Facultatis Pharmaceuticae Universitatis Comenianae 7, 15 (2003).

1286 For example, http://www.shop-apotheke.com/arzneimittel/6456801/esomeprazol-ratiopharm-40mg-hartkapseln.htm?know=search%3Aesomeprazole~. (Last accessed on December 20, 2013).

1287 See subsection V.A.1.b).

cessfully delayed the launches of generic versions for a good number of years.

Example of Clarinex®

Another famous example is the story of Clarinex®, which is a repeat of the Nexium® story. Clarinex®, the metabolite of Claritin® of Schering-Plough successfully replaced its parent drug before its patent expired, thanks in large part to the massive promotional campaign that made the brand ubiquitous.[1288] As Angell properly noted, Clarinex was approved for additional use, i.e. indoor allergies, "only because the company decided to test it for that use. If they had tested Claritin [the parent drug] for indoor allergies, it would undoubtedly have been the same as Clarinex – because it is the same."[1289]

The scope of the patent on enantiomer does not cover the racemate. Thus, generic companies can principally sell the racemate form. However, if the whole market moves to the enantiomers due to the efforts of the company, generics which include the "old" racemate form, are seen as "outdated" or perceived as "less effective" even if no actual benefit results. This market switch to the new version, in turn, is very useful for the innovating company in extending patent exclusivity.

d) Along with very specific patents on the secondary products

Life cycle management strategy for maximizing the period of exclusivity includes a complex combination of patents, which are sometimes too specific and hard to invalidate. The narrow scope of second generation patents often provides ineffective protection, since their limited scope allows generic manufacturers to design around the patent and launch the generic version without infringing the patents.[1290] In addition, these second generation patents are often challenged with regard to validity over their own basic patent disclosures. On the other hand, once the patentee overcomes the challenge, some of these incredibly specific scopes can be extremely valuable in stopping generic entries.

1288 *Angell*, 2004, 78.
1289 *Angell*, 2004, 78-79.
1290 *Roin*, 87 Tex. L. Rev. 503, 548 (2009).

There is a tension between regulatory requirement and patent infringement for generic products. On the one hand, to meet the regulatory requirement, i.e. bioequivalency of the generic version, the product should be as close to the reference drug as possible, since the similarity to the reference drug really matters in the market place. Namely, a generic drug maker may have marketing approval by showing that their versions are the same dosage form, contain the same dose and the same chemical form, and are equivalents of the innovator's drug.[1291] Thus, they will likely copy the reference product exactly to avoid the expense and time of clinical trials required by the FDA for an even slightly different version.[1292] In other words, some slight change in dosage form, route of administration, strength, or the like, which can be normally covered by second generation patents, would most likely trigger clinical trials.[1293]

On the other hand, to avoid a patent infringement, the same generics should be as different as possible. Thus, because the patent covering the new version of a product is too specific to avoid it and survived after the validity challenge, the generic manufacturers will be hard pressed to bring the generic versions to market. One of the most specific claims would be the one claiming certain pharmacokinetic parameters related to the formulation.[1294] In the case of the European Patent No EP0973527, covering the "Extended release formulations of clarithromycin,"[1295] claim 1 is as follows:

1291 *Rosenbaum*, 2011, 195-198 (further explaining the *bioavailability* of a dosage form is the rate, and extent to which, the drug reaches the systemic circulation; *bioequivalence* is a special type of relative bioavailability; and two or more products would be regarded as *bioequivalent* when it is shown that the products have essentially the same bioavailability.).

1292 *Scherer*, 351 New Eng. J. Med. 927, 927 (2004) (noting "[d]rug patents provide particularly strong protection against competition from other companies because even a slightly different molecular variant must undergo the full panoply of clinical tests required by the FDA"); *Voet,* 2011, 62-63.

1293 *See e.g.,* 21 U.S.C. § 505(b)(2) (this application procedure also allows a company to rely, at least in part, on the FDA's finding of safety and/or efficacy for the reference drug, and to save money and time).

1294 *Grubb/Thomsen*, 2010, 268.

1295 European Patent No. EP0973527 (B1) (November 5, 2003, under the title of "Extended release formulations of clarithromycin").

1. A pharmaceutical composition for extended release of clarithromycin in the gastrointestinal tract, to be administered orally, comprising clarithromycin and a pharmaceutically acceptable, hydrophilic, water-soluble polymer,

which releases clarithromycin so that after a regimen of a single 1000 mg dose on day 1 and a multiple dose regimen of 1000 mg on days 3, 4 and 5, the maximum plasma concentration is reached after 6.9 ± 3.3 hours, and the area under the plasma concentration time curve 0-24 hours is 40.2 ± 13.8 μg·h/mL, or

which releases clarithromycin so that after a single 500 mg dose, the area under the plasma concentration time curve 0-∞ is 15.0 ± 6.5 μg·h/mL.

The specificity of the claim is apparent, i.e., claim 1 claims the composition of the formulation, its dosage regime, and the pharmacokinetic profiles after the administration of the formulation, such as C_{max}, T_{max},[1296] and AUC[1297]. Since pharmacokinetics includes the study of the mechanisms of absorption and distribution of an administered drug, and the like, if a patent covers not only the composition of the formulation but also what the body does to the drug, it will be very difficult to design around. Thus, once the market is moved to this second generation product, the generic drug of the older version will not sell well, and the launch of the generic of the new version should be postponed until the second generation patents expire. At this point, one clear option for the generic company to launch its product would again be trying to invalidate the second generation patents through litigation.[1298]

4. Analysis and conclusion

Life cycle management or evergreening has been discussed in this section especially in respect of whether it can unfairly hinder a generic's market entry. Such tactics can be deployed on the basis of second generation patents. However, contrary to the prevailing perception, not all kinds of selection inventions can prevent entrance of a generic version once the basic patent expires. To the extent that second generation patents can prevent the entry of generics, a second generation patent granted thanks to the relaxed patentability requirement can prevent the marketing of generics for another some years. The argument on the purposely delayed filing of second generation patent applications to delay the entry of generics was shown not to be justified.

1296 A "C_{max}" is the peak plasma concentration of a drug after its administration, and a "T_{max}" is the time at which the peak plasma concentration of a drug occurs, *see Rosenbaum*, 2011, 164-195.

1297 An "AUC" is a measure of the body's exposure to the drug, and proportional to the effective dose, *see Rosenbaum*, 2011, 196.

1298 See subsection V.A.1.c).

Many serious concerns were found in other fields. The pendency of patent applications on second generation inventions would create much increased legal uncertainty and make it more difficult for the generic companies to assess their positions and legal security. Moreover, the active market shift to the newer version of the product based on second generation patents, along with the very specific scope thereof could make the market for generics unattractive. This is possible with the specificities of the pharmaceutical markets, such as high loyalty, disconnection between the decision-makers and buyers, and the like. In addition, although the case would be limited to the United States, the new list up in the Orange Book could seriously delay generic entry.

E. Summary and conclusion

Lowered patentability requirements on second generation inventions naturally increases the number of second generation patents.[1299] In particular, the relaxed novelty requirement has led to concerns about the patent disclosure depending on the language, reducing the examination of patentability *de facto* to the examination of novelty, and other potential concerns about the applications of disclosure requirements in other fields of patent law. This greatly increased number of second generation patents has amplified the patent exclusivities, thereby creating a more complicated and uncertain landscape. This has also caused companies to incur more costs in their search for the freedom to operate, in the process of obtaining second generation patents, and in the litigation and invalidation of such patents. The relaxed patentability requirements could be one of the reasons why basic patentees greatly increased the spending attributable to line extensions and why short-term priorities encourage marginal inventions that provide more reliable returns on investment at the expense of major changes.[1300] Eventually, the market becomes flooded with second generation products,[1301] which results in more imitative research and fewer breakthroughs and drugs[1302] and which hinders real pharmaceutical innovation and could threaten health.

1299 *Thomas*, 52 Am. U. L. Rev. 771, 773 (2003).
1300 *Munos*, 8 Nat. Rev. Drug Discov. 959, 966 (2009).
1301 *NIHCM*, 2002, 18-19.
1302 *Munos*, 8 Nat. Rev. Drug Discov. 959, 966 (2009).

The increased number of marginal patents with the case law involving the patent term extensions on second generation patents seems to promote more work on the second generation inventions rather than on the basic inventions. Namely, patent term extensions seem to be granted based on the extent to which, if they are patented, they will be distinctive from the basic substances and can enjoy the extensions of terms.[1303] In the end, after the patent term and the SPC of the basic patent, which is desirable, many additional years of patent term on the second generation invention can be obtained. In addition, unlike other patent term extension systems, the calculation system of SPC seems to penalize even the basic inventions, the R&D for which takes longer.[1304] In contrast, since the disclosure requirement does not seem to be lower, there is little influence on the breadth of the second generation patents.

The implications on the competition in the industry were also discussed. Firstly, contrary to the dominant perception, there are fewer cases in which the exploitation of the basic patent was held to infringe the second generation patents. Secondly, only to the extent that second generation patents can prevent a generic's entry can second generation patents stop the marketing of generics for additional periods of years. Thirdly, the common argument on the purposely delayed filing of second generation patent applications was shown to have no merit.

Serious concerns were found in other areas. The automatic thirty-month stay and new list up in the Orange Book in the United States could seriously delay generic entry. The pendency of patent applications on second generation inventions increases legal uncertainty and makes it difficult for the generic companies to assess their legal security. Moreover, the active movement of the market to the new version of the product based on second generation patents, along with the very specific scope thereof, can make the market unattractive for generics.

1303 See subsectionV.C.2..

1304 See *supra* 1173 -1175 and accompanying texts.