I. Introduction

Innovations are mostly derived from already existing technologies that may or may not have been patented.

Selection inventions have been an important issue in the area of patent law from various aspects including novelty, inventive step, sufficiency of disclosure, and the like. Among these issues, novelty is one of the most fundamental issues in patentability and/or validity assessment, to have been hotly discussed in the field of chemical, biotechnological, or pharmaceutical inventions.

It is hard to find statutory definitions of what a selection invention is. However, the expression "selection invention" might be generally understood as an invention that has a specific concept selected from a prior broader or larger generic concept of invention, and that pertains superior or advantageous properties to the broader concept which have not been disclosed in the prior art. Selection can be generally categorized as two types,[1] but, in fact, has various forms, such as selection of (a member of) compound(s), processes, dimensions, a range of values, parameters, crystal forms, nanoscales and so on from the class, the broader range, or the various forms of previously disclosed inventions.[2] Thus a selection invention is an invention which falls under the scope of prior art disclosure, but has not been individually disclosed in the prior art.[3]

On the one hand, patent laws require a claimed invention to be new, to involve an inventive step (non-obviousness), to be susceptible of industrial application (utility)[4] and to be sufficiently supported by description (sufficiency of disclosure).[5] Although the requirement of novelty varies slightly from jurisdiction to jurisdiction, an invention generally is considered to be new if it does not form part of the

1 Guidelines for Examination in EPO C-IV. 1.C.4. ((a) chemical substances and group of substances in respect or general formulae (Markush formulae) under which they fall (b) products or processes defined by parameter ranges as against known products or processes characterized by wider or overlapping parameter ranges).

2 *See generally* Chris P. Miller ET AL., The Chemist's Companion Guide to Patent Law 15 (2010). *See also* Richard T. Jackson, *A Lockean Approach to the Compulsory Patent Licensing Controversy,* 9 J. Tech. L. & Pol'y, 116, 119 (2004) (discussing similar concept, namely, the concept of an improvement patent or dependent patent, which can be defined as one that cannot be used without infringing an earlier, existing patent.).

3 *See, e.g.,* Israel Agranat et al., *Intellectual property and chirality of drugs.* 4 Drug Discov. Today 313, 313-314 (1999).

4 *See, e.g.,* European Patent Convention (hereinafter 'EPC') Art. 52 (1).

5 *See, e.g.,* EPC Art. 84; 35 United States Code (hereinafter 'U.S.C.') § 112.

state of the art.[6] Novelty is a prerequisite for patentability for preventing something which already existed in the public domain being monopolized. On the other hand, a selection invention, by nature, is selected from the broader concept of a "previously known" invention; therefore construction of the concept of novelty in selection inventions has been debated.

Patents play different roles in different fields of technology. There is no dispute that the pharmaceutical industry as one of the most technology-based industries is one of the industries that depends most on the patent system,[7].[8] Thus, barring of patentability of selection inventions has an especially heavy impact in the pharmaceutical industry in several of the above aspects as follows, although the selection issue is not limited to pharmaceutical or chemical inventions.[9]

Innovative pharmaceutical companies have suffered loss of revenues due to expirations of patents on so-called blockbuster products. The numbers of these expirations are expected to reach their peak around 2011. They have not managed to compensate the loss with new follow-up innovations.[10] This may also explain the active merger and acquisition activities in pharmaceutical sectors[11] worldwide. Low productivity of R&D can be observed when looking at recorded statistics from 1998 to 2008. The cost of R&D over the past decade has increased by about 80%, but the number of NMEs (new molecular entities) has decreased by around 40% (see Fig. 1) .[12] This result becomes even more surprising considering the fact that i) the average cost to bring an NME to market is estimated to be up to around $1.8 billion,[13] ii) this has happened during the most technological and scientific period

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6 *See, e.g.,* EPC 54 (1); 35 U.S.C. § 102.

7 *See also* Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why Manufacturing Firms Patent (or Not)* 23-24, Nat'l Bureau of Econ. Res., working Paper No. 7752, (2000) (reporting that the pharmaceutical industry, whose product is a discrete product like medication is the most efficient industry to exploit patents to create revenues from them either by commercializing the invention by the patent owner itself or by licensing them).

8 *See also* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability,* 87 Tex. L. Rev. 503, 513 (2009) (indicating that "[i]t is well known that pharmaceutical companies generally refuse to develop new drugs unless they have strong patent protection over them.").

9 *See also* Mark J. Davison et al., Australian Intellectual Property Law, 434 (2008) (providing exemplary cases of selection issues in mechanical and electrical inventions.).

10 *See, e.g.,* Steven M. Paul et al., *How to improve R&D productivity: the pharmaceutical industry's grand challenge*. 9 Nat. Rev. Drug Discov. 203, 203 (2010).

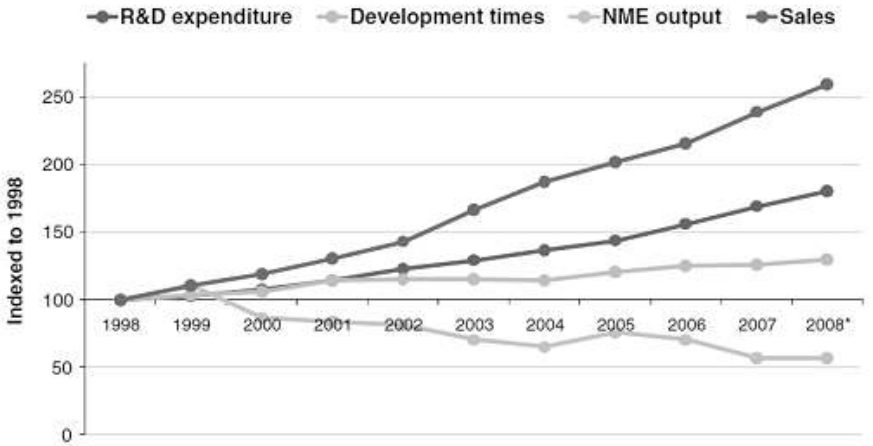
11 Among several reasons for this activity in the global pharmaceutical industry, the absence of proper R&D activities, expiry of patents and recalls of high-profile blockbusters can be counted.

12 Article in Press: H.-J Federsel, *Process R&D under the magnifying glass: Organization, business model, challenges, and scientific context*. Bioorg. Med. Chem. Doi:20.1016/j.bmc.2010.06.029.

13 Paul et al., *supra* note 10, at 204; *see also* Peter Landers, *Cost of Developing a New Drug Increases to About $1.7 Billion*, Wall St. J., Dec. 8, 2003, at B4 (2003).

of development ever, and iii) there is an urgent unmet need for new medications especially in the field of oncology and CNS (central nervous system) diseases.

Figure 1:
Global R&D expenditure, development times, global pharmaceutical sales and new molecular entity output 1998-2008.



Source: CMR International (2009 FactBook) & IMS Health.

It is much more difficult to bring a new medication to market because of several reasons including increased regulatory requests for study data relating not only to efficacy but also to safety, higher failure rate of targeting novel mechanisms, and advances in science and technology.

Over the last decade, observed market withdrawals for safety based reasons have brought the regulatory bodies' attention to the safety of drugs, which was intensified after the withdrawal of Vioxx® in 2004. The withdrawal of Vioxx from the market cast serious doubts on the reliability of clinical data and on the regulatory bodies' approval process, which created demands for higher transparency of data and resulted in lower approval rates of NMEs. This situation made innovative companies more cautious, and did hardly encourage them to conduct new research because the potential for more frequent failure to obtain regulatory approval for new medications may mean a zero return on the investment in R&D.[14] In addition, even after launching a new drug, innovative companies can never just celebrate and relax. This is because litigations related to safety-based withdrawals and the costs asso-

14 For instance, Vioxx's successor Arcoxia has been denied for its approval in April 2007, which meant a return of zero dollars to Merck.

ciated with it have undeniably and sharply soared. For instance, Merck spent around one billion dollar for the defense in 27,000 cases regarding product liability for Vioxx and related class actions within two years after the withdrawal thereof.[15]

It was shown that an R&D process based on unprecedented (novel) targets has a lower success rate (3 to 5%) than one based on precedented (traditional) targets (8%),[16,17] This means that an innovative pharmaceutical company should investigate several hundred more novel targets to be able to launch a single new product, which partly explains the negative net present value in regards to NCE (New chemical entity) developments.[18]

The lower success rate in new drug development than before might also be attributed to the fast development of technology. In fact, there is a higher proportion of pipeline dropouts because of undesired toxicity.[19] More technologies are involved and employed to predict toxicity and safety,[20] however, this developments may provide higher specificity and lower detection limit of trace elements and in turn leads to possible candidates or even targets dropping out in their early stages than before.

The above reasons may contribute to the trend that pharmaceutical companies focus research more on improving the characteristics of medications with which they have extensive experience in the market after approval by the regulatory body, than on developing entirely new medications. The recent report of the European Commission on the pharmaceutical sector,[21] for example, shows the following trend with innovative companies: i) a markedly sharp increase of the number of patent applications in pharmaceutical inventions was observed during the period of 2000 to 2007;[22] ii) 93% of the pending applications were classified as selection inven-

15 *See* Thomas N. Tiedt, *The Drug Safety System Conundrum,* 62 Food & Drug L.J. 547, 548 (2007).

16 Philip Ma et al., *Value of novelty?,* 1 Nat. Rev. Drug Discov. 571, 581-572 (2002). The precedented targets normally mean that those that has been successful in development of human medication.

17 Article in Press: David A. Fryburg, *Do technical and commercial biases contribute to the pharmaceutical industry's productivity problems? An analysis of how reordering priorities can improve productivity.* Drug Discov. Today. doi:10.1016/j.drudis.2010.06.010 (2010.).

18 *Id.*

19 *See* Gary W. Caldwell, *Compound Optimization in Early- and Late-phase Drug Discovery: Acceptable PharmacokineticProperties Utilizing Combined Physicochemical, in vitro and in vivo Screens,* 3 Curr. Opin. Drug Discov. Dev. 30, 30-31 (2000).

20 *See e.g.,* Dale E. Johnson, *Predicting Human Safety: Screening and Computational Approaches,* 5 Drug Discov. Today, 445, 445 (2000).

21 *See* European Commission's pharmaceutical sector inquiry report, available at http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf.

22 This statistics was based on the IPC (International Patent Classification) A61K with some exceptions (e.g.: preparations for dentistry(A61K6) and so on), which can be regarded as the closest proxy for pharmaceutical applications.

tions;[23] and iii) 84% of the granted patents were categorized as selection inventions as well. Examples of these efforts which may be categorized as selection inventions are salts, polymorphs, esters, isomers, metabolites, prodrugs, pharmacokinetic profiles, and combinations of innovative medications.[24]

This trend, together with ferocious attacks from generic drug makers, resulted in rich jurisprudence on the patentability of selection inventions with quite diverging decisions. This was true in European jurisdictions e.g., as far as Germany is concerned, until the "*Olanzapine*[25]" decision of the German Federal Court of Justice related to a chemical selection invention, with which the German approach became to be in line with the EPO case law by deviating from the "Fluoran" decision[26] . The ruler pronounced in this decision is confirmed by the later "*Escitalopram*" decision[27] directed to another important class of medications known as chiral drugs, which brought the German Federal Court of Justice case law into conformity with corresponding decisions in the U.K. and U.S.A. as well.

This thesis will start by giving some background information on Markush type claims, and chemistry of enantiomers. Then the jurisprudence on the patentability requirements for selection inventions will be given, first in terms of novelty, then followed by the nonobviousness requirement. Then discussions about the anticipation and obviousness issues in view of the *Olanzapine* and the *Escitalopram* decisions will be provided. This paper will then turn to the issues raised after granting of selection inventions. Lastly some different views in other jurisdictions will be provided as well.

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23 The terminology in the pharmaceutical Sector Inquiry is "secondary patent (application)" which is an application not related to the first the patent (application) for the active molecules. for which the contrary category of 'primary patent (application)' is used.

24 So-called 'life cycle management' or 'evergreening' of pharmaceutical patents; *See also* IV.C.1.

25 A blockbuster marketed by Eli Lilly, called Zyprexa®.

26 Bundesgerichtshof[BGH] [Federal Court of Justice] (hereinafter, 'Fluoran') Jan. 26, 1988 International Review of Intellectual Property and Competition Law [IIC, hereinafter 'IIC'] IIC 736, 1989 (Ger.). Since official translations of materials in language other than English are not always available, the author did it by consulting other's translation or by herself. For accuracy, please check its original version.

27 Bundesgerichtshof [BGH] [Federal Court of Justice] (hereinafter, 'Escitalopram, Federal Court of Justice') Sept. 10, 2009, Gewerblicher Rechtsschutz und Urheberrecht [GRUR, hereinafter 'GRUR'] 123, 2010 (Ger.).