VII. FINAL CONCLUSIONS

A steady supply of new medications is vital to public health. The patent system and patent exclusivity have been among the most important incentives in encouraging continuing investment in the research and development ("R&D") of innovative medications. In addition, to ensure an efficient flow of medicines to society, competitive pressure plays an important role in lowering drug prices.

Pharmaceutical inventions are generally divided into basic inventions, which can be further developed into new medical entities, and second generation inventions. The latter include species selection inventions, optical isomers, crystalline forms, metabolites, prodrugs, esters, salts, dosage forms, combinations of active ingredients, new uses or new methods of treatment, dosage regimes, processes, intermediates, and more.[1657] Products in the pharmaceutical field fall into the categories of new medical entities, me-too products, second generation products and generic drugs.[1658] This dissertation has focused mainly on chemical selection inventions, such as species selection inventions, optical isomers, crystalline forms, and metabolites, as representatives of second generation inventions. Species selection inventions can also represent basic inventions, since, unlike other second generation inventions, they can be the basis for further improvements or applications, as long as they are developed to New Medical Entities ("NMEs").

The pharmaceutical industry differs from other industries in various ways. It is one of the few industries that bears high regulatory burdens, especially on initial innovations. The development process of these innovations is long and costly, and it includes production of the information needed to meet regulatory requirements. Transforming an invention into an NME involves enormous scientific, regulatory, and market uncertainties.[1659] These uncertainties raise the cost of developing new medications even further, since manufacturers must also absorb the costs incurred by all of their failures. In contrast, imitation involves negligible costs and significantly reduced risks.

1657 See subsection II.C.
1658 See subsection II.D.
1659 See subsection III.A.1.c).

This is one of the main reasons why the pharmaceutical industry depends so greatly on patent protection.[1660]

Despite the existing patent system, the number of NMEs has decreased, especially during the last decade, which has been the most technologically advanced period in history.[1661] This has caused great concern, since NMEs have made important contributions to reductions in morbidity and mortality of the population. In comparison to the declining number of new medical entities, the number of second generation inventions and products has increased dramatically over the same period.[1662] The industry is accused not only of neglecting its real mission of providing new medications while it generates second generation inventions, but also of preventing less expensive generic products from entering the market. Thus, this dissertation has reviewed and analyzed whether these concerns are justified.

To begin with, this dissertation analyzed whether the patent system has changed, especially in conjunction with chemical selection inventions. The novelty requirements of a species selection invention and optical isomer inventions were found to have become less stringent. For species selection inventions, Germany and the United Kingdom have changed their earlier strict ways of assessing novelty according to the *Fluoran* decision and the *IG Rule* respectively.[1663] In the United States, the size of the genus in the prior art from which the species selection was made, has become an important factor in the assessment of novelty. Assessment of novelty of these inventions seems to be based on the difficulty of identifying and selecting a specific species which has a therapeutic effect distinguishing it from the rest of the genus.[1664] For optical isomers, based on the enablement requirement for assessing anticipation of the prior art,[1665] novelty is established over racemic mixtures, if purification of one isomer from the racemate is not disclosed, and this is difficult, even if the structure is clearly disclosed. In the past novelty standards of inventions were based on the difficulties of isolation or separation just as they are today, however, more advanced techniques have now incomparably decreased those difficulties, and the isolation of isomers is made out of a well-known targeted mixture. Thus, the novelty

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1660 See subsection III.A.3.b).
1661 See subsection III.B.2.
1662 See subsection III.B.5.
1663 See subsections IV.A.4.a).
1664 See supra 558 - 559 and accompanying texts.
1665 See subsections IV.A.3. and IV.C.2.b)(1).

standards of inventions connected with purification, such as the isolation of an optical isomer have relaxed over the past century. For crystalline forms, the issue of novelty arises mainly when the claimed crystalline forms are produced according to the process disclosed in the prior art, in which case novelty generally is not found. Similarly, though their reasoning was different, the courts in the United Kingdom and in the United States both held that metabolite invention was not novel.[1666] To some extent, the ruling in this case is natural, because the patent on the metabolite is a repetition of the prior art, insofar as it precludes the use of the parent drug as an anti-histamine treatment.[1667] Therefore, except for the crystalline forms, this thesis concludes that satisfaction of the novelty requirement for selection patents has become less demanding.

Furthermore, the inventive step requirement for selection inventions was found to have been significantly reduced. For species selection inventions, the courts in each jurisdiction acknowledged advantageous effects over the prior art. In addition, the size of the genus from which the selection invention is made is important for establishing the inventive step. Due to the changed inventive step requirement, however, the superior effects do not need to be shown over the whole scope of the prior art. For optical isomers, the early rulings held that the different effects of one enantiomer from the other were known, and that it was routine both to produce an enantiomer and to test its activity. Thus, even advanced effects were not considered evidence of the inventive step.[1668] However, the BOA held that an enantiomer invention establishes the inventive step based on a radically different problem and a solution disclosed by the original patent specification; the BGH held the same based on the difficulty of separating the racemate, and the decision was similarly reached in the United Kingdom. The earlier decision held that the enantiomer was obvious because resolution of a racemate was common knowledge.[1669] However, unless there was enough motivation to resolve the racemate or the separation was predictable, the Court found an inventive step in the enantiomer invention.[1670] In the United States, even acknowledging that there was ample motivation to separate an enantiomer, an inventive step

1666 Because of the bifurcate system in Germany, the Court on the same metabolite issue held only the non-infringement of selling the parent drug.
1667 *Jacob*, IIC 1996, 170, 171.
1668 See *supra* 790 and accompanying texts.
1669 See *supra* 803 -804 and accompanying texts.
1670 See *supra* 809 -811 and accompanying texts.

of the enantiomer was found based on the difficulty of separation. However, the Korean Supreme Court ruling contrasted sharply with those in other jurisdictions. For example, the Federal Circuit found one enantiomer to be inventive, because the fact that one enantiomer was responsible for the biological activity and the other for the side effect was not predictable. In the corresponding case, the Korean Supreme Court held that the invention was obvious, because a two-fold superiority in therapeutic effect and the 1.6-fold superiority in acute toxicity in comparison with the racemate were not significantly better than the activity of the racemate.[1671] For crystalline forms, the inventive step was denied either because of a reasonable expectation of success or because of a clear expectation that a crystalline form would provide more desirable characteristics. The Korean Supreme Court held that the properties of crystalline forms were well known, that it was a common practice to confirm the existence of polymorphism of a substance, and specifically the Court could not acknowledge the improved "pharmaceutical effect" achieved by the improved physical characteristics of a crystalline form.[1672] For metabolite inventions, novelty was the central issue, and the inventive step was not. Therefore, except for the crystalline form, the inventive step requirements of species selection inventions in the selected jurisdictions have been lowered or are lower than the standard in Korea.

For these reasons, it was concluded that the patentability standards of second generation inventions in selected jurisdictions have a tendency toward a lowered novelty requirement and a significantly relaxed inventive step requirement. In a certain sense, the case law seems to be more harmonized, although the observed direction of the changes may be worrisome.

These lowered patentability requirements have led to an increased number of superfluous second generation patents and to greater uncertainties on the landscape of exclusivities. Moreover, considering that manufacturers have finite resources, these lowered requirements may siphon off resources and divert them away from breakthrough drug developments, thus potentially hindering future pharmaceutical innovations. Furthermore, they result in

1671 See *supra* 836 and accompanying texts (with the comparison that the administration of one enantiomer gave around 2-fold better effects than that of a racemate which is a 1:1 mixture of enantiomers).

1672 See *supra* 863 -867 and accompanying texts.

higher cost for searches, prosecutions, and especially litigations,[1673] which are incurred both in the attack and the defence of these patents. Since second generation patents are also eligible for patent term extensions, this provides further incentives for those companies whose drugs contain older active ingredients to extend their R&D efforts, marketing resources, and capital on second generation inventions.

The scope of patent term extensions on second generation patents seems to encourage R&D efforts to focus more on second generation inventions. Since, another SPC or patent term extension can be granted if the derivatives are covered by the patent,[1674] this can lead the original patentee to work more on trivial modifications of those active moieties which were already authorized in previous products. This concentration on trivial modifications is exacerbated by the fact that lowered patentability requirements make it easier to patent derivatives.

Furthermore, the patent term extension system apparently compensates for the cost and period of R&D more on second generation inventions than on NMEs.[1675] This is especially so for medications that require more extensive safety testing, toxicity testing, or both. For example, for medicines to treat chronic diseases, Alzheimer's disease, or cancers, the maximum cap of five years to an extension risks discouraging the companies from pursuing research in these fields.[1676] The situation in Europe may be more serious, because the calculation system for the SPC is much more favourable to secondary products than to new medical entities. Unlike medications that take five to ten years from the patent application date to acquire market approval, those that need more than ten years can never enjoy fifteen years of the maximum effective patent term.[1677] The gap between the two dates should be much shorter for second generation products, ideally less than ten years,

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1673 For example, in the United States, litigation costs to take a patent case through to appeal range from $650,000 to $4.5 million. In Germany, the overall cost for each party of a small to middle-scale patent case ranges €50,000 to €250,000 at first instance, and ranges €90,000 to €190,000 at second instance for both validity and infringement. In the U.K., the cost of a similar case ranges from €150,000 to €1.5 million at first instance and €150,000 to €1 million at second instances, and an average patent case in the U.K. lies well over €1 million. *EPO*, 2006, 10-12; *see also Holderman/Guren*, 2007 U. Ill. J.L. Tech. & Pol'y 101, 110 (2007).

1674 See subsection V.C.2.

1675 See also subsection VI.D.2.a)(1).

1676 *Domeij*, 2000, 282.

1677 See subsection V.C.3.

which would increase the chances for them to enjoy maximum effective patent term.[1678]

The impacts of increased second generation patents on generic manufacturers, which are referred to as life cycle management or evergreening, must also be mentioned. Against the grain of prevailing perceptions, only in a few specific cases can selection inventions impact the entry of generic versions of older products.[1679] To the extent that second generation patents can prevent the entry of generics, the patent term and term extension of second generation patents can cause delays. What is more noteworthy is the manufacturers' augmented legal uncertainty and insecurity in the preparation of its generic versions because of the increased patent pendency of second generation inventions. Furthermore, although the case has limited application in the United States, the automatic thirty-month stay and the new listing in the Orange Book, which are usually based on second generation patents, effectively delay the entry of generics. In addition, the active market movement to second generation versions in conjunction with the very specific scope of second generation patents make the market for the older version very unattractive. The disconnect between decision-makers and payers for a medicine may also help to diminish the attractiveness of older medications, considering that there is probably no other industry where quality is so disparaged on account of lower prices.[1680]

The nature of a species selection invention is different from that of other selection inventions because the former can be developed into NMEs. In addition, whereas the value of the former is that it has been identified from among millions of candidates, the nature of the latter is in the isolation or separation from a mixture. Isolated or separated inventions have been patented for over a century. However, many of these decisions were taken a century ago[1681] when the pharmaceutical industry was arguably not yet research-based but a manufacturing industry. In addition, the average skilled person has since become dramatically more knowledgeable. More importantly, even if other selection inventions were available to the public for the first time, the public already has access to older versions developed from the basic inventions. In addition, patentability of the majority of the other selection inventions is based on the difficulty of separation from a well-known mix-

1678 See subsection V.C.3.
1679 See subsection V.B.3.
1680 *Steele*, 5 J. Law Econ. 131, 142 (1962).
1681 See subsection VI.B.2.b).

ture. Accordingly, one might doubt whether the absolute product protection afforded by a patent is appropriate for second generation inventions. On the basis of the different sets of values inherent in selection inventions and the needs of society, this dissertation has analyzed and proposed optimal ways for patent law to help bring more NMEs to the public.

Firstly, to move research capacity and investments from second generation research to basic research on NMEs, the main arguments for granting a broader scope of patent protection to the basic invention were explored. However, because of the unpredictable character of selection inventions, the granting of a broader scope of patent protection is not regarded as a proper tool for the promotion of pioneering innovations.[1682] Because of the problem presented by the already broad scope of the genus patent, several possible solutions were explored for acquiring the freedom to operate the species selection invention. Although scholars have offered many proposals for voluntary license agreements,[1683] pharmaceutical companies usually do not want to undermine their exclusivities based on licensing. Consequently, licensing does not seem to be of practical use. Instead, application of the lesson from the *eBay* case, implementation of the statutory compulsory license system or improved use of the reverse doctrine of equivalence were put forward as more desirable solutions to resolving the blocking issue. The same solutions can be applied to the situation in which the basic patent stops the use of new dosage forms, combinations of active ingredients, or especially new medical uses. Secondly, given that the pharmaceutical industry is one of the few that is sensitive to the term of protection, and that the patent term extension system is more favourable to second generation inventions, a provision that guarantees fifteen year patent exclusivity from the time of market approval is proposed for new medical entities.[1684] Thirdly, in order to assess the novelty requirement of species selection inventions, application of the teaching in the *Olanzapine* decision is recommended, which requires "clear and unambiguous" prior art disclosure to destroy a claimed invention.[1685] This recommendation is based on the observation that a patent system is a double-edged sword for the pharmaceutical industry, which differs from the prevailing conception. Fourthly, this dissertation recommends that post-invention costs and uncertainties in the course of product development be

1682 See subsection VI.C.2.
1683 See subsection VI.C.3.a).
1684 See subsection VI.D.2.a).
1685 See subsection VI.E.2.b).

considered as secondary considerations in accessing the inventive step requirement of basic inventions such as species selection inventions.[1686]

For other second generation inventions, it is firstly proposed that, if the biologically active moiety is the same and the earlier one enjoyed a patent term extension, no further patent term extension should be granted.[1687] Secondly, the therapeutic contribution of these inventions is recommended as a secondary consideration in judging the inventive step.[1688]

Even though these observations were made for selection inventions, the same rationale could be applied to other second generation inventions. Through these efforts, much R&D could be directed toward new medical entities, and more new medications could be offered to patients who are awaiting them at this very moment.

Further research directions

This dissertation also proposes a series of additional research questions. Crucial among these are detailed evaluation and refinement of proposals that were made in chapter 6. Further, an in-depth study on competition issues, including movement of the market to second generation products would be desirable.

Considering that pharmaceuticals are information-rich substances, changes in other regimes that protect the information itself, such as regulatory exclusivities,[1689] could be further researched and compared with the protection provided by patent law. In particular, further exploration and analysis would be warranted to determine whether it would be proper to extend exclusivity in the regulatory regime and, if so, how the non-disclosure problem in "data protection" could be resolved, or even, in the end, whether both systems should be run parallel but in a different manner from existing ones.

Pharmaceutical companies are facing an increasing number of challenges from private and governmental health systems, which put companies under pressure to reduce prices.[1690] These intensified price controls, including changing reimbursement mechanisms, significantly reduce the funding

1686 See subsection VI.E.3.b).
1687 See subsection VI.D.2.b).
1688 See subsection VI.E.3.c).
1689 *Roin*, 87 Tex. L. Rev. 503, 564-68 (2009).
1690 *Wilson*, The New York Times, March 6, 2011.

available for R&D,[1691] and they may also add to the already substantial costs involved in bringing new products onto the market.[1692] For instance, curtailing reimbursement impacts on the company's marginal rate of return on innovation, and reduces R&D expenditure on future projects. [1693] Considering the high failure rate in developing new medical entities, the decrease in reimbursement could significantly affect innovations which would otherwise have market potential.[1694] The effect would be even greater since lower profits for pharmaceutical companies discourage investment in R&D and clog the pipeline for new drug treatments, which in turn shortens expected life spans.[1695] Considering the fact that the two largest pharmaceutical markets, i.e. the United States and Germany, are not, or were not until recently, subject to price controls by the government, it also would be interesting to study the relationship between pharmaceutical innovation and price regulation. Therefore, it would be advisable to research the relationship between pharmaceutical R&D and reimbursement mechanisms in order to propose measures such as pricing schemes that would promote R&D on both basic inventions and second generation inventions.

1691 *Vernon*, Regulation, 22, 25 (2002-2003, Winter); *U.S. Department of Commerce International Trade Administration*, 2004, x.

1692 *McGuire/Drummond/Rutten,* 2004, 131-32.

1693 *McGuire/Drummond/Rutten,* 2004, 131-32; *U.S. Department of Commerce International Trade Administration*, 2004, x-xi.

1694 *McGuire/Drummond/Rutten,* 2004, 131-32.

1695 *Lakdawalla, et al.*, 28 Health Affairs w138, w148-w149 (2009); *Holmes*, 379 Lancet 1863, 1864 (2012).