IV. STANDARDS OF PATENTABILITY FOR PHARMACEUTICAL SELECTION INVENTIONS

So far we have explored specificities and recent developments in the field of pharmaceuticals. As noted, patent protection is crucial for pharmaceutical innovation. Based on these observations, such as high regulation in the industry, the characteristics of the technology, market factors, as well as the norms that dictate the behaviour of researchers in universities or institutes, we have seen a trend towards second generation inventions, products and patents. In this chapter, we explore the patentability of these second generation inventions.

In order to obtain a patent, patent law requires a claimed invention to be new, to involve an inventive step (non-obviousness), to be susceptible to industrial application (utility), and to be sufficiently supported by a description (sufficiency of disclosure), although these elements are expressed slightly differently from jurisdiction to jurisdiction.[441] It is difficult to interpret these requirements of patentability and the requirements are judicially determined, administered by the patent offices, and litigated in courts.[442] To determine whether there is any correlation between the drastic increase of second generation inventions and patentability standards, this chapter examines the basic test for patentability requirements as they are applied to selection inventions. It will also analyze whether or how the present requirements in Europe and in the United States have been lowered by comparing the former requirements in those jurisdictions with those of Korea, respectively.

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441 It was noted that these requirements as a series of doors through which an applicant should pass in order to acquire a patent right. *See e.g. In re Bergy*, 596 F.2d 952, 960 (C.C.P.A. 1979). One thing to note is, no Patent law, in fact, provides the definition of invention, although some provide what shall not be regarded as an invention. *E.g.* EPC Art. 53.

442 *Luski/Wettstein*, 1 Probl. Perspect. Manage. 31, 42-43 (2004) (further noting that there were no fixed set of rules to judge patents in the court, but the decisions are rather very discretionary in nature.); *Scotchmer/Green*, 21 RAND J. Econ. 131, 131-32 (1990).

A. Novelty and anticipation

1. Introduction

The novelty requirement is not controversial.[443] It is a concept that is fundamental to patentability[444] and "a separate examination" step from other requirements when examining patentability.[445] There are several concepts of novelty that have been applied to inventions in different jurisdictions, such as absolute novelty,[446] local novelty,[447] or mixed novelty.[448] Novelty of an invention is required to avoid double patenting,[449] to prevent patenting in-

443 *Duffy*, 71 U. Chi. L. Rev. 439, 502 (2004).

444 *Jacob*, IIC 1996, 170, 170; *Chou/Haller*, 1995, 1 (noting along with "inventive step," novelty is the most important patentability criteria).

445 *BGH/Olanzapine, IIC 2009,* 596, 599 (noting "with regard to the purpose of the (separate) examination of novelty").

446 *Anten*, 54 J. Pat. Off. Soc'y 75, 76 (1972) (noting absolute novelty means "the invention cannot have been made known by prior publication or prior use anywhere in the world."); *Dessemontet*, 1976, 195 (noting "absolute novelty means the novelty that exists in relation to the world state of the technique, without limit in time or space, and by relative novelty is understood that situation which exists within a given country, or within a specific period of time"); *Green Lane Products Ltd v. PMS International Group Plc & Ors* [2008] EWCA Civ 358, para 20.

447 "Local novelty" means the rule that a prior publication or use have to occur within the country in order to destroy the novelty of invention. *Grubb/Thomsen*, 2010, 62 (providing example of this system, which is the early days of patents in England, when patents were frequently granted for inventions, that, although it was known abroad, were brought into the kingdom for the first time by the patentee to U.K.).

448 *Grubb/Thomsen*, 2010, 63-64; *See also Anten*, 54 J. Pat. Off. Soc'y 75, 76 (1972) (noting "mixed novelty" system have been applied in some countries, like USA, that a later patent application is rendered invalid by written publication anywhere in the world, but by oral publication or use of the invention only in USA.).

449 *Tilmann*, IIC 2010, 149, 151-152 (noting "[o]utdated, because, according to Art. 54(2) EPC, not only a patented invention may destroy novelty but any kind of prior art information. And even if there is a prior patented (or applied for, Art. 54(3) EPC) invention, "avoiding double patenting" (as the alleged aim of the novelty requirement) is not restricted to mean, that the claims of that patented invention are the same as the claims of the invention under examination; the disclosure may also be given by the description or by the drawings of the first patented invention."). Double patenting is not acknowledged under the EPC.

formation that already exists in the public domain by a first disclosure,[450] and thus to assure that information remains in the public domain for the free use of the public.[451] An invention is generally considered new if it does not form part of the state of the art.[452] If the concept of an invention is completely disclosed within a single piece of prior art, [453] it lacks novelty, regardless of whether it was independently developed from the earlier invention.[454] "Anticipation" is a conclusion as to the failure of the invention to meet the novelty requirement.[455] A claim is said to be "anticipated" by a prior art that identically discloses the claimed invention,[456] when the prior disclosure en-

450 *Bayer/Diastereomer*, T 12/81 OJ EPO 1982, 296, 301 (noting "[t]he purpose of Article 54(1) EPC is to prevent the state of the art being patented again."); *Dupont/Copolymer*, T 124/87, OJ EPO 1989, 491, 495; *Tilmann*, IIC 2010, 149, 151-152; *Seymore*, 60 Duke L. J., 919, 919, 931 (2011) (noting "novelty serves to safeguard the public's right to enjoy what it already possesses."); *Jacob*, IIC 1996, 170, 170 (noting this concept was described as a "golden thread" running through patent jurisprudence).

451 *Aronson v. Quick Point Pencil Co.,* 440 U.S. 257, 262 (1979); *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 148 (1989) (holding "[s]ections 102(a) and (b) operate in tandem to exclude from consideration for patent protection knowledge that is already available to the public.").

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

453 *Spenner*, 90 J. Pat. & Trademark Off. Soc'y, 477, 510 (2008). Prior arts cannot be combined to show the elements of the claimed invention.

454 *Mauer/Scotchmer*, 69 Economica 535, 535 (2002) (noting "patents differ from other forms of intellectual property in that independent invention is not a defense to infringement."); *cf. Diener/Shear*, T305/87, OJ EPO 1991, 419, 429 (holding it was not permissible to combine separate items belonging to different embodiments described in one and the same document (which was a catalogue) merely because they were disclosed in that one document, unless of course such combination had been specifically suggested there.).

455 *Chisum*, 15 AIPLA Q. J. 57, 58 (1987).

456 *Chisum*, 15 AIPLA Q. J. 57, 58 (1987).

ables the entire claimed invention in addition to disclosing each and every element of the invention.[457]

2. Examination of novelty

Assessing the novelty requirement may on the face of it appear fairly straightforward.[458] The sole test of novelty is the comparison between the invention and the whole knowledge from the prior art, and the invention will be determined as novel if there is a difference from the prior art.[459] However, the determination of novelty is not as simple as it sounds. Firstly, the determination involves multiple factors and is dominated by standards that apply to various elements as with the determination of other patentability requirements.[460] For example, to determine whether an invention is anticipated in an enabling manner, we should judge the level of ordinary skill of a person skilled in the art and the degree of experiments which would be regarded as "undue,"[461] In addition, to determine what is "undue," several factors must

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457 *Kieff/Schwartz/Newman*, 2011, 490-91; *See. e.g., Elan Pharmaceuticals., Inc. v. Mayo Foundation*, 346 F.3d 1051, 1054 (Fed. Cir. 2003) (holding a reference is enabled when its disclosures are sufficient to allow one of skill in the art to make and use the claimed invention, quoting *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001)); *See also Atlas Powder Co. v. Ireco, Inc.,* 190 F.3d 1342, 1346 (Fed. Cir. 1999) (holding that in order to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently, quoting *In re* Schreiber, 128 F.3d 1473 (Fed. Cir. 1997)); *RCA Corp. v. Applied Digital Data Systems, Inc.,* 730 F.2d 1440, 1444 (Fed. Cir. 1984) (noting "[a]nticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention."); *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 14 (noting if an earlier published document discloses the claimed invention and a person skilled in the art can perform the claimed invention when he tries to do so by using the matter disclosed in the earlier document and-or his common knowledge, the claim is anticipated by the earlier document.).

458 *Kieff*, 45 B. C. L. Rev., 55, 86-87 (2003); *Grubb/Thomsen*, 2010, 67.

459 *Dessemontet*, 1976, 195.

460 *Duffy*, 51 Wm. & Mary L. Rev. 609, 638-639 (2009).

461 *Duffy*, 51 Wm. & Mary L. Rev. 609, 638 (2009); *see also* Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed. Cir. 2000) (holding that anticipation requires describing every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation).

be determined.[462] To judge "inherent anticipation" – "[the invention] is inherently disclosed only if it is the natural result flowing from the explicit disclosure of the prior art" –[463] it should first be decided what is to be regarded as a "natural result."[464] Secondly, the determination of novelty also depends on the developmental status of inventions. The novelty requirement is usually easier to achieve for fundamental inventions (e.g. basic patents) than for improvement inventions[465] taking into consideration the accumulated amount of prior arts over time. Thirdly, the complexity of determining novelty varies according to the field of technology. Determining novelty is more straightforward in relatively predictable fields, like electrical or mechanical engineering; however, it is more difficult for chemical, biotechnological, or pharmaceutical inventions, which lie in unpredictable fields.[466] Considering these complexities, one may be surprised to learn that anticipation is a finding of fact "with which an appellate court should be reluctant to interfere."[467] Last but not least, the novelty requirement, including the level of enablement, depends on the jurisdiction and on the developmental status of law, as will be discussed in chapter IV.A.4.

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462 *See e.g.* MPEP§ 2164.01(a) (providing exemplary multi-factors to determine "undue" experiments as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure, quoting *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)).

463 *For details,* see subsection IV.A.3.

464 *Duffy*, 51 Wm. & Mary L. Rev. 609, 638 (2009); *See also Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (holding "a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from'' the explicit disclosure of the prior art.").

465 *See also Van Dijk*, 44 J. Ind. Econ. 151, 152-153 (1996); see the differences and difficulties in pharmaceutical art in subsection VI.E.2.b).

466 *Seymore*, 60 Duke L. J., 919, 933-936 (2011).

467 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 38; *Merck v. Teva Pharmaceuticals USA*, 347 F.3d 1367, 1369 (Fed. Cir. 2003) ("Anticipation is a question of fact, and after a bench trial is reviewed under the clearly erroneous standard"); *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006) (anticipation is a question of fact, including whether or not an element is inherent in the prior art and the prior art reference must disclose each and every feature of the claimed invention, either explicitly or inherently).

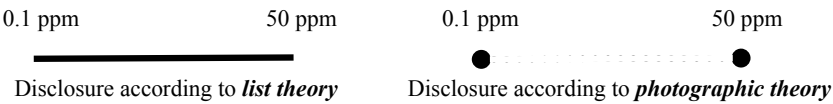
The construction of the concept and the assessment of novelty differ among patent offices. In Europe, an invention is considered new if it does not form part of the state of the art,[468] which comprises everything made available to the public before the critical date of patent filings.[469] To test this novelty, ***EPO***, representatively, uses a strict definition of the disclosure of a prior art, the so-called "*photographic novelty approach,*" as in T 12/81 through "*purposive selection*" as in T 198/84, which is contrary to "arbitrary selection."[470] Consider a range selection as an example: Although a range of value falls within the scope of a previously disclosed range, it could be found novel when the selected interval i) is narrower; ii) is sufficiently far removed from the preferred alternatives in the prior art; and iii) is not an arbitrary choice from the prior art but results in a better effect ("purposive selection").[471] This "non-arbitrary" but "purposive selection" can be found when only the selected range has some better properties, not over the whole known range, which in turn makes the selection a new invention.[472] The novelty will be denied only when a skilled artisan could have seriously contemplated the claimed invention by applying the technical teaching of the prior art in the overlapping range.[473] According to this approach, an implicit disclosure of an invention in the prior art may not be sufficient to deny the novelty thereof, which can allow some pieces of existing knowledge to be patented.[474] Some scholars have even warned that this kind of novelty requirement could be met just by cleverly drafting a patent application.[475]

Until the *Olanzapine* decision, the greatest discrepancy between the EPO's and the ***German*** interpretation of novelty was the one between this "photographic" theory and the "list" theory.[476] Germany had a typical interpretation for assessing the novelty of a selection invention - the so-called

468 EPC Art. 54(1); German Patent Act 2011 ("GPA") Section 3(1); UK Patents Act 1977 (as amended 2011, "UK Patents Act 1977"), Section 2(1).
469 EPC Art. 54(1); GPA Section 3(2); UK Patents Act 1977, Section 2(2).
470 *Weaver/Perakis/Riolo*, 15 World Pat. Info. 81, 83 (1993).
471 *Hoechst/Thiochloroformates*, T198/84, OJ EPO 1985, 209, 209; *see also Texaco/Novelty*, T279/89 (1991), point 4.1.
472 *Hoechst/Thiochloroformates*, T198/84, OJ EPO 1985, 209, 214, point 7.
473 *Unilever/Washing Composition,* T 666/89, OJ EPO 1993, 495, 503; *see also Toshiba/Thickness of Magnetic Layers*, T 26/85, OJ EPO 1990, 22, 22.
474 World Bank, 2003, 180.
475 *See e.g., Correa*, 2006, 3.
476 *Singer/Lunzer*, 1995, 54.15B.

"*Bruchhausen doctrine*".[477] The BGH held that, in the absence of any other indication, patent claims would lead a person skilled in the art to expect that the desired result can be achieved in all values within the specified range.[478] It further held that this was because, according to the rules of arithmetic, the indication of a quantitative range, e.g. 0.1-50 ppm, was a simplified representation of all conceivable intermediate values within the range.[479] In the *Inkrustierungsinhibitoren* case, where the disclosure of prior art was questioned, while explicitly disagreeing with the EPO's jurisprudence, the BGH confirmed that, since the indication of a quantitative range was a simplified representation of the continuous intermediate value, all intermediate values were as a rule to be regarded as disclosed.[480] The range of disclosure according to these two theories can be well understood by the following diagram, and the same principle was applied to selection inventions:

Figure 6: The scope of disclosure of "0.1-50 ppm" according to both theories[481]



The ***British*** novelty test, which is referred to as the "*clear and unmistakable direction test"*, is set out in the *General Tire v. Firestone* case[482] as follows: A claim is regarded as anticipated either if the prior art included a clear disclosure to do something that would infringe the patentee's claim, or if following the direction provided by the prior art would result inevitably in something that would fall within the patentee's claim.[483] Lord Hoffman affirmed that when a prior art disclosing the subject matter that would unavoidably have infringed the patent if it performed after granting the patent,

477 *Singer/Lunzer*, 1995, 54.15B.
478 *BGH/Crackkatalysator (Cracking catalyst)*, GRUR 1990, 510, 512.
479 *BGH/Crackkatalysator (Cracking catalyst)*, GRUR 1990, 510, 512.
480 *BGH/Inkrustierungsinhibitoren (Incrustration inhibitors)*, GRUR 2000, 591, 593-94.
481 This figure is prepared by the author on the basis of *Hansen/Hirsch*, 1997, 141.
482 *General Tire v. Firestone* [1972] RPC 457.
483 *General Tire v. Firestone* [1972] RPC 457, 485-86.

this prior art anticipated the later claimed invention.[484] Further, since whether a person is working or not an invention is an objective fact, the person's awareness of what he is doing does not matter.[485] However, as the House of Lords acknowledged, there is one exception to this test, i.e. an act performed secretly or without knowledge of the relevant facts, even if it would amount to infringements afterwards, will not anticipate the invention before.[486]

In the ***United States***, even though the law regarding novelty is more complicated,[487] basically, novelty is destroyed by a previous disclosure, a prior use, or other forms of public communication. As Learned Hand J stated, "a prior art patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated." [488] In ***Korea***, the invention should be considered as novel, unless it is (i) an invention publicly known or worked in the Republic of Korea or a foreign country or (ii) an invention described in a publication distributed in the Republic of Korea or a foreign country, or iii) an invention publicly available through certain telecommunication lines before the filing date of the patent application.[489]

In the case of a compound invention, the ability to produce the compound in question is the common basic requirement in many jurisdictions, i.e., the novelty-destroying prior art must enable the compound. However, if all elements of the claimed invention are disclosed in a single reference, other references as common knowledge might be used to show that the claimed

484 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, paras 22-24.
485 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 22.
486 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, para 29 (noting there is a gap between the tests for infringement and anticipation after the 1977 Act.).
487 35 U.S.C. (2007) § 102 and 35 U.S.C. (2011) § 102.
488 *Dewey & Almy Chemical Co v. Mimex Co.*, 124 F.2d 986, 989 (2nd Cir. 1942) (further holding "[i]f the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation.").
489 Korean Patent Act, Art. 29 (1).

invention is enabled.[490] In any event, it is unclear what is common knowledge and what is simply another publication.[491]

3. Inherent anticipation and enablement

> "It would certainly not be absurd to say that no one can obtain a claim that literally covers an item described in a prior art reference even if a method of making the described item was not disclosed or known in the art. In such a situation, it can be argued that a person who later invents a method of making that item is entitled to no more than that - a process claim to the method of making. Nevertheless, the contrary view that a prior art publication or a patent must be enabling in order to constitute an anticipation is the prevailing one today."[492]

The basic novelty question is whether the public already "possesses" the invention,[493] and the question of possession matters more when inherent anticipation is to be determined, which is more diverse from one jurisdiction to another. To constitute an anticipation of an invention, a description in a prior art must be sufficient to place the invention in the possession of the public, i.e. it must be *enabling*.[494] Namely, a prior art disclosure must enable the invention either explicitly or inherently, such that the person skilled in the art could practice the invention without undue experimentation.[495] The House of Lords reformulated the novelty test in the *General Tire* case with-

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490 *See e.g. In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) (noting "even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. […]It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.); *See also, In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973) (noting "[e]very patent application and reference relies to some extent upon knowledge of persons skilled in the art to complement that disclosed in order that it be "enabling" within the meaning of § 112 and to satisfy the requirements of a reference under § 102. […] In closer cases, where it might be reasonably doubted that a reference or patent application satisfies § 102 or § 112, other references can be cited as evidence of the level of skill in the art.").

491 *Grubb/Thomsen*, 2010, 67.

492 *Chisum*, 15 AIPLA Q. J. 57, 59-59 (1987).

493 *Seymore*, 60 Duke L. J., 919, 929 (2011).

494 *Holbrook*, 59 SMU L. Rev. 123, 151 (2006); *Chisum*, 15 AIPLA Q. J. 57, 61 (1987).

495 *See Kieff/Schwartz/Newman*, 2011, 174-75, 182-83; *see also Smithkline Beecham Corporation v. Apotex Corp.,* 403 F.3d 1328, 1329-30 (Fed. Cir. 2005); *see* also *In re* Brown, 329 F.2d 1006, 1011 (C.C.P.A. 1964).

out significant change, and confirmed that anticipation had two requirements, prior disclosure and enablement,[496] and that the requirement of each was distinct from the other.[497] Similarly, in the United States, this enablement requirement in the context of anticipation has been consistently affirmed.[498]

Under ***EPO*** practice, assessing novelty requires determining not what may have been "inherent" in what was made available, but what was "made available" to the public, for example, by a written description or by a prior use.[499] A hidden or secret use is not a ground for rejection.[500] Since these secret prior uses do not make the invention available to the public, it seems that there is no such thing as an inherent lack of novelty[501] before the EPO. This approach was followed by the House of the Lord in a metabolite case, i.e. *Merrell Dow Pharmaceuticals v. HN Norton*.[502] ***In the United Kingdom***, since an invention is a piece of information and making it available to the public requires the communication of information, for an invention to be anticipated by prior use, the use must have made the necessary information available.[503] Thus, acts performed secretly or without the knowledge of the relevant facts, even if they would amount to infringements, will not anticipate the invention.[504] On the other hand, if the procedure in the prior art that inevitably produces the substance is part of the prior art, so is the substance made by the procedure.[505]

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496 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 19.
497 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, paras 28-33.
498 *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1083-85 (Fed. Cir. 2008).
499 *Mobil Oil/Friction Reducing Additives, G2/88,* OJ EPO 1990, 93, 111.
500 *Mobil Oil/Friction Reducing Additives, G2/88,* OJ EPO 1990, 93, 111; *Bayer/Plant growth regulating agent*, G 6/88, OJ EPO 1990, 114, 123.
501 *Grubb/Thomsen*, 2010, 248; *CPC/Flavour concentrates*, T 303/86 (1988), para 2.1. (Once the technical Board of Appeal held it was sufficient to destroy the novelty of the claimed process, when the claimed process and the process in the prior art were identical with respect to starting materials and reaction conditions, since processes identical in these features must inevitably yield identical products.).
502 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14.
503 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, para 28.
504 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, para 29.
505 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, para 44.

In the United States, a prior art may be anticipating despite being silent about a feature of the claimed invention when that missing descriptive matter was necessarily present or inherent in the single prior art.[506] A prior art includes the inherent feature when it is the "natural result" flowing from the explicit disclosure of that prior art.[507] This inherent feature of a prior art reference does not need to be perceived as such by a person skilled in the art at the time of invention.[508] A secret or confidential use of an invention could give rise to the public use bar.[509] For instance, a product constitutes prior art although the knowledge needed to produce the product was not publicly available. Such a product is called a "non-informing" product.[510] In the *Metallizing Engineering* case, the patentee used a secret process to recondition worn metal parts for its customers before the critical date of the relevant patent application, and this fact rendered the patent invalid.[511] The principle underlying this doctrine of inherent anticipation is to ensure that the public remains free to exploit the invention, regardless of whether they understand its makeup sufficiently to allow them to operate.[512] The Federal Circuit in *Atlas Powder v. Ireco* held as follows:

> "Anticipation of a patent claim requires a finding that the claim at issue 'reads on' a prior art reference. In other words, if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art."[513]

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506 *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

507 *In re Kratz*, 592 F.2d 1169, 1174 (C.C.P.A. 1979); *Eli Lilly & Co. v. Barr Labs.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

508 *Atlas Powder Co. v. Ireco, Inc.,* 190 F.3d 1342, 1348-49 (Fed. Cir. 1999); *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1378 (Fed. Cir. 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1321 (Fed. Cir. 2004) (holding "the fact that a characteristic is a necessary feature or result of a prior-art embodiment […] is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

509 35 U.S.C. § 102(b); *see, e.g., Metallizing Engineering Co. v. Kenyon Bearing & Auto Parts Co.*, 153 F.2d 516 (2nd Cir, 1946).

510 *Merges/Duffy*, 2011, 395-96.

511 *Metallizing Engineering Co. v. Kenyon Bearing & Auto Parts Co.*, 153 F.2d 516 (2nd Cir, 1946).

512 *Atlas Powder Co. v. Ireco, Inc.,* 190 F.3d 1342, 1348 (Fed. Cir. 1999).

513 *Atlas Powder Co. v. Ireco, Inc.,* 190 F.3d 1342, 1346 (Fed. Cir. 1999).

In Korea, anticipation is not a concept which appears in the determination of novelty of inventions.

4. Novelty of selection inventions

"Selection" is an act of selecting or rejecting one or more things. In other words, the selected item has already existed before, or at least at the time of selection. This initiates the whole discussion on the novelty of selection inventions.

a) Species selection inventions

A single prior art disclosing a species within a patent's claimed genus reads on the generic claim; thus, the species prior art anticipates the genus claim.[514] Therefore, to acquire a patent, an applicant must limit the claim to an extent which does not overlap with the prior art disclosure of species. A genus prior art, however, does not stop the applicant from filing a selection patent to claim species with certain useful properties.[515] As long as no member of the narrow subgroup is *specifically* disclosed in the publication, the compounds in the subgroup are considered novel, though they may have been described in general terms.[516] Therefore, although the species invention was disclosed in the prior genus invention, a patent on the species invention

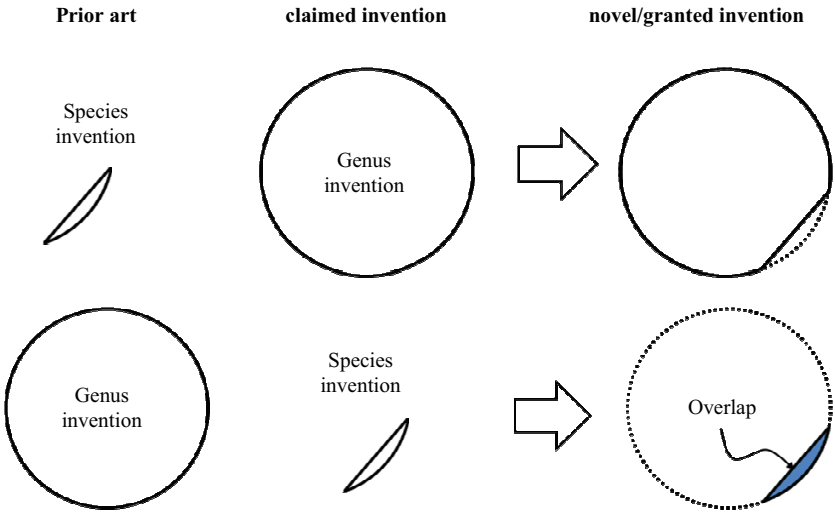
514 *Atlas Powder Co. v. Ireco, Inc.,* 190 F.3d 1342, 1346 (Fed. Cir. 1999) (holding it is also true for the range selection inventions); *see also Titanium Metals Corp. v. Banner*, 778 F.2d 775, 783, 782 (Fed. Cir. 1985) (holding "a claim covers several compositions, the claim is 'anticipated' if one of them is in the prior art.").

515 *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003), *cert. granted*, 545 U.S. 193 (2005).

516 *Robinson*, IIC 1972, 139, 143 (noting "[t]he selected group is regarded as novel because the disclosure, by generalization from a few specific investigated products, of a general class, comprising hundreds or thousands or even millions of members, cannot be considered a disclosure specifically of each member of that class."); *Grubb/Thomsen*, 2010, 64; *Chisum*, 2012, § 3.02[2][b]; *Metabolite Laboratories, Inc. v. Laboratory Corporation of America Holdings*, 370 F.3d 1354, 1367-68 (Fed. Cir. 2004) (holding that a prior art reference that discloses a genus still does not inherently disclose all species within that broad category); *See also Meier-Beck*, GRUR 2009, 893, 895.

can be granted. Thus, there can be overlapping scope of patents between a prior genus patent and a species patent. See Figure 7.

Figure 7: Genus v. species invention[517]



In the EPO

The teaching of a prior art is not confined to the detailed information given in the examples of how the invention is carried out, but embraces any information in the claims and description enabling a person skilled in the art to carry out the invention.[518] However, a generic disclosure does not generally deprive specific compounds of novelty.

The BOA distinguished between the following two situations; (i) if the subject matter of a claimed invention is a second family of compounds that

517 This figure is prepared by the author.

518 *Bayer/Diastereomer*, T 12/81 OJ EPO 1982, 296, 301 (holding the disclosure of the starting substance and the reaction process is always prejudicial to novelty because those data inevitably establish the end product, however, if two classes of starting substances are required to prepare the end products and examples of individual entities in each class are given in two lists of some length, then the resultant from the reaction of a specific pair from the two lists can nevertheless be regarded as new.).

partially covered the first class in the prior art, the invention is not new;[519] and (ii) if the subject matter is a defined compound, whereas the prior art discloses a family of compound defined only by a general formula covering the defined compound but not describing it explicitly, the invention must be considered novel.[520]

The former is the case where the invention was not found novel when a major part of the previously disclosed class was claimed. In T 133/92, the prior art was a product patent where part of the structural formula was an alkyl between 1 and 20 carbon atoms, and preferably the alkyl group was alkyls with between 6 and 15 carbon atoms (C_6-C_{15} *alkyl group*).[521] The application in suit claimed alkyl groups with between 6 and 10 carbon atoms (C_6-C_{10} *alkyl group*), which totally fell within the scope of the earlier patent, but no part of the compounds had been explicitly disclosed in the earlier patent. Though the Board noted an improved effect within the selected area, since the selection comprised almost half of the generic disclosure, the selection lacked novelty.[522] The Board further found that the selection of the alkyl groups between 6 and 8 carbon atoms (C_6-C_8 *alkyl group*) was not novel, but the selection of five specific examples (*n-hexyl, n-octyl, 2-ethylhexyl, 3,5,5-trimethylhexyl or n-decyl group*) was narrow enough and novel.[523] The Board reiterated the EPO's position as follows:

> "[A] distinction must be drawn between the novelty of a group of compounds defined by a general formula, and the novelty of particular individual compounds, because of the concept of individualisation which only applies to the structural definition of a single compound […]."[524]

It is not clear from this decision, however, if the five compounds had been defined in a general formula, whether the same selection would have been found to lack novelty. This would barely be reasonable. Meanwhile, it is assumed that in the case where the selection was made from relatively small numbers of a group disclosed in the prior art, it would be more problematic

519 *Dupont/Copolymer*, T 124/87, OJ EPO 1989. 491, 497.

520 *Draco/Xanthines*, T 7/86, OJ EPO 1988, 381, 385 (holding the novelty was in question in the case a prior document disclosed a class of compounds and the claimed invention was concerned with the selection of a class of compounds, not the specific individual compounds).

521 *AKZO/Bleaching activators*, T 133/92, 1994, point 4.2.2.

522 *AKZO/Bleaching activators*, T 133/92, 1994, point 2.1.3.

523 *AKZO/Bleaching activators*, T 133/92, 1994, point 2.1.3.

524 *AKZO/Bleaching activators*, T 133/92, 1994, point 4.2.2.

to establish the novelty thereof; thus, the general disclosure might be regarded as the disclosure of each member.[525]

Other than the relative size of the selection, the distinction between the disclosure of a generic formula and that of individual substances in prior art seems to be a separate criteria and to have taken root within the EPO case law to assess novelty.[526] In T181/82, it was held that, when the products of the reaction of specific compounds with a 'C_{1-4} alkyl bromide' was disclosed, a product as a result of the reaction with C_1 alkyl bromide is the only lack of novelty. This was because, among eight alkyl bromides,[527] only methyl bromide was disclosed, since C_1 was mentioned as the lower end of the range and was only the methyl.[528] This decision was interpreted in the later decision[529] as holding that only methyl bromide was disclosed in an individualized form, and that no special alkyl group with more than two carbon atoms was disclosed, and that the four individual groups comprised in the upper basic value (C_4) were disclosed only as a generic term.[530]

In Germany

The patentability of a "selection invention" was widely debated in Germany, especially right after the prohibition against product protection was repealed

525 *Grubb/Thomsen*, 2010, 234; cf. *Vivian*, IIC 1989, 303, 306 (noting the size of genus itself is normally not decisive as to the question of anticipation regardless of whether the selection was one from a class of 10 million or one from a class of two.).

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

527 C1-C4 alkyls are 8 alkyls as follows: C1 alkyl is methyl; C2 alkyl is ethyl; two C3 alkyls are n-propyl and isopropyl; and four C4 alkyls are n-butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

528 *Ciba-Geigy/Spiro compounds,* T 181/82, OJ EPO 401 (1984).

529 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206.

530 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206; *see also PFIZER/Penem Derivatives*, T 1048/92, point 2.1.

as of January 1, 1968.[531] In the *Fluoran* decision, the BGH held that a Markush claim disclosure in the prior art would be enough to be a novelty-destroying reference of a selection invention and to be regarded as disclosing an individual species, when a person skilled in the art was able to implement the invention on the basis of the indications given regarding the contested compound of the prior art publication.[532] It further held that "[t]he fact that a chemical compound falls within a previously published formula says nothing about the question of novelty […]. The only decisive factor is whether the information contained in a previous publication alone enables a person skilled in the art to make the invention relating to this chemical compound, i.e. to produce the substance in question."[533] Thus, the compounds were not novel, because a person skilled in the art could have worked the invention. After this decision, it was very difficult to get patents for selection inventions until the *Olanzapine* decision in late 2008.

In the *Olanzapine* case, the BGH held that all compounds embraced by a generic formula would not automatically be regarded as individually disclosed.[534] Lilly's patent in suit[535] was on a single chemical compound "olanzapine."[536] One of the most relevant prior arts was a patent document that was also filed by Lilly and that was acknowledged in the very patent specification.[537] This patent document disclosed a general formula covering theoretically millions of individual compounds, identified around 100 com-

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531 *Katzenberger*, IIC 1972, 357, 364-365 (providing arguments against granting selection patent such as, i) anticipatory prior art effect of the patent covering that group of compounds and ii) prohibition against double patenting; and arguments for selection patent such as, discovery of a new and valuable compound from a group of compounds valued as much as discovering a new group of compounds.); *see also Schmied-Kowarzik*, IIC 1970, 190, 196 (arguing selection inventions must be able to obtain an absolute product protection); *see also Nastelski*, IIC 1972, 267, 291-294 (especially arguing selection patent shouldn't be deemed to be novel, even if the products have not been individually designated, "if the producibility of an appropriate variety and number of individual representatives of the group is experimentally proven so that in accordance with the decision the manufacture or existence of the remaining products belonging to the group has also been substantiated for the skilled artisan"); *see also Vossius*, GRUR 1976, 165, 171.

532 *BGH/Fluoran*, GRUR 1988, 447.

533 *BGH/Fluoran*, GRUR 1988, 447, 449.

534 *BGH/Olanzapine*, IIC 2009, 596.

535 EP 0,454,436, US 5,229,382.

536 a widely prescribed anti-psychotic agent used for the treatment of schizophrenia.

537 GB 1,533,235.

pounds by name, but did not disclose olanzapine specifically. Another prior art ("Chakrabarti" article)[538] document disclosed the Structure-Activity-Relationship[539] observations of a group of compounds and several compounds closely structured to olanzapine, but did not disclose olanzapine. The questions at issue were the effect of a particular kind of disclosure, namely, a "Markush" formula, the consideration of structural similarity of compounds, and whether a person skilled in the art could have modified or supplemented the prior art's teaching to determine the disclosure of prior art.

The Federal Patent Court of Germany ("BPatG") held that, since a skilled person would be able to obtain all necessary information[540] to manufacture olanzapine from *Chakrabarti* prior art, it was a novelty-destroying disclosure of olanzapine.[541] In contrast to this ruling, the BGH held that it was not necessary to determine in what form a person skilled in the art could perform a certain general teaching, using his technical knowledge, or how he can modify this teaching, if necessary.[542] The important point was exclusively what a person skilled in the art derived from the prior publication as the content of the specific (general) teaching.[543] The BGH went on to say that the decisive question was rather what can be "*directly and unambiguously*" derived from a document, from the point of view of a person skilled in the art, which was in line with the jurisprudence of the BOA of the EPO.[544]

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538 *Chakrabarti, et al.*, 28 J. Med. Chem. 874 (1980).

539 This is the relationship between the chemical 2D or 3D structure of a molecule and its biological activity. This analysis enables to determine the chemical groups responsible for a target biological effect. This in turn makes modification of the effect or potency of the medication by changing its chemical structure. The chemists uses this relations ship to insert or delete some chemical groups into/from the compound and test the modification, and finally modify its biological effect.

540 The court illustrated this information as follows: lead structure of formula I, a group of only 12 compounds, 3 specific compounds immediately "neighboring" olanzapine, neuroleptic activity of compounds which is useful for treating diseases such as schizophrenia.

541 *Barth/Zimmer*, 27 Biotechnol. Law Rep. 532, 532-533 (2008).

542 *BGH/Olanzapine*, IIC 2009, 596, 599.

543 *BGH/Olanzapine,* IIC 2009, 596, 599.

544 *BGH/Olanzapine,* IIC 2009*,* 596, 599; The Federal Court of Justice cited the relevant BOA decision as follows: *Bayer/Diastereomer*, OJ EPO 1982, 296; *Ciba-Geigy/Spiro compounds,* T 181/82, OJ EPO 1984, 401, 411; *Draco/Xanthines*, T 7/86, OJ EPO 1988, 381, 38; *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206-207; *Hoechst/Diastereomers of 3-cephem-4-carboxylic acid-1-(isopropoxy-carbonyloxy) ethyl ester*, T 940/98 (2003); *See also Meier-Beck*, GRUR 893, 895 (2009); *Grubb/Thomsen*, 2010, 64.

The BGH held that the determination of what was not explicitly mentioned in the characteristics of the claim, and in the text of the specification, but was obvious for a person skilled in the art to implement the teaching being protected and therefore did not require any special disclosure, was not aimed at supplementing the disclosure with the technical knowledge.[545] The purpose was not different from determining the meaning of a claim, i.e. the technical information that a person skilled in the art derives from the source with the background of his technical knowledge.[546] Citing the *Elektrische Steckverbindung* decision,[547] the BGH held that modifications would be allowable only if the modifications were so obvious to a person skilled in the art in the entire content of the document that they were easily evident when reading the document attentively, paying attention less to the words than to their meaning, so that he essentially "*reads them along"* in his thoughts.[548]

The BGH then applied this principle to the chemical compound invention as follows: "The decisive factor is whether the concrete compound is disclosed or not, and for this purpose, information that easily enables a person skilled in the art to specifically implement the invention relating to this chemical compound, i.e. to obtain the specific substance, is required."[549] The BGH clarified its position against the *Fluoran* decision by explaining that the *Fluoran* case was decided under the Patent Act of 1968 and that the Court did not adhere to this decision for the current law. The BGH held further that an individual compound that was not explicitly disclosed could only be considered to have been disclosed if a person skilled in the art "read it along" in the sense of the *Elektrische Steckverbindung* decision, for example, because it was familiar to him as the usual implementation of the stated general formula and therefore occurred to him as also having been meant when he read the general formula.[550] Otherwise, the disclosure of the individual compound was necessary to destroy novelty.[551]

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545 *BGH/Olanzapine,* IIC 2009, 596, 599.
546 *BGH/Olanzapine,* IIC 2009, 596, 599.
547 *BGH/Elektrische Steckverbindung (Electronic Plug-in connection)*, GRUR 1995, 330.
548 *BGH/Olanzapine,* IIC 2009, 596, 599.
549 *BGH/Olanzapine,* IIC 2009, 596, 600.
550 *BGH/Olanzapine,* IIC 2009, 596, 600.
551 *BGH/Olanzapine,* IIC 2009, 596, 600.

In the United Kingdom

Species selection inventions have been patentable for many decades following a specific rule for these kinds of inventions established by Maugham J in the *I.G. Farbenindustrie's A.G.'s Patent* case ("*IG Rule*"). [552] The *IG Rule* stated the following three traditional requirements: i) a selection patent to be valid must be based on some substantial advantage to be secured by the use of the selected members (the phrase will be understood to include the case of a substantial disadvantage to be thereby avoided); ii) the whole of the selected members must possess the advantage in question; and iii) the selection must be in respect of a quality of a special character that can fairly be said to be peculiar to the selected group.[553] Although the second requirement was criticized as impractical, it was well followed in the United Kingdom in other cases, without distinguishing between novelty and inventive step.[554]

Jacob LJ declared the end of the IG Rule's life in the *Olanzapine* decision.[555] In his opinion, Jacob LJ firmly rejected the argument that "every chemical class disclosure discloses each and every member of the class" for two reasons: i) being an *a priori* consideration and ii) not being consistent with the jurisprudence of the BOA of the EPO, particularly the *Hoechst/ Enantiomers* decision.[556] He reiterated that "an anticipation is an 'individualized description' of the later claimed compound or class of compounds."[557] With respect to the *a priori* consideration, he argued as follows:

> "An old question and answer runs as a[sic] follows: 'Where does a wise man hide a leaf? In a forest.' It is, at least faintly, ridiculous to say that a particular leaf has been made available to you by telling you that it is in Sherwood Forest.

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552 *I.G. Farbenindustrie's AG's Patent* 47 R.P.C. 289, 322-3 (1930); *see also Blanco White,* 1983, 105-106.

553 *I.G. Farbenindustrie's AG's Patent* 47 R.P.C. 289, 322-3 (1930); *see also Blanco White,* 1983, 105-106.

554 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, paras 36-39.

555 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, para 37 (holding that the IG rule was just "a part of legal history," but not part of the living law (post-1977 law)); *See also* Manual of Patent Practice - UK Patents Act 1977, paragraph 3.89-3.90 (October 2012).

556 *Hoechst/ Enantiomers,* T296/87, OJ EPO 1990, 195.

557 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, para 30.

> Once identified, you can of course see it. But if not identified you know only the generality: that Sherwood Forest has millions of leaves." [558]

Jacob LJ noted that the "selection invention" rule of *I.G. Farbenindustrie's Patent* was developed to avoid a finding of anticipation, it did not draw a distinction between lack of novelty and obviousness, and it was too strict, because it is difficult to show that a group (compound) has a "substantial advantage" over the whole prior class without an enormous range of experiments.[559] Lord Neuberger noted that this issue was "not dissimilar from the enantiomer/racemate issue"[560] and recognized the difficulty in the application of the *IG Rule*, where the prior class of compounds was very large.[561] Consequently, when the invention can be found novel in the first place, there is no longer any need to consider whether it is a valid selection invention according to the *IG Rule*.[562]

In the United States

Unlike other jurisdictions, the U.S. American ("American") patent law does not use the term "selection inventions" as a category of invention. Instead, the terms "genus" and "species" are often used in practice, though not as a statutory category, and a significant body of case law has evolved.

In *In re Petering*,[563] the Court held that a prior art reference disclosing a limited genus of twenty compounds rendered every species within the genus unpatentable. The Court pointed out that the significance was not in the mere

558 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, paras 25-30. This argument was in line with the separate judgment of Neuberger L. *see* para 108.

559 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, paras 36-39.

560 *Generics Ltd. v. Lundbeck* [2009] UKHL 12.

561 *Generics Ltd. v. Lundbeck* [2009] UKHL 12, paras 103-104.

562 *See e.g., Fitt*, 20 Biotechnol. Law Rep. 17, 18 (2010).

563 *In re* Petering, 301 F.2d 681 (C.C.P.A. 1962).

number of compounds in the prior document,[564] but in the total circumstances, including the limited number of variations for R, only two alternatives for Y and Z, and a large unchanging patent structural nucleus.[565] The Court further held that, on reading the prior publication, a person skilled in the art would "envisage each member of" the genus and that "it is no moment that each compound is not specifically named or shown by structural formula in that publication."[566] In *In re Schaumann*, in which the prior art disclosure taught only fourteen possible compounds,[567] the Court held that, when a prior art disclosure embraced "a very limited number of compounds," it would inevitably be concluded that "the reference provides a description of those compounds just as surely as if they were identified in the reference by name." [568] In *Bristol-Myers Squibb v. Ben Venue Laboratories*, the Federal Circuit also noted that "the disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited."[569] Thus, when the genus embraces a limited number of compounds, the individual

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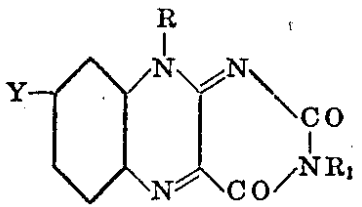
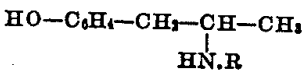
564 U.S. Patent No. 2,155,555 (April 25, 1939, under the title of "Iso-alloxazine derivatives and process for the manufacture of same"), and the generic formula was as follows:



565 *In re* Petering, 301 F.2d 681, 681-82 (C.C.P.A. 1962).

566 *In re* Petering, 301 F.2d 681, 682 (C.C.P.A. 1962).

567 *In re* Schaumann, 572 F.2d 312, 314 (C.C.P.A.1987); the prior patent was U.S. Patent No. 2,344,356 (March 14, 1944, under the title of "Chemical compounds beta-(meta-hydroxyphenol)-isopropylamines") and the disclosed generic formula with single variable (R) was read as:



568 *In re* Schaumann, 572 F.2d 312, 316-17 (C.C.P.A.1987).

569 *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001).

description does not seem to be necessary to destroy the novelty of a species invention.[570]

In the *Olanzapine* decision, the defendants argued that the Chakrabarti article anticipated the patent in view of the holdings in *In re Petering* and *In re Schaumann*. However, in his opinion, Rader J distinguished the *Olanzapine* case, where the Chakrabarti article disclosed millions of compounds, from these two cases, because limited numbers of specific preferences, namely "some 20 compounds," or "14 compounds" were disclosed, respectively. He reiterated that, "[t]o anticipate, a prior art reference must place the inventive compound or composition in the possession of the public. Thus, the prior art reference must disclose each and every feature of the claimed invention, either explicitly or inherently."[571] He then noted that the Chakrabarti patent document had not "expressly spelled out a definite and limited class of compounds that enabled a person of ordinary skill in the art to at once envisage each member of this limited class."[572] Rader J also stated that "one would have to depart from the teaching of the article and recombine the components of the specific illustrative compounds *with hindsight"* to make the olanzapine starting from another prior art disclosing structure and activity relationship.[573]

In Korea

As it is reiterated by the Korean Patent Court in the Olanzapine case,[574] it is established case law that, to deny the novelty of selection invention, the prior art document should specifically disclose the concept of a selection invention, and it could also be that a person skilled in the art could directly learn the existence of the selection invention from the prior document based on

570 *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1262 (Fed. Cir. 1989) (rejecting once the argument "a claim to a genus would inherently disclose all species" as wholly meritless).

571 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006).

572 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006). In fact, this was the first decision among four jurisdictions which upheld the validity of Olanzapine patent.

573 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc*., 471 F.3d 1369, 1377 (Fed. Cir. 2006).

574 *Korean Patent Court/Olanzapine*, 2010Heo371, Nov. 11, 2010.

the disclosure thereof and on common knowledge at the time of application.[575]

In this case, the Korean Patent Court held the novelty of selection invention was not denied, since (i) olanzapine was not specifically disclosed in the prior art references, (ii) though olanzapine was included in the preferred compound groups, the number of compounds comprised in the preferred compound groups was too large for a skilled person to directly learn the existence of Olanzapine, and (iii) there was no indication in the prior art for a skilled person to directly recognize olanzapine.[576]

b) Optical isomers

It seems that the narrower the selection is made with regard to the generic term, the more likely the selection can be deemed novel. What, then, if one is selected out of two? Indeed, the optically active form of a racemate can be considered an extreme example of selection inventions, and it has been arg ued that this invention cannot be novel if the racemate is known, since the racemate can be considered an equimolar mixture of each enantiomer.[577] More generally, the enantiomer invention is about a substantially or totally pure compound that is not contaminated by other possible stereoisomers.[578]

In the EPO

In the early decision on the novelty of optical isomers, the Board stated that "[a] substance selection can come about in various ways, e.g. if an unmentioned compound or group of compounds having formula covered by the state of the art is found, in the absence of any information as to the starting substance or substances."[579] Namely, a specific compound covered by a generic formula of the prior art will be novel if the prior art does not provide any specific information, given in the examples of how the invention was carried out, but embraces any information in the claims and the description

575 *Korean Patent Court/Olanzapine*, 2010Heo371, Nov. 11, 2010, para 3.Ka.
576 *Korean Patent Court/Olanzapine*, 2010Heo371, Nov. 11, 2010, para 3.Na.2).
577 *Grubb/Thomsen*, 2010, 236.
578 *Eli Lilly/Enantiomer*, T 600/95 (1996), point 3.2.
579 *Bayer/Diastereomer*, T 12/81 OJ EPO 1982, 296, 303.

enabling a person skilled in the art to carry out the invention.[580] Afterwards, it was often confirmed by the Boards that the conceptual disclosure of two possible configurations without any pointer to the individual member was insufficient for the novelty to be denied.[581]

In T 296/87, in which the claimed invention was a mixture containing 80% of D-enantiomer, and the prior art made no mention of enantiomers and indicated only a chemical substance with an asymmetric carbon atom, i.e. the racemate, the Board presented the "photographic approach" to test the novelty in the enantiomer invention and held as follows:

> "The novelty of the D- and L-enantiomers is therefore not destroyed by the description of racemates. The situation is different if the state of the art includes enantiomers – however designated (D, d, L, l or + or -) – which are specifically named and can be produced. […] the only technical teachings prejudicial to novelty are those which disclose a substance as the inevitable result of a prescribed method or in specific, i.e. individualized, form."[582]

This decision demonstrates that novelty was already established when a choice between two possibilities was made. The Board further held that the configuration of one enantiomer was different from the racemate, and the fact that the prior art disclosed only racemates in detail did not disclose the enantiomer's specific configurations.[583] However, it is the context of basic organic chemistry, and once a person skilled in the art sees the chemical structure having chiral carbons, he will automatically know the special configuration of each enantiomers.

In addition, before the EPO, it seems that, even though a skilled person could have successfully separated the racemate into the enantiomers with the help of general knowledge, the claimed enantiomer would be regarded as novel over the previously disclosed racemate. This can be seen in the following paragraph of the decision:

> "In taking this view the Board is aware that the two enantiomers, far from falling merely intellectually within the definition of the structure in question, actually

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580 *Bayer/Diastereomer*, T 12/81 OJ EPO 1982, 296, 303 (The Board, however, did not acknowledge the novelty of a compound because it would have been inevitably produced according to the disclosed method and the starting materials).

581 *Pfizer/Penem Derivatives,* T1048/92 (1994), point 2.5; *see also ZENECA/Enantiomer*, T1046/97 (1999), point 2.1.1.6. (held optically-active form in the prior art provides no information about any specific stereochemical form(s) of the chemical compound.).

582 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206-207.

583 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990,195, 195.

> exist unseparated in the racemate. Generally, the latter can also be separated by converting the enantiomers into a mixture of diastereomers, e.g. using optically active substances, then resolving the mixture and recovering the enantiomers from the resulting products. These considerations are immaterial to the question of novelty, however, and will be more usefully applied to the examination as to inventive step."[584]

Furthermore, an enantiomer was found novel despite the prior patent holder's attempt to include all individual isomers and all mixtures. [585] Namely, even a disclosure conveying the previous patentee's desire to cover all possible isomers does not destroy the novelty of a later selection of an isomer, if the previous patent did not disclose the specific isomers.

To sum up, it is EPO's consistent jurisprudence that, unless the prior art contains both an individualized disclosure and a particular method and starting materials that will inevitably lead to the claimed compound, this kind of a chemical selection will be found novel over the racemate disclosed in the prior art.[586]

In Germany

In its early decision, where the patentability of an epimer[587] over the prior art description of the presence of an asymmetric carbon atom of the compound was issued, the BGH held that "[a] chemical compound is no longer novel if it is identified in a previous publication as a chemical individual and a skilled person was able to produce [it]. It is insignificant whether the compound had actually already been manufactured."[588]

A case was decided in 2007, in which the patent in issue claimed an enantiomer of atorvastatin[589] over the prior patent disclosing structure of atorvastatin with the wedges and dashes.[590] Referring to *Elektrische Steckver-*

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584 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990,195, 207.

585 *Pfizer/Penem Derivatives,* T1048/92 (1994), points 2.3-2.5. (holding "as will be appreciated, various optically active isomers of the new compounds are possible. ***The present invention embraces such optically active isomers and mixtures thereof***."[Emphasis added]).

586 *E.g.*, *Eli Lilly/Enantiomer*, T 600/95 (1996) (holding one isomer is not novel over the prior art description of the very isomer and of the method to obtain it).

587 See *supra* 115 .

588 *BGH/ α-aminobenzylpenicillin,* GRUR 1978, 696, 698.

589 Atorvastatin is the active ingredient of an anti-cholesterol drug sold under the brand name Lipitor® which was the best selling drug in the world.

590 *BPatG/Atorvastatin*, Beck-Rechtsprechung ("BeckRS") 2007, 18183.

bindung and *Schmierfettzusammensetzung*,[591] the BPatG held that, according to the jurisprudence of the BGH, the disclosure of a document belonging to the prior art was not limited to the literal description, but encompassed everything that the skilled person supplemented self-evidently or nearly essentially, or that he recognized directly with his careful study of the document and read along in thoughts.[592] The Court further held that

> "These principles which refer to the disclosure content of a prior publication in the field of mechanics are applicable in the field of chemistry, provided that a chemical compound is viewed as prejudicial to novelty, when a prior publication or a document with earlier priority date conveys to the skilled person a concrete indication to the compound in question, that is that a skilled person easily reads this compound in his thoughts and because of this indication he is directly put in the position of laying his hands on the compound in question. It is not necessary to that the compound has actually already been prepared. The mere possibility of its preparation and, thus thereby being made available suffices (referring α-Aminobenzylpenicillin, Fluoran, and Herbicid wirksames Enantiomer)."[593]

The Court further held that the novelty of stereoisomer (epimer, enantiomer, diastereomer) was thus already to be denied, when the stereoisomer was recognizably described to the skilled reader in the form of a mixture of its stereoisomers, and was accessible to him without difficulties by means of conventional separation methods from this mixture.[594] The Court also properly stated that "an indication or an explicit naming of the stereoisomer in question is as little necessary as a specification or description of method to its isolation."

However, the BGH confirmed its new position on this issue in the *Escitalopram* decision, the first decision on the patentability of an enantiomer after its *Olanzapine* decision.[595] The main issue for debate was again whether the prior patent disclosure of racemate, Citalopram,[596] allowing a person skilled in the art clearly to recognize two enantiomers, i.e. (S)- and (R)-

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591 *BGH/Schmierfettzusammensetzung(Grease composition)*, GRUR 2000, 296.
592 *BPatG/Atorvastatin*, BeckRS 2007, 18183, point II.1.a).
593 *BPatG/Atorvastatin*, BeckRS 2007, 18183, point II.1.a).
594 BPatG/*Atorvastatin*, BeckRS 2007, 18183, point II.1.a).
595 *Zu Waldeck und Pyrmont*, Gewerblicher Rechtsschutz und Urheberrecht, Praxis im Immaterial- und Wettbewerbsrecht ("GRUR-Prax"), 2010, 13 (stating that the Escitalopram decision seems to show that the Court continues its new line regarding the concept of disclosure stated in its Olanzapine decision.).
596 Citalopram is a selective serotonin reuptake inhibitor anti-depressant.

enantiomers, was enough to destroy the novelty of a patent on the (S)-enantiomer, ES-Citalopram. [597]

In this case, the BPatG held that the patent was invalid for lack of novelty for the similar reasons that a chemical compound having one chiral atom was no longer novel when claimed in the form of an enantiomer, if specific indication of the enantiomer in a prior publication had been given, and if a skilled person was able to produce the compound on the basis of this indication and his general knowledge.[598] The Court found that the person skilled in the art would easily have been able to separate the Escitalopram from the racemic mixture disclosed in the prior art patent specification in a way that was commonly used before the priority date of the Escitalopram patent.[599]

While admitting that the person skilled in the art on the basis of his general knowledge was able to recognize that citalopram having a chiral carbon had two different structures, the BGH stated nevertheless that this fact did not lead to a disclosure that was detrimental to novelty.[600] Citing the *Olanzapine* decision, the Court said that, to "make them [the individual enantiomers] available to the skilled person for the purpose of novelty examination, further information was as a rule required, in particular with regard to their individualization."[601] The Court concluded that, since the prior document did not directly and unambiguously disclose the individual enantiomers to the person skilled in the art, and since he had to find a way to resolve the racemate, the prior patent was not detrimental to novelty.[602]

In the United Kingdom

The *Ranbaxy v. Warner-Lambert* case concerned two patents owned by Warner-Lambert, one of which covered a class of compounds including

597 EP 0,347,006, U.S. RE34, 712.
598 *BPatG/Escitalopram*, BeckRS 2007, 14624, para II, especially II b).
599 *BPatG/Escitalopram,* BeckRS 2007, 14624, para II, especially II b).
600 *BGH/Escitalopram*, GRUR 2010, 123, 125.
601 *BGH/Escitalopram,* GRUR 2010, 123, 126.
602 *BGH/Escitalopram*, GRUR 2010, 123, 126.

atorvastatin[603] and the other covered a single enantiomer of atorvastatin (Lipitor®).[604] Ranbaxy appealed against the decision refusing a declaration of non-infringement of the previous patent with respect to its particular compound, enantiomeric atorvastatin calcium salt, and Warner-Lambert cross-appealed the decision ruling that the enantiomer patent was invalid for lack of novelty and obviousness.[605] The Court of Appeal held that the patent claiming an enantiomer was anticipated by the prior art, which did not disclose the salt of the pure enantiomer, but clearly taught that one of the things that could be made was the single enantiomer, and the way of carrying out the teaching of the earlier patent application would necessarily infringe the later claim of an enantiomer.[606] This case was slightly different from other cases, because the general formula of the earlier patent on the compounds showed a three dimensional arrangement. [607]

In *Lundbeck v. Generics*, while citing *Synthon BV v. Smithkline Beecham Plc,*[608] Lord Hoffmann restated that, to anticipate a patent, the prior art must have disclosed the claimed invention and enabled a ordinary skilled person to perform it. He also stated that it was settled jurisprudence in the EPO[609] that disclosure of a racemate did not in itself amount to disclosure of each of its enantiomers.[610] Regarding the plaintiff's argument that claim 1 was

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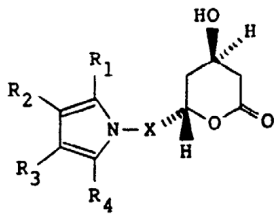
603 EP No. 0247633 (January 30, 1991, under the title of "Trans-6-(2-(3- or 4-carboxamido-substituted pyrrol-1-yl)-alkyl)-4-hydroxypyran-2-one inhibitors of cholesterol synthesis"), claim 1: A compound of structural formula



(I)

I

[…].

604 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876.

605 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, para 1.

606 *Ranbaxy (UK) v. Warner-Lambert*, [2006] EWCA Civ 876, paras 36-40.

607 See subsection II.C.1.b).

608 *Synthon BV v. SmithKline Beecham plc*, 20 October 2005, [2005] UKHL 59.

609 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311 (citing the decisions T 296/87 (OJ EPO 1990, 19, point 6.2), T 1048/92 and T 1046/97).

610 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 9.

not only directed to the isolated enantiomer, namely that claim 1 could include the racemate, thus, to that extent the claim was anticipated by the prior art, Lord Hoffmann noted that the claim did not include an unresolved part of the racemate, based on the title of the patent ("new enantiomers and their isolation"), and the knowledge of a person skilled in the art.[611] Jacob LJ stated further that this was a pure question of construction, namely whether claim 1 covered the (+) enantiomer when in the racemate, and he held that claim 1 obviously did not – the patentee was plainly not intending to cover the racemate, thus, how much more than 50% of the (+) enantiomer must have been present for a product to fall within the claim was simply a moot point as far as the case was concerned.[612]

After this decision, the Court in *Generics (UK) v. Daiichi Pharmaceutical* reaffirmed, since the prior patent on a racemate (ofloxacin, an anti-microbial agent) neither taught nor suggested the resolution of racemate into enantiomers, and the prior art disclosing ofloxacin did not anticipate one enantiomer, i.e. levofloxacin.[613]

In the United States

Unlike other jurisdictions, challenges to the patentability of chiral molecules based on novelty and non-obviousness have been asserted since as early as 1948, and have been met with a rule favorable to pharmaceutical companies.[614] In *In re Williams,* while quoting the famous Aspirin® case, the Court held that "the existence of a compound as an ingredient of another substance does not negative novelty in a claim to the pure compound, although it may, of course, render the claim unpatentable for lack of invention."[615] Apart from the Aspirin® case, which was decided in 1910, among the three countries where patents for aspirin were granted, the American patent was the only

611 *Lundbeck v. Generics*, [2008] EWCA Civ 311, paras 10-13.
612 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311*,* para 50; Since the challenge based on lack of novelty had failed in both courts below, it was not renewed before the House of Lords. *See Generics Ltd. v. Lundbeck* [2009] UKHL 12, paras 11, 43, 65 (also noting that the patentee would not have intended to cover racemate).
613 *Generics (UK) v. Daiichi Pharmaceutical* [2008] EWHC 2413 (Pat), para 317-18.
614 *In re Williams*, 171 F.2d 319 (C.C.P.A. 1948); *Darrow*, 2 Stan. Tech. L. Rev. 1, para 13 (2007).
615 *In re Williams*, 171 F.2d 319, 320 (C.C.P.A. 1948).

one that survived.[616] Furthermore, in *In re May* in 1978, the Court held that the novelty of an optical isomer was not negated by the prior art disclosure of its racemate;[617] and, in *Brenner v. Ladd* in 1965, the Court held it did not matter even that a racemate may dissociate in the solution.[618]

In *Sanofi-Synthelabo v. Apotex, Inc.*, the prior art patent disclosed clopidogrel,[619] in which there was one chiral center and which consisted of two enantiomers, and claimed that the invention related both to each enantiomer and their mixture.[620] Like the BOA,[621] the Federal Circuit, while mentioning the difficulty of separating enantiomers and the unpredictability of their properties, held that a reference that did not enable the separation of those enantiomers, would not have enabled a person skilled in the art to obtain clopidogrel substantially separated from the l-enantiomer.[622]

In *Forest Labs., Inc. v. Ivax Pharms., Inc.,* the District Court found that the alleged prior art did not disclose "substantially pure" *Escitalopram* and did not enable the person skilled in the art to obtain the product, since the separation technique at the time of the invention was relatively new and unpredictable, and the inventor himself failed to separate the enantiomer several times.[623] The Federal Circuit did not find errors in the District Court's

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616 *Kuehmsted v. Farbenfabriken of Elberfeld Co.*, 179 F. 701 (7th Cir. 1910) (holding that a pure compound might be patentable, under certain conditions, over the same compound in an impure form.); *cf. infra* 1335 -1338 and accompanying texts; Among three patent applications claiming Aspirin in US, UK, and Germany, those patents in UK and Germany were invalidated on the ground of lack of novelty.

617 *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978); *see also Pfizer Inc. v. Ranbaxy Laboratories Ltd*., 405 F.Supp.2d 495, 519 (D.Del. 2005), remanded in a different ground (holding "a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate or render the individual isomers of the racemate obvious.").

618 *Brenner v. Ladd*, 247 F.Supp. 51, 56 (D.D.C. 1965) (holding enantiomer should not be considered to be anticipated by the solution of racemate disclosed in the prior art, even though a racemate may dissociate in solution).

619 Clopidogrel is an antiplatelet agent used to inhibit blood clots, and this antiplatelet agent is used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease.

620 U.S. Patent No., 4,529,596 (July 16, 1985, under the title of "Thieno [3,2-c] pyridine derivatives and their therapeutic application"), column 1, lines 39-41.("These compounds having an asymmetrical carbon may exist in the form of two enantiomers. The invention relates both to each enantiomer and their mixture.").

621 *See Pfizer/Penem Derivatives,* T1048/92 (1994), points 2.3-2.5.

622 *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1085 (Fed. Cir. 2008).

623 *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1265 (Fed. Cir. 2007).

conclusions.[624] The Federal Circuit affirmed that, since the prior art, which in effect did state Escitalopram, did not enable the person skilled in the art to prepare the enantiomer and did not anticipate the claimed invention.[625]

In any case, this rule of novelty of enantiomers over their racemates seems to have been consistently applied for over a century. The difficulty of separation with the technology in the early 20th century is understandable and the novelty should be decided from case to case. However, one may doubt whether it is still as difficult as it was a hundred years ago to separate one ingredient from another.

In Korea

In the *Clopidogrel* case*,* [626] a patent on d-enantiomer[627] of clopidogrel was challenged,[628] with the same relevant facts as *Sanofi-Synthelabo v. Apotex, Inc.* in the United States.[629] The Supreme Court of Korea reiterated that to deny the novelty of selection invention, the prior document should specifically disclose the concept of a selection invention, and it could also be that a person skilled in the art could directly learn the existence of the selection invention from the prior document based on the disclosure thereof and on common knowledge at the time of application.[630] Based on the same disclosure,[631] however, the Court stated that the prior document disclosed the claimed d-enantiomer of clopidogrel, because the prior document i) disclosed clopidogrel itself, and ii) noted that the invention related both to each enantiomer and their mixture and the each enantiomer of clopidogrel was d- and l-enantiomer, respectively.[632] Further, the Court held that the use of

624 *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1267 (Fed. Cir. 2007).
625 *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268-69 (Fed. Cir. 2007).
626 *Korean Supreme Court/Clopidogrel*, 2008Hu736 & 2008Hu743, Oct. 15, 2009.
627 "Dextro-rotatory" and "levo-rotatory" is another way of indicating the chirality of each enantiomer. However, there is no fixed relation to the (R)- or (S)- enantiomer. For example, an (*R)* isomer can be either dextro-rotatory or levo-rotatory.
628 The prior patent disclosed especially "[…] is an asymmetric carbon atom. In fact, this formula represents both the dextro-rotatory molecule claimed as well as its levo-rotatory enantiomer.".
629 See *supra* 619 -622 and accompanying texts.
630 *Korean Supreme Court/Clopidogrel* , 2008Hu736 & 2008Hu743, Oct. 15, 2009, para 1.Ka.
631 See *supra* 622 ; both enantiomer and mixture.
632 *Korean Supreme Court/Clopidogrel*, 2008Hu736 & 2008Hu743, Oct. 15, 2009, para 1.Na.

clopidogrel also lacked novelty, since the prior art already disclosed clopidogrel and its use.[633] The Court finally held that, since it was specifically disclosed and the person skilled in the art would have acknowledged the racemate, its d-enantiomer, and l-enantiomer as separate compounds, *it was not necessary* that the method of separation or possibility of separation of enantiomers from racemates to obtain enantiomers be disclosed *unless the invention is directed to the method of separating d-enantiomer*.[634]

In *Warner Lambert v. CJ et al*.,[635] the issue was the same as the BPatG/Atorvastatin in Germany.[636] While citing the *Clopidogrel* case,[637] the Supreme Court held that, even though only the racemate of R-trans-heptanoic acid and S-trans-heptanoic acid was disclosed, considering that a carboxamide compound of formula I was acknowledged as separate 4 enantiomers and not as a mixture, a person skilled in the art could have acknowledged formula I's open-ring form, namely, R-trans-heptanoic acid and S-trans-heptanoic acid, as separate enantiomers, too, and, thus, the prior art disclosed the R-trans-heptanoic acid.[638] The Court restated that the selection invention was recognized as separate enantiomers, not as a mixture in the prior document, and that it was not necessary to disclose the method of separation or the possibility of separation of the enantiomer from racemates unless the invention was directed to the method of separating the dextrorotatory enantiomer.

However, most patent offices consider the optical isomer of known racemates as novel per se as long as the individual enantiomers have not been explicitly disclosed or separated.[639]

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633 *Korean Supreme Court/Clopidogrel*, 2008Hu736 & 2008Hu743, Oct. 15, 2009, para 1.Na. (describing the use as "a therapeutic composition having blood-platelet aggregation inhibiting activities and antithrombotic activities containing the above compound and a pharmaceutically acceptable carrier.").

634 *Korean Supreme Court/Clopidogrel*, 2008Hu736 & 2008Hu743, Oct. 15, 2009, para 1.Na.

635 *Korean Supreme Court/Atorvastatin*, 2008Hu3469, Mar. 25, 2010.

636 See *supra* 590 .

637 *Korean Supreme Court/Clopidogrel.*, *supra* 626 .

638 *Korean Supreme Court/Atorvastatin*, *supra* 635 , at para 1.Na.

639 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206-207; *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978) (holding "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate.").

c) Crystalline forms

In the EPO

The Board held that a chemical substance was new once it differed from a known substance in a reliable parameter.[640] Since the physicochemical properties of the polymorphs are different from each other, which can be represented by reliable parameters, as long as the applicants can prove the differences, it would be held novel.

In *SmithKline Beecham/Paroxetine methanesulfonate*, the parameters indicating the polymorph in the prior art and those of the claimed invention were not identical.[641] The Board, however, held that this difference did not mean that the two crystalline forms are different because the list of peaks was not limiting; the claimed invention had no further distinctive technical features other than the parameters;[642]and the claimed form was sufficient to be produced by a skilled person.[643]

The prior document for the crystal forms, of course, must enable the invention in question. The Board held that, even if the prior art unambiguously taught that finasterid existed in two polymorphic differentiations, since there was no indication of how the polymorph form I might be prepared, the prior art was not an enabling disclosure and was not a novelty-destroying disclosure for the claimed invention.[644] While noting that the submission was not supported by any evidence, the Board did not accept the examining division's submission that the crystal forms were accessible by means of any known crystallisation method and that a skilled person would not have had

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640 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 196, headnote (this case was about the patentability of an enantiomer).

641 The Claim 1 of granted patent EP-B-0 970 955: "1. Paroxetine methane sulfonate in crystalline form having inter alia the following characteristic IR peaks:1603, 1513, 1194, 1045, 946, 830, 776, 601, 554, and 539 4 cm–1; and/or the following characteristic XRD peaks [...] .".
The disclosure of prior art: Preparation of crystalline paroxetine mesylate, which was characterized by the following list of IR peaks:3023, 2900, 2869, 2577, 1615, 1515, 1500, 1469, 1208, 1169, 1100, 1038, 962, 931, 838, 777, 546, and 531 cm–1 (and no XPRD spectrum).

642 *Smithkline Beecham/Paroxetine methanesulfonate,* T 0885/02 (2004), points 3.4.10-3.1.13.

643 *Smithkline Beecham/Paroxetine methanesulfonate,* T 0885/02 (2004), points 3.6 and 3.7.

644 *Merck/Finasteride,* T605/02 (2005), point 3.2.1.

any difficulty in finding out under which crystallisation conditions either of two polymorphic forms could have been obtained.[645] Thus, even if the prior art discloses the claimed invention, if it does not enable the invention, it is not novelty destroying. In the case where the novelty of the crystalline forms of *Famotidine* was issued, the Board held that the product prepared according to the process disclosed in a prior art was the same as the claimed polymorph, thus the polymorph was not novel.[646]

In Germany

In the *Kristallformen,* the BPatG held that a compound, in the sense of patent law, was every individual chemical that could be reliably differentiated from another, if they provide sufficient and appropriate parameters.[647] This case involved two polymorphic forms of an already known antibiotic, Cefaloridin, which showed non-hygroscopicity. The Court further ruled that compounds having the same chemical composition were basically identical, did not apply for special forms of compounds, if these forms could not have been produced.[648]

In the United Kingdom

Smith Kline & French Laboratories v. Evans Medical involved a polymorph of the first H2-blocker Cimetidine (Tagamet®).[649] After some years of filing of the basic patent application covering cimetidine, the patentee claimed one polymorphic form of the same compound.[650] The Court dismissed the case noting that this patent was anticipated over its basic patent because the claimed form A of cimetidine was inevitably obtained by following the process disclosed in the prior art.[651]

Similar to the BOA's decision,[652] in the case on a crystal form of *Paroxetine methansulphonate,* the House of Lords held that the incorrect data indicating that the claimed invention was different from the subject disclosed

645 *Merck/Finasteride,* T605/02 (2005), point 3.2.1.
646 *Richter Gedeon/Famotidine,* T 226/98, OJ EPO 2002, 498, 509-514.
647 *BPatG/Kristallformen(Crystal forms),*Entscheidungen des Bundespatentgerichts ("BPatGE") 20, 6, 6.
648 *BPatG/Kristallformen,* BPatGE 20, 6.
649 *Smith Kline & French Laboratories v. Evans Medical* [1989] F.S.R. 561.
650 *Smith Kline & French Laboratories v. Evans Medical* [1989] F.S.R. 561, 561.
651 *Smith Kline & French Laboratories v. Evans Medical* [1989] F.S.R. 561, 579.
652 *SmithKline Beecham/Paroxetine methanesulfonate,* T 0885/02 (2004).

in the prior art were irrelevant because the evidence showed that the claimed invention would have inevitably resulted from the prior art and that the prior art was enabling, because the person skilled in the art would have tried a different solvent if the solvent in the main example was not suitable for crystallization.[653]

In *Laboratories Servier v. Apotex,* while noting that "the individual peaks of the table should not have too much significance attached to them – it is the overall set that matters," Jacob LJ held that the claimed polymorph was not novel when it would inevitably be obtained by carrying out the process disclosed in the earlier patent for the basic substance.[654] While pointing out that the exclusivity based on this crystalline form could have extended to 2020, Jacob LJ remarked that "[i]t is the sort of patent which can give the patent system a bad name." [655]

In the United States

In *Abbott Laboratories v. Geneva Pharmaceuticals*, the novelty of an anhydrous crystalline form IV of Terazosine hydrochloride ("THC")[656] over sales of a product containing this form of THC without the parties' knowledge was in issue.[657] The Federal Circuit held that the third party's sales of the anhydrous crystalline form of THC before the patent filing date rendered the patent on that particular anhydrous crystalline form of THC invalid, even though the parties to those sales did not know that they were dealing with the particular form claimed in the patent.[658] The Court further clarified that if a product offered for sale inherently possesses each of the limitations of the claims, then the invention was on sale, whether or not the parties to the

653 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, paras 34-38.
654 *Laboratoires Servier v. Apotex* [2008] EWCA Civ 445, paras 21-38 (a case about the novelty of one crystal form of the t-butylamine salt of perindopril).
655 *Laboratoires Servier v. Apotex*, [2008] EWHC Civ 445, para 9.
656 Terazosin is a medication for the treatment of hypertension and benign prostatic hyperplasia.
657 *Abbott Laboratories v. Geneva Pharmaceuticals, Inc*., 182 F.3d 1315 (Fed. Cir. 1999).
658 *Abbott Laboratories v. Geneva Pharmaceuticals, Inc*., 182 F.3d 1315, 1315 (Fed. Cir. 1999).

transaction recognized that the product possessed the claimed characteristics.[659]

In *SmithKline Beecham v. Apotex*, Apotex, which was seeking to practice the invention in the prior art, was found to have infringed the patent, based on which, logically, the prior art should have anticipated the claim before the patent filing date.[660] The Federal Circuit held that the patent covering crystalline Proxetine Hydrochloride ("PHC") *hemihydrate*[661] was invalid, because it was inherently anticipated based on the fact that the process of making PHC *anhydrate* in the prior art, which did not discuss PHC *hemihydrate*, inherently resulted in the production of at least trace amounts of the hemihydrates.[662]

There is no equivalent case law regarding novelty of crystalline form in Korea.

d) Metabolite

In the United Kingdom

Merrell Dow was a patentee of an anti-histamine called terfenadine (Teldane®). The subsequent research on the product showed that the anti-histaminic effect was due to a specific metabolite. After the determination of the structure of the metabolite, called Fexofenadine (Allegra®), Merrell Dow filed a new patent application. After the basic patent for the terfenadine expired in 1992, the patent holder for the metabolite, Merrell Dow, sued a generic company selling Terfenadine for infringing not the basic patent but the metabolite patent, which would not expire until 2000.[663] Merrell Dow argued that the supply of terfenadine provided the essential means for making the patent protected metabolite, and thus for puting the patented inven-

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659 *Abbott Laboratories v. Geneva Pharmaceuticals, Inc*., 182 F.3d 1315, 1319 (Fed. Cir. 1999) (further noting "The question is not whether the sale, even a third party sale, 'discloses' the invention at the time of the sale, but whether the sale relates to a device that *embodies* the invention.").

660 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1341 (Fed. Cir. 2005).

661 See *supra* 140 .

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

663 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, paras 7-8.

tion into effect.[664] The House of Lords found that the acid metabolite of the anti-allergic drug terfenadine lacked novelty. It held that the metabolite was not novel, not because of its previous use but because of the previous disclosure of "a part of the chemical reaction in the human body produced by the ingestion of terfenadine and having an anti-histamine effect," which contained sufficient information and enabled the public to work the invention to make metabolites in their livers by taking the medication.[665] The Lords rejected the argument that the metabolite was made available to the public by the clinical trials of terfenadine, because they did not make the necessary information of its metabolite available, i.e. they did not enable anyone to perform the metabolite invention.[666] The Lords seemed to accept that the metabolite could be patented provided that the claim was limited to the metabolite produced by methods other than metabolism in the body.[667]

In Germany

The same case that was litigated in the United Kingdom[668] was appealed to the Munich Higher Regional Court in 1992, which held that the patent of metabolite was not infringed, since it was not manufactured, sold, or kept for filing by the defendants.[669] Because of the bifurcated system in Germany, the Court could not rule on the validity of the patent in issue.

In the United States

After first construing the word "compound" in the patent on metabolite, the District Court limited the patent scope only to the synthetically produced version of acid metabolite of terfenadine.[670] However, the Court did not question the patentability of the metabolite patent in this case. In *In re Bu-*

664 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, para 8.
665 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, paras 22-48.
666 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, paras 22-48; *Jacob*, IIC 1997, 880, 880-81.
667 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14, para 15; *Jacob*, IIC 1997, 880, 881.
668 *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd* [1995] UKHL 14.
669 *OLG München/Terfenadine*, GRUR, 1994, 746.
670 *Marion Merrell Dow Inc. v. Baker Norton Pharmaceuticals, Inc.*, 948 F.Supp. 1050, 1055-56 (S.D.Fla.,1996), appeal dismissed, 152 F.3d 941 (Fed. Cir. 1998).

spirone Patent Litigation, the District Court held that the fact that the use of the parent drug was described in a package insert of the parent drug and that it was prescribed more than one year prior to the filing date of metabolite patent application alone were sufficient to decide the issue of invalidity.[671]

In *Schering Co. v. Geneva Pharmaceuticals*, the Federal Circuit held that a metabolite of Loratadine was anticipated over the prior art, which disclosed the administration of loratadine to a patient, since it "necessarily and inevitably" resulted in the formation of the metabolite.[672] The Federal Circuit further held that inherent anticipation required neither the recognition of the person skilled in the art, nor the actual creation or reduction to practice of prior art subject matter before the priority date, i.e. the actual administration of the patent drug to any patients, but required only enabling disclosure.[673] Unlike the House of Lords, the Federal Circuit also restated that "that which would literally infringe if later in time anticipates if earlier."[674] Interestingly, Rader J noted that these metabolites might not receive protection via bare compound claims, which were defined by structure only, since the scope of these claims could include the compounds in any surroundings, including those with the body as metabolites of a drug. However, he stated that it could be claimed in its pure and isolated form,[675] since the prior art would not provide an enabling disclosure to anticipate such claims.[676] Thus, in the United States, as in the United Kingdom, a metabolite may be patentable if it is claimed in its pure and isolated form.[677]

Novelty of metabolites has not been issued in Korea.

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671 *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 340, 360 (S.D.N.Y., 2002).
672 *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1378 (Fed. Cir. 2003).
673 *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1378-80 (Fed. Cir. 2003), quoting *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).
674 *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1379 (Fed. Cir. 2003), quoting *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001).
675 Examples were a pharmaceutical composition, a method of administering the metabolite or the corresponding pharmaceutical composition.
676 *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1381 (Fed. Cir. 2003).
677 *Schering Co. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1381 (Fed. Cir. 2003).

5. Analysis and conclusion

For species selection inventions, the EPO has the most extreme approach, i.e. to destroy the novelty of a species selection invention, the prior art must disclose the same, as it is the photograph of a later invention.[678] Germany and the United Kingdom relaxed their previous stringency in this regard to allow assessment of the novelty of species selection inventions, and it was declared by the courts that the *Fluoran* decision or the *IG Rule* exist only in history; therefore, the novelty requirement is much lowered. The United States, where the decision on Olanzapine was first held, appears to consider the size of the genus from which the selection was made. Although there are some differences from jurisdiction to jurisdiction, a species selection invention will be found novel unless it is individually spelled out in the prior art. This seems to be based on the difficulty of identifying and envisaging a specific species selection invention with effects that distinguish it from the millions of others as per Jacob J's *a priori* consideration.[679]

This lowered novelty requirement applied to the optical isomers inventions, although differently. The novelty of an optical isomer is already established over the racemic mixture, if its structure is clearly disclosed and it is acknowledged by the person skilled in the art that one or the other would exert its pharmacological effect, unless purification of that isomer from the racemate is not disclosed and is difficult. For example, while referring to the *Olanzapine* decision, the BGH held that an enantiomer was not available to the public, since the prior document did not directly and unambiguously disclose an enantiomer because the person skilled in the art should find the way to resolve the racemate. This is also because anticipation requires the *enablement* of the invention.

For the crystalline forms, the issue of novelty arose mainly because the claimed crystalline forms were inevitably produced according to the process disclosed in the prior art, and novelty was generally not found. If a new crystalline form were shown, it would have no difficulty being found novel.

The reasoning on novelty of metabolites in the United Kingdom and the United States shows an interesting contrast. In the United States, where a *secret or confidential use* of an invention could give rise to the public use bar, so that "non-informing" prior art can be the prior art, the Federal Circuit

678 This extreme approach could make novelty test be subject to the skill of drafting person.

679 See *supra* 558 .

found that it was not-novel based on its rule that "that which would literally infringe if later in time, anticipated if earlier." However, the House of Lords held that the metabolite was available not by the previous use of its parent drug, but by a disclosure which was common knowledge.[680] This is because, in the United Kingdom, to make something available to the public, the communication of information is required,[681] but the use of the parent drug does not present any information about the metabolite. Thus it could not be a prior art. Through this effort, it seems that the House of Lords invoked the "golden thread" that a patent cannot stop someone from doing something that was old,[682] which is the basis of the novelty requirement. Since the non-enabling/communicating use – the ingestion of the parent drug - does not constitute the prior art, if the Court could not have found another way, the metabolite patent could ultimately have prevented the public from practicing the parent drug. Thus, the Court held that the metabolite lacked novelty based on the prior disclosure, which merely described the same non-enabling use, while the use would inevitably produce the metabolite. Indeed the patent on the metabolite precisely patents the state of the art again, insofar as it precludes the use of the parent drug as an anti-histamine treatment.[683]

B. Inventive step / Non-obviousness[684]

> "We are like dwarfs on the shoulders of giants, so that we can see more than they, and things at a greater distance, not by virtue of any sharpness on sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size."[685]

No invention occurs in a vacuum, and every invention is built upon previous inventions. The inventive step requirement in patenting ensure that patented invention is qualitatively distinguised from previous invention.

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680 See *supra* 665 -666 and accompanying texts.
681 See *supra* 666 and accompanying text; *see also Jacob*, IIC 1996, 170, 171 (arguing the disclosure of a process made available to the public, for the purposes of that process, everything that inevitably took place as part of the process, whether appreciated or not.).
682 *Jacob*, IIC 1997, 880, 880.
683 *Jacob*, IIC 1996, 170, 171.
684 "Inventive step" and "non-obviousness" are used in this thesis without distinction.
685 *Bernard of Chartres*, 1130 AD.

1. Inventive step in patentability requirements

The novelty requirement is not controversial, and utility will be found on a relatively trivial showing.[686] The two other requirements are arguably relatively "mild"[687] compared to the rigor of the inventive step requirement. The inventive step requirement is considered the "final gatekeeper of the patent system"[688] and the "ultimate condition of patentability."[689] In other words, even if relatively trivial changes to the prior art could survive these two requirements, inventive step functions as the ultimate requirement and filters the patentable from the unpatentable.[690]

The inventive step requirement has been traditionally justified as a corollary to the "reward theory" of patent law.[691] The purpose of having this requirement is to encourage invention, while not over-rewarding it.[692] The inventive step asks whether a development is a significant enough technical advance to merit the award of a patent.[693] Without this requirement, the possibility of using the variations of prior art from everyday practice would be jeopardized.[694] The requirement guarantees that the information inherent in the claimed invention has a minimum threshold quantum of value in exchange for a patent.[695] As Lord Hoffman noted, "[t]he question was whether, in accordance with this policy, the patent in suit disclosed something sufficiently inventive to deserve the grant of a monopoly."[696] This requirement is also to ensure that the patent system rewards those inventions that would

686 *Duffy*, 71 U. Chi. L. Rev. 439, 502-03 (2004).
687 *Merges/Duffy*, 2011, 619.
688 *Merges/Duffy*, 2011, 619-20 (also noting "nonobviousness can accurately be described as a 'non-triviality' requirement in patent law.").
689 *Witherspoon*, 1980.
690 *Merges/Duffy*, 2011, 620.
691 *Duffy*, 71 U. Chi. L. Rev. 439, 503 (2004) (noting "[n]ew and useful creations that are also relatively obvious do not deserve the reward of a patent because the social benefits of the invention are outweighed by the social costs of the patent monopoly.").
692 *Merges*, 7 High Tech. L. J. 1, 3 (1992).
693 *Merges/Duffy,* 2011, 620.
694 *Kraßer*, 2009, 301-02; *Grubb/Thomsen*, 2010, 68.
695 *Merges*, 7 High Tech. L. J. 1, 18-19 (1992).
696 *Societe Technique de Pulverisation Step v. Emson Europe Ltd. and others* [1993] R.P.C. 513.

not have been created without the inducement of a patent.[697] Thus, the inherent problem was to develop some means of selecting out those inventions.[698]

One cannot claim a patent right on a subject matter that, though it is not fully anticipated, would nevertheless be obvious to a person skilled in the art at the applicant's date of invention or of filing.[699] Thus, the inventive step assures that, although the invention may be novel in some technical sense, it is not merely a straightforward extension, a simple application of some familiar invention,[700] or an incremental development of technology.[701]

2. Examination of inventive step

An invention may be obvious to the person skilled in the art over more than one piece of prior arts.[702] In other words, if a subject matter is obvious to the person skilled in the art over the entire state of the prior art, a patent will not be granted. This judgment of whether an invention involves an inventive step is one that is intrinsically much more difficult than that of novelty, since to some extent judgement of the inventive step is rather subjective.[703] Thus, the assessment of the inventive step raises largest single cause of uncertainty

697 *Graham v. John Deere Co.*, 383 U.S. 1, 11-17 (1966); *Kitch*, 1966 Sup. Ct. Rev. 293, 301 (1966) (noting if an invention would not have been developed absent the prospect of a patent, it should be granted); *Gilfillan*, 31 J. Pat. & Trademark Off. Soc'y 611, 611 (1949) ("A patent is helpful and proper when it rewards sufficiently useful creative work *which might not have been done without* that prospective reward.").

698 *Graham v. John Deere Co.*, 383 U.S. 1, 11 (196) (holding "[t]he inherent problem was to develop some means of weeding out those inventions which would not be disclosed or devised but for the inducement of a patent.").

699 *Chisum*, 15 AIPLA Q. J. 57, 58 (1987).

700 *Grady/Alexander*, 78 Va. L. Rev. 305, 340 (1992).

701 *Holbrook*, 59 SMU L. Rev. 123, 170 (2006).

702 *Spenner*, 90 J. Pat. & Trademark Off. Soc'y, 477, 510 (2008); EPO Examination Guidelines G-VII, 6; Examination Guidelines for Patent and Utility Model in Korea ("Korean Examination Guidelines"), January 2011, Ch 5.1.

703 *Grubb/Thomsen*, 2010, 67.

about the validity of patents, and has thereby resulted in a rich jurisprudence.[704]

In the EPO

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.[705] Even though the BOA held that this approach was no more than one possible route to assessing inventiveness,[706] the practice in the EPO basically applies the "problem-and-solution approach" to assessing the inventive step. This can be divided into three main stages:

> "(i)Determining the 'closest prior art'
> (ii) Establishing the 'objective technical problem' to be solved; and
> (iii)Considering whether or not the claimed invention, starting from the closest prior art and the objective technical problem, would have been obvious to the skilled person."[707]

This approach is based on the principle that every invention is a solution to a technical problem. "The objective technical problem" in the second step concerns the aim and the task of modifying or adapting the closest prior art to provide the technical effects of the invention over the closest prior art, which may be different from what is presented as "the problem" in the patent application, and this in turn could require the reformulation.[708] While noting that the "reformulation" involved the court artificially, creating a problem that was supposed to be solved by the invention, Jacob LJ pointed out that

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704 *Cornish/Llewelyn/Aplin*, 2010, 210 (noting "[t]he evaluative issue that this introduces is the largest single cause of uncertainty about the validity of patents and hence a frequent inflator of the scale and length of patent disputes.").

705 EPC Art. 56, first sentence; GPA Section 4, first sentence; UK Patents Act 1977, Section 3.

706 *Alcan/Aluminium alloys*, T 465/92, OJ EPO 1996, 32, 50 (holding that "[T]he problem and solution approach ought to be considered as one amongst other possible approaches, each of which has its own advantages and drawbacks.").

707 EPO Examination Guidelines-G-VII, 5.; *See e.g.*, *Bayer/Carbonless copying paper*, T 1/80, OJ EPO 1981, 206; EPC Rule 42(1)(c) (The description shall disclose the invention, as claimed, in such terms that the technical problem, even if not expressly stated as such, and its solution can be understood, and state any advantageous effects of the invention with reference to the background art.).

708 EPO Examination Guidelines-G-VII, 5.2 (further noting this could be specially the case when "the prior art cited in the search report may put the invention in an entirely different perspective from that apparent from reading the application only.").

this reformulation might be the weakest part of the problem-and-solution approach.[709] To answer the question in the third step, the word, "would" must be defined. The point here is not whether the skilled person could have arrived at the invention, i.e. that it was within their technical ability, but whether he would have done so because the prior art motivated him to do so while wishing to solve the objective technical problem or expecting some improvement or advantages.[710] It is not sufficient that the person skilled in the art *could* have arrived at the invention from the prior art; it must be shown that he *would* have done so.[711] This last step is similar to the TSM test in the United States.[712]

Some secondary considerations are relevant to the last step again, especially in determining whether the person skilled in the art "would" have made the claimed modifications to the closest prior art to solve the objective technical problem, and include unexpected or synergistic technical effects, long-felt need or commercial success.[713] However, commercial success is not to be regarded as a sole criterion and needs to be coupled with evidence of long-felt need.[714]

In the United Kingdom

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.[715] The British Court's approach to assessing the inventive step was set out in *Pozzoli v. BDMO*, which provided four steps:

"1. a) Identify the notional "person skilled in the art"
   b) Identify the relevant common general knowledge of that person;
2. Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

709 *Actavis UK Ltd v. Novartis AG* [2010] EWCA Civ 82, paras 30-34; *see also Ranbaxy UK & Anor v. Warner-Lambert* [2005] EWHC 2142, para 71 (noting this kind reformulation of the problem could provide a substantial risk that would lead to a finding of non-obviousness based on the after-discovered advantages.).

710 EPO Examination Guidelines-G-VII, 5.3.

711 *Actavis UK Ltd v. Novartis AG* [2010] EWCA Civ 82, para 46 (further commenting this seemed, however, to be self-evident).

712 See *infra* 732 -733 and accompanying texts.

713 EPO Examination Guidelines-G-VII, 10.

714 EPO Examination Guidelines-G-VII, 10.3.

715 UK Patents Act 1977, Section 3.

3. Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
4. Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"[716]

Jacob LJ explained that (i) the only thing that mattered for step 2 was what was claimed, and (ii) the meaning of "obvious" for the purpose of step 4, which is the key statutory step, was technically rather than commercially obvious.[717]

In the United Kingdom, obviousness is a multifactorial question. Namely, the Court makes a full multifactorial assessment of all relevant facts of each case, which may include commercial success, a long-felt want, a motive to find a solution to the problem, the number and extent of the possible avenues of research, the effort involved in pursuing them, and the expectation of success.[718] Unexpected results can only fail to defend against an obviousness attack, when there is a real motivation to use the idea apart from that advantage, since only then will the person skilled in the art more or less inevitably bump into the unexpected advantage.[719]

In Germany

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.[720] In *Betrieb einer Sicherheitseinrichtung,* the BGH placed the focus on whether the person skilled in the art had motivation to develop the prior art further in the direction of the claimed subject matter. [721] The BGH held that seeing the use of an approach that deviated from previous approaches as not only possible but as obvious to the skilled person required additional im-

716 *Pozzoli v. BDMO* [2007] EWCA Civ 588, para 122 (reviewing the English Court's approach in the earlier case, *Windsurfing v. Tabur Marine* [1985] RPC 59.).
717 *Actavis UK Ltd v. Novartis AG* [2010] EWCA Civ 82, paras 18-21.
718 *Actavis UK Ltd v. Novartis AG* [2010] EWCA Civ 82, paras 26, 41 (citing *Conor Medsystems Inc v. Angiotech Pharmaceuticals Inc & Ors* [2008] UKHL 49, para 42).
719 *Napp Pharmaceuticals v. Ratiopharm* [2009] EWCA Civ 252, para 115.
720 GPA Section 4, first sentence.
721 *BGH/ Betrieb einer Sicherheitseinrichtung (Operating a Safety Device)*, GRUR 2009, 746.

pulses, stimuli, suggestions or other motives going beyond discernability of a technical problem to prompt the skilled person to solve the technical problem by inventive means.[722] However, there seems to be no formal approach to assessing the inventive step.

The secondary indications cannot establish or replace the inventive step. Further, they may only be the occasion in exceptional cases for a particularly critical review of the solutions known in the state of the art to determine whether they provide sufficient indications for the obviousness of the subject matter of the claimed invention against the background of general technical knowledge and whether they merely appear to contain a suggestion leading to the invention from a post-hoc point of view.[723] Secondary considerations often applied are economic success based on the invention, overcoming difficulties, satisfaction of a long lasting need, evidence of others' failures, unexpected technical progress, overcoming prejudices, and unexpected results.[724]

In the United States

A patent may not be obtained if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.[725]

Under the *Graham* decision,[726] which established a basic framework for judging non-obviousness, courts must identify (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention, and (3) the level of ordinary skill in the art. Then, they must determine whether the subject matter of the claimed invention is obvious.[727] These are referred to as the "Graham factors." The Graham Court further held that secondary considerations, which are subsequently called the fourth

722 *BGH/ Betrieb einer Sicherheitseinrichtung (Operating a Safety Device)*, GRUR 2009, 746, 748.
723 *BGH/Dreinahtschlauchfolienbeutel (Three-Seam Tubular Sachet)*, GRUR 2010, 44, 46-47.
724 *Pagenberg*, GRUR Int 1986, 83 *et seqq*.
725 35 U.S.C. § 103(a).
726 *Graham v. John Deere Co.*, 383 U.S. 1 (1966).
727 *Merges/Duffy,* 2011, 670.

Graham factors,[728] such as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to determine obviousness.[729] However, the *Graham* decision does not specify precisely how a court is to make this ultimate determination.[730] The imaginary person, typically referred to in the United States as a PHOSITA (a person having ordinary skill in the art), is the yardstick by which the bar to obtaining patent protection can be adjusted to specific technological fields.[731]

Soon after its creation, the Federal Circuit articulated what would become its exclusive test for deciding obviousness, which was known as the "Teaching, Suggestion or Motivation" or the so-called TSM test.[732] The Federal Circuit held that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination."[733] However, this test came under increasing scrutiny, and the Supreme Court granted certiorari on the question whether the Federal Circuit had erred in holding that a claimed invention could be deemed "obvious" by applying the TSM test too rigidly.[734]

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728 *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1348-49 (Fed. Cir. 2012).

729 *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *cf. Newell Companies, Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988) (holding although secondary considerations must be considered, they do not necessarily control the obviousness conclusion); *cf. Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1372 (Fed. Cir. 2007)*, reh'g denied, cert. denied.*

730 *Merges/Duffy,* 2011, 670.

731 *Strandburg*, 1 UC Irvine L.R.,265, 267 (2011); For the PHOSITA, see MPEP § 2141.03, citing *In re GPAC*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *Custom Accessories, Inc. v. Jeffrey Allan Industries, Inc*., 807 F.2d 955, 962-63, (Fed. Cir. 1986); *Environmental Designs, Ltd. V. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983) (noting "the factors that may be considered in determining the level of ordinary skill in the art may include: (A) type of problems encountered in the art; (B) prior art solutions to those problems; (C) rapidity with which innovations are made; (D) sophistication of the technology; and (E) educational level of active workers in the field. And in a given case, every factor may not be present, and one or more factors may predominate.").

732 *Merges/Duffy*, 2011, 672.

733 *ACS Hosp. Systems, Inc. v. Montefiore Hosp.,* 732 F.2d 1572, 1577 (Fed. Cir. 1984) (further noting "[u]nder section 103, teachings of references can be combined only if there is some suggestion or incentive to do so.").

734 *KSR Intern. Co. v. Teleflex Inc.,* 548 U.S. 902 (Mem) (2006).

In *KSR v. Teleflex*, the Supreme Court held that "[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." The Court rejected the Federal Circuit's "rigid approach" to obviousness in favour of a more "expansive and flexible" approach.[735] The Court held that "any need or problem known in the field of endeavour at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed."[736] The Court added an "obvious to try" test: "When there is a design need or market pressure to solve a problem; and there are a finite number of identified predictable solutions; then a person of ordinary skill has good reason to pursue the known options, and this leads to the anticipated success."[737]

When evaluating obviousness, the American patent system further uses a procedural device called the "*prima facie* case of obviousness," which differs from obviousness and was established to shift the burden of proof to the applicant.[738] The *prima facie* case of obviousness is initially established by an examiner based on the application of the first three Graham factors and maintained unless and until the applicant provides sufficient evidence to demonstrate non-obviousness, such as "secondary considerations."[739] To establish *prima facie* obviousness in the field of chemistry, size of the genus, structural similarities, and reasonable expectation of success can be used. To rebut the *prima facie* obviousness in the field, in addition to the factors presented in *Graham*, industry acclaim, unexpected results, prior art teaching away from the invention,[740] industry praise, copying, industry scepticism, and licensing are secondary considerations. [741] Regarding a "teaching away," a court found that a prior art reference "taught away" from combining references could alone defeat an obviousness claim.[742] For commercial suc-

735 *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 401, 415 (2007).
736 *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 401, 420 (2007).
737 *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 401, 421 (2007).
738 *In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984).
739 MPEP § 2142; *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990) (noting the applicants can prevail this prima facie obviousness if they overcome it by providing evidences).
740 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006); In re Sullivan, 498 F.3d 1345, 1351 (Fed. Cir. 2007).
741 *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340 (Fed. Cir. 2012).
742 *Alza Corp. v. Mylan Labs. Inc.*, 388 F. Supp. 2d 717, 738 (N.D. W. Va. 2005), *aff'd*, 464 F.3d 1286 (Fed. Cir. 2006).

cess, the Federal Circuit declared that the presence of certain secondary considerations of non-obviousness were not sufficient as a matter of law to overcome its conclusion that the evidence supported only a legal conclusion that claims would have been obvious.[743]

Recently, however, while referring to *Stratoflex, Inc. v. Aeroquip Corp*,[744] the Federal Circuit further held that the evidence of secondary considerations must have been "considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art. Thus, in order to determine obviousness, the decision maker must be able to consider all four *Graham* factors." [745]

In Korea

If a person with ordinary skill in the art to which the invention pertains would have easily been able to perceive the invention based on the prior art, the patent shall not be granted for such an invention.[746] To assess the inventive step, one shall consider the overall state of the art, the purpose, technical structure, and advantageous effects of the invention, while paying attention to the opinion of the applicant, in consideration of its specific purpose and effectiveness, and the difficulty of the technical structure of the claimed invention. [747] The main factors to be considered are: (a) whether the prior art provides any motivation to a person skilled in the art to reach the claimed invention; (b) whether the difference between the prior art and the claimed invention is considered as an exercise of ordinary creativity; and (c) whether the claimed invention has any advantageous effects over the prior art. [748] Regarding the motivation to reach the claimed invention, the Korean Patent Court held that to say the claimed invention could have been easily conceived by the combination of the cited references, there should be a suggestion of combination in the cited references.[749]

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743 *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006).

744 *Stratoflex, Inc. v. Aeroquip Corp*., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

745 *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

746 Korean Patent Act, 2012, Art. 29(2).

747 Examination Guidelines for Patent and Utility Model in Korea ("Korean Examination Guidelines"), January 2011, Ch3. 5.

748 Korean Examination Guidelines, January 2011, Ch3. 5.

749 *Korean Patent Court/Kimchi fridge*, 2002Heo8424, Sept. 04, 2003, para 2.Na.(3)(Ba).

Secondary considerations, such as teach away, long-felt but unmet need, and commercial success, can be considered to assess the inventive step.[750] However, while commercial success alone is not enough, it can be considered as indicative of the inventive step when the applicant proves that the success was derived from the technical features of the invention.[751] Based on overwhelming commercial success, the Korean Patent Court found the invention nonobvious once, because, in contrast to the prior inventions, which failed to be commercialized or were withdrawn right after being on the market, the product based on the claimed invention achieved commercial success owing to the significant effects derived from the claimed invention.[752] For the long-felt but unmet need, the Korean Patent Court held that the claimed invention could not have been easily conceived from the cited invention considering the fact that the claimed invention had not emerged over eight years.[753]

3. Inventive step requirement for selection inventions

a) Species selection invention

In the EPO

The EPO Examination Guidelines provides an exemplary case when the selections from the Markush formula are found to be obvious (a) if they are neither described as having nor shown to possess any advantageous properties not possessed by the prior art examples; or (b) if they are described as possessing advantageous properties compared with the compounds specifically referred to in the prior art, but these properties are ones which the person skilled in the art would expect such compounds to possess, so that he is likely to be led to make this selection.[754] Once the selection of compounds is regarded as novel, then the compounds must show either the advantageous properties over those *not* possessed by the prior art examples or unexpected advantageous properties that were possessed by the prior art examples.

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750 Korean Examination Guidelines, January 2011, Ch3. 8.
751 Korean Examination Guidelines, January 2011, Ch3. 8 (2).
752 *Korean Patent Court/Kimchi fridge*, 2002Heo8424, Sept. 04, 2003, para 2.Na.(3)(Ba).
753 *Korean Patent Court/A combining method*, 98Heo8397, Apr. 23, 1999, para 3.Na.
754 EPO Examination Guidelines G-VII Annex 3.1.(iv.).

In Germany

In *Olanzapine* decision, the BGH held that the claimed compound was not obvious to the person skilled in the art over either the "Chakrabarti" document or other prior art in any other manner.[755] In this case, the BGH made it clear that its position was not in line with the EPO's way of determining obviousness, in "only" applying the so-called "problem-solution approach,"[756] which started from its fundamental step in identifying the "closest prior art." While disagreeing with the BPatG's assumption that a person skilled in the art would have chosen the Chakrabarti document first, the Court stated that there was no such higher ranking of the "closest prior art" and that only from a retrospective view did it become clear which prior publication came closest to the invention and how an inventor could have approached the problem to arrive at the solution according to the invention.[757] It appears that the BGH was concerned about the risk of hindsight if, as a starting point for the determination of an inventive step, one selected the closet prior art. The Court also stated that the selection of the starting point therefore required the justification that generally lay in the efforts of a person skilled in the art to find a better solution for a specific purpose than the known state of the art makes available.[758]

While elaborating the structure and activity relationship of the disclosed compounds, the Court held that, since the "Chakrabarti" document taught away or did not provide a skilled person the information, according to which the further research appeared to be interesting or promising, it was not obvious.[759]

In the United Kingdom

In the Patent Court of olanzapine case,[760] Floyd J employed the structured approach of the obviousness test developed in the *Windsurfing v. Tabur*

755 *BGH/Olanzapine,* IIC 2009, 596, 601.
756 See *supra* 707 and accompanying texts.
757 *BGH/Olanzapine,* IIC 2009, 596, 601.
758 *BGH/Olanzapine,* IIC 2009, 596, 601-602.
759 *BGH/Olanzapine*, GRUR 2009, 382, 387.
760 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345.

Marine case.[761] He found the "skilled addressee" to be a team of scientists with a particular interest in finding anti-psychotics led by a medicinal chemist having access to other disciplines such as pharmacology and toxicology,[762] found "common general knowledge," such as medicinal chemistry, including structure-activity-relationships, psychological disorders and associated side effects,[763] and held the patent was not obvious over all prior arts argued.[764] Considering that the determination of what a person skilled in the art perceived at the filing date was crucial to judging obviousness,[765] this Court seems to start from the very basic element. In addition, he found that "commercial success" is not helpful in deciding obviousness, since that fact alone did not support obviousness if olanzapine was technically obvious.[766] He emphasized that the commercial success was not because the third parties had not appreciated the advantages of olanzapine, but because the basic patent covering olanzapine had prevented the manufacture and sale of olanzapine.[767]

On appeal, Jacob LJ stated that the objection of obviousness could be made where there was "no real technical advance" in the art, since the patent monopoly could be justified by the technical contribution to the art.[768] While endorsing Jacob LJ's position on this issue, Lord Neuberger noted that it

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761 *Windsurfing International Inc. v. Tabur Marine (GB) Ltd*. R.P.C. 59 (1985). (4 step tests to the obviousness: (1) (a) Identify the notional "person skilled in the art" (b) Identify the relevant common general knowledge of that person; (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it; (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed; (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?").

762 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345, para 140.

763 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345, paras 141-148.

764 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345, paras 149-184.

765 *Spenner*, 90 J. Pat. & Trademark Off. Soc'y, 477, 477 (2008).

766 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345, para 185.

767 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345, para 186.

768 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, paras 40-52.

should be asked whether the selection was arbitrary or whether the teaching of prior art established that the selection achieved "a particular technical result."[769] If there was no technical advance, it was just an arbitrary selection that was obvious. However, since olanzapine provided its superior therapeutic effect to the prior art, and selection from almost millions of compounds could not be regarded as random,[770] it was nonobvious over the prior art.

In the United States

In the *Olanzapine* case, the Federal Circuit held that several prior art references, in fact, taught away from exploring the compounds that did not possess an electron-withdrawing group in one benzene ring, because olanzapine has exactly one hydrogen atom, which was an electron-withdrawing group.[771] While the Court recognized the structural similarity with a compound that has an ethyl group ("ethyl-olanzapine") instead of a "methyl" group of olanzapine, the Court noted that patentability for a chemical compound did not depend only on structural similarity, but also accounted for the unexpected beneficial significant properties that might render the invention nonobvious.[772] After Rader J noted the similarity with the case of *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*,[773] he stated that the defendants did not sufficiently show the motivation for a person skilled in the art to select the above "ethyl-olanzapine" as a lead compound that did not contain an electron-withdrawing group.[774] This analogy is interesting, since, in *Yamanouchi*, an entire complex combination was required, selecting and combining separate parts of two embodiments followed by further

769 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, para 109.

770 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, [2009] EWCA Civ 1362, paras 54-57, 98-101, 109-115.

771 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006).

772 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1378-80 (Fed. Cir. 2006).

773 *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344 (Fed. Cir. 2000) (holding that [The ANDA filer] did not show sufficient motivation for person skilled in the art at the time of invention to take any necessary steps to reach the patented invention from the prior arts).

774 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1378-79 (Fed. Cir. 2006).

chemical reactions to produce the patented compound. However, there was only a single difference between the compounds in the prior art (ethyl group) and that in the patent at issue (methyl group) in the *Olanzapine* case. While citing *Yamanouchi* again, he stated that to make obvious the combination as a whole was not the mere identification in the prior art of each component, but rather a motivation to select the reference and to combine them in the particular claimed manner to reach the claimed invention.[775] The Court held that it was not obvious based on the above "teaching away" and extensive "secondary considerations of non-obviousness" such as (i) a long-felt and unmet need; (ii) failure of others; (iii) industry acclaim; and (iv) unexpected results.

The size of the genus has special impacts on the finite obvious to try case; where there is a finite number of possibilities from which to start, a technique that is within the grasp of the person skilled in the art is used to modify the prior art to arrive at the claimed invention, and the results are not unexpected, then the invention is obvious.[776] In *Pfizer v. Apotex*, a prior patent claimed amlodipine and its pharmaceutically acceptable salts, disclosed maleate as the best salts, but did not explicitly disclose besylate.[777] A later patent application claiming amlodipine besylate salt was rejected on the basis of a reasonable expectation of success over the above prior patent in combination with the *Berge* reference that disclosed fifty-three FDA-approved, commercially marketed anions that were useful for making pharmaceutically-acceptable salts and included besylate.[778] The Court found the fact that there were a limited number of choices to start from, and a reasonable probability

775 *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals. Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006).

776 *See Spenner*, 90 J. Pat. & Trademark Off. Soc'y, 477, 510 (2008).

777 *Pfizer, Inc. v. Apotex, Inc*, 480 F.3d 1348, 1353 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied* 552 U.S. 941 (2007).

778 *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1355 (Fed. Cir. 2007) *reh'g denied*, 488 F.3d 1377, 1383-84 (Fed. Cir. 2007) (This denial of rehearing *en banc* decision was not unanimous, i.e., Judges Newman, Lourie, and Rader wrote their own dissents. Regarding the "obvious to try" analysis, Judge Rader stated that since a salt selection was unpredictable, there would not have been a reasonable expectation of success.).

of success to make the salt, prevented its unexpected results from rebutting the *prima facie* obviousness.[779]

In Korea

In August, 2012, the Korean Supreme Court upheld the validity of Eli Lilly's patent on olanzapine.[780] The Supreme Court reiterated that for the inventive step of a selection invention not to be denied, all specific concepts in the selection invention must exhibit *qualitatively different or qualitatively the same but quantitatively superior effects* over the prior invention, and that these effects should be clearly disclosed in the specification of the selection invention patent by either a description of qualitative differences or data supporting any quantitative advantages.[781] The Supreme Court did not acknowledge the therapeutic superiority of olanzapine over prior art, since the superiority of parameters comparing the therapeutic effects thereof were not consistent.[782] Based on the description of the patent specification regarding the avoidance of side effects,[783] however, the Supreme Court held that such effects were qualitatively different, since these were not disclosed in the prior art, and a person skilled in the art could not anticipate from the prior art that olanzapine would have such effects.[784] Further, the Supreme Court noted that where a selection invention had multiple effects, the selection invention could be recognized as showing qualitatively different effects compared to a prior art, even if only a part of the effects of the selection invention, not all of the effects, was recognized as being qualitatively different or quantitatively remarkable compared to the prior art.[785]

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779 *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1372 (Fed. Cir. 2007) *reh'g denied*, *cert. denied* (holding "even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case.").

780 *Korean Supreme Court/Olanzapine*, 2010Hu3424, Aug. 23, 2012 (this was the first case to upheld the validity of a selection invention).

781 *Korean Supreme Court/Olanzapine*, 2010Hu3424, Aug. 23, 2012, para 1.

782 *Korean Supreme Court/Olanzapine*, 2010Hu3424, Aug. 23, 2012, para 2.Na.

783 Korean Patent No. 195566, 11-3 (noting "[i]n dog toxicity studies with a closely analogous compound (ethyl olanzapine), at a dosage of 8 mg/kg, it was observed that four out of eight dogs showed a significant rise in cholesterol levels, whereas the compound of the present invention (olanzapine) did not show any rise in cholesterol levels.").

784 *Korean Supreme Court/Olanzapine*, 2010Hu3424, Aug. 23, 2012, para 2.Da.

785 *Korean Supreme Court/Olanzapine*, 2010Hu3424, Aug. 23, 2012, para 2.Ra.

b) Optical isomers

Considering that the novelty of the optical isomer is not negated by the earlier disclosure of disclosed racemate, the patentability of this invention would more likely hinge on the question of the inventive step. To establish the inventive step, the inventor should show that the optical isomer has surprisingly superior properties in comparison with the known racemate.[786] One may recall that the existence of the chiral center means the existence of optically active forms, and it is generally recognized that one optical isomer normally has higher activity than the others.[787]

In the EPO

Initially BOA found the invention of a mixture containing at least 80% of one of two enantiomers novel over the prior art disclosing a mixture of two enantiomers containing 50% of each. However, BOA found it lacking an inventive step.[788] The Board noted that test of different ratios of mixture to analyze their effects was a routine procedure.[789]

> "Long before the contested patent´s priority date, it was generally known to specialists that, *in physiologically active substances* (e.g. herbicides, fungicides, insecticides and growth regulators, but also pharmaceuticals and foodstuffs) with an asymmetrical carbon atom enabling them to occur in the form of a racemate or one of two enantiomers, *one of the latter frequently has a quantitatively greater effect than the other or than the racemate.* If – as here - the aim is therefore to develop agents with increased physiological activity from a physiologically active racemate the obvious first step - before any thought is given, say, to synthesizing structurally modified products - is to produce the two enantiomers in isolation and test whether one or the other is more active than the racemate. *Such tests are routine.* Under established Board case law, *an enhanced effect cannot be adduced as evidence of inventive step if it emerges from obvious tests.* Since, in the present case, tests with the enantiomers were obvious in view of the task at hand, discovery of the claimed effect of the D-enantiomers

786 *Grubb/Thomsen*, 2010, 236.

787 *See e.g., Forest Labs., Inc. v. Ivax Pharms., Inc.,* 501 F.3d 1263, 1269 (Fed. Cir. 2007) (Forest's argument: "the general expectation in the art that one enantiomer would be more potent than the other provided reason for a person of ordinary skill in the art to isolate the enantiomers").

788 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206, 209.

789 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206, 209.

compared with corresponding racemates does not involve an inventive step."[790] [Emphasis added]

Ten years later in T 229/97,[791] however, the Board held that a patent on hemicalcium salt of R-enantiomer of atorvastatin (Lipitor®)[792] involved an inventive step over the prior patent claiming sodium salt of the racemate of atorvastatin.[793] Based on the experimental evidence of favourable handling properties of a claimed invention submitted just one month before the appeal hearing, the Board held that i) the problem to solve was providing a hypocholesterolemic compound having improved handling properties, i.e. improved hygroscopicity and solubility, and that ii) the closest prior art gave no hint of how to solve the problem nor any incentive to modify those salts of the racemates in the hemicalcium salt of the particular R-enantiomer. Thus, the claimed invention involved the inventive step.[794] However, the original patent specification as filed did not mention either the problem of handling the substance nor the solution thereof, i.e. the evidence showed a radically different problem and solution disclosed by the original patent specification. As Pumfrey J noted, this reformulation of the problem i.e. the better handleability of calcium salt of atorvastatin over the sodium salt, could provide a substantial risk that would lead to a finding of non-obviousness based on the later discovered advantages.[795]

In Germany

In the *Atorvastatin* decision in 2007, after holding that claims 1 to 3 directed to product invention were not novel,[796] the BPatG held that claim 4 directed to the process to produce atorvastatin did not involve the inventive step, since a person skilled in the art would have been able to manufacture it according to the method described in the prior art.[797]

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790 *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206, 209.
791 *Warner-Lambert/Atorvastatin,* T 0229/97 (2000).
792 EP No. 0,409,281 (October 31, 2001, under the title of "(R-(R*R*))-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl-3-phenyl-4((phenylamino)-carbonyl)-1H-pyrrole-1-heptanoic acid, its lactone form and salts thereof").
793 U.S. Patent No. 4,681,893 (July 21, 1987, under the title of "Trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-one inhibitors of cholesterol synthesis").
794 *Warner-Lambert/Atorvastatin*, T229/97 (2000), paras 4.2.-4.7.
795 *Ranbaxy UK & Anor v. Warner-Lambert* [2005] EWHC 2142, para 71.
796 See *supra* 589 -594 and accompanying texts.
797 *BPatG/Atorvastatin*, BeckRS 2007, 18183, para II.4.

In the *Escitalopram* decision, the BPatG held that it was obvious to resort to the method of chiral chromatography to separate the enantiomers.[798] The BGH agreed with the BPatG in that a person skilled in the art had reason as of the date of priority to attempt to produce or isolate the citalopram's enantiomers, since it was known that one enantiomer can have a better effect and another might have the opposite or a side effect.[799] However, based on the fact that there was no obvious way to obtain the escitalopram as of the date of priority, that it was not certain which way would provide an industrially useful scale production, that there was not enough motivation to choose the method, that there was uncertain expectation of success, and that there were many failures to separate it, the Court held that the invention was not obvious.[800] All of the reasoning was directed to the *difficulty of the method* in separating escitalopram, and it was the precisely reason for finding that the escitalopram was "novel."

In the United Kingdom

The differences from the EPO approach were drawn into sharp focus in the *Ranbaxy v. Warner-Lambert* case. In this case, the Patent Court found that a patent relating to the hemi-calcium salt of atorvastatin (Lipitor®) was invalid for the lack of obviousness.[801] This contrasted markedly with an earlier decision of the EPO's Technical Board (T 229/97), in which the same patent was found to involve an inventive step over an equivalent piece of prior art.[802] The Court noted the following: i) by 1989 resolution of racemates with pharmaceutical activity was well established; ii) for the family of statins, the skilled person would have known that the activity would reside in a specific enantiomer; iii) the salts would likely be more soluble than the free acid; and iv) testing the properties of salts was standard practice.[803] The Court also held that the difference between the claimed invention and the prior art was most certainly obvious, since the resolution of the racemate was common general knowledge, and the seven salts were specifically described including calcium.[804] The Court further explained that, according to

798 *BPatG/Escitalopram,* BeckRS 2007, 14624, para II.1.b).
799 *BGH/Escitalopram*, GRUR 2010, 123, 126.
800 *BGH/Escitalopram*, GRUR 2010, 123, 127-130.
801 *Ranbaxy UK & Anor v. Warner-Lambert* [2005] EWHC 2142.
802 See *supra* 791 -794 and accompanying texts.
803 *Ranbaxy (UK) v. Warner-Lambert* [2006] EWCA Civ 876, paras 55-57.
804 *Ranbaxy (UK) v. Warner-Lambert* [2006] EWCA Civ 876, para 62.

the *IG Farbenindustrie AG's Patents* case, although the selection of a single element having advantageous properties from a class was possible, the prior disclosure had to be a disclosure of a class rather than a disclosure of the individual members of that class.[805] In the appeal, the Court noted that it was unnecessary to consider the obviousness point.[806]

However, in *Lundbeck v. Generics Ltd.*, a patent for an enantiomer (escitalopram) of the known drug citalopram was held valid. Before the Court of Appeal, whether the so-called amino diol route for resolving the racemate would have been obvious was an issue.[807] Lord Hoffmann stated that the Court might reverse the trial judge's finding when the error of principle occurred, because the judge failed to consider whether it was obvious for the skilled person to try the reaction to see if it worked, as in the *Biogen*[808] case.[809] While stating that Kitchin J applied the state of the law correctly to the facts of this case, Lord Hoffmann rejected the obviousness argument. Jacob LJ rejected the plaintiff's argument that a person skilled in the art could have come to the invention by doing a short and simple experiment, stating that, by itself, it was insufficient, as one could say that "with hindsight" of many inventions, and as it was not enough motivation for a skilled person to carry it out. Therefore, the invention was not obvious.

On appeal, the obviousness was not a major issue before the House of Lords, since the attack based on obviousness failed in both courts below. On the other hand, Lord Neuberger summarized basic knowledge that had long been known about enantiomers as follows: i) Two enantiomers could have different properties from each other; ii) a racemate's therapeutic effect might be mainly dependent on one enantiomer; iii) the other enantiomer might have toxic or side effects; iv) the only way to tell which one had which effect was to separate one from another and to compare; v) however, that was not possible to predict yet.[810] He continued that the notion to obtain a pure therapeutic form from a racemate was obvious, but to obtain a pure form was not obvious, and it was particularly difficult to separate (S)-citalopram from the

805 *Ranbaxy (UK) v. Warner-Lambert* [2006] EWCA Civ 876, para 63.
806 *Ranbaxy (UK) v. Warner-Lambert* [2006] EWCA Civ 876, para 32.
807 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 14.
808 *Biogen Inc v. Medeva Plc* [1996] UKHL 18.
809 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 23.
810 *Generics Ltd. v Lundbeck* [2009] UKHL 12, para 61.

racemate.[811] The difficulty of separating the racemates again seemed to be weighted to determine obviousness.

After this *Escitalopram* case, the Court of Appeal again held that an enantiomer of ofloxacin, i.e. *Levofloxacin,* was not obvious over a prior art disclosing the method of producing other compounds having the same core structure as ofloxacin.[812] Specifically, Jacob LJ held:

> "I am not sorry to reach this conclusion. Daiichi's work led to a better medicine than ofloxacin. Levofloxacin is not just twice as active as ofloxacin (which might have been expected) but is a lot more soluble and less toxic than was predictable. It can be used in higher dosages than might have been expected with corresponding medical benefit."[813]

In the United States

Unlike the *Levofloxacin* case in the United Kingdom where the equivalent prior art was found not to provide enough motivation to resolve the levofloxacin, the *Ortho-McNeil* Court found that the prior art provided ample motivation to separate optical isomers of the racemate in question.[814] However, the Court held that, even though the prior art enabled the production of enantiomer and provided enough motivation, the patent was not invalid, since there was no evidence showing that the improved result was reasonably expected in light of secondary considerations.[815] Simply put, the *prima facie* obviousness that was established by enabling the difficult way of production was rebutted based on its unexpected effect.[816]

The *Atorvastatin* case in the United States was somewhat simpler. In *Pfizer, Inc. v. Ranbaxy,* the Federal Circuit held that one claim at issue over *Atorvastatin* was invalid for failure to satisfy 35 U.S.C. § 112 and remanded

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811 *Generics Ltd. v Lundbeck* [2009] UKHL 12, paras 61-65.

812 *Generics (UK) Ltd v. Daiichi Pharmaceutical* [2009] EWCA Civ 646, paras 30-44.

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

814 *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 752 (N.D.W.Va. 2004), *aff'd,* 161 Fed.Appx. 944 (quoting a part of the book "[W]ith the development of synthesis methods via stereoselection and improvement in the analytical methods of optical isomers in the recent years, many came to believe that only one of the enantiomers is the important substance and that the other one is, if bluntly said, almost an impure substance.").

815 *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 752-62 (N.D.W.Va. 2004), *aff'd,* 161 Fed.Appx. 944.

816 *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 754 (N.D.W.Va. 2004), *aff'd*, 161 Fed.Appx. 944 (noting "levofloxacin is pharmaceutically superior to ofloxacin in virtually every relevant aspect").

the case to the District Court.[817] However, since Pfizer sought to reissue the patent at issue to correct the above error and provided Ranbaxy with a covenant not to sue Ranbaxy on all remaining claims of the original patent,[818] and since the patent was unenforceable, the District Court dismissed this allegation.[819]

In *Forest Labs. v. Ivax Pharms.*, the District Court found that the alleged prior art did not provide a reasonable expectation of success of obtaining the enantiomer (escitalopram) for similar reasons to those that supported a finding of enablement regarding the same prior art.[820] The Court further found that one of ordinary skill in the art at the time of the invention would generally have been motivated to develop new compounds rather than undertake the difficult and unpredictable task of resolving a known racemate.[821] In the appeal, the Federal Circuit noted that Ivax emphasized only the evidence that was favorable to its desired outcome without addressing the evidence favorable to Forest, such as the failure of the inventors to resolve citalopram without undue experiments, and so on,[822] and concluded that it was not obvious to the person skilled in the art. Considering that this decision was rendered several months after *KSR*, the decision is interesting, because the Federal Circuit did not consider more than the ordinary view regarding obviousness while relying on the District Court's finding based on *Graham v. John Deere Co*.

One week after the *Escitalopram* decision, the Federal Circuit answered the same question, i.e. whether the one stereoisomer of Ramipril with five chiral centers, 5(S) Ramipril was obvious over its prior racemate. [823] While quoting the *KSR* decision, the Federal Circuit reasoned that requiring an explicit teaching to purify the 5(S) stereoisomer was precisely the sort of rigid application of the TSM test that was criticized in *KSR*.[824] The Federal

817 *Pfizer, Inc. v. Ranbaxy Laboratories Ltd*., 457 F.3d 1284, 1291-92 (Fed. Cir. 2006).
818 *Pfizer, Inc. v. Ranbaxy Laboratories, Ltd.*, 525 F.Supp.2d 680, 684 (D.Del.,2007).
819 *Pfizer, Inc. v. Ranbaxy Laboratories, Ltd.*, 525 F.Supp.2d 680, 685 (D.Del.,2007).
820 *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1267 (Fed. Cir. 2007).
821 *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1267 (Fed. Cir. 2007); *contra BGH/Escitalopram*, GRUR 2010, 123, 126; *contra Darrow*, 2 Stan. Tech. L. Rev. 1 paras 21 and 39 (2007).
822 *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007).
823 *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1300 (Fed. Cir. 2007).
824 *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007).

Circuit found that the prior art motivated a person skilled in the art to isolate 5(S) Ramipril and taught how to do so, based on the facts (i) that one therapeutically active racemate contained only two enantiomers, namely SSSSS and SSSSR,[825] (ii) that the person skilled in the art would have reasons to believe that the mixture derived properties from particular components of the compound,[826] and (iii) that the prior art taught that the stereoisomers of ramipril "can be separated by conventional chromatographic or fractional crystallization methods."[827] The Federal Circuit also held that there was no evidence that separating 5(S) Ramipril from the above therapeutically active racemate was beyond the capability of a person skilled in the art and the patentee failed to prove unexpected results over the above mixture, since the potency of an isomer precisely varied with the absolute amount of the isomer in the racemate.[828]

In *Sanofi-Synthelabo v. Apotex, Inc*., experts testified about the degree and kind of stereoselectivity of a selected enantiomer, i.e. a situation where one enantiomer having biological activity and the other having toxicity was rare and could not have been predicted, since usually if one enantiomer has better biological activity than the other, that activity also includes the adverse as well as the beneficial properties.[829] The Federal Circuit held that these unexpected and unpredictable properties of *Clopidogrel* would not be what one would have expected in the *Ramipril* case.[830] In response to the argument that potential regulatory pressure for the separation of enantiomers would have motivated to resolve the racemate, the Court found that the resolution was undertaken not because of the potential regulation but because of the purpose to study the adverse neurological effects.[831]

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825 This seems to be similar to the situation one enantiomer was selected from a racemate with one chiral center.

826 Prior art provided the molecules with close structural relationship to Ramipril, such as enalapril or captopril were more active in the (S) form.

827 *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007).

828 *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007).

829 *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1081 (Fed. Cir. 2008).

830 *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1089 (Fed. Cir. 2008); *see Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) (holding that the ramipril isomer's potency was "precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers.'').

831 *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1089-90 (Fed. Cir. 2008).

Even though the motivation to resolve the racemate could be found and the separation method in general may be known, particular enantiomers may not be obvious, since various factors, including the obviousness of the resolution method, may play a role in determining obviousness.[832]

In Korea

With regard to obviousness in the *Clopidogrel* decision, [833] the Supreme Court held that, for the inventive step not to be denied, all specific concepts in the selection invention must show effects that are *qualitatively different or qualitatively same but quantitatively superior* to those of the prior invention,[834] and these effects should be clearly disclosed in the specification of the selection invention by either a description of qualitative differences or data supporting any quantitative advantages.[835] The Court further noted that a two-fold superiority in platelet aggregation inhibition or around 1.6-fold superiority in acute toxicity to the racemate in the prior art could not be regarded as superior considering that the administration of one enantiomer yielded approximately 2-fold better effects than that of a racemate, which is a 50:50 mixture of enantiomers.[836]

In the Atorvastatin decision, the Supreme Court determined that the enantiomer invention was also obvious, since, even under the consideration of hygroscopicity or solubility, which were argued by the patentee, there was no special disclosure in the specification which could show any qualitatively different or qualitatively identical but quantitatively superior effects.[837]

c) Crystalline forms

The systematic investigation of a compound to determine whether it is prone to polymorphism as well as the nature of polymorphism is routine practice

832 *Spenner*, 90 J. Pat. & Trademark Off. Soc'y, 477, 487-88 (2008).
833 *Korean Supreme Court/Clopidogrel*, 2008Hu736 & 2008Hu743, Oct. 15, 2009.
834 This requirement seems to be similar to those of *I.G. Rule* in U.K.
835 *Korean Supreme Court/Clopidogrel*, 2008Hu736 & 2008Hu743, Oct. 15, 2009, Headnote 2.
836 *Korean Supreme Court/Clopidogrel*, 2008Hu736 & 2008Hu743, Oct. 15, 2009, para 2.Na.
837 *Korean Supreme Court/Atorvastatin*, 2008Hu3469, Mar. 25, 2010, para 2. Na.

in pharmaceutical pre-formulation studies.[838] This understanding forms the part of the common general knowledge in the art.

In the EPO

In T 51/97, where an issue was whether one crystalline form of a compound established its inventive step over another modified form of the same compound, the Board held that it was obvious over the combination of the closest prior art which was acknowledged in the specification of the patent in suit and another prior art which indicated the incentives and a concrete hint as to how to solve the dispersion instability at high temperatures.[839] The Board further held that it was not necessary to establish that the success of a solution of a technical problem was predictable with certainty; it was sufficient to establish that the skilled person would have done so with a reasonable expectation of success. [840]

One recent Technical BOA decision that attracted considerable attention in the pharmaceutical industry was T 777/08, where crystal forms II and IV of atorvastatin were claimed, and two closest prior arts each disclosing amorphous forms of atorvastatin were identified.[841] After explaining the common knowledge at the priority date of the patent in suit [in 1995],[842] the Board held that, in the absence of any technical prejudice, the mere provision of a crystalline form of a known pharmaceutically active compound could not be regarded as involving an inventive step.[843] The Board further held as follows:

> "[I]n view of his general knowledge, as reflected in this excerpt from [another prior art], the skilled person, starting from the amorphous form of a pharmaceutically active compound as closest prior art, would have a clear expectation that a crystalline form thereof would provide a solution to the problem [to pro-

838 *Caira*, 1998, 165.
839 *Nippon/Crystalline dye,* T 0051/97 (2000), points 2.6. and 2.7.
840 *Nippon/Crystalline dye,* T 0051/97 (2000), point 2.7.3.
841 *Warner-Lambert/Atorvastatin polymorphs,* T 0777/08 (2011).
842 *Warner-Lambert/Atorvastatin polymorphs,* T 0777/08 (2011), Headnote 1 ("At the priority date of the patent in suit, the skilled person in the field of pharmaceutical drug development would have been aware of the fact that instances of polymorphism were commonplace in molecules of interest to the pharmaceutical industry, and have known it to be advisable to screen for polymorphs early on in the drug development process. Moreover, he would be familiar with routine methods of screening.").
843 *Warner-Lambert/Atorvastatin polymorphs,* T 0777/08 (2011), point 5.2.

> vide atorvastatin in a form having improved filterability and drying characteristic]. Although this might not be true of every crystalline form obtained [examples], it was nevertheless obvious to try this avenue with a reasonable expectation of success without involving any inventive ingenuity. […] [A]n arbitrary selection from a group of equally suitable candidates cannot be viewed as involving an inventive step."[844]

Thus, it must be expected that the inventiveness of a new polymorph can be acknowledged only if it is associated with an unexpected pharmaceutical activity, while improved physical and/or physicochemical properties will not be sufficient. As the Board also noted, one should not overlook the fact that it is not always the case that every single polymorph provides improved characteristics. As *McCrone* famously noted in 1965, "[…] every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound."[845]

In the United Kingdom

In the case on a crystal form of *Paroxetine methansulphonate,* obviousness was not the issue.[846] In another case on a crystal form of *t-butylamine salt of perindopril*, the Court of Appeal held that the claim on the process to produce the crystal form, i.e. a solution "is heated at reflux and is then cooled gradually until crystallisation is complete," which differed from the prior art procedure only in the qualification "gradually," was obvious over the prior art.[847]

In *Leo Pharma v. Sandoz*, where a single crystalline form of *Calcipotriol*[848] monohydrate which was said to have superior stability and technical properties useful in the manufacture of suspension formulations, the inventive step of claimed crystalline form over the prior art disclosed anhydrous form of crystalline calcipotriol was one of the issues in the appeal.[849] The Court found this case unusual, since Sandoz argues that the skilled person

844 *Warner-Lambert/Atorvastatin polymorphs,* T 0777/08 (2011), point 5.2.
845 Cited in *Bernstein*, 2002, 9; indeed there are a good number of companies who are specialized in polymorph screening, such as Analytics-Pharm, Poly Crystal Line, Crystal Pharmatech, Avantium and the like.
846 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59.
847 *Laboratoires Servier v. Apotex* [2008] EWCA Civ 445, paras 13-20 (a case about the novelty of one crystal form of the t-butylamine salt of perindopril).
848 Calcipotriol is a Vitamin D3 analogue.
849 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188.

would, using his technical knowledge, have come across the invention (namely the hydrate and its beneficial technical properties) without any expectation of successfully finding a better product.[850] Sandoz argues that, given the instructions disclosed in the prior art for an aqueous suspension cream containing calcipotriol, it was obvious to find and use calcipotriol monohydrate. The Court of Appeal considered the four different approaches argued by Sandoz against the finding of non-obviousness,[851] but held in each case that the lower court's conclusion could not be faulted. The Court further held that it was not universal practice to conduct a polymorph screen and that a skilled team would not regard such a screen as mandatory.[852] The Court held that the demand of the regulatory authorities could not be equated to knowledge of the person skilled in the art.[853] The Court held that it was not obvious to use the screen and so to find the hydrate as a part of a routine check in the course of stability studies or in anticipation of a regulatory requires, since it was not proven that the above investigation would reveal the hydrate.[854] The Court of Appeal further held that, although the wet-milling[855] was accepted at first instance to be an obvious variant to dry milling, as the hydrate would have been produced only 50% of the time, the lower court was correct to conclude that it did not make the hydrate obvious.[856] The Court of Appeal also rejected the argument that routine crystallisation experiments would have produced the hydrate, since the nature

850 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188, para 9.

851 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188, para 11 ((i) obviousness over the acne use patent because it was obvious to conduct a full polymorph screen, during which the monohydrate and its properties would have been discovered; (ii) obviousness over the acne use patent because a product screen would have revealed the monohydrate and its technical properties; (iii) obviousness over the acne use patent because wet milling instead of dry milling would have produced the monohydrate and its technical properties would have then been revealed; (iv) obviousness in the light of common general knowledge alone because experiments into crystallisation would have revealed the monohydrate and its technical properties.).

852 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188, paras 51-63; *contra Warner-Lambert/Atorvastatin polymorphs,* T 0777/08 (2011), point 5.2. (noting it was the routine tasks of the skilled person involved in the field of drug development to screen for solid-state forms of a drug substance); *contra McCrone*, cited in *Bernstein*, 2002, 9.

853 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188, para 54.

854 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188, paras 64-68.

855 Milling is one of the most efficient methods of producing small particle size. And wet milling is a process in which the substance is steeped in water.

856 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188, paras 69-71.

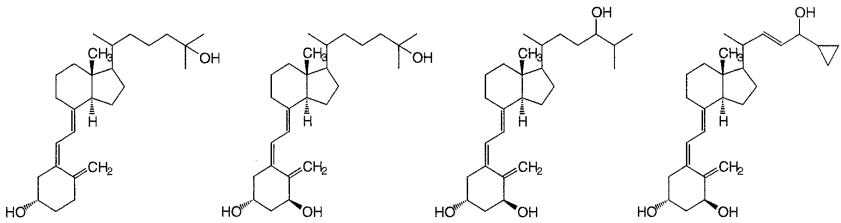
of the experimental programme was neither established nor sufficiently defined to enable a conclusion as to what it would have uncovered.[857]

The problem with each approach outlined by Sandoz was that the skilled person would not have necessarily had any expectation of finding calcipotriol monohydrate. On the one hand, all approaches pursued by Sandoz were essentially plausible; on the other hand, a non-obviousness challenge based on "obvious to try" must have a fair expectation of success for the skilled person. The British courts seem to require a relatively high standard for a non-obviousness case based on "obvious to try."

In Germany

Unlike the British case, where it was mainly argued that the way to make monohydrates was part of the common knowledge of a skilled person, the same prior arts disclosing three other Vt. D3 monohydrates were used as main references to challenge the inventive step of the claimed crystalline form of calcipotriol mononhydrate. Figure 8 presents the respective structures of three other Vt D3 analogues and Calcipotriol.

Figure 8: The structures of Vt D3 analogues and Calcipotriol



25-Hydroxy-Cholecalciferol 1α,25-Dihydroxy-Cholecalciferol 1α,24-Dihydroxy-Cholecalciferol Calcipotriol

The BGH held that, in the assessment of inventive step, the question of whether the skilled person had an incentive to adopt the measurement described in the prior art and to apply a known scheme to a known subject matter grew in importance depending on whether the skilled person could reasonably expect to succeed this way in solving the technical problem.[858] The BGH further held that these requirements were fulfilled in this case,

857 *Leo Pharma v. Sandoz Ltd* [2009] EWCA Civ 1188, paras 73-76.
858 *BGH/Calcipotriol-Monohydrat*, GRUR 2012, 803, 807.

since, based on those three prior arts, the skilled person had the incentive to adopt the described measurement – solution of the solid in organic solvent with the addition of water – and to apply it to the Calcipotriol; consequently, he could have obtained the calcipotriol monohydrate.[859] The implementation of these measurements would have been with a view to the structurally related Vt. D analogues in the prior art and a possible similar reaction of calcipotriol coupled to the reasonable expectation of success; moreover, the effort to be introduced – use of organic solvents and water – in relation to an expected result was to be proportionate.[860]

In the United States

Obviousness was not the issue in either *Abbott Laboratories v. Geneva Pharmaceuticals*[861] or *SmithKlein Beecham v. Apotex*.[862]

In Korea

The Supreme Court reiterated the inventive step requirement for crystalline form as follows:

> "It is well-known in the field of pharmaceutical compounds that the same compounds may have various crystalline forms and that the pharmaceutical properties thereof, such as solubility, stability, etc., may vary. Thus, prior to designing a preparation method of a compound, it is common to first confirm the existence of polymorphism of the compound. Accordingly, an invention for a compound having a specific crystalline form, which is different from a compound disclosed in the prior art only in terms of the crystalline form, namely, an invention relating to a crystalline form, is recognized as having an inventive step only if the effect thereof is qualitatively different from a compound disclosed in the prior art or is quantitatively very different, but not necessarily qualitatively different, from a compound disclosed in the prior art. Although not absolutely required to provide comparative experimental data with the prior art, the specification of the invention relating to a crystalline form must clearly describe the above effect, in order for the effect to be considered when determining the inventive step of the invention. If the effect is questionable, the applicant or the patentee must specifically demonstrate the effect through reliable comparative experimental data after the filing date of the application."[863]

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859 *BGH/Calcipotriol-Monohydrat*, GRUR 2012, 803, 807.
860 *BGH/Calcipotriol-Monohydrat*, GRUR 2012, 803, 807.
861 *Abbott Laboratories v. Geneva Pharmaceuticals, Inc*., 182 F.3d 1315 (Fed. Cir. 1999).
862 *SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331 (Fed. Cir. 2005).
863 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 1.

In this case, the Supreme Court acknowledged that the results of experiments regarding the bioavailability, solubility, and reduced batch-to-batch variability were clearly described in the patent specification.[864] Since the bioavailability disclosed in the patent specification was based on the blood concentration of the claimed racemate of Lercanidipine hydrochloride, the submitted result of bioavailability on the prior art was based on the blood concentration of S-enantiomer of Lercanidipine hydrochloride, and, even though each condition of the experiment could not be acknowledged by the submitted document, the Court held that the superior bioavailability of claimed crystalline form over the prior art could not be recognized.[865] In addition, for argument that the solubility of the claimed crystalline form was improved, the Court noted that according to the submitted experimental data, it was not confirmed whether the crystalline form compared to those of prior art was also non-hydrate as those disclosed in the prior art, and it was already known at the time of patent filing that 5~10 times of improved solubility could be obtained by the change of crystalline form.[866] The Court further held that, since it was not recognized what kind of *specific pharmaceutical effect* was achieved by the 5 times improved solubility of claimed crystalline form, the 5 times improved solubility could not be regarded as a superior effect.[867] The reduced batch-to-batch variability in mono-crystalline form was a logical result, since less variability would have been derived from the mixture ratio of different crystalline forms.[868] Accordingly, the Court held that, since the claimed crystalline form was not recognized as having a different or quantitatively remarkable effect in comparison to the compound disclosed in the prior art, the invention lacked an inventive step.[869]

In *Ibandronate* case, the Supreme Court noted that the patent specification disclosed the stability of the crystalline form under certain conditions and the particle size distribution of the claimed crystalline form. However, the experimental data submitted by the plaintiff included only the results of testing the stability of the claimed crystalline form without providing comparative experimental results with the compound disclosed in the prior

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864 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 2.
865 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 2.
866 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 2.
867 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 2.
868 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 2.
869 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 3.

art.[870] Thus, the Supreme Court held that, since the degree of improvement of the claimed invention over the prior art could not be confirmed and *the pharmaceutical effect* achieved by the improved stability of particle size distribution of the claimed crystalline form could not be confirmed, the claimed crystalline form was not recognized as having a different or quantitatively remarkable effect in comparison to the compound disclosed in the prior art. Thus, the invention lacked an inventive step.[871]

d) Metabolites

The case laws on the patentability of metabolites have focused mainly on the novelty of inventions, and inventive step thereof has not been the issue.

4. Analysis and conclusion

For species selection inventions, the courts in each jurisdiction acknowledged the advantageous effects over the prior art, i.e. the technical advance in the art through the selection; subsequently, the selection was regarded as non-arbitrary. The size of the genus from which the selection invention is made is important in establishing an inventive step. However, because of the lowered inventive step requirement, the advantageous effects do not need to be shown over the whole scope of the prior art.

For the optical isomers, the much lower inventive step requirements are distinctly observed. Unlike the early rulings that the stereochemistry and the different effect of one enantiomer from another were known, and that the production of an enantiomer and the testing of the activity thereof were routine, meaning even the advanced effects could not be the evidence of inventive step,[872] the BOA held an enantiomer invention established an inventive step based on the radically different problem and solution from those disclosed in the patent specification as filed.[873] In addition, in Germany, after the Olanzapine decision, the BGH held an enantiomer invention established its inventive step simply based on the difficulty of separating the racemate.

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870 *Korean Supreme Court/Ibandronate*, 2010Hu3554, Sept. 8, 2011, para 2.
871 *Korean Supreme Court/Ibandronate*, 2010Hu3554, Sept. 8, 2011, para 2.
872 See *supra* 790 and accompanying texts.
873 See *supra* 791 -794 and accompanying texts.

The same seems to be true in the United Kingdom. In contrast to the decision holding that the enantiomer was obvious because the resolution of the racemate was common general knowledge,[874] even if these facts regarding the enantiomer invention were known, there was either not enough motivation to resolve the racemate or the separation was not predictable, such that the inventive step of racemate was established.[875] In the United States, acknowledging that there was ample motivation to separate an enantiomer, based on the difficulty of separation, or even based on the expectation that the person skilled in the art would have worked on the new compounds rather than try to resolve the racemate, the enantiomer inventions were held to be non-obvious. At best, a two-fold increase in activity could be expected,[876] and this modest increase in activity would be offset by the difficulty and complexity of resolving the racemates.[877]

The decisions on the inventive step of enantiomer of clopidogrel in the United States and Korea showed quite stark differences. The Federal Circuit acknowledged the inventive step of one enantiomer, because the fact that one enantiomer was responsible for the biological activity and the other one was responsible for the side effect was not predictable. However the Korean Supreme Court held that it was obvious because a two-fold superiority in the therapeutic effects and around 1.6-fold superiority in acute toxicity to the racemate could not be regarded as better than that of the racemate considering 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.[878]

For the crystalline forms, the inventive step of one crystalline form was denied either because it was sufficient to establish that the person skilled in the art could have done so with a reasonable expectation of success, or because it was a clear expectation that a crystalline form would provide a solution to the performance of substance. The Korean Supreme Court held that the properties of crystalline forms were well known, and it was a common practice to confirm the existence of polymorphism of a substance.[879] The

874 See *supra* 803 -804 and accompanying texts.
875 See *supra* 809 -811 and accompanying texts.
876 *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 747 (N.D.W.Va. 2004), *aff'd*, 161 Fed.Appx. 944 (stating "a difference in [activity] of two, a two-fold difference ordinarily would not be considered to be a substantial difference.").
877 *Pfizer Inc. v. Ranbaxy Laboratories Ltd*., 405 F.Supp.2d, 495, 517 (D.Del. 2005).
878 See *supra* 836 and accompanying texts.
879 See *supra* 863 and accompanying texts.

Supreme Court specifically held that it could not acknowledge the improved "*pharmaceutical effect*" achieved by the improved physical characteristics of a crystalline form,[880] and it further noted that the reduced batch-to-batch variability in mono-crystalline form was just a logical consequence.[881]

For the metabolite inventions, the novelty was the central issue, and the inventive step was not.

The tendency to a lowered inventive step requirement is also observable from the fact that even if there is clear motivation leading to the invention, the unexpected effects from the obvious test was well adapted to defend the non-obviousness attack. In other words, unexpected or enhanced results could fail to establish the inventive step when there is a real motivation to use the idea, i.e. the effects emerged from obvious tests.[882] Of course, no recipe to obtain separation of enantiomers[883] or crystalline forms is infallible, and the separation can be a paradigm of trial and error.[884] However, decisions to develop either a single enantiomer or racemates as a drug substance are already a key milestone in the drug R&D process.[885] There is also the regulatory pressure to require separation of enantiomers from its racemic mixture.[886] The situation is similar in crystalline form identification and development.[887] However, either the courts do not acknowledge these as motivation,[888] or the motivation is countervailed by unexpected results.

The case law could develop and change, but the current direction of the changes seems to be going against or at least not considering the development of scientific technology.

880 See *supra* 867 and accompanying texts.
881 See *supra* 868 and accompanying texts.
882 *Napp Pharmaceuticals v. Ratiopharm* [2009] EWCA Civ 252, para 115; *Hoechst/Enantiomers*, T296/87, OJ EPO 1990, 195, 206, 209.
883 *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088 (Fed. Cir. 2008).
884 *Sanofi-Synthelabo v. Apotex Inc.*, 492 F.Supp.2d 353, 370 (S.D.N.Y.,2007).
885 *Beary*, 339 Lancet 495 (1992); *Caldwell*, 16 Hum. Psychopharm. S67, S69 (2001); *Mansfield/Henry/Tonkin*, 43 Clin. Pharmacokinet. 287, 287 (2004).
886 *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1089-90 (Fed. Cir. 2008).
887 *Korean Supreme Court/Lercanidipine*, 2010Hu2872, Jul. 14, 2011, para 1.
888 *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1089-90 (Fed. Cir. 2008).

C. Disclosure requirement

The concept of "possession" or "occupancy" is one of the most fundamental concepts in property,[889] which provides the boundaries of what is mine or another's. Due to the nature of intellectual property, the object that someone possesses, such as an invention, is intangible. This is the fundamental reason why patent law sets out the disclosure requirement, which is divided into a written description and the enablement.[890] In general, the written description requirement helps to define the boundary of possession of the invention, and the enablement requirement works to prove that the inventor did not just describe the invention but really possessed the invention at the time of filing. As evidence of possession, either the embodiment that was physically created and existed or the disclosure that enabled others to do so without many difficulties will usually be provided.

The purposes of this disclosure requirement are i) to permit others to make use of a patented invention once the patent expires, thereby ensuring that the invention will ultimately enter the public domain, and ii) to enable others to improve on the patented technology, either by designing around the patent, or by developing improved versions.[891] Thus, this disclosure requirement is

889 *See generally, Rose*, 52 U. Chi. L. Rev. 73 (1985).

890 EPC Art. 84, the second sentence ("[The claims] shall be clear and concise and be supported by the description) and EPC Art. 83 ("The European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art."); 35 U.S.C. § 112 ("The specification shall contain (i) a written description of the invention, (ii) and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, (iii) and shall set forth the best mode contemplated by the inventor of carrying out his invention."); the best mode requirement of U.S. patent law would not be discussed in this dissertation; *Chisum*, 15 AIPLA Q. J. 57, 58 (1987); *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 19 (stating two requirements for anticipation is prior disclosure and enablement).

891 *Burk/Lemley*, 17 Berkeley Tech. L.J. 1155, 1161 (2002).

the *quid pro quo* for granting patent exclusivity.[892] This requirement for the chemical invention, however, has seldom been the subject of decisions at the highest legal level, and most of the litigation has been fought in the areas of novelty and the inventive step.[893] Thus, the disclosure requirement will be only briefly discussed.

1. Written description requirement

As a result of disclosure, later inventors can build on their own inventions based on the information disclosed, and the overall knowledge of society increases. Thus, courts have regarded disclosure as a crucial standard for the patent system.[894] As Newman J stated, this requirement sets forth what was invented and sets boundaries for what can be claimed.[895] This requirement limits the claims to the extent that they are adequately disclosed in the specification.[896] To the question of whether the claims constitute a description, the *Gardner* Court once answered that the claim, which was an original

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892 *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 971 (Fed. Cir. 2002), *reh'g denied,* (Lourie, J., concurring) ("The statute states that the invention must be described. That is basic patent law, the *quid pro quo* for the grant of a patent; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time."); *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005) (noting "[t]he written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity."); *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Intern., Inc.*, 534 U.S. 124, 142 (2001) ("The disclosure required by the Patent Act is 'the quid pro quo of the right to exclude.'"); *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co*., 598 F.3d 1336, 1361 (Fed. Cir. 2010); *Beecham Group v. Bristol Laboratories S.A.* [1978] RPC 521, 579 ("The quid pro quo for the monopoly granted to the inventor is the public disclosure by him in his specification of the special advantages that the selected members of the class possess.").

893 *Hansen/Hirsch*, 1997, 51 (further noting recently this got to play a role at the area of biotechnology, such as the inventions involving gene technology).

894 *Anonymous*, 118 Harv. L. Rev. 2007, 2011 (2005) (noting courts had embraced the disclosure rationale as a centerpiece of patent policy. However, the author has a contrary opinion.).

895 *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 975 (Fed. Cir. 2002) , *reh'g denied,* (Newman, J., concurring) (noting "[t]he description of invention has always been the foundation of the patent specification. It sets forth what has been invented and sets boundaries of what can be claimed.").

896 *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998).

claim, in itself constituted a description in the original disclosure equivalent in scope and identical in language to the total subject matter being claimed, and nothing more was necessary to comply with the description requirement.[897]

The written description requirement traditionally played a role in limited circumstances: i) When determining whether the claims were entitled to the application's filing date after claims were amended or newly-added, ii) when assessing whether a patentee was entitled to the benefit of the filing date of an earlier application claiming a priority date, and iii) when an interference mattered.[898] More recently, the requirement has been invoked against claims that were not originally filed as part of the written description, although commentators have heavily criticized this as a heightened written description requirement. [899]

In Europe, separately from the enablement requirement embodied in Art. 83 EPC, the written description requirement is set out in Art. 84 EPC, which requires that the claim be clear and concise and be supported by the

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897 *In re Gardner*, 475 F.2d 1389, 1391 (C.C.P.A., 1973), *reh'g denied* 480 F.2d 879, 879-80 (holding that the original claim in itself adequate written description of the claimed invention, and whether the descriptive part of the specification should be amended to include the language of the claim in suit was more of an administrative matter.).

898 *Janis*, 2 Wash. U. J. L. & Pol'y 55, 57, 59-60 (2000); *Rai*, 34 Wake Forest L. Rev. 827, 830 (1999); *In re Wright*, 866 F.2d 422, 424 (Fed. Cir. 1989) (holding the essence of written description requirement is to judge whether the newly claimed subject matter was described in the patent application as filed, in the case that the scope of a claim has been amended and directed to a different invention than the original claim.).

899 *Sampson*, 15 Berkley Tech. L.J. 1233, 1262 (2000) (The primary argument against the Federal Circuit's heightened written description requirement for biotechnological invention is that … it also 'reduces incentives to invest in innovation by depriving potential patentees of the opportunity to fully benefit from their research.'"); *Rai*, 34 Wake Forest L. Rev. 827, 834-35 (1999) ("the Lilly court used the written description requirement as a type of elevated enablement requirement." "[T]he CAFC's is based on its view that DNA-based technology is simply a subset of chemical technology generally."); *Mueller*, 13 Berkeley Tech. L.J. 615, 617 (1998) ("The *Lilly* decision establishes uniquely rigorous rules for the description of biotechnological subject matter that significantly contort written description doctrine away from its historic origins and policy grounding. The *Lilly* court's elevation of written description to an effective 'super enablement' standard of uncertain scope and applicability […]"); *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1326 (Fed. Cir. 2003).

description. The BOA explained that a principle purpose of this requirement in Art. 84 is to ensure that the monopoly given by a patent normally corresponded to the invention described in the application, and that the claim is not drafted so broadly that it dominates activities that do not depend upon the invention described in the application.[900] The Board further made clear that the term "supported" applies to a claim in a generalized form.[901] In the *Exxon* case, the Board noted that "a claim might be well supported by the description in the sense that it corresponded to it, but still encompassed subject-matter that was not sufficiently disclosed within the meaning of Art. 83 EPC, as it cannot be performed without undue burden, or vice versa." [902]

In the United States, a written description was not a separate requirement from the enablement requirement before 1967. That year, however, the Court in *In re Ruschig*[903] created a new written description doctrine for the sole purpose of enforcing priority issues.[904] It could have been based on the historical rationale derived from the Supreme Court's interpretation of a predecessor to § 112 in *Evans v. Eaton*, which was decided when American patent law had not required to contain claims.[905] In *Evans v. Eaton*, the Supreme Court held that a patent specification had two objects: (i) To enable artisans to make and use the invention, and (ii) to put the public in possession of what the party claimed as his own invention.[906] Some scholars argued that the distinction between the written description and the enablement requirement was arbitrary and redundant.[907] However, the Federal Circuit recently reaffirmed the distinction between these two requirements in the *Ariad v. Lilly* case.[908]

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900 *Xerox/Amendments*, T 133/85, OJ EPO 1988, 441, 448.

901 *Xerox/Amendments*, T 133/85, OJ EPO 1988, 441, 448. .

902 *Exxon/Fuel oils*, T 409/91, OJ EPO 1994, 653, 662; *see also Mycogen/Modifying plant cells*, T 694/92, OJ EPO, 1997, 408, 414-15 (noting "it follows that, despite being supported by the description from a purely formal point of view, claims may not be considered allowable if they encompass subject-matter which in the light of the disclosure provided by the description can be performed only with undue burden or with application of inventive skill.").

903 *In re Ruschig*, 379 F.2d 990, 995-96 (C.C.P.A. 1967).

904 *See*, *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1323 (Fed. Cir. 2003); cf. *Janis*, 2 Wash. U. J. L. & Pol'y 55, 57, 62-69 (2000) (arguing this distinction between the written requirement and enablement requirement is artificial.).

905 *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991).

906 *Evans v. Eaton*, 20 U.S. 356, 433-34 (1822).

907 *See e.g., Janis*, 2 Wash. U. J. L. & Pol'y 55, 80-88 (2000).

908 *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336 (Fed. Cir. 2010).

In Korea, the written description is set out in the Korean Patent Act, Art. 43(4), which requires the claim to be supported by the description and to define the invention clearly and concisely. The enablement requirement is set out in Art. 42(3) which requires the detailed description of an invention states the invention clearly and fully in a manner that allows a person skilled in the art to carry out the invention easily.

2. Enablement requirement

a) Enablement requirement

The enablement requirement requires that patent applicants disclose the description of the invention sufficiently to enable the person skilled in the art to make and use it.[909] This disclosure, which is a trade off between the patentees and the public, is one of the fundamental functions of patent law.[910] This can be read in the U.S. Supreme Court's language: "[T]o obtain a utility patent, a [patentee] must describe the [invention] with sufficient specificity to enable others to 'make and use' the invention after the patent term expires."[911]

This requirement ensures that the invention is available to be taught to the public once it is published and to enable others to practice the invention once the patent term expires.[912] This is the proper way to answer the question of "possession" of an invention by the inventor,[913] and, at the same time, guar-

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909 *See e.g.*, EPC Art. 83, 35 U.S.C. § 112.

910 *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 489 (1974); *Burk/Lemley*, 17 Berkeley Tech. L.J. 1155, 1161 (2002).

911 *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Intern., Inc.*, 534 U.S. 124, 142 (2001).

912 *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 186-87 (1933) (" An exclusive enjoyment is guaranteed him for seventeen years, but, upon the expiration of that period, the knowledge of the invention inures to the people, who are thus enabled without restriction to practice it and profit by its use."); *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Intern., Inc.*, 534 U.S. 124, 142 (2001).

913 *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 988 (Fed. Cir. 2002) , *reh'g denied,* (Linn, J., dissenting) ("The question presented by 35 U.S.C. § 112, paragraph 1, is not, 'Does the written description disclose what the invention is, or does it merely describe what it does?' The question is, 'Does the written description describe the invention recited and described in the claims-themselves part of the specification-in terms that are sufficient to enable one of skill in the art to make and use the claimed invention?'").

antees that the public will be in possession of the invention.[914] In other words, this requirement seeks to ensure that the inventor actually has conceptual possession of the invention at the time of filing.[915]

To meet the enablement requirement, the specification, which is part of the application for a patent, must describe not only the invention but also the manner of making and using the invention in sufficiently full terms as to enable a person skilled in the art to make and use the invention without resort to "undue" experimentation.[916] The patent specification does not need to disclose all of the ways to enable the invention. For example, even if only one way of performing the invention is disclosed, it can be sufficient as long as it allows the person skilled in the art to perform the invention in the whole range that is claimed.[917] Accordingly, the scope of enablement inversely varies with the degree of unpredictability of the factors and the arts involved.[918] The patentee is entitled only to a scope that is commensurate with the scope of his innovation, which is represented by the disclosure in the

914 *Janis*, 2 Wash. U. J. L. & Pol'y 55, 63 (2000); *See generally, Holbrook*, 59 SMU L. Rev. 123 (2006) (noting this teaching function of patent disclosure was rather limited, however, functioned more to demonstrate the inventor's possession of the invention.).

915 *Burk/Lemley*, 89 Va. L. Rev. 1575, 1653 (2003) (further explaining that after the written description requirement was served by the claim in the United States, this requirement had evolved to serve a new purpose, i.e. enablement); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998).

916 *Chisum*, 15 AIPLA Q. J. 57, 58 (1987); *see also Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, paras 28-33; *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (noting "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.", quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)); *In re* Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988); *see also* subsection IV.A.3.

917 *BGH/Textilgarn*, GRUR 1959, 125, 125; *Exxon/Fuel oils*, T 409/91, OJ EPO 653, 662-63 (1994) point 3.5.(further noting the disclosure of the invention was sufficient if it enabled the skilled person to obtain substantially all embodiments falling within the ambit of the claims.).

918 *Brandi-Dohrn*, GRUR Int 1995, 541.

patent specification.[919] Thus, this demarcation is especially important in the field of unpredictable arts. Given that it is harder to predict the technical result in chemical reactions, and especially physiological responses, than to predict those in other fields, the level of enablement in pharmaceutical art seems to be naturally higher than those in other fields. Conducting a large number of tests to monitor the results of a minor structural change would be of little value. However, the extent to which the invention should be enabled is not certain and must be determined in each case.[920]

The effort to be expected of the person skilled in the art is the total sum of the experimental effort necessary to advance successfully step-by-step toward the desired final goal, even though each individual experimental step can be considered feasible with a certain amount of trial and error.[921] "Without undue experimentation" therefore means that it allows certain sensible degree of trial and error. In Europe, this experimentation must lead to the desired result with "an acceptable statistical expectation rate" in case of random experiments.[922] In the United States, the relevant factors to determine this include "the quantity of experimentation that was actually needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology."[923] The determination of "undueness" is "not a single, simple factual determination,

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919 *See e.g., Chiron Corp. v. Genentech, Inc*., 363 F.3d 1247, 1263 (Fed. Cir. 2004) (Bryson, J., concurring) (noting the proper approach is "to address cases of new technology by construing claims, where possible, as they would have been understood by one of skill in the art at the time of the invention, and not construing them to reach the as-yet-undeveloped technology that the applicant did not enable. That approach preserves the benefits of patent protection for the invention that the applicant has actually conceived and enabled, without extending those benefits for an invention that the applicant may not have conceived and certainly has not enabled.").

920 In the pharmaceutical field where there is narrower room for the person skilled in the art could have known the inventor's possession of the invention, the broader variants need to be shown to be enabled.

921 *MIT/Biopolymers*, T639/95 (1998), point 15; *Molecular Biosystems/Oligonucleotide therapeutic agent*, T 994/95 (1999), point 9.

922 *Unilever/Stable bleaches*, T 0226/85, OJ EPO 1988, 336, 340.

923 *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1085 (Fed. Cir. 2008).

but rather a conclusion reached by weighing many factual considerations." [924]

However, the enabling disclosure of the specification must be correlated with the scope of the claim under consideration.[925] A specification may only enable part of a claim. For example, the chemical embodiments in the specification might not include the whole number of the generic class of compounds. Similarly, a specification might enable a broader scope than the claim. For example, a claim may be narrowed down by adding a limitation, but the specification fails to provide sufficient information as to the limited scope of the claim. These limitations are imposed, because a patent should not control inventions that it does not enable.[926] In the *Exxon/Fuel Oils* case, the application was refused, because, while it claimed fuel oils containing certain crystals with an average particle size of "less than 4000 nm," it provided only an example thereof with a crystal particle size of 1200 nm and gave no further teaching regarding the production of smaller particles.[927] The Board held that, to fulfil the requirement of Art. 83 EPC, the application as filed should have contained sufficient information to allow a person skilled in the art, using his common general knowledge, to carry out the invention within the whole area that was claimed.[928]

As the BGH held, "claims for chemical compounds, in which generic formulae characterise the claimed compounds, may not cover compounds which it is established were not available to the skilled person at the time of the patent application."[929] In traditional chemistry, however, since the information in the patent application has made it feasible to manufacture the compounds with generally available starting materials and standardized reactions, the more valuable information concerns the use of the compounds,

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924 *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

925 *Chisum*, 15 AIPLA Q. J. 57, 61 (1987); *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.,* 166 F.3d 1190, 1195-96 (Fed. Cir. 1999) (noting "[t]he enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims."); MPEP § 2164.08 ("All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled.").

926 *Merges/Nelson*, 25 J. Econ. Behav. Organ. 1, 18 (1994).

927 *Exxon/Fuel oils*, T 409/91, OJ EPO 653, 657 (1994) point 2.

928 *Exxon/Fuel oils*, T 409/91, OJ EPO 653, 657 (1994) point 2.

929 *BGH/7-Chlor-6-demethyltetracyclin*, GRUR 1978, 162, 165.

not the way to manufacture them.[930] Self-evidently, each invention should lead to the described results as well, when one applies the relevant technical teaching.[931]

b) Enablement requirements in the patent law

Although there was a case requiring enablement in the context of obviousness rejection, [932] enablement requirements are generally found in the disclosure requirement and in the novelty requirement.

(1) Enablement as a requirement for anticipation

As discussed in chapter IV.A.3, an enabling disclosure is required in addition to the disclosure requirement for anticipation of the invention in main jurisdictions. For example, the BGH held in the *Olanzapine* decision that the concept of disclosure was exclusively what a person skilled in the art directly and unambiguously derived from the prior art as the content of teaching, thereby enabling him specifically to carry out the invention.[933] The House of Lords explained that there is a difference in the role of the person skilled in the art for the two requirements of anticipation. For the disclosure requirement, the person skilled in the art is taken to be trying to understand what the author of the prior art meant, and, once the meanings of the prior disclosure are determined, the author has no further part to play.[934] For the purpose of the enablement requirement, however, the question is no longer what the skilled person would think the disclosure meant, but whether he would have been able to work the invention.[935] Enablement has played a key

930 *Domeij*, 2000, 45.
931 *Hansen/Hirsch*, 1997, 56.
932 *In re* Payne, 606 F.2d 303, 314 (C.C.P.A. 1979) ("References relied upon to support a rejection under 35 USC 103 must provide an enabling disclosure, i. e., they must place the claimed invention in the possession of the public.").
933 *BGH/Olanzapine*, IIC 2009, 596, 599.
934 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 32.
935 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 32.

role in the context of anticipation; however, it has rarely been discussed.[936]

(2) Basic similarity of the two enablement requirements

The BOA held that any prior art cited under the novelty provisions must contain an enabling disclosure to destroy novelty and that this enabling requirement was identical to that under Art. 83 EPC. Thus, the cited document must have disclosed the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.[937] In other words, the same degree of clarity and practical usefulness is required regarding the possibility of using the invention, which is part of the state of the art, and that of using the invention in the application filed.[938] *Tilman* also noted that the prior art document must have clarity, such as a patent claim would have, and that this requirement comes close to the wording of Arts. 83 and 84 EPC. Thus it was correct to require that the information in a prior art disclosed "directly and unambiguously" the subject matter of a claim to avoid double patenting.[939] Lord Hoffman mentioned that he could think of no reason why there should be any difference between the test of enablement of a prior disclosure for the purpose of anticipation and the test of enablement of the patent itself for the purpose of sufficiency.[940] He held that the authorities on section 72(1)(c) regarding the grounds for the revocation of a patent were equally applicable to enablement for the purpose of sections 2(2) and (3) regarding novelty.[941] Thus, the tests of enablements may seem to have no difference.

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936 *Seymore*, 60 Duke L. J., 919, 925 (2011); *see also, e.g., Chester v. Miller*, 906 F. 2d 1574, 1576 n.2 (Fed. Cir. 1990) (noting that for being prior art under section 102(b), the reference must place the anticipating subject matter at issue into the possession of the public through an enabling disclosure).

937 *See e.g., ICI/Herbicides*, T 206/83, OJ EPO 1987, 5, 9; *Collaborative/Preprorennin*, T81/87, OJ EPO 1990, 250, 257.

938 *Domeij*, 2000, 136.

939 See *Tilmann*, IIC 2010, 149, 152.

940 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 27 (noting "[i]n the present case the Court of Appeal was reluctant to say that the test of enablement of a prior disclosure for the purpose of anticipation was the same as the test of enablement of the patent itself for the purpose of sufficiency. But I can think of no reason why there should be any difference […].").

941 *Synthon BV v. SmithKline Beecham plc* [2005] UKHL 59, para 27.

(3) Differences between the two enablement requirements

The differences between enablement as a requirement for anticipation and as a requirement for sufficiency of disclosure can be summarized as follows. The first distinction depends on whether the requirement is introduced by legislation or by judicial bodies. The statutes clearly state the enablement requirement (sufficiency of disclosure) for obtaining a patent.[942] However, the enablement requirement for anticipation is specified neither in Art. 54 EPC, nor 35 U.S.C. § 102, nor anywhere else in the patent statutes. This requirement for anticipation was established by the courts.[943]

The second difference depends on whether the utility of the invention is to be enabled as well. The Federal Circuit in *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp*.[944] confirmed that the standard for enablement of a prior art reference for purposes of anticipation under § 102 differed from the enablement standard under 35 U.S.C. § 112; namely, the specification should enable a person skilled in the art to "use" the invention to meet the requirement under § 112, but the specification need not do so to meet the requirement under § 102.[945]

The third difference is whether the scope of the invention has to be enabled when the prior art reference is a patent (application) itself. To meet the enablement requirement for the "patent-obtaining purpose" under Art. 83 EPC

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942 EPC Art. 83 (2010); 35 U.S.C. § 112 ¶1 (2006); Korean Patent Act Art. 42(3).

943 *Mueller/Chisum*, 45 Hous. L. Rev. 1101, 1137-38 (2008) (stating "the courts have read the enablement requirement into anticipation under § 102(b)."); *see also In re LeGrice*, 301 F.2d 929, 939 (C.C.P.A. 1962) (holding that anticipation under § 102(b) "requires that the description of the invention in the printed publication must be an 'enabling' description").

944 *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp*., 424 F.3d 1347, 1355 (Fed. Cir. 2005); *Rasmusson v. SmithKline Beecham Corp*., 413 F.3d 1318, 1325 (Fed. Cir. 2005).

945 *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp*., 424 F.3d 1347, 1355 (Fed. Cir. 2005) (citing *In re Hafner*, 410 F.2d 1403, 1405 (C.C.P.A.1969) stating "section 102 makes no such requirement as to an anticipatory disclosure."); *see also In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992) (citing *In re Donohue*, 632 F.2d 123, 126 (C.C.P.A. 1980) ("proof of utility is not a prerequisite to availability of a prior art reference under 35 U.S.C. § 102(b)"); *see also Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.,* 246 F.3d 1368, 1379 (Fed. Cir. 2001)) (holding that "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art."). This can be viewed differently in different jurisdictions.); *Rasmusson v. SmithKline Beecham Corp*., 413 F.3d 1318, 1325 (Fed. Cir. 2005).

or 35 U.S.C. § 112, the specification must enable the whole scope of the claimed invention. In contrast, to meet the enablement requirement for the "patent-defeating purpose", it is enough to enable the scope of the invention at issue.[946] Thus, the description of a single embodiment for a broad claim in an earlier patent (application) can enable the invention for anticipation purposes, but the same embodiment alone may not be enough to provide a sufficient description for the earlier patent (application) itself.[947] However, even in this case, the single embodiment of the prior art reference (earlier patent) could have enabled a narrower claim scope in the earlier patent covering at least the embodiment itself.

3. Disclosure requirement of selection inventions

Unlike novelty or inventive step requirements, the disclosure requirement for the chemical invention has seldom been the subject of decisions at the highest legal levels.[948] Thus, only a few relevant cases are discussed under this title.

a) Species selection invention

In *Dr Reddy's Laboratories v. Eli Lilly* in the United Kingdom, the lack of sufficiency was challenged by Dr. Reddy's Laboratories. The main ground raised before the Patent Court was that the patent specification did not disclose alleged superior advantages to other members of preferred classes in the prior art,[949] which was required to meet a selection invention. In other words, this insufficiency attack was based on the premise that the patent could be upheld over the prior disclosure only if it was a valid selection patent. However, since the Patent Court found that the patent was valid without relying on the selection principles, the insufficiency attack lost its

946 *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991); *see also Kieff/Schwartz/Newman*, 2011, 207-211.

947 *In re Lukach*, 442 F.2d 967, 970 (C.C.P.A. 1971) (noting the difference of the enablement requirement for the patent obtaining purposes from that for the patent defeating purposes).

948 *Hansen/Hirsch*, 1997, 51.

949 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345, para 188.

ground.[950] Jacob LJ on appeal restated that, since Lilly had not complied with the 'old selection rules', it was unnecessary to discuss this issue.[951]

b) Optical isomers

In the first instance of the *Escitalopram* decision in the United Kingdom, while citing the *Biogen* decision,[952] Kitchin J held that the claims were not sufficient, basically because the scope of protection was broader than the invention's technical contribution. He restated that enantiomer's inventive idea is only one way to make it, neither on the discovery of the enantiomer nor on its medicinal effect.[953] He further stated that, since the claim in issue was to a monopoly of that enantiomer but the specification provided only one way to make it, the patentee was not entitled to a monopoly of every way of making it i.e. a product *per se* claim. Consequently, the claim was not sufficient.[954]

While distinguishing a product-by-process claim, as in the *Biogen* case, from an ordinary product claim, Lord Hoffmann[955] held that, "since the product itself is the invention, it is sufficiently enabled if the specification and common general knowledge enables the skilled person to make it and one method is enough."[956] The difference between this case and *Biogen* was whether the product made by the inventive procedure was available before the invention. While agreeing with the EPO's decision on the *Exxon* case,[957] Lord Hoffmann concluded that, "if the patentee had found a non-obvious way of making the product, he was entitled to a product claim, with

950 *Dr Reddy's Laboratories (UK) Ltd v. Eli Lilly & Company Ltd* [2008] EWHC 2345, para 189.
951 *Dr Reddy's Laboratories Ltd v. Eli Lilly & Company Ltd*, EWCA Civ 1362, paras 75-76.
952 *Biogen Inc v. Medeva Plc* [1996] UKHL 18, para 75.
953 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 26.
954 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 26.
955 Lord Hoffmann the very who gave *Biogen* decision specially stepped down an instance and sat on the Court of Appeal where he had served more than ten years ago.
956 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 27.
957 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 59 (citing the Technical Board of Appeal said in Exxon/ Fuel Oils T409/91 as "The extent of the patent monopoly, as defined by the claims, should correspond to the technical contribution to the art in order for it to be supported or justified.").

the full monopoly of the product which that conferred."[958] Jacob LJ noted that the product claim actually provides a broader monopoly[959] and concluded that the fact that the patentee should not have more than he deserved did not form part of the statutory test for sufficiency.[960]

The House of Lords' reasoning was very much in line with Lord Hoffmann's. Lord Walker noted the discussion before the House of whether "inventive concept" meant the same as "technical contribution to the art." He stated that they are certainly connected, but that "inventive concept" was concerned with the identification of the core of the invention, while the invention's "technical contribution to the art" was concerned with the evaluation of its inventive concept.[961] Lord Neuberger stated that based on the fact that the patentee's "technical contribution" was to make the invention available for the first time, the patentee was entitled to claim the enantiomer. This decision brought the British patent courts into line with EPO jurisprudence and with a more patentee friendly disposition.

c) Crystalline forms

In T1066/03, where a process for the preparation of amorphous atorvastatin (Lipitor ®) and hydrates was claimed, the Board revoked the patent based on the lack of sufficiency, since the patent did not enable the skilled person to produce without undue burden the crystalline form I of atorvastatin, i.e. the starting material (seed crystal) to be used in the claimed process.[962]

D. Conclusion

The patentability requirements on selection inventions have been explored and analyzed. Regarding species selection invention, the novelty requirement has been lowered in Germany and the United Kingdom, where the courts declared that their established patentability requirements for the species selection invention were no longer valid. To establish novelty re-

958 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 37.
959 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 54.
960 *Lundbeck v. Generics Ltd.* [2008] EWCA Civ 311, para 57.
961 *Generics Ltd. v. Lundbeck* [2009] UKHL 12, para 30.
962 *Warner-Lambert/Polymorphic Atorvastatin*, T 1066/03 (2006), para 2.6.

quires overcoming the difficulty of identifying and isolating a specific member from the genus disclosure. The inventive step of a species selection invention was mainly established based on its advantageous effects.

The novelty of optical isomers was based on the difficulty of separation, regardless of the extent to which the structures were clearly disclosed in the prior art and regardless of whether it was well-known to a person skilled in the art that one or the other would exert its pharmacological effect. The difficulty of resolution was key in assessing novelty, because for an invention to be anticipated by a prior art, it must not only disclose the element of invention but also enable the invention. The much relaxed inventive step requirement on optical isomers was glaring. For example, the routine test became the non-routine test after ten years. In many jurisdictions except Korea, unlike their earlier rulings, it was held that the inventive step was re-established based on the difficulty of separation or on the fact that the separation could not have been achieved with reasonable expectation thereof, even though there was ample motivation to do so.

For crystalline forms, the issue of novelty was mainly about the extent to which the claimed crystalline forms were inevitably produced according to the process disclosed in the prior art, and novelty was generally not found. In addition, the inventive step for crystalline forms was denied either because there was a reasonable expectation of success or because the argued better effects were expected. The Korean Supreme Court noted that the improved pharmaceutical effect achieved by the altered physical characteristics of a crystalline form was not acknowledged.

Even though the reasoning behind the novelty of metabolite inventions in the British and American decisions was different, it was very clear that the courts acknowledged that the new exclusivity could have prevented the public from continuing to do something that was done before. If the metabolite had been found to be novel, the patent would have been granted on it, and the scope of the metabolite patent could have covered the metabolite generated by the body, thereby leading to an absurd result.

In addition, by granting these patents with lowered patentability requirements, the patent system could have influenced manufacturers to do the research on it separately or laterally. For example, the inventive step for optical isomers was identified because of the difficulty of resolution or the unpredictability of which isomer among the racemic mixture would exert the pharmacological effect of the racemate and which isomer would exert the side effects thereof. If this is so, should the manufacturers not be encouraged to do so from the very beginning, not after the research on the racemates is

done? This would be tantamount to exposing the public to drugs containing risky components.[963]

The low quality of pharmaceutical patents can also be seen in the report by the American Federal Trade Commission ("FTC"). The FTC report presented data from the litigation that resulted from paragraph IV challenges from 1992 to 2000, in which 73% of the para. IV filers prevailed.[964] Although winning a suit not only invalidates the challenged patent or leads to abandonment by the reference drug company, it also means non-infringement of the generic version. The high number is enough to imply that the quality of these patents is poor. The Pharma Sector Inquiry further confirmed that the opposition rate before the EPO was consistently higher for the pharmaceutical sector (about 8%) than it is in the organic chemistry sector (about 4%) and across all sectors (overall EPO average was about 5%).[965] The Pharma Sector Inquiry further reported that generic companies exclusively opposed second generation patents and prevailed in approximately 60% of the final decisions rendered by the EPO (including the BOA) in the period 2000 to 2007, and that the scope of the originator patent was restricted in another 15% of cases.[966] Furthermore, an empirical study on completed patent litigation on all drugs that first became eligible for challenges between 2000 and 2008 (covering 277 patents and 147 drugs) reported i) that for the patents at issue in settled litigation, 89% were secondary patents,[967] and ii) that for the patents litigated to completion (not settled), the brand name companies nearly always won a suit asserting an NMEs (92%), however, they usually lost suits asserting secondary patents (32% wins).[968]

Patentability requirements are assessed by a person skilled in the art. Thus, these lowered patentability requirements could well mean that a person skilled in the art has even fewer skills in the most scientifically developed era. Further, the much relaxed patentability requirements made both the newer version of products and the older versions concurrently available in

963 *Daniels/Nestman/Kerr*, 31 Drug Inf. J. 639, 643 (1997) (noting regulatory bodies would be more interested with the toxicological aspects of the stereochemistry issues, and they would expect full toxicological evaluation of each enantiomer if the toxicity had been detected.).

964 *FTC*, 2002, 20.

965 *DG Competition*, 2009, 239-253.

966 *DG Competition*, 2009, 239-253.

967 *Hemphill/Sampat, Bhaven N.*, 339 Science 1386, 1387 (2013).

968 *Hemphill/Sampat, Bhaven N.*, 339 Science 1386, 1387 (2013).

the market.[969] Although the case law may develop and change, the direction of the changes seems to be running counter to or at least not to be taking into consideration the development of scientific technology.

969 *Hutt/Valentová*, 50 Acta Facultatis Pharmaceuticae Universitatis Comenianae 7, 8 (2003).