II. PHARMACEUTICAL INVENTIONS, INNOVATIONS & PRODUCTS

A. Cumulative nature of inventions

Most inventions have been developed based on previous inventions.[30] This has never been so accentuated as in the current evolution of high technologies.[31] The cumulative nature of technological innovation poses a problem for operating an optimal patent system,[32] namely, today's patent can hinder tomorrow's innovations.[33] Thus, every potential inventor can be a potential infringer,[34] although this is not always immediately obvious.[35]

The literature on law, economics or patents is inconsistent in its use of terms to describe previous inventions and subsequent inventions.[36] Representative terms would be first/second generation, earlier/later inventions,[37]

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30 *E.g.*, "[d]*warfs standing on the shoulders of giants,*" in Latin: *nanos gigantium hemeris insidentes*, Wikipedia, available at: http://en.wikipedia.org/wiki/ Standing_on_the_shoulders_of_giants; it is a Western metaphor meaning "one who develops future intellectual pursuits by understanding the research and works created by notable thinkers of the past. (Last accessed on December 20, 2013).

31 *Scherer/Ross*, 1990, 264 (noting "growth of technology is cumulative and richly interactive"); *Scotchmer*, 5 J. Econ. Perspect. 29 (1991) (stressing the importance of the cumulative nature of innovation); *Arrow*, 1962, 616-619 (noting that today's invention is the input for future innovations); *Vossius*, 59 J. Pat. Off. Soc'y 180, 180 (1977) (noting "[a] completely pioneer invention is a rare occurrence in today's world.").

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

33 *Luski/Wettstein*, 1 Probl. Perspect. Manage. 31, 31 (2004).

34 *Merges/Nelson*, 90 Colum. L. Rev. 839, 916 (1990); *O'Donoghue*, 29 RAND J. Econ. 654, 655 (1998); *Heller/Eisenberg*, 280 Science 698 (1998) (noting strong IP right would rather impede research than promote it).

35 *Scotchmer*, 27 RAND J. Econ. 322, 329 (1996).

36 *Cf. Janis*, 40 Harv. Int'l L. J. 151, 151-152 (1999) (using "second tier patent" as a generic label encompassing utility models, petty patents, and so on which is different from the regular patent system.).

37 *Gallini/Scotchmer*, 2002, 65.

primary/secondary patents, basic inventions/applications,[38] pioneer/subsequent patents,[39] broad/subservient patents,[40] dominant/subservient patents,[41] and basic/future inventions. [42] Similarly, terms that refer to the inventors of both inventions include first/second inventors, initial/later inventors, or original developer/subsequent improvers.[43] The earliest invention or patent has been referred to as the original invention, the breakthrough invention, the initial patent, [44] the originating patent, or the parent patent. Another comparable notion is upstream invention and downstream invention.[45] The terms will be disambiguated in the following sections, and "basic invention" and "second generation invention" will be adhered to in this paper.

1. Basic and second generation inventions

An invention that is a breakthrough or pioneering invention, which provides the roots and routes for future innovations, is often called a **basic invention**.[46] In contrast to basic inventions, second generation inventions are generally improvements and applications of the basic inventions. A class of invention called a "selection invention" is particularly relevant in pharmaceutical and chemical inventions and is discussed in detail below.

38 *Matutes/Regibeau/Rockett*, 27 RAND J. Econ. 60, 60-61 (1996); cf. basic/applied research: *Eisenberg*, 56 U. Chi. L. Rev. 1017, 1017 (1989). (basic research which directed solely toward expanding human knowledge vs applied research which directed toward solving practical problems),.
39 *Merges/Nelson*, 25 J. Econ. Behav. Organ. 1, 13 (1994).
40 *Merges/Nelson*, 25 J. Econ. Behav. Organ. 1, 21 (1994).
41 *Chang*, 26 RAND J. Econ. 34, 49 (1995).
42 *Friebel et al.,* 2006, 26.
43 *Lemley*, 75 Tex. L. Rev. 989 (1997).
44 *Matutes/Regibeau/Rockett*, 27 RAND J. Econ. 60, 60-61 (1996).
45 *Heller/Eisenberg*, 280 Science 698 (1998).
46 *Friebel et al.,* 2006, 26-29.

a) Improvement inventions

An improvement invention refers to an invention that essentially builds upon a basic invention,[47] or to an invention that could not have occurred until the basic invention was available.[48] Thus, improvement inventions can only occur in the wake of basic inventions are the outcome of research activities directed to improvements or applications of previous inventions.[49] In the context of patent law, an improvement invention may be referred to as a dependent invention, which may not be used without infringing the basic patent, until it expires.[50] Improvement inventions are ubiquitous as most technological progress builds upon previous inventions.[51] They are most commonly found in the software industry, where incremental improvement is endemic for various reasons.[52]

b) Selection inventions

Improvements can also be achieved through selection in some technical fields. Although it is difficult to find a statutory definition, a "selection invention" is generally understood as an invention that has a particular concept which is selected from a prior broader or larger generic concept of an invention and that presents superior or advantageous properties compared to

47 *Bessen/Maskin*, 40 RAND J. Econ. 611, 612 (2009) (improvement inventions as an example of sequential inventions).
48 *Denicolò/Zanchettin*, 20 Int'l. J. Indus. Org. 801, 804 (2002).
49 *Gallini/Scotchmer*, 2002, 65.
50 See e.g., Korean Patent Act, Art. 98 (Relation to Patented Invention etc. of Another Person) *Jackson*, 9 J. Tech. L. & Pol'y, 117, 119 (2004); *Gallini/Scotchmer*, 2002, 65.
51 *CFMT, Inc. v. Yieldup Intern. Corp*., 349 F.3d 1333, 1340 (Fed. Cir. 2003).
52 *See in general, Burk/Lemley*, 89 Va. L. Rev. 1575, 1620-24 (2003).

the broader concept, which were not disclosed in the prior art.[53] It is an invention that falls under the scope of the prior art disclosure, but has not been individually disclosed in the prior art.[54] A patent document from which a selection invention is derived is referred to as a dominant patent.[55]Selection inventions are also referred to as "improvement inventions" since they usually provide some unexpected results or benefits, which also help to overcome challenges to patentability based on assertions of the obviousness thereof.[56] Selection inventions can be generally categorized into three types, according to the selection of an individual element, sub-sets, or sub-ranges respectively.[57]

Selection inventions can be found in various technical fields. When a class of a mechanical invention is a group of structural elements, one of which is

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53 *Bayer/E-Isomers of N-alpha-(2-Cyan-2-alkoximino-acetyl)-amino acid derivatives and peptides*, T12/90 (1990), point 2.7 (stated "the term 'selection' is the singling out of a narrow portion from a relatively broad scope immanent.", quoting *Bayer/Diastereomer*, T 12/81 OJ EPO 1982, 296, 301); *see also Nastelski*, Review of Intellectual Property and Competition Law ("IIC") 1972, 267, 291 (describing a selection invention as an invention providing a particular representative (or a subgroup) of already disclosed product group by the first inventor which showing particularly distinguishing effects when used as indicated by the first inventor or has the possibility of a different type of use.); *see also Vossius*, Gewerblicher Rechtsschutz Und Urheberrecht ("GRUR") 1976, 165, 165 (describing that a chemical selection exists when an second inventor has select one or more representatives from a group of substances, one component from a mixture, or a narrower range of alloy components from a [broader] alloy area.); *see also Grubb/Thomsen*, 2010, 232 (describing selection invention as an invention that is the selection of a particular compound or relatively small group of compounds from the larger group previously disclosed in broader terms, and the compound or the small group of compounds are individually new but fall within an earlier discloser.); *see also, Blanco White,* 1983, 104-106 (noting "[a] special case arises where, although the subject-matter of the claim concerned has never specifically been disclosed before, there has been a prior publication covering that subject-matter in general terms; or (in other words) there is an earlier document which "contains a broad description or claim covering the whole area within which the subsequent selection falls.").

54 *See, e.g., Agranat/Caner*, 4 Drug Discov. Today 313, 313-314 (1999).

55 *Miller/Evans*, 2010, 14-15.

56 *Miller/Evans*, 2010, 14, fn12.

57 Guidelines for Examination in the European Patent Office, June 2012, (herein after "EPO Examination Guidelines"), G-VI, 8 ("Selection inventions deal with the selection of individual elements, sub-sets, or sub-ranges, which have not been explicitly mentioned, within a larger known set or range").

selected as being particularly useful, it is a selection invention.[58] Examples of such inventions can be found in the field of alloys, where a specific range of compositions are chosen, or in the field of engineering and manufacturing, where specific operating conditions are selected. Selection inventions are typically encountered in pharmaceutical and chemical technologies. In the field of chemistry, any competent researcher who invents one compound and discovers its usefulness, can enumerate derivatives that may be equally useful, even though it remains beyond the power of the researcher to manufacture more than a few of those compounds at the time of filing.[59]

Although second generation patents can be found in all technological fields, this thesis will focus on those in the pharmaceutical industry. Pharmaceutical selection inventions could be a selection of a compound or of compounds, the use of a compound, a chemical process, dimensions, a range of values, parameters, crystal forms,[60] nanoscales, dosage regimes, and so on.[61] A more extreme case of a selection invention would be claiming a known compound with a very high level of purity.[62]

B. Inventions and innovations in pharmaceutical field

1. Inventions and patents in pharmaceutical field

Categories of pharmaceutical patents are not generally different from patents in different fields of technology. Compounds and processes can be subject to patent protection, but a new use of a known compound can be patented depending on the particular jurisdiction. Typical pharmaceutical patents can protect active ingredients and their metabolites, hydrates, salts, esters, intermediates and the like combinations of more than two active ingredients, methods of manufacturing the active ingredient and its intermediates, different methods or uses of medical treatment of known medications (includ-

58 *Grubb/Thomsen*, 2010, 64.

59 *See e.g., Blanco White,* 1983, 104.

60 *Smith Kline & French Laboratories v. Evans Medical* [1989] Fleet Street Report ("F.S.R.") 561,563 (Aldous J. noted "the *polymorph patent is said to be a selection patent*, in that the [basic] patent disclosed Cimetidine makes no mention that it can exist in A, B or C [crystal] form."[Emphasis added]).

61 *See generally Miller/Evans*, 2010, 14-15; for the dosage regime, refer *Abbott Respiratory/Dosage Regime*, G 2/08 (2010), para 6.3.

62 *Grubb/Thomsen*, 2010, 237.

ing dosage regimes), and formulations of a drug, including new dosage forms, devices such as patches, drug delivery systems.[63] These inventions and patents will be explained in detail in chapter II.C. The protection covers various aspects of pharmaceutical innovation. It is possible to form a hierarchy among compound, use or process claims of patents based on the scope of protection that the patents provide.

a) Product invention and the absolute character of its protection

A claim to structures rewards patentees with exclusive rights to all properties and manufacturing processes thereof, regardless of whether properties or processes discovered subsequently were acknowledged by the applicant at the time of filing. If the product is a compound, this is called "absolute compound protection",[64] which differs from "purpose-limited protection", where the patent can cover only the purpose of the compound as indicated in the patent application.[65] Regarding the broader scope of the exclusivity of the product, Jacob LJ noted:

> "[A]ny product claim is apt to give the patentee "more than he has invented" – and in two ways. Firstly such a claim will have the effect of covering all ways of making the product including ways which may be inventive and quite different from the patentee's route. Secondly it will give him a monopoly over all uses of the patented compound, including uses he has never thought of."[66]

Although there are arguments for purpose-limited protection,[67] the Federal Supreme Court of Germany ("BGH") clearly addressed the effect of absolute chemical protection on the pharmaceutical industry. In the *Klinische Ver-*

63 *Voet*, 2011, 59.

64 *Kraßer*, 2009, 130 *et seqq*.; *Bacher/Melullis* in: Benkard *et al.*, 2006, § 1 Rdns 12 and 16; *Deutsches Patent- und Markenamt* ("DPMA"), 2008, 29; *Merges/Duffy*, 2011, 393; *cf.* Case C-428/08, *Monsanto Technology LLC v. Cefetra BV and Others*, E.C.R. 2010, I-06765 (holding the Art. 9 of Council Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions did not confer absolute protection to the patented product, i.e. a patented DNA sequence, when it was contained in soy meal, where it did not perform the function for which it was protected); *see also Kilger/Feldges/Jaenichen*, 87 J. Pat. & Trademark Off. Soc'y 569 (2005) (for the German perspectives of purpose-limited compound protection for the sequences of human genes in German Patent Act).

65 DPMA, 2008, 29.

66 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 54.

67 *Domeij*, 2000, 85 *et seqq*.; *Merges/Duffy*, 2011, 399.

suche case, the BGH held that as a consequence of dependent patents, the product patent kept its economic value, since in order to exploit the use patent, the later patentee would need the approval of the product patentee. Accordingly, the earlier patent retained its full validity with respect to third parties regarding the use protected by the later patent. [68] This increases the value of the product patent and allows the holder to exploit the exclusive right of the earlier patent.[69]

b) Hierarchy of pharmaceutical patents

The hierarchy of pharmaceutical patents can be established according to the scope of patents. The most valuable is *a compound patent*, because it affords absolute compound protection in that it covers a product independent of its formulation, manufacture, or use and without regard to how much of the patented compound it contains, as long as it contains an active ingredient covered by the compound patent.[70]

A medical use patent covers the (un)approved second or further medical use of a previously patented compound with a first medical use.[71] Since this type of patent also covers any product claiming the protected medical use, it is the second most valuable patent. However, given the problems of enforcement associated with this type of patent, it is not easy to encourage pharmaceutical manufacturers to invest their R&D resources in this new use of old drugs. [72] Induced infringement can be found only when a drug product has an instruction for the other's patent-protected medical use. The off-label

68 *BGH/Klinische Versuche (Clinical Trials)*, GRUR 1996, 109, 115. 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.

69 *BGH/Klinische Versuche (Clinical Trials)*, GRUR 1996, 109, 115.

70 *Nastelski*, IIC 1972, 267, 271-72 (noting an unlimited protection provided to the patented product which has no definite external form, and only the patentee is authorized to make the product or the chemical substance commercially, to bring it into commerce, to offer it for sale or to use it.); *Grubb/Thomsen*, 2010, 77' *Voet*, 2011, 60; *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1341-42 (Fed. Cir. 2005) (holding no matter how small the amount is, as long as the product contains a compound protected by a patent, it infringes the compound patent.).

71 *Voet*, 2011, 60.

72 *Eisenberg*, 5 Yale J. Health Pol'y L. & Ethics 717, 724-25 (2005).

use by the doctors[73] - the prescription of a medication in a manner different from that approved by regulatory authorities - can be a serious problem for the patentee of a new medical use seeking to enforce his patent right.

The remaining types of patents can be ranked below the previous two. The scope of these patents is normally narrow, and sometimes excessively specific. Consider, for example, the scope of a patent covering a product manufacturing process. As the Imperial Supreme Court of Germany held in 1888, the protection of a manufacturing process included those products made directly by the protected process.[74] However, it cannot prevent anyone from making the same products by a completely different method, if any.[75] In addition, a patent might be less useful for a process than a product, because it is more difficult to prove patent infringement for a process.[76] A process patent can be enforceable when the use of that process invention can be determined from the end-product or from other evidence, such as trace impurities.[77] For this reason, TRIPS requires that the onus of proof is reversed and imposed upon the alleged infringer of the patented process if the compound is novel.[78]

This narrow but overly specific claim often makes it very difficult to design around the patent. A patent with a very narrow scope of protection can therefore be extremely valuable in preventing the market entry of generic versions.[79] As patents for compounds, new uses and processes offer different strategic values to the patent holder, industries often recognize the hierarchical differences and strategically seek protection accordingly.

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73 *Stafford*, 358 N. Engl. J. Med., 1427 (2008).

74 *Methylenblau*, 22 Reichsgericht in Zivilsachen 8 (holding "the product manufactured by means of the (protected) process does not fall outside of subject-matter of invention, and constitutes the end-point as characterized by patent law. Thus the process comprises the product manufactured by the by said process as part of the subject-matter of the invention.").

75 *Grubb/Thomsen*, 2010, 77-78; *Nastelski*, IIC 1972, 267, 272 (a third party patent on method of preparation or forms of use of the product is dependent on the product patent, and he cannot practice his patent commercially without the approval of the holder of the product patent.).

76 *Cohen/Nelson/Walsh*, 2000, 10.

77 *Grubb/Thomsen*, 2010, 245.

78 TRIPS Art. 34 (Process Patents: Burden of Proof), In other words, the court would assume that it has been produced by the patented process unless the alleged infringer would prove otherwise.

79 See subsection V.D.3.d).

2. Innovations in pharmaceutical field

The pharmaceutical industry has been referred to as one of the best examples of an industry for which patents are regarded as socially desirable, since incentives arising from patents appear to be prerequisites for the vast majority of pharmaceutical innovations. If there is an invention that cannot be categorized as such, however, its protection might be unjustified. Therefore, it will be helpful to define what pharmaceutical innovation is and what it is not.

a) Invention v. innovation

The distinction between invention and innovation returns us to Schumpeter's Theory of Economic Development.[80] Schumpeter distinguishes the act of innovation, which is a new combination of known and/or unknown means of production, from the act of invention, which creates a new means of production.[81] He further argues that invention of itself does not produce an economically relevant effect.[82] In contrast, innovation brings incessant changes in economics through a so-called "process of creative destruction."[83] Eisenberg notes that an innovation may be defined as putting existing inventions to practical use.[84] Svatos argues that the innovation is the final product that appears on the market and is different from the invention for which a patent was granted.[85] He further argues that patents therefore stimulate a combi-

80 *Nelson/Winter*, 1982, 263.

81 *Schumpeter*, 1964, 100-101 (Innovation comprises: (1) the introduction of a new good or of a new quality of a good; (2) the introduction of a new method of production which includes a new way of handling a commodity commercially; (3) the opening of a new market for the good, irrespective of the prior existence of the market; (4) the conquest of a new source of supply of raw materials or half-manufactured goods; (5) the carrying out of the new organization of any industry, such as the creation of a monopoly position or the breaking up of a monopoly position.); *Schumpeter*, 1942, 139-140 (mentioning the competition of these types of innovations); He distinguished these two without mentioning "innovation," which appears in his later publication, *Business Cycle*, 1939, 84).

82 *Schumpeter*, 1939, 80.

83 *Schumpeter*, 1942, 137-38.

84 *See e.g., Eisenberg*, 56 U. Chi. L. Rev. 1017, 1036-37 (1989).

85 *Svatos*, 13 Soc. Philos. Policy 113, 122 (1996).

nation of invention and marketing skill.[86] Merges similarly holds that "[a]n invention refers to the practical implementation of the inventor's idea. […] An innovation is the 'debugged' and functional version of the invention: the version first offered for sale."[87] He further contends that the innovation significantly differs from the invention because of the changes necessary to turn the invention into a commercial product.[88] While the distinction between invention and innovation is somewhat simplified, since the process of development is a continuum,[89] the two ends, i.e. invention and innovation are relatively easy to distinguish.

Chronologically, once an invention has been made, substantial investment is often needed to ready the invention for the market.[90] Such investment can involve the construction of a new plant or equipment, promotion or advertisement.[91] Indeed, innovation, in conjunction with investment and development, is more sensitive to economic variables than invention.[92] Converting inventions into innovations is a core feature of technological progress.[93]

b) NMEs as the core of pharmaceutical innovation

Every product available on the pharmaceutical market which is developed from an invention can be considered an innovation. However, the significance of an innovation can vary substantially between a second generation product and new medical entities ("NMEs").[94] In other words, for some products, such as NMEs, substantial investment in preclinical and clinical trials to meet regulatory requirements must be made to bring the invention to market, in contrast to second generation products. More importantly, NMEs are basic inventions that bring constant changes in market economics

86 *Svatos*, 13 Soc. Philos. Policy 113, 122 (1996).
87 *Merges*, 76 Cal. L. R. 803, 807 (1988).
88 *Merges*, 76 Cal. L. R. 803, 807 (1988) (also noted this distinction between invention and innovation has been criticized as a simplified dualism by some economists, who argue that the process of development is actually much more of a continuum).
89 *Nelson/Winter*, 1982, 263-64; *Merges*, 76 Cal. L. R. 803, 807 (1988).
90 *See e.g., Eisenberg*, 56 U. Chi. L. Rev. 1017, 1037 (1989).
91 *See e.g., Eisenberg*, 56 U. Chi. L. Rev. 1017, 1037 (1989).
92 *Scherer*, 1984, 26.
93 *Chandy, et al.*, 43 J. Marketing Res. 494 (2006).
94 See subsection II.D.1.

through various second generation products. Thus, NMEs are the really valuable innovations in the pharmaceutical industry. In this context, we must question whether current patent protection for pharmaceuticals incentivizes R&D of truly valuable innovation.

C. *Second generation inventions and patents in pharmaceuticals*

As noted above, some evidence in the cases involving second generation inventions is complicated.[95] After a basic research period, leading to the identification of a "lead compound", the typical procedure in developing a medicine can be briefly summarised as follows: "With the selection of the lead compound, the chemist and biologist embark on an extensive program to improve its potency, the specificity of biological effect with concomitant reduction in toxicity, oral absorption, duration of action, metabolic profile and pharmacokinetic pattern. This typically involves extensive structure-activity relationship ("SAR") studies."[96]

The lead compound or the lead compound series are to be patentable,[97] and generally, the outputs from subsequent developments are also the objects of patent protections. Using the concept of basic and second generation inventions, the lead compound will be the *basic invention*, and the following inventions will be *second generation inventions*. The second generation inventions from the lead compound can be salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, com-

95 *Laboratoires Servier v. Apotex*, [2008] EWHC Civ 445, para 41.
96 *deStevens*, 1990, 266; *Domeij*, 2000, 26.
97 *deStevens*, 1990, 266; *Domeij*, 2000, 26.

plexes, combinations and other derivatives of known substance, and the like. These inventions are eligible for patent protection in most jurisdictions.[98]

Beyond second generation, there can be (n+2) generation inventions, such as, a new crystal form of a known salt of a basic medication,[99] a new use of a known metabolite, [100] solvates or hydrates of a known salt form, and the like. However, all of these types of invention will be comprehensively referred to as second generation inventions in this dissertation since all such inventions arise subsequent to the basic invention.

The relevant inventions, patents and types of claims for second generation inventions are explained briefly here, according to the three types, i.e. product patents, use patents, and process patents.

1. Product inventions and patents

a) Species selection inventions

In the U.S., the United States Patent and Trademark Office ("USPTO") defines *a species selection invention* as an invention that is a different embodiment or a species that could fall within the scope of a generic invention.[101] Further, a generic invention should require no material element ad-

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98 In some jurisdictions, such as India, these cannot be patent eligible if these second generation inventions are regarded as the mere discoveries of new properties or new uses for a known substance. *See* Sec. 3(d) of Indian Patents Act, 1970 ("The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant."); *see further* Manual of Patent Office Practice and Procedure in India, 08.03.05.04 (Ver. 01.11, as modified on March 22, 2011) ("Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance ***shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy***." [Emphasis added]).

99 *E.g.*, *Laboratoires Servier v. Apotex*, [2008] EWHC Civ 445 (crystalline forms of tert-butylamine salt of perindopril were claimed).

100 *E.g., Teva v. Merrell* [2007] EWHC 2276 (Ch) (the new uses of a metabolite of a known substance were claimed).

101 U.S. Patent & Trademark Office, Manual of Patent Examining Procedure (8th ed 2010) ("MPEP"), § 806.04; *see also Chisum*, 2012, § 12.03[3].

ditional to those required by a species invention and each species invention must require all of the limitations of the generic invention.[102] Similarly, in Europe, EPO considers that a selection invention deals with the selection of individual elements, which have not been explicitly mentioned within a larger known set as a selection invention.[103]

Markush type claim

The use of a Markush type claim[104] was first reported in a U.S. case involving Eugene Markush, who filed a patent application in 1924 for pyrazolone dyes where a generic structure was claimed.[105] This type of claim is used when no generic term describes the desired individual species that share common significant features, similar properties or activities, or at least one common function, or which have an equivalent basis for categorization in the same group.[106] The scope of this kind of claim in chemistry is limited by the compounds that can be manufactured by combining various alternatives mentioned for the different positions in the formula. One famous example is a claim in respect of a cheese cigarette filter, which reads: "A cigarette filter according to claim1 in which the cheese comprises grated particles of cheese selected from a group comprising Parmesan, Romano, Swiss and Cheddar cheeses."[107]

Although there are some downsides to using it,[108] this type of claim is very popular and common as it has several advantages. It may offer broader protection for the patentee and it is easier to file as one multinational patent

102 MPEP § 806.04 (d).

103 EPO Examination Guidelines"), G-VI, 8.

104 Markush type claims are one of the formats of claiming, such as Jepson type claims, product-by-process claims, means-plus-function claims, step-plus-function claims, and the like.

105 *Fitt*, 20 Biotechnol. Law Rep. 17, 18 (2010).

106 *See e.g.*, *Durham*, 1999, 57; *Valance*, 1 J. Chemical Documentation, 87, 87-88 (1961); *Miller/Evans*, 2010, 146-48.

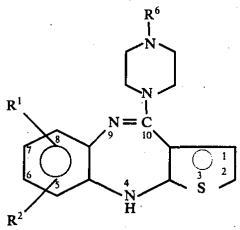
107 U.S. Patent No. 3,234,948 (February 15, 1966, under the title of "Cheese-Filter Cigarette").

108 These disadvantages could be the difficulty to search through the normal database, increased prosecution time and examination errors, undermining their status as the prior arts, and being unclear in their scope of protection, *see e.g. Brown*, 31 J. Chem. Inf. Comp. Sci. 2, 3-4 (1991) (also noting "it is unreasonable to expect that so many compounds will exhibit activity similar to the activity shown by substances for which practical data is supplied.").

application rather than several separate patent applications. Furthermore, it can provide the licensor with a stronger basis for cross-licensing agreements with licensees, who own improvement (selection) patents that use the licensor's invention.[109]

The following is an example of a Markush type claim in U.S. Patent No. 4,115,574,[110] which can also be referred to as a "*genus" claim*.

1. A thieno[2,3-b][1,5]benzodiazepine compound of the formula



or a pharmaceutically acceptable acid addition salt thereof, wherein R^1 and R^2 independently represent hydrogen, C_{1-4} alkyl, halogen, C_{1-4} haloakyl, nitro, amino, C_{1-4} alkoxy, C_{1-4} alkylthio or a group of the formula $—SO_2N(R^4)_2$ where R^4 is C_{1-4} alkyl; wherein R^6 is hydrogen, phenyl, halophenyl, C_{1-4} alkyl, C_{1-4} carbalkoxy or $—(CH_2)_nOH$ where *n* is 2 or 3; and wherein the thiophene ring is unsubstituted or is substituted by a C_{1-4} alkyl group in the 2-position.

(Underlines added).

109 *Brown*, 31 J. Chem. Inf. Comp. Sci. 2, 2-3 (1991); *see also Miller/Evans*, 2010, 146-48 (noting "the power of Markush claiming is most evident when combinations of Markush groups are all used within the same claim. The number of possible embodiments of the invention multiplies in a combinatorial fashion not practically reproduced by drawing all of the embodiments separately.").

110 U.S. Patent No. 4,115,574 (September 19, 1978, under the title of "Benzodiazepine derivatives"), this claim was simpler than the correspondent claim of a U.K. patent, and is a good example of a basic invention.

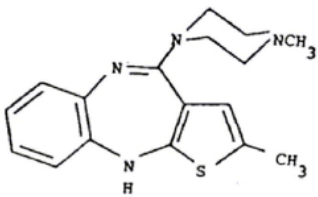
A species claim

About 15 years after U.S. Patent No. 4,115,574 was granted, a combination of the optional variables mentioned above, such as R^1, R^2, and the substitution in the thiophene ring, was filed by the same applicant as follows:[111]

1. 2-Methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine, or an acid addition salt thereof.

This is referred to as a *"species" claim* because it is a claim directed to a specific species from a genus.

The compound named above has the following chemical formula:



One can arrive at this formula *by selecting the underlined groups from the above "genus" claim* 1 of the U.S. Patent, i.e., C_1 alkyl($-CH_3$) group for R^6; hydrogens for both R^1 and R^2; and the thiophen ring, which is substituted by a C_1 alkyl ($-CH_3$) group in the 2-position. This compound was later named "Olanzapine". It is evident that the structure of the compound itself was already disclosed in the prior art as one of the possible combinations, although it was not disclosed specifically. This kind of invention, like the invention of "Olanzapine" is achieved through a specific and particular selection from a group disclosed in the prior art, and thus is referred to as a species selection invention.

111 U.S. Patent No. 5,229,382 (July 20, 1993, under the title of "2-methyl-thieno-benzodiazepine").

b) Optical isomers

Organic chemical compounds contain carbon atoms ("C"s) which are covalently bonded to other atoms. Each carbon atom normally forms four bonds.[112] If a carbon atom has four single bonds, the four other atoms around the carbon atom usually form a tetrahedral spatial arrangement (See Figure 1).[113] Compounds with the same molecular formula or atomic composition, but with a different spatial arrangement are called *stereoisomers*. *Optical isomers*[114] are one type of stereoisomers and can be classified further into enantiomers and diastereomers.[115] *Enantiomers* are a pair of stereoisomers that differ only in their spatial arrangements and have at least one "stereocenter," which is a carbon atom (C) with four different groups attached.[116] The spatial structure is the nonsuperimposable mirror image of the other, designated "chiral," which is derived from the Greek *cheir*, meaning "hand."[117] Its three dimensional molecular structure is depicted with wedges and dashes and the enantiomers of the amino acid alanine are presented in Figure 1 as an example. Various naming conventions are used to distinguish between the enantiomers, such as "(+)" or "(-)", "(d)" or "(l)", "(D)" or "(L)",

112 *William* 1999, 18.

113 *Macomber*, 1996, 97 (Further noting the study of this kind of three-dimensional structure of molecule and the spatial relationship among the atoms is called stereochemistry. *Macomber*, 1996, 189).

114 This is because a pure enantiomer rotates plane-polarized light in a particular direction, such as clockwise, or counterclockwise.

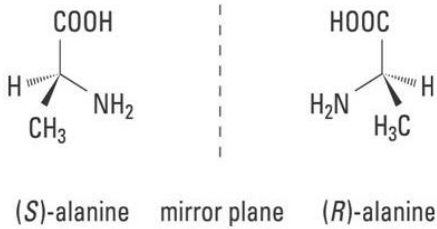
115 ***"Diastereomers"*** are the optical isomers which occur when there are more than one chiral centers in the compound and which are non-superimposable, non-mirror images of others. And ***"epimers"*** are diastereomers that differ in configuration of only one stereogenic center.

116 For example, two different mirror-imaged forms are a "right handed form" and a "left-handed form." In Figure 5, the carbon atom in the center is a stereocenter to which four different groups has been attached, namely –COOH, $-NH_2$, $-CH_3$, and H. The solid wedge is used to indicate that the methyl group (–CH3) is projecting out of the page (toward to the viewer), while the hashed line indicates that the hydrogen atom (H) is behind the page (away from the viewer). Some compounds having more than two chiral centers result in multiple possible three-dimensional arrangements which are known as diastereomers.

117 *See generally William* 1999, 612-613; *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 720 (N.D.W.Va. 2004), *aff'd*, 161 Fed.Appx. 944 (these kinds enantiomeric compounds are thus often analogized to a person's left and right hands).

and "(R)" or "(S)",[118] and for the racemates, "(±)" or "(dl)" or (RS) are used.[119] A "*racemic mixture*" or a "*racemate*" refers to an equal mixture of R and S enantiomers.[120]

Figure 1: Example of an enantiomer - an amino acid, alanine.



Research into drug chirality has been underway since 1874.[121] Although enantiomers have nearly identical physical properties, they often have different activities and side effect profiles. This has long been recognized both by academia, by industry and by regulatory authorities.[122] These are the medications that are separated from the racemate mixtures; the components obtained are responsible for beneficial pharmacological action, while other components that are usually responsible for side effects are excluded.[123] More than half of the drugs listed in the *Pharmacopoeia*[124] are chiral

118 These systems are not interchangeable.
119 Unless otherwise indicated, R/S system is used in this paper.
120 Racemates are normally produced through a chemical reaction which prepares a chiral compound from an achiral compound in normal conditions.
121 *Mansfield/Henry/Tonkin*, 43 Clin. Pharmacokinet. 287, 287 (2004).
122 *Caldwell*, 16 Hum. Psychopharm. S67, S67, S70 (2001) (noting the existence of optical enantiomer was recognized in 1848, and the research into enantiomers has become to be more active since 1980s according to the technical progresses on separation, analysis, and production on an industrial scale of enantiomers); *Darrow*, 2 Stan. Tech. L. Rev. 1, para 7 (2007) (noting enantiomers can exhibit substantially different biological, pharmacological, or toxicological activity).
123 *The National Institute for Health Care Management Research and Educational Foundation ("NIHCM")*, 2002, 5.
124 *Pharmacopoeia* is a book containing directions for the identification of samples and the preparation of compound medicines, and published by the authority of a government or a medical or pharmaceutical society.

molecules,[125] including many of the world's best-selling products, such as Lipitor®, Plavix® and Nexium®.[126] Other well-known chiral drugs include Ibuprofen, Claritin®, Allegra®, Prilosec®, Zyrtec®, and even thalidomide.[127]

Enantiomer patents claim selected individual enantiomers of racemic mixtures that were previously disclosed in the prior art, mainly, their basic patents. For this reason, an enantiomer patent may be categorized as a selection invention. The importance of enantiomer patents is reflected in the "patent cliff"[128] threat by the expiration of enantiomer patents on blockbuster chiral drugs.[129] Knowledge of the structure of one enantiomer, or of a racemate, necessarily furnishes a person skilled in the art with knowledge of the structure of the other or both enantiomers.[130] This leads to a fundamental inquiry regarding the novelty or obviousness of enantiomer inventions.[131] The validity of enantiomer patents has often been challenged, mostly by generic pharmaceutical companies on the grounds of lack of novelty, lack of inventive step, lack of utility, double patenting, and insufficiency of disclosure.[132]

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125 *Ariëns/Wuis*, 42 Clin. Pharmacol. Ther.361, 361-62 (1987) (showing 949 out of 1675 drugs listed in the *Pharmacopoeia* were chiral, 461 of the 469 natural or semi-synthetic chiral products (98.3%) are single enantiomers, but only 58 of 480 synthetic chiral products (12.1%) are single enantiomers).

126 *IMS Health*, 2010 (the top three best-selling global drugs from 2007 to 2009 and top three out of top four best-selling global drugs in 2010 are single enantiomers).

127 *Darrow*, 2 Stan. Tech. L. Rev. 1, para 2 (2007).

128 *See* chapter III.B.3; *See also Mansell*, 1 Scrip Executive Briefing 1, 1–16, (2008) (explaining that "patent cliff" is a term for the loss of revenue which occurs when the monopoly granted by patents is lost and the generic versions of drugs enter into the market. It is expected that the patent cliff reaches its peak in 2010-2011 as patents of many blockbusters including SanofiAventis' Clopidogrel, Pfizer's Atorvastatin, and others expire.).

129 *Agranat/Wainschtein*, 15 Drug Discov. Today, 163, 169 (2010).

130 *Darrow*, 2 Stan. Tech. L. Rev. 1, paras 5-6 (2007).

131 *See e.g., Darrow*, 2 Stan. Tech. L. Rev. 1, paras 5-6 (2007).

132 *Agranat/Wainschtein*, 15 Drug Discov. Today, 163, 163 (2010); *Darrow*, 2 Stan. Tech. L. Rev. 1, para 3 (2007) (noting the patentability of chiral molecules has taken on increased significance and is a subject of litigation.).

c) Crystalline forms

Polymorphs are different crystalline forms of the same compound. Polymorphism denotes the ability of a material to exist in more than one form or crystal structure. It was discovered in the 19th century that many substances could be crystallized into solids with different melting points and crystal habits.[133] The molecules in the crystalline form are arranged in an organized pattern called a "lattice"; which is different from an amorphous form, in which the molecules are randomly distributed.[134] Among the substances that exist in crystalline form, some can be in one crystalline form, which is referred to as a monomorphic substance, for example, wax or common window glass. Others that exist in more than one organized pattern, such as the cocoa butter in chocolate,[135] are referred to as polymorphs. According to the shape of the crystals, polymorphs can often exhibit different physico-chemical properties, such as stability, solubility, hygroscopicity,[136] and hardness,[137] although their chemical composition is identical in all forms. Examples among drugs include Ranitidine (Zantac®), Paroxetine (Deroxat®), and Cefnidir (Omnicef ®). A patent for a polymorph can be extremely valuable when the patent covers the most stable form at ambient conditions, considering that less stable forms may spontaneously convert to the most stable form.

Co-crystals such as solvates or hydrates are called *pseudo-polymorphs*. If the substances are dissolved in a solution, they are normally recovered by evaporation of the solvent. [138] If this evaporation is conducted with carefully controlled parameters (e.g. "in water solvent," such as humidity, or drying / evaporating), some substances can retain a certain number of water

133 *Brittain*, 2009, 1.
134 *Giron*, 73 J. Thermal Analysis & Calorimetry 441, 441-42 (2003).
135 Cacao butter could exist in six different crystalline forms; the most thermodynamically stable form (form VI) has a dull surface and soft texture; however, form V is the most appreciated by consumer and shows the crispy hardness and glossy surface. In order to make chocolates crystallize exclusively in the preferable form (form V), the crystallization process must be controlled by a sophisticated temperature regime, *see in general, Von der Freien*, 39 Chemie in Unserer Zeit, 416, 423 (2005).
136 "Hygroscopicity" means the readiness of a substance to absorb moisture from the atmosphere.
137 *Brittain*, 2009, 2-3.
138 *Seager/Slabaugh*, 2010, 279.

molecules as part of the solid crystalline structure.[139] This type of crystalline form is called a "*hydrate.*"[140] If the same procedures are followed "in a solvent other than water," the resulting crystalline form is called a "*solvate*".[141]

Claims to polymorphs can be suitably drafted by using their physicochemical parameters, which are determined by Single crystal X-ray diffraction (SXD), X-ray powder diffraction (XRPD), Infrared(IR)- or Raman spectroscopy, solid state 13C-Nuclear Magnetic Resonance (NMR) spectroscopy, and the like. Thus, in a properly drafted claim for polymorphs, many figures are listed.[142]

d) Metabolites and prodrugs

Metabolites are substances produced in the body through the metabolism of other substances and in some cases are responsible for the pharmacological effects observed. The *metabolism* of substances absorbed in the body makes the ingested substance more water-soluble and readily excreted by the kidney.[143] This is one of the major pathways by which a xenobiotic substance, such as a medication, is inactivated.[144] However, it is not uncommon to find that a metabolite itself has pharmacological effects, while the parent medication that is metabolized to it does not.

Prodrugs are bioreversible derivatives of active drugs. The active ingredients exerting the pharmacological effects are released through biotrans-

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139 *Seager/Slabaugh*, 2010, 279.

140 *Seager/Slabaugh*, 2010, 279 (the retained water in the crystalline structure is called the water of hydration, and according to the number(n) of water molecules in the crystalline structure, they are called anhydrate (n=0), ***hemihydrates*** (n=1/2), monohydrate (n=1), dihydrate (n=2), and the like.).

141 *Giron*, 73 J. Thermal Analysis & Calorimetry 441, 442 (2003) (further noting solvates were new crystalline compounds formed with the solvent, i.e. were the combination of solvent molecules with the compound molecules).

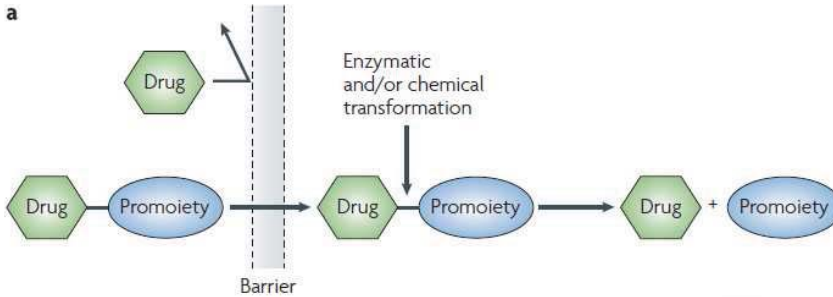
142 Claim 1 of GB Patent No. 1,543,238 (March 28, 1979, under the title of "Polymorph of Cimetidine")
A substantially crystallographically pure polymorphic form of Cimetidine (Cimetidine A) which is characterised by an infra red spectrum (1% KBr disc) having very strong, broad peaks at 1400 and 1385cm^{-1}, a strong, sharp peak at 1205 cm^{-1} and a medium-sharp peak at 1155 cm^{-1} and having no peak at 1180 cm^{-1}.

143 *Ionescu/Caira*, 2005, 3.

144 *Ionescu/Caira*, 2005, 41.

formation in the body. Prodrugs account for 5-7% of the drugs approved worldwide.[145] Prodrugs are chemicals with little or no pharmacological activity, but they are used to improve the efficacy of established drugs.[146] Through this approach, one can improve the bioavailability of the active drugs or make oral administration possible by overcoming poor solubility, instability, insufficient oral absorption, local irritation, and the like.[147] Examples of prodrugs include the well-known proton pump inhibitor[148] Omeprazole, the ACE inhibitor[149] Enalapril, and the antibiotic Hetacillin.[150]

Figure 2: A simplified representative illustration of the prodrug concept[151]



a | The drug–promoiety is the prodrug that is typically pharmacologically inactive. In broad terms, the barrier can be thought of as any liability or limitation of a parent drug that prevents optimal (bio)pharmaceutical or pharmacokinetic performance, and which has to be overcome for the development of a marketable drug. The drug and promoiety are covalently linked via bioreversible groups that are chemically or enzymatically labile, such as those shown here. The 'ideal' prodrug yields the parent drug with high recovery ratios, with the promoiety being non-toxic.

145 *Rautio, et al.*, 7 Nat. Rev. Drug Discov. 255, 255 (2009); *Oellerich/Armstrong*, 47 Clin. Chem. 805, 805 (2001).
146 *Ionescu/Caira*, 2005, 372.
147 *Rautio, et al.*, 7 Nat. Rev. Drug Discov. 255, 255 (2009); *Oellerich/Armstrong*, 47 Clin. Chem. 805, 805 (2001).
148 A proton pump inhibitor has long-lasting effect to reduce the gastric acid production and used for the treatment of a couple of disorders related to the over-secretion of gastric acid, such as gastritis or peptic ulcer disease.
149 An ACE inhibitor is an "angiotensin-converting-enzyme" inhibitor and used for the treatment of hypertension and congestive heart failure.
150 *Hansen/Hirsch*, 1997, 342.
151 *Rautio, et al.*, 7 Nat. Rev. Drug Discov. 255, 256 (2009).

How substances are categorized depends on when their characteristic is identified. Two main cases may be distinguished. If the pharmacological effect of a medication is due to the transformation of a drug into a metabolite, the medication may be called "a drug" and an "active metabolite". If, on the other hand, said effect is due to the release of the drug from a larger chemical entity, then the medication may be called "a drug" and "a prodrug".

e) Esters and salts

Esters are chemical compounds that react with water to produce alcohols and organic or inorganic acids. Thus, when a medication is in alcohol form, it can be converted to its ester form via reaction with acids. In turn, when this ester form is administered to the patient, it will be hydrolyzed in the physiological condition to yield alcohols or acids that will have pharmacological effects.[152] Aspirin, which is remarkably versatile, is an acetyl *ester* of salicylic acid.[153]

Salts are compounds that result from the neutralization reaction of a base and an acid. Salts are composed of positively charged ions (cations) and negatively charged ions (anions); and can be organic or inorganic (metallic).[154] Salt forms may enhance absorption in the body or the stability of product, or they may be formulation-friendly.

f) Dosage forms

A dosage form is the entity administered to patients in order that that they receive an effective dose of a drug, such as tablets, capsules, injections, and transdermal patches.[155] These kinds of inventions may include different strengths, an extended release form, or another delivery system such as an inhaler, or implanted device.[156] A sustained release drug delivery system, for example, aims to maintain therapeutic blood levels of the drug for an extended period by controlling the rate of release of the drug from the dosage

152 *Seager/Slabaugh*, 2010, 481-82.
153 *Seager/Slabaugh*, 2010, 481.
154 *Seager/Slabaugh*, 2010, 278-79.
155 *Mahato/Narang*, 2012, 15-16.
156 *NIHCM*, 2002, 5.

form.[157] This can be achieved by providing multiple doses of a drug within a single dosage form, which are released at periodic intervals, or by delaying the timing of the first release.[158] Over the past forty years, the sustained release drug-delivery system has attracted considerable attention, since it can reduce the frequency of dosing, increase effectiveness of the drug by reducing the dose required, reduce the incidence of adverse effects, provide uniform drug delivery, and simplify dosing regimes.[159]

g) Combinations of active ingredients

A new product can be provided by combining the active ingredient of an approved drug with one or more other active ingredients.[160] As in other technical fields, a mixture of known substances can be patentable if it meets the requirements of patentability. For example, the combination of aspirin and another pain-killer, such as Naproxen,[161] can be created to enhance their analgesic or anti-inflammatory therapeutic effect; or a combination of two diuretics (amiloride and hydrochlorothiazide) with different mechanism of action can exhibit more than additive effects. Thus, said combinations can be claimed.[162]

2. Use inventions

a) New Use/New method of treatment

A medical indication is a symptom or particular circumstance indicating the advisability or necessity of a specific medical treatment or procedure. The nature of a medical use invention is based on a newly identified effect, and

157 *Jantzen/Robinson*, 2002, 748.
158 *Jantzen/Robinson*, 2002, 748.
159 *Jantzen/Robinson*, 2002, 747; *see also Actavis UK Ltd v. Novartis AG* [2010] EWCA Civ 82, para 62 (Jacob LJ noted a sustained release might provide better efficacy or fewer side effects or better compliance).
160 *NIHCM*, 2002, 5.
161 *E.g., Willkens/Segre*, 19 Arthritis & Rheumatism 677, 680-81 (2006).
162 *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804 (Fed. Cir. 1989), *cert. denied,* 493 U.S. 975 (1989) (holding the patent was invalid because of lack of inventive step over prior art).

is a new teaching that results from that discovery.[163] Often, pharmaceuticals have several different indications. For example, aspirin was discovered as a highly effective pain-killer in 1897 by Hoffmann, Eichengrün and Dreser at Bayer. However, the mechanism of its action, namely the inhibition of the biosynthesis of prostaglandins from arachidonic acid, was first discovered by John Vane at the Royall College of Surgeons as late as 1971.[164] Since then, it has turned out to have many more additional therapeutic indications, especially in preventing heart attacks and strokes.[165] Revisiting old drugs in this way may lead to therapeutically interesting new discoveries, and new benefits to the patients. The industry has coined this repositioning approach "teaching an old drug new tricks."[166]

Patent law deals with medical treatment differently from other methods or use claims related to medicines. Medical treatment and procedures are often excluded subject matter for patenting, as is the case in Europe.[167] If a previously unknown substance is proven to have a novel therapeutic or diagnostic effect, a patent applicant can obtain an exclusive right to all uses of the substance.[168]

The prohibition in Europe has been relaxed by the introduction of the new provision of Art. 54(5) of the European Patent Convention ("EPC") 1973 regarding *first medical use*. The first medical use of a known substance can be patented, and has come to be regarded as a product patent. Moreover, if one can prove a second medical use for a substance, which was known to have a first therapeutic effect, it is possible to claim a second medical use as well. For a second medical use, the applicant would have exclusivity only on the *second medical use* in Europe.[169] The practice was derived from the EPO's G 5/83 decision[170] and various technical board of appeal cases regarding second medical use, is now finally based on the statutory language of the Art. 54(5) of EPC 2000. In the United States, however, patents on uses

163 *Klöpsch*, IIC 1982, 457, 467.
164 *Dutfield*, 2009, 17-20.
165 *Dutfield*, 2009, 20.
166 *Scudellari*, The Scientist, April 1, 2011.
167 European Patent Convention, Art. 53 (c).
168 Cf. However, in the past, if the substance was known, a patent could be granted neither on the product, which would be lacking in novelty, nor on the new use, as the patent grant would contravene the provision banning patents for medical procedures.
169 *Eisai/Second medical indication*, G 5/83, OJ EPO 1985, 64.
170 *Eisai/Second medical indication*, G 5/83, OJ EPO 1985, 64.

are limited to a particular "method-of-use", which does not protect the product as such.[171]

b) Dosage regime

Dosage regime provides instructions for the proper way to take a medication, such as "three times per day after a meal," "once a day before sleep," or "40 mg once a day in the morning for 4 to 8 weeks." For example, if the single novel feature of an invention is the direction "once a day prior to sleep" of a well-known substance to cure the same illness, the Enlarged BOA held that this use was not excluded from patentability under the EPC. [172]

3. Process inventions

a) Process

A chemical process invention denotes the invention of a process to manufacture a product. In Germany, since the *Kongo-Rot* decision in 1889,[173] so-called "analogous chemical processes"[174] are also patentable if the product resulting from the process demonstrates unexpected and advantageous characteristics or effects in comparison to known chemical products.[175] In the United Kingdom and under EPO practice, if a compound is patentable, both the claims directed to the compounds and to the process for the manufacture

171 *LabCorp v. Metabolite, Inc.*, 548 U.S. 124 (2006); *UNCTAD-ICTSD,* 2005, 356.

172 *Abbott Respiratory/Dosage Regime*, G 2/08 (2010) (a referral to the Enlarged Board of Appeal for the decision that a feature of a claim relating to a specific dosage regime reflected a medical activity which was excluded from patentability under Art. 52(4) EPC 1973, *Kos Lifesciences/ Dosage regimen*, T 1319/04, OJ EPO 2009, 36).

173 *Kongo-Rot*, Decision of the Reichsgericht (Imperial Supreme Court) of May 8, 1889, Patentblatt 1889, 209, 212.

174 "Analogous chemical processes" are processes for making a new chemical product. These processes are neither chemically new nor unusual, have different starting materials but with an analogous constitution, interacting with one another in the same procedural manner (or same starting analogous procedural manner) to obtain definite new chemical products of a new constitution corresponding to specific expectation.

175 *Nastelski*, IIC 1972, 267, 269-70.

of that compound are patentable, even if the starting material and the process are already known.[176] In the United States, this type of analogous process patent is considered to be obvious,[177] unless it is a biotechnological process.[178]

b) Intermediates

Intermediates are compounds that normally have no pharmaceutical activities on their own, but can be used in a chemical process to manufacture an active pharmaceutical ingredient. They are patentable either by their function in a chemical method of production or by the novel properties of the new end product.[179] A patent on an intermediate essential to produce the basic medicine could effectively prolong the control of the resulting drugs' markets.

D. Pharmaceutical products in the market

Although the value and size of innovation vary, every product available on the market developed from an invention, can be an innovation. Pharmaceutical innovations, namely, pharmaceutical products – more commonly known as medicines or drugs – are a fundamental component of both modern and traditional medicine.[180] It is essential that such products are safe, effective, and of good quality, and that they are prescribed and used rationally.[181] For this reason, they are heavily regulated and influenced by the types of pharmaceutical products that are already on the market. Incentives for a new innovation in this market need to account for market regulations. Accordingly, this chapter will explore the types of marketed products.

176 *Grubb/Thomsen*, 2010, 246.
177 *In re Durden*, 763 F.2d 1406, 1410 (Fed. Cir. 1985).
178 35 U.S.C. (2007) § 103(b).
179 *Hansen/Hirsch*, 1997, 345.
180 *WHO*, Pharmaceutical products, available at: http://www.who.int/topics/pharmaceutical_products/en/. (Last accessed on December 20, 2013).
181 *WHO*, Pharmaceutical products, available at: http://www.who.int/topics/pharmaceutical_products/en/. (Last accessed on December 20, 2013).

1. New medical entities, new molecular entities

An NME is an active ingredient that has never been marketed before in any form, or in the product containing it.[182] Thus, the manufacturers must prepare all of the efficacy and safety data through experiments and trials.[183] The first product with an International Non-proprietary Name ("INN") of an active ingredient can also be regarded as an NME. An INN is a unique name that is globally recognized; it is public property;[184] and it is given to a pharmaceutical substance as designated by the World Health Organization ("WHO"). The significance of NMEs and the current status of new drug development will be further elaborated in chapter III.B.2.

2. Similar or equivalent "me-too" products

Once a new medical structure with interesting pharmacological properties has been reported to the public, many other companies perform their own research around said identified structure, and the research that they undertake regarding the new medical structure is sometimes called "me-too" research.[185] A product resulting from this research is often derogatorily called a "me-too" product, because it follows the research prospects that others have already successfully identified. A "me-too" product can be any drug entity that is in the same class and is used for the same main indication as the prototype drug.[186] These may be also NMEs, and they will be subject to all preclinical and clinical trials to prepare the data necessary to meet the regulatory requirements.

In the sense that the research follows a relatively easier path of a previously identified medical structure, the follow on research leading to similar

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182 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 203 (2010); *FDA*, Drugs@FDA Glossary of Terms, available at: http://www.fda.gov/Drugs/informationondrugs/ucm079436.htm#M (Last accessed on December 20, 2013); *Pisano*, 2006, 119 (noting "new molecular entities (NMEs)-both small molecules and biologics-").

183 *NIHCM*, 2002, 4.

184 *WHO*, International nonproprietary name, available at: http://www.who.int/medicines/services/inn/en/ (Last accessed on December 20, 2013); this INN can be also called as a "generic name" that is contrasting to the "brand name," however, in order to avoid any future confusion, this term is not used in this thesis.

185 *Hansen/Hirsch*, 1997, 324.

186 *Wertheimer/Santella/Chaney*, 17 J. Pharmaceut. Marketing Manage. 25, 29 (2005).

or equivalent products are viewed negatively. Furthermore, with regard to the efficacy of me-too products, some argue that a me-too drug has diminished value, serving merely to increase a pharmaceutical company's profits.[187] However, they provide several advantages. Firstly, they may offer wider choice for physicians and patients and can contribute to cost-containment in pharmaceutical care.[188] They enable physicians to treat diverse patients with precision and provide options when the first medicine treated is either ineffective or not tolerated.[189] In addition, they have been also associated with overall cost savings, especially through competition among drugs in a therapeutic class.[190]

Secondly, a me-too product differs from second generation products in that it is a product that is based on an NME. As they are based on new molecules, the improvement through me-too products is sometimes more valuable than improvement through second generation products. This is mainly because analogous studies provide molecules which have different characteristics. These molecules "are as different from the parent molecule as a recent car compared to a 40-year-old model."[191] Furthermore, once the drug is on the market, more people will be exposed to it. This may reveal rarer side effects, which sometimes cause the manufacturer to withdraw the drug from the market. However, it may also lead to the identification of further medical uses of the drug, such as in the cases of Minoxidil[192] or Sildenafil.[193]

Thirdly, they may manifest entirely new properties, which can lead a therapeutic derivative to become a new lead structure. A representative example of this is Imipramine synthesized as an analogue of the antipsychotic drug Chlorpromazine. Imipramine demonstrated antidepressive activity and has provided an effective therapy for the treatment of depression since

187 *See e.g.*, *Angell*, 2004, 75-76, 80-83; *Avorn*, 309 Science 669, 669 (2005).
188 *Wertheimer/Levy/O'Connor*, 2001, 79-82.
189 *Wertheimer/Levy/O'Connor*, 2001, 80-81.
190 *Wertheimer/Levy/O'Connor*, 2001, 100-105.
191 *Wermuth*, 2008, 129; *see also Wertheimer/Levy/O'Connor*, 2001, 78-79 (arguing that it was better to have multiple drugs in the same class).
192 *Zins*, 6 Clin. Dermatol. 132 (1988), minoxidil's hair growth activity was observed on the patents who took it for the treatment of hypertension.).
193 *Ghofrani/Osterloh/Grimminger*, 5 Nat. Rev. Drug Discov. 689 (2006); *Kling*, 1 Modern Drug Discov. 31 (1998), The sildenafil, an active ingredient of Viagra® was initially synthesized and studied for use in the treatment of hypertension and then of angina pectoris (a symptom of ischaemic heart disease).

1954.[194] Thus, a new drug that may seem similar to an older one can provide a major advance in pharmaceutical technology[195] and can become a true pharmaceutical innovation.

3. Second generation products

Second generation products result from follow-up R&D essentially based on an existing product (an NME) and have essentially the same mode of action. [196] These second generation products may have the same INN as the first product (e.g., second products involving *inter alia* new formulations, crystalline forms, particle sizes or medical uses) or a different one (e.g. combinations, individual stereoisomers separated from mixtures or metabolites of an existing INN).[197] They are also called Incrementally Modified Drugs ("IMDs"), which either rely on an active ingredient present in a drug already approved for the market, a closely related chemical derivative of such an ingredient,[198] or have been modified by the manufacturer, such as new formulations, combinations, salts or esters, and the like.[199] Although some commentators use different definitions for second generation products,[200] or for follow-on products,[201] this thesis will use the term "second generation products" according to the definition set out above.

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194 *Wermuth*, 2008, 129.

195 *Wertheimer/Santella/Chaney*, 17 J. Pharmaceut. Marketing Manage. 25, 29-30 (2005) (reporting 81% of the drugs in the list of essential medicines by the World Health Organization were me-too products).

196 *DG Competition*, 2009, 351; *in general, Scotchmer*, 27 RAND J. Econ. 322, 329 (1996) (defining "improvements" as a new version of the patented product with greater commercial value).

197 *DG Competition*, 2009, 351.

198 Such as new salts or esters.

199 *NIHCM*, 2002, 4.

200 *Den Exter*, 17 Eur. J. Health L. 125, 131 (2010) (noting second generation drug as me-too products).

201 *Wertheimer/Santella/Chaney*, 17 J. Pharmaceut. Marketing Manage. 25, 29 (2005) (considering "follow-on drugs" as those that had approved indication in addition to their originally approved indication).

Re-evaluation of old drugs, such as single enantiomers, can be successful on occasions,[202] which can lead some companies specializing in chiral synthesis to develop single isomers and, subsequently, to enter into licensing agreements with the originators of the racemate.[203] These second generation products can certainly provide a high return on investment. The development of a medicine using an active ingredient, the safety and efficacy of which have already been established, is normally less time consuming, less expensive, and less risky than using a compound about which little is known. The high cost potential for IMDs can make modifying older products attractive.[204]

4. Generic drugs

A generic drug, or a "generic", is identical to or bioequivalent to a brand name drug in dosage, safety, strength, route of administration, quality, performance, and intended use. [205] A generic drug product must contain identical amounts of the same active ingredient(s) as the brand name product and have equal effect and little difference when substituted for the brand name product.[206] Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantially discounted prices from the branded prices. The U.S. Food and Drug Administration ("FDA") has noted that generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies, and billions more can be saved when hospitals use generics.[207]

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202 *Hutt/Valentová*, 50 Acta Facultatis Pharmaceuticae Universitatis Comenianae 7, 14 (2003) (noting failure of developing single enantiomers, such as dilevalol, sotalol, and fluoxetine).

203 *Tucker*, 355 Lancet 1085, 1085 (2000) (providing Sepracor as an example of these specialized companies); *see also Darrow*, 2 Stan. Tech. L. Rev. 1, para 113 (2007) (noting Sepracor obtained patents on single enantiomer versions of sixteen chiral drugs previously sold as racemates by other firms.).

204 *NIHCM*, 2002, 4.

205 *FDA*, available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ ucm100100.htm (Last accessed on December 20, 2013).

206 *FDA*, available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ ucm100100.htm (Last accessed on December 20, 2013).

207 FDA, Generic Drugs: Same Medicine, Lower Cost, available at: http://www.fda.gov/downloads/ ForConsumers/ConsumerUpdates/UCM340458.pdf (Last accessed on December 20, 2013).

E. Summary

Since no invention can occur in a vacuum, today's technology depends upon yesterday's.[208] The path of invention and innovation in pharmaceutical technology is no exception. Inventions in pharmaceuticals can thus be divided into basic inventions and second generation inventions. When there is investment, these inventions become innovative products that reach the market.[209]

In this chapter, we have explored the disctinction between basic and second generation invention. As seen above, basic inventions can be developed into NMEs, which can then lead to second generation inventions, and the products that usually follow successful NMEs. Among the second generation inventions, species selection inventions have been shown to be different. Unlike other second generation inventions, a species selection invention can be another basic invention, in the sense that it can also be developed into an NME, which can in turn lead to other second generation inventions. In this sense, a species selection invention has a dual nature – it can be both a basic and a second generation invention.

In the product market, in addition to NMEs and second generation products, there are "me-too" products and generic drugs in the pharmaceutical market place. A me-too product is a drug entity that is in the same class and used for the same medical purposes as the prototype drug. However, these are also NMEs, since they are active ingredients that are marketed for the first time. In contrast, generic products are the bioequivalents of a reference drug in dosage, safety, strength, route of administration, quality, performance, and intended use, but are sold at a much lower price.

The definitions and concepts of inventions and products are crucial to understanding the law on the patentability of inventions, the market situation where the products a play role, and the phenomena that we are facing.[210] As presented in chapter I.C, selection inventions will be the focus of the discussion as representatives of second generation inventions.

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208 *Luski/Wettstein*, 1 Probl. Perspect. Manage. 31, 31 (2004).
209 *Chandy, et al.*, 43 J. Marketing Res. 494 (2006).
210 See chapter III.B.