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Assessment of Disclosure In European Prodrug Patent Claims

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ASSESSMENT OF DISCLOSURE IN EUROPEAN PRODRUG PATENT CLAIMS

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ABSTRACT

The article discusses the concept of disclosure in European patent applications involving prodrugs and active metabolites thereof. The article begins with an introduction to the scientific aspects of prodrug design to understand their meaning and difference from common drugs. It is followed by legal analysis discussing the notion of "disclosure" as an element of assessing novelty and inventive step. The article argues that the "disclosure" should be broken off into scientific disclosure affecting novelty criteria and disclosure as an element of enablement to judge the inventive step. The arguments of the article is based on the ruling of the United Kingdom ("UK") landmark case *Merrell Dow Pharmaceuticals v. Norton Limited and Penn Pharmaceuticals* that has dealt with the assessment of novelty criteria by separating scientific disclosure from disclosure through use. As analyzed in the article, novelty assessment based on the disclosure doctrine may destroy the novelty criteria because of scientific "gaps" that may exist in the parent drug leading to potential infringement by the second-generation claim. The article also discusses the applicability of the inventive step requirement by analyzing relevant case law concluding that differently from the novelty criteria, the later should be applied differently considering explicitly available information about prior art or in other words, enablement of disclosure. Therefore, the notion and extent of the disclosure have a versatile impact on the assessment of the patentability criteria depending on whether it targets the novelty or the inventive step requirement.

I. THE SCIENCE BEHIND PRODRUGS

Many of the most common medicines are not effective in treating a large number of patients because of the genetic makeup that is responsible for determining how a specific drug reacts in a human body. The common

drug research involving a vast quantity of drug molecules cannot provide targeted solutions that can overcome physiochemical, biological or other barriers in drug efficiency and/or toxicity. Because of the genetic makeup, some people metabolize drugs slowly leading to toxic accumulation of the drug or some people metabolize drugs too quickly which may result in inefficiency of the drug action in the human body. When a new chemical entity shows barriers or limitations about its utility, it cannot be developed further into a therapeutic agent.[1] During the research phase, the most common problem related to the development of new drugs concerns solubility problems. Even with the use of current computational "filters" to minimize this problem,[2] compounds that are active in vitro may lack adequate pharmacokinetic properties and/or may be difficult to formulate.[3] Striving to improve the properties of a given drug and overcome the negative side effects of an existing drug, prodrugs have become valuable tools for modern drug development. A prodrug is a pharmacologically inactive substance[4] that must go through a chemical or enzymatic transformation to become effective inside the body. Thus, the therapeutic rationale behind prodrugs is to enhance the properties of the parent drug once metabolized in the body.

According to Huttunen, prodrug strategy has been used to increase the selectivity of drugs for their intended target.[5] These types of drugs are striving to offer safer and better-targeted treatment options in modern medicine. Metabolites[6] that are closely related to prodrugs are eventually formed as a result of a natural biochemical process of degrading and eliminating compounds. Therefore, to differentiate between prodrugs and metabolites, it can be said that if the pharmacological effect of a medication is due to the transformation of a drug into a metabolite, the medication may

1. *See generally* Valentino J. Stella, *Prodrugs: Some Thoughts and Current Issues*, 99 J. PHARM. SCI. 4755 (2010).

2. Jarkko Rautio et al., *Prodrugs: Design and Clinical Applications*, 7 NAT. REV. DRUG DISCOV. 255, 255 (2008).

3. A study conducted with the top 200 oral drug products in Japan, Great Britain, United States, and Spain revealed that approximately 37 percent of drugs had solubilities of less than 0.1 mg/mL *See* Toshihide Takagi et al., *A Provisional Biopharmaceutical lassification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan*, 3 MOL. PHARM. 631, 635 (2006).

4. The prodrug itself is often biologically inactive but may also possess biological activity—serving as a drug itself.

5. Kristiina M. Huttunen et al., *Prodrugs – from Serendipity to Rational Design*, 63 PHARMACOLOGICAL REVIEWS, 750, 751 (2011).

6. Edward D. Harris, *Biochemical Facts behind the Definition and Properties of Metabolites*, https://www.fda.gov/ohrms/dockets/ac/03/briefing/3942b1_08_Harris%20Paper.pdf (last visited Mar. 18, 2019).

be called "a drug" and an "active metabolite".[7] If, on the other hand, the said effect is due to the release of the drug from a larger chemical entity, then the medication is called "drug" and "prodrug."

Prodrugs can masked forms of active drugs that are designed to be activated after an enzymatic or chemical reaction once they are into the body.[8] Considering that during the R&D process of the parent drug it is not always possible to foresee all its properties, prodrugs as second-generation products seek to modify some of the shortcomings of the parent drug pertaining to absorption, distribution or metabolism. The active metabolite that is eventually responsible for the drug's *in vivo* pharmacological effect differs structurally from the existing prodrug that is administered to the patient.[9] A small structural modification, however, may result in major differences in biological activity.[10] Thus, second generation products can not only serve as a more efficient treatment option but also provide a high return on investment for a pharmaceutical company. The development of medicine using an active ingredient, the safety, and efficacy of which have already been established, is normally less time consuming, less expensive, and less risky than using a compound about which little is known.[11]

From the intellectual property law perspective, it is important to consider that prodrugs are inactive derivatives of drug molecules that were already contained in the parent drug that is developed to overcome therapeutic barriers in drug delivery. It means that in most cases prodrugs are simple chemical derivatives that are only one or two chemical or enzymatic steps away from the active parent drug as it incorporates an active molecular entity within another molecular structure. To illustrate this, according to a study, 49 percent of all prodrugs are targeted at the formation of esters, which means that they are structurally like the parent drug.[12] Some of the recently approved prodrugs include a very controversial Sofosbuvir that is challenged by the European Patent Office ("EPO").

7. HYEWON AHN, SECOND GENERATION PATENTS IN PHARMACEUTICAL INNOVATION, 19 MIPLC STUDIES 47-49 (2014).

8. *See generally*, Peter Ettmayer et al., *Lessons Learned From Marketed and Investigational Prodrugs*, 47 J. MED. CHEM. 2393, 2394 (2004); See *generally* Valentino J. Stella, *Prodrugs: Some thoughts and current issues*, 99 J. PHARM. SCI., 4755, (2010).

9. See *generally* Ralph Minderop et al., *Prodrugs and Metabolites – In the Twilight Zone of Patentability?*, 2 IP IN THE LIFE SCIENCES INDUSTRIES 9, (2013).

10. Case T 0939/92, Triazoles (1995).

11. Nat'l Inst. for Health Care Mgmt., Changing Patterns of Pharmaceutical Innovation (2002), http://nihcm.org/pdf/innovations.pdf.

12. Jarkko Rautio et al., *Prodrugs: Design and Clinical Applications*, 7 NATURE REVIEWS 255, 256 (2008).

From a legal point of view, prodrugs may offer a valuable opportunity to extend the life cycle of the parent drug. It is estimated that prodrugs account for 5-10 percent of the overall global drug market.[13] Most patents targeting prodrugs are related to oncological research although the range of truly innovative drugs is, according to the same study, not more than 5-10 percent, which suggests that many of these patents are small improvements or adjustments of currently existing drugs.

Considering that prodrugs are mainly applied for as secondary patents, they can add 6.3 additional years to the product life cycle.[14] According to Kapczynski, depending on the category of independent secondary patents, formulation patents when applied as secondary independent claims add approximately 6.5 years of patent life, secondary independent claims for salts, polymorphs, esters, etc., add 6.3 years and independently claimed a method of use claims add 7.4 years.[15] According to the European Pharmaceutical Sector Inquiry executed by the European Commission, applications on second generation patents for bestselling medicines is a common strategy to evergreen product lifecycle. The number of second generation patents rises significantly at the end of basic patents.[16] The Inquiry found that in 40 percent of cases first-generation patents are followed by second-generation patents and the average time before the launching of the second-generation patent was estimated to take place 1.5 years before the expiry of the basic patent.[17] Kapczynski has observed that independent secondary patents are not obtained randomly but rather the propensity to obtain secondary patents increases after successful sales suggesting they reflect deliberate attempts by branded firms to lengthen their monopoly for more lucrative drugs.[18] The EC Pharmaceutical Inquiry Report revealed a primary to a secondary patent ratio of 1:7 meaning that the number of secondary patents is much higher in comparison to initial patents obtained in

13. Jarkko Rautio et al., *Prodrugs – Recent Approvals and a Glimpse of the Pipeline*, 109 EUR. J. PHARMACEUTICAL SCI. 109, 146–61 (2017).

14. Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "'Secondary" Pharmaceutical Patents*, 7 PLOS ONE 49470(2012), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049470.

15. *Id.*

16. EUROPEAN COMM'N, PHARMACEUTICAL SECTOR INQUIRY REPORT (2009), http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

17. *Id.*

18. Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "'Secondary" Pharmaceutical Patents*, 7 PLOS ONE 49470 (2012), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049470.

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the beginning of drug lifecycle.[19] The interesting aspect of second-generation patents is that most studies analyze and estimate the effects of patenting strategies based on calculations related to the filing date of first-generation patents[20] thus, ignoring the potential effects of second-generation filings to the patent portfolio lifetime. If secondary patents are frequently obtained later in the invention cycle then chemical compound patents, this will underestimate patent life, perhaps substantially.[21]

Considering that a prodrug is structurally similar to its parent drug, two questions arise regarding patentability standards of these drugs. The first question that arises is the extent of disclosure or free use after the expiry of the parent drug in case a prodrug is claimed later during the life cycle process. The second question, connected to the first, is the validity of the prodrug patent in the light of fulfillment of the novelty and inventive step requirements. This article provides insight into these problems in the following sections and discusses the normative uncertainties by analyzing the most relevant case law.

II. THE IMPACT OF DISCLOSURE IN FIRST-GENERATION CLAIMS TO PRODRUG PATENT APPLICATIONS

Based on the data retrieved from the European Patent Register, it seems that most patents for prodrugs are claimed as second-generation patents. There can be several reasons that could explain it. It is possible that, at the time of filing the first-generation claim, potential shortcomings of the parent drug were not known which later caused the filing of the second-generation claim. It is also possible that the shortcomings in the first-generation drug were actually known already during the first filing, but the second-generation patent was later used as part of product life cycle management.

It is a fundamental principle of patent practices that after the expiry of the basic patent the subject matter falls in the public domain meaning that it becomes accessible to anyone without having to worry about the infringement. When the subject matter falls in public domain, no further patent should be granted to the same subject matter; otherwise it would lead to double patenting. If anyone attempted to craft a patent application covering the earlier subject matter, under the assumption that the earlier

19. EUROPEAN COMM'N, PHARMACEUTICAL SECTOR INQUIRY REPORT (2009), http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

20. See *generally* Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT'L. J. TECH. MGMT. 98 (2000).

21. See *generally* C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents?*, 8 J. EMPIRICAL LEGAL STUD. 613 (2011).

disclosure was complete and enabling enough, it would destroy the novelty and/or the inventive step requirement. However, considering that prodrug applications are line extensions of the parent drug, there are a few aspects to consider.

For a new claim to be patent eligible, a complete and enabling disclosure is required which is then assessed from the practical point of view. This means that the disclosure of the claim should be complete enough to enable a person skilled in the art to perform the invention without undue burden. Article 84 of the European Patent Convention ("EPC") states the following: "*The claims shall define the matter for which protection is sought. They shall be clear and concise and be supported by the description*."[22] In its case law, the EPO has clarified that Article 84 of the EPC requires that the claims define the subject matter for which patent protection is sought. It signifies that the disclosure should specify all the essential features needed to define the invention and that the meaning of these features should be clear for the person skilled in the art from the wording of the claim.[23] Based on the EPO Board's interpretation in case T 409/91, the underlying purpose of Article 83, directed to the disclosure of the invention, is the same as is stated in Article 84 of the EPC, Namely, to secure the grant of the proper breadth of patent exclusivity that can be justified by the technical contribution to the art.[24] The well-established jurisprudence of the EPO in respect to the interpretation of Article 84 of the EPC, requires that to be patentable, an independent claim must recite all the essential features which are necessary for clearly and completely defining a particular invention.[25] Therefore, the claim should define the subject matter by reference to all its essential technical features.[26] Although the disclosure must contain sufficient information for the skilled person to perform the invention, there is no requirement that the inventor should have full scientific understanding behind the invention. In many situations, it is not possible to add the full disclosure in the patent application, especially in the case of biotechnological patents and pharmaceutical patents, as it is not possible to delimit the invention. From the legal point, the reason why it is relevant to differentiate between the scientific disclosure and practical (enabling) disclosure is that it

22. *See* Convention on the Grant of European Patents art. 84, Oct. 5, 1973, 1065 U.N.T.S. 199 [hereinafter European Patent Convention].

23. Case G 0001/04, Diagnostic Methods, OJ EPO 2006, ¶ 6.2.4.

24. Case T 0409/91, Fuel Oils, OJ EPO 1994, 3.5.

25. Case G 0001/04, Diagnostic Methods, OJ EPO 2006, ¶ 6.2.4.

26. Case G 0001/04, Diagnostic Methods, OJ EPO 2006, ¶ 6.2..

defines the extent of the subject matter for which protection is sought and how it reflects the evaluation of novelty and the inventive step requirements. It is especially relevant for patents involving prodrugs as a small piece of scientific information in the disclosure to determine the perspective for patentability.

According to Article 83 of the EPC, the claim must also contain sufficient technical disclosure of the solution to the problem.[27] EPO Guidelines for Examination clarify that a detailed description of at least one way of carrying out the invention must be given. Therefore, the description should disclose any essential feature for carrying out the invention by the person skilled. When the first-generation patent is claimed for the parent drug, the disclosure should include a number of examples, alternative embodiments or variations of the subject matter extending over the area protected by the claim.[28]

In its case T-0409/91 the EPO Boards of Appeal has held that "The essential features of the invention, which must be used for defining the matter for which protection is sought, in accordance with Art. 84 EPC in combination with Rule 29(1) and (3), are all those technical features which are necessary to define an invention which is patentable under the EPC, including any feature which is necessary to define matter which also meets the requirement of sufficient disclosure pursuant to Article 83."[29]

Defining the essential features in the first-generation patent has an impact on the assessment of novelty in the second-generation patent application. The scientific disclosure is in direct conflict with the novelty criteria but according to Art. 54 of the EPC, novelty is judged based on the information made available at the time of the application. The novelty is thus judged by the (scientific) knowledge available. The inventive step requirement, on the other hand, refers to the enabling aspect of the invention to be carried out by the person skilled in the art. or these reasons, the extent of disclosure should be analyzed from two different angles, the scientific disclosure, which is connected to the novelty, and the enabling aspect of the disclosure, which is connected to the inventive step.

27. *See* European Patent Convention, *supra* note 22, art. 83.

28. European Patent Office, *Guidelines for Examination*, pt. F, ch. III, § 1 (2018), https://www.epo.org/law-practice/legal-texts/html/guidelines/e/f_iii_1.htm.

29. Case T 198/84, Hoechst ex parte, OJ EPO (1985). In the EPO Case T 292/85 it was stated that in certain cases a description of one way of performing the claimed invention might be sufficient to support broad claims with functionally defined features. For example, where the disclosure of a new technique constitutes the essence of the invention and the description of one way of carrying out the invention enables the person skilled in the art to obtain the same effect of the invention in a broad area by use of suitable variants of the component features. *See* Case T 0292/85, Genentech, OJ EPO (1988).

In the case of prodrugs, although being structurally similar to the parent drug, the main challenge does not arise from the scientific disclosure because these types of inactive derivatives of original drugs usually contain improved scientific knowledge. The inability to guarantee a patent for prodrugs stems rather from the inability to come to terms with the practical aspect of the disclosure because it raises questions whether a person skilled in the art was expected to reach to a specific result already during the assessment of the first-generation claim or not. Differently from prodrugs, the active metabolites that are the molecules (end products) of a drug (or prodrug) are generally considered as being already included in the first-generation claim in Europe from both the scientific, as well as practical, point of view their "behavior" during metabolism is a natural consequence, therefore they are excluded from patentability. As a consequence, they do not fulfill even the novelty requirement.

Still, under some circumstances, the scope of the patent is not limited to the version that the inventor invented, but could cover the subsequently modified versions if each falls within the scope.[30] It can be deduced that the inventor is not expected to include a "complete" scientific disclosure in the patent application, but should provide sufficient information to the examiner to carry out the invention. For some types of inventions, it can mean that the disclosure, although sufficient from the practical point of view, may contain "gaps" from the scientific aspect regarding any of its specific elements. These elements, on the other hand, can themselves be patentable subject matter, or may already be encompassed in the disclosure without being directly referred. For example, prodrugs and especially metabolites thereof can be viewed as anticipated inventions although they may not have been previously disclosed in the parent claim. At the same time, prodrugs can be viewed as a separate subject matter eligible for a new patent. The polemics here is whether these second-generation prodrug claims should automatically be refused to avoid a situation where the subject matter of the first claim is indirectly encompassed in the second-generation claim or find the prodrug patent valid which could mean that the first-generation invention is delayed before entering the public domain. The extent of disclosure and its effects on the novelty and inventive step requirements will be dealt with in the following sections of this article.

30. Changing Patterns of Pharmaceutical Innovation, *supra* note 11, at 19.

III. ASSESSMENT OF NOVELTY – THE MERRELL DOW CASE

Prodrugs are chemically modified versions of the pharmacologically active agent that must transform *in vivo* to release the active drug.[31] Considering that claims involving prodrugs usually refer to minor modifications of the structure or the chemical makeup of a molecule[32] meaning that they are only a few steps away from the parent drug, the main challenge for patenting prodrugs as product related second-generation claims comes from potential structural similarities to the parent drug of the first-generation claim. In other words, potential challenges arise from destroying the novelty and/or inventive step requirements of Articles 54 and 56 of the EPC. Article 54 requires that "for the invention to be considered novel, it should not form part of the state of the art."[33] If the concept of an invention is completely disclosed within a single piece of prior art, it lacks novelty, regardless of whether it was independently developed from the earlier invention.[34] Thus, the novelty connects to the availability of already existing information on prior art and the anticipation thereof. In case the invention is already claimed in an earlier (first generation) invention, the prior disclosure enables the entire claimed invention in addition to disclosing each and every element of the invention.[35] According to John F. Duffy,[36] whether the disclosure forms part of the state of the art depends whether there is a natural result, meaning that it should be decided whether the later invention is the natural result flowing explicitly from the earlier disclosure. What has to be established in the examination as to novelty is whether the state of the art is such as to make the subject matter of the invention available to the skilled person in a technical teaching.[37]

In the case of prodrugs and active metabolites, the question that arises is how to judge the extent of the scientific disclosure because this type of second-generation inventions may already have been disclosed in the first application without being disclosed. In other words, the question is how to

31. *Id.* at 2.

32. Case T 198/84, Hoechst ex parte, OJ EPO (1985) at 2–3.

33. See European Patent Convention, *supra* note 22, art. 54.

34. Stephen M. Mauer & Suzanne Scotchmer, *The Independent-Invention Défense in Intellectual Property*, 69 ECONOMICA 535–47 (2002).

35. Synthon BV v. SmithKline Beecham plc [2005] H.L. 59, at ¶14.

36. See *generally* John F. Duffy, *Rules and Standards on the Forefront of Patentability*, 51 WM. & MARY L. REV. 638, (2009).

37. Case T 198/84, ¶ 6, A generic disclosure does not destroy the novelty of any of the specific possibilities falling within the disclosure unless it claims a specific generic feature that encompasses the latter.

define the extent of the disclosure for the assessment of novelty in the case of prodrugs and metabolites thereof if they fall within a scientific "gap." This means that although they are not explicitly disclosed in the first-generation application, they are nevertheless anticipated even when the inventor had no knowledge about such an effect.

What has to be established in the examination as to novelty is whether the state of the art is such as to make the subject matter of the invention available to the skilled person in a technical teaching.[38] However, different from the evaluation over the inventive step is that compared and analyzed to the existing technical criteria, novelty is evaluated not on what it adds to the existing technical teaching, but whether it can be considered a new invention overall. In other words, it is whether the subject matter of the invention is available to the person skilled in the art in technical teaching, which thus should be an absolute novelty, not a natural result of the existing disclosure.[39] Differently, from assessing the inventive step, it is not the newly discovered effect that is evaluated for novelty, but the new disclosure has to form a new invention *per se*. For assessing novelty of second-generation claims, it is not important whether there is a technical effect present over the prior art as this is evaluated at the stage of analyzing the existence of the inventive step. However, what is important about the technical teaching in the context of novelty is that the second-generation patent should not disclose a teaching that is anticipated by the examiner as a "natural result" of the first-generation claim.

When the first-generation claim covering the parent drug already included a possible (future) prodrug derivative, the novelty criteria in the second-generation claim could not be met. The teaching of the prior art is not confined to the detailed information given in the examples of how the invention is carried out[40] but relies on the information available in the claims and the description of the application that becomes the starting point for the person skilled in the art to carry out the invention and test novelty. For this reason, according to the established EPO case law,

> In the case of one of a number of chemical substances described by its structural formula in a prior publication, that substance's particular stereospecific configuration (thereof form) - though not explicitly

38. *Id.* at ¶ 6.

39. The new disclosure should not be a mere embodiment of the prior disclosure but is expected to form another invention. *See* Case T 0279/89, *In re* Texaco Dev. Corp., OJ EPO (1991) ¶ 4.1.

40. Case T 0012/81, *In re* Bayer AG, OJ EPO (1982).

> mentioned - is anticipated if it proves to be the inevitable but undetected result of one of a number of processes adequately described in the prior publication by indication of the starting compound and the process.[41]

Thus, when deducting this reasoning to prodrugs, if the second-generation family of the compound partially already covered what was disclosed in the first-generation disclosure, novelty cannot be approved. But at the same time, "if the (second-generation) subject matter is a defined compound, whereas the prior art discloses a family of [a] compound defined only by a general formula covering the defined compound, but not describing it explicitly, the invention must be considered novel."[42]

Deducing from the EPO case law, the second-generation claim may nevertheless fall within the scope of the parent claim, even if it was not explicitly described as the disclosure of the parent claim that could already anticipate the subject matter of the other claim due to the scientific "gap" or, in other words, explicit anticipation. Therefore, the success of the second-generation patent application relies on available knowledge, the extent of disclosure, and the wording of the patent application concerning what is claimed.

The validity of prodrug and metabolite patents in Europe has been dealt with in the landmark case *Merrell Dow v. H.N. Norton & Co. Ltd.* in the UK[43]. The case concerned a metabolite of Terfenadine, which was a line extension of the original drug patented in the 1970s. Considering that the second-generation patent involving a metabolite was patented a decade later, a generic drug company Norton challenged the metabolite patent as a *de facto* extension of the original drug based on validity and/or infringement. The case was under discussion in the U.S., Germany and the UK. In the first two countries, the main challenge was about patent infringement whereas the litigation brought up in the UK was the only country challenging the validity of metabolite claims. Therefore, the questions regarding novelty and inventive step arose in the context of challenging patent validity. Generally,

41. *See supra*, Section II.

42. The Board stated the following*:* "If a mere precisely structurally defined (described by a chemical reaction) class of chemical compounds with only one generically defined substituent does not represent a prior disclosure of all the theoretical compounds encompassed by an arbitrary choice of a substituent definition, it must be clearly valid for a group of chemical substances, the general formula of which has two variable groups. Therefore, in the present case, a class of chemical compounds, defined only by a general structural formula having at least two variable groups does not specifically disclose each of the individual compounds which would result from the combination of all possible variants within such groups." Case T 0007/86, DRACO v. Napp Labs. Ltd., OJ EPO (1987) ¶ 5.1.

43. Merrell Dow Pharms. Inc v. Norton & Co. Ltd., [1996] 3 RPC 76 , 87 (H.L.).

for a patent in the second-generation application to be held invalid for the lack of novelty, the prior art should disclose the same invention. In *Merrell Dow*, Lord Hoffmann invalidated the patent for having been anticipated by disclosure.[44] The notion and extent of the disclosure were addressed in detail. Referring to Art. 54 of the EPC, it was found that what constitutes anticipation is not simply something that was done before.[45] To determine the extent of the disclosure and consequently, judge novelty, it should be clarified what constitutes prior art in terms of "use" and (scientific) and "disclosure." Lord Hoffmann made a distinction between these terms as he considered that for the prior art to have a destructive impact on the assessment of novelty through use required that the information should have been made public through its use which, in this specific case, was not an issue. Instead, the judge found that the disclosure does not mean everything made available to the public in a written form or by public statement. The view was the disclosure by itself can contain information without being made public through use, meaning that the result of the metabolite action in the human body was due to the scientific disclosure (which was not, at the time, known to the inventor) rather than due to the communication to the public through its use. Thus, the second-generation invention should be anticipated based on the (scientific) disclosure that enables a person skilled in the art to convey sufficient information to work the invention.[46] This means that the anticipation by "use" has a different basis than anticipation by (scientific) "disclosure".

For purposes of clarifying the difference between these terms, Lord Hoffmann stated the following referring to the *CPC/Flour Concentrate* case[47]:

> if the recipe which inevitably produces the substance is part of the state of the art, so is the substance as made by the recipe. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee.[48]

It seems what the judge had in mind is that when the subsequent invention was performed based on the disclosure, it would necessarily have led to the infringement of the initial patent. Thus, the outcomes of performing

44. Merrell Dow Pharms. Inc v. Norton & Co. Ltd., [1996] 3 RPC 76 , 87 (H.L.).
45. *Id.* at 84.
46. *Id.* at 34
47. *Id.*
48. *Id.* at 90.

the second-generation invention should not be one of the possible options or result, but it should be based on the information disclosed even when it was not explicitly described in the patent. It should be anticipated. If it is one of the possible consequences, one cannot say that performing this invention would infringe.[49] This statement is supported by *Union Carbide Corporation v. Basf AG, Dow Chemical Co. and NV DSM*. Here, the EPO Boards of Appeal concluded that:

> "[i]t may be easy, given a knowledge of a later invention, to select from the general teachings of a prior art document certain conditions, and apply them to an example in that document, so as to produce an end result having all the features of the later claim. However, success in so doing does not prove that the result was inevitable. All that it demonstrates is that, given knowledge of the later invention, the earlier teaching is capable of being adapted to give the same result. Such an adaptation cannot be used to attack the novelty of a later patent."[50]

In the case of metabolites that make an effect on the molecular level as the end products after being metabolized, it is expected that when performing the first-generation invention involving a drug it would necessarily result in the same effects as the second-generation metabolites do. Therefore, the result should be expected in the first-generation patent. Also, as discussed in *Merrell Dow*, the (scientific) disclosure that sets the basis for the evaluation of novelty may not be known to the inventor himself[51] Nevertheless, it does not make the following claim valid. What matters is the disclosure must necessarily result in an infringing invention in the second-generation claim once performed. This is what sets novelty apart from the practical enablement or in other words, inventive step requirement. In *Merrell Dow*, the ingestion of terfenadine by hay-fever sufferers, which was the subject of prior disclosure, necessarily entailed the making of the patented acid metabolite in their livers.[52] It was, therefore, an anticipation of the acid metabolite, even though no one was aware that it was being made or even that it existed. A similar view regarding the assessment of novelty in light of judging the extent of disclosure was seen in *Synthon v. SmithKline Beecham* in the UK, which contested a patent for a crystalline form of paroxetine

49. Lord Hoffmann said, ". . . the prior disclosure must be construed as it would have been understood by the skilled person at the date of the disclosure and not in the light of the subsequent patent." *Id.* at 84.

50. Case T 0396/89, Union Carbide Corp. v. BASF Aktiengesellschaft et al., OJ EPO (1991) ¶ 4.4

51. Synthon BV v. SmithKline Beecham plc [2005] H.L. 59, at 23.

52. *Id.* at 23.

Methosulfate.[53] In *Synthon*, the judge sought to separate the notion of disclosure from enablement since disclosure concerns novelty and enablement concerns the obviousness/inventive step.[54]

As for assessing the novelty criteria in the light of prior disclosure, the judge came to a similar conclusion as in *Merrell Dow*. The judge concluded that relying on prior art should disclose the subject matter in a manner that, if performed, it would necessarily result in patent infringement.[55] Based on these judgments, it can be concluded that for the assessment of novelty concerning prodrugs and/or active metabolites the main doubt concerns the extent of the scientific disclosure within the first-generation claim. In evaluating disclosure, it does not matter whether the second-generation subject matter was explicitly mentioned in the parent claim because, from the scientific point of view, this type of subject matter is anticipated. The existence and advantages of the second-generation subject matter are generally, in this situation, disclosed because carrying out the invention would inevitably lead to the production of the second-generation product by the person skilled in the art. Although the concept of the invention is not completely disclosed in the first claim, if the subject matter of the second-generation claim would fall within the scientific "gap" disclosed in the parent drug, the result would inevitably lead to the construction and or effects of the prodrug/metabolite claim. The Court interpreted the novelty provision to find that the earlier patent had put information about the Terfenadine metabolite into the public domain, despite not publicly teaching the 'missing element' in the patent specification.[56] The findings and reasoning of the decision in *Merrell Dow* are well-suited for justifying the inexistence of novelty in the following patent application to avoid evergreening attempts as part of drug life cycle management. Certainly, each case is judged based on its contents, but the UK judgment has followed the same approach denying metabolite patents in Europe as did the EPO. However, prodrugs are still patentable subject matter in Europe as they are in the UK, but the passing of the novelty test based on the contents of the disclosure depends on the wording of a claim and the extent of the scientific disclosure. The following section of the article discusses the understanding of disclosure within the

53. *Id.* at 23.

54. *Id.* at 66.

55. *Id.* at 22.

56. *See generally* H. Samuel Frost, *The Unique Problem of Inventions which are Fully Enabled and Fully Described but not Fully Understood(Merrell Dow's Terfenadine Revisited)*, 15 INTELL. PROP. J. 2,(2007).

notion of enablement as a means of assessing the inventive step in prodrug and metabolite patent applications in Europe.

IV. DISCLOSURE AS AN ELEMENT OF ENABLEMENT FOR ASSESSING THE INVENTIVE STEP

It has been an accepted legal principle that the extent of the patent monopoly should correspond to and be justified by the technical contribution to the state of art.[57] Therefore, the extent to which an invention is sufficiently disclosed as an element of enablement is highly relevant for the evaluation of second-generation patent applications. The inventive step requirement is considered the "final gatekeeper of the patent system."[58] This means that even if relatively trivial changes to the prior art could survive the novelty and industrial applicability requirements, the inventive step will function as the ultimate requirement and filter the patentable from the unpatentable.[59] The relevance of the inventive step requirement is to guarantee there is a technical advancement in the teaching in comparison to the state of the art. It should not be an extension or incremental development of technology,[60] which may pass the novelty check but would add nothing to the level of technological advancement.

The inventive step can only be assessed when the invention is deemed novel. In comparison to the novelty, the inventive step seems to have higher standards of applicability. Art. 56 of the EPC defines the inventive step in the following manner: "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."[61] While both of these definitions deal with the state of art the novelty criteria is informative. To pass the evaluation, the main factor considered is the available information of prior art as discussed in the previous section. Novelty is judged based on the scientific disclosure, which may mean that this information can fall in the scientific "gap," which nevertheless can destroy novelty. The inventive step requirement, on the other hand, refers to the technical teaching, which means in addition to being novel to the examiner, the invention should contain a new technical

57. Case T 0409/91, *In re* Exxon Chem. Patents, Inc., (1993) at 3.3 (Eur. Pat. Bd. of App.).

58. R. P. MERGES & J. F. DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 619–20 (LexisNexis, 5th ed. 2011).

59. *Id.* at 620.

60. Mark F. Grady & Jay L. Alexander, *Patent Law and Rent Dissipation*, 78 VA. L. REV. 305, 340 (1992).

61. *See* European Patent Convention, *supra* note 22, art. 56.

contribution to the state of the art. While the novelty requirement puts the examiner in a passive state,[62] the inventive step requirement has the opposite effect as it requires the active participation of the person skilled in the art to perform tests and make the ultimate evaluation. The inventive step requires that the invention, based on the prior art, is not obvious to the examiner. For assessing the inventive step, the *problem-solution approach* is used. This means that the second-generation claim should provide a technical problem over the prior art that needs to be "solved" to see whether the solution can be considered inventive (non-obvious) in comparison to the existing knowledge.[63] Thus, an unexpected advantage that could not have been predicted from the prior art is taken as evidence of an inventive step. In this light, for the fulfillment of the inventive step requirement, the newly claimed compound/molecule should present a special technical property that is not previously disclosed. It means that the second-generation claim should offer a "surprising" technical effect to the existing prior art. In the case of prodrugs, it can be either a new property or a better activity in comparison to the existing invention.

In the case of chemical inventions concerning potential structural similarity, the EPO has taken the view[64] that "to deny the patent for the lack of the inventive step, a skilled person should be expected to find the same or similar usefulness in comparison to the known compound as means of overcoming the technical problem." What makes the difference is the range of structural differences of the second-generation drug when compared to the parent compound. If these differences are lacking or very small, they would have an insignificant bearing on those properties that are essential for solving the technical problem at issue. Because of structural similarities with the parent drug, the inventive step for a prodrug often turns on the structural similarities and differences between the claimed compound and prior art.[65] In T 2402/10 the board stated "in the field of drug design any structural modification of a pharmacologically active compound is, in the absence of an established correlation between structural features and activity, a priori

62. *Id.*; Frost, *supra* note 56, at 19.

63. In assessing the inventive step, the EPO has applied the following three-step test: "1. Determining the 'closest prior art'; 2. Establishing the 'objective technical problem' to be solved; and 3. 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." *See* Implementing Regulations – to the Convention on the Grant of European Patents of 5 October 1973.

64. Case T 0358/04, Retroviral protease inhibitors/G.D. SEARLE, OJ EPO (2006) ¶ 4.5.3 .

65. JARKKO RAUTIO, PRODRUGS AND TARGETED DELIVERY: TOWARDS BETTER ADME PROPERTIES 73 (Wiley 2011).

expected to disturb the pharmacological activity profile of the initial structure."[66] In the case of prodrugs, the structural similarities in the first- and second-generation claims can otherwise lead to double patenting if the inventive step is not approached with caution. Double patenting can be raised where the subject matter of the granted invention is encompassed by the claim later put forward.[67] However, what makes the difference whether the inventive step stage is passed successfully or not is whether the second-generation claim has distinguishing features in comparison to the first-generation claim. Under this condition, the subject matter of the second-generation claim and the first-generation claim cannot be considered as "the same subject matter. Thus, the evaluation of the inventive step has stricter standards in Europe when compared to the assessment of the novelty criteria. The inventive step has to occur for the entire selection range, but the novelty criteria is fulfilled when the claimed subject matter is distinguished from the prior art in the range of overlap by a new technical element.[68]

As discussed in the previous section, to destroy novelty, the disclosure must infringe the invention If the performance of an invention would make the second-generation subject-matter obvious to the person skilled in the art but not necessarily infringe the first one, then one can discuss the practical enablement in judging the inventive step, not novelty.[69] Therefore, while *Merrell Dow* divided the destruction of novelty into two categories, namely disclosure by use and scientific disclosure, the inventive step requirement is connected to the practical enablement of the disclosure. Enablement means that a person skilled in the art should be able to perform the invention, which satisfies the requirement of disclosure.[70] Thus, the inventive step can be judged based on what is previously disclosed, meaning that for the destruction of the inventive step, either the prior disclosure of the invention or general common knowledge would have enabled a person skilled in the art to make it.[71] The inventive step depends on what is disclosed in the prior art making it different from novelty, which may be judged, based on *Merrell Dow*, also on the "missing" information (the scientific "gap") in the disclosure made available.

In *Union/Carbide*, the EPO Boards of Appeal clarified that:

66. Case T 2402/10, Prostaglandin derivatives / Pfizer, OJ EPO (2012).
67. Case T 0307/03, ARCO/Double patenting, [2007] (Eur. Tech. Bd. of App.).
68. Case T 0012/90, Bayer AG, OJ EPO (1990).
69. *Id.*; Synthon BV v. SmithKline Beecham plc [2005] H.L. 59, at 49.
70. *Id.*; Case T 0396/89, Union Carbide Corp. v. BASF Aktiengesellschaft et al., OJ EPO (1991).
71. Asahi Kasei Kogyo KK's Application [1991] RPC 485 (HL).

> It may be easy, given a knowledge of a later invention, to select from the general teachings of a prior art document certain conditions, and apply them to an example in that document, so as to produce an end result having all the features of the later claim. However, success in so doing does not prove that the result was inevitable. All that it demonstrates is that, given knowledge of the later invention, the earlier teaching is capable of being adapted to give the same result. Such an adaptation cannot be used to attack the novelty of a later patent.[72]

If the disclosure of prior art would make it obvious to the skilled person how to adapt the invention in a manner that could eventually result in infringement, one can challenge the inventive step but not novelty because the infringement would be based on the existing available information of prior art. Secondly, enablement would not mean an automatic and inevitable infringement, but it is one of the possibilities that may lead to such infringement if adaptions are made. In other words, enablement means that for the destruction of the inventive step, the skilled person is expected to perform the invention, which satisfies the requirements of disclosure. Based on *Hill v. Evans*,[73] for the assessment of novelty, no further experiments with the subject matter are performed as it is judged based on the (scientific) disclosure. Given *Merrell Dow*, the argument in *Union/Carbide* and *Hill v. Evans* is different because of the case's substantial circumstances. Namely, the intriguing aspect of *Merrell Dow* was that the second-generation invention disclosed in the prior art was not the same as claimed in the invention itself, but if performed by the examiner, it would infringe the claimed invention. In this case, the debate concerned whether the disclosure contained in the prior art enabled the examiner to make Terfenadine, not whether it enabled him to make metabolites. This makes judging novelty different from the inventive step and the questions that were raised regarding validity in *Merrell Dow* concerned novelty, not the inventive step.

72. *Id.*; Case T 0396/89, Union Carbide Corporation v. BASF Aktiengesellschaft et al., OJ EPO (1991) ¶ 4.4.

73. In *Hill v. Evans* in the UK, the House considered what would amount to disclosure of an invention. Lord Westbury LC said "I apprehend the principle is correctly thus expressed: the antecedent statement must be such that a person of ordinary knowledge of the subject would at once perceive, understand and be able practically to apply the discovery without the necessity of making further experiments and gaining further information before the invention can be made useful. If something remains to be ascertained which is necessary for the useful application of the discovery, that affords sufficient room for another valid patent." Hill v. Evans, (1862) 31 LJ (NS) 457, 463.

CONCLUDING REMARKS

Although second-generation patents are sometimes seen as lacking true inventiveness and, therefore, should perhaps not be granted,[74] it is not always the case. The main concern about drug patent has been the issuing of secondary patents with questionable value, meaning that although a patent can qualify from the technical point of view for a new patent but it may not necessarily have any significant therapeutic value from the medical aspect. It has therefore been questioned whether these types of patents rather reflect their input and true innovative value. Lemley and Shapiro have pointed out that among the vast number of patents filed most of them have little value and such patenting leads to a situation where third parties have no meaningful opportunity to participate in the patent granting system.[75] Burdon and Sloper state that "[a] key element of any lifecycle management strategy is to extend patent protection beyond the basic patent term for as long as possible by filing secondary patents, which are effective at keeping generics off the market."[76] According to the Pharmaceutical Sector Inquiry, which studied the tendencies of European pharmaceutical companies to use sequential patents, the primary-to-secondary patent ratio is 1:7, and interestingly, the ratio for pending patents is much higher in comparison to granted patents.[77] Another study conducted in the U.S. market suggested that around half of pharmaceutical products are additionally covered with follow-on patents.[78]

Lemley and Shapiro[79] argue that "[m]odern technologies incorporate not one but a number of combinations of patents for different components of the basic invention." A study conducted by Stella has suggested that, in many cases, a look at the structure of the active drug with the additional claim of prodrugs suggested that prodrugs would serve minimal advantage.[80] According to his estimation, the vast majority of prodrug patents contain

74. *Id.*; Asahi Kasei Kogyo KK's Application [1991] RPC 485 (HL).

75. *See generally* Mark A. Lemley & Carl Shapiro, *Probabilistic patents*, 19 J. ECON. PERSP. 75 (2005).

76. Michael Burdon & Kristie Sloper, *The Art of Using Burden Secondary Patents to Improve Protection*, 3 INT'L J. MED. MARKETING, 226, 266 (2003).

77. EUROPEAN COMM'N, PHARMACEUTICAL SECTOR INQUIRY REPORT (2009), http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

78. *See generally* Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "'Secondary" Pharmaceutical Patents*, 7 PLOS ONE 49470 (2012).

79. *See generally* Mark A. Lemley & Carl Shapiro, *Patent Holdup and Royalty Stacking*, 85 TEX. L. REV. 1992 (2007).

80. *See generally* Valentino J. Stella, *Prodrugs: Some thoughts and current issues*, 99 J. PHARM. SCI. 4755 (2010).

little true novelty either in the chemical or biological sense meaning that less than 5-10 percent of the patents represent true creativity.[81] Correa has made a similar conclusion arguing that "[a] claim on a prodrug will generally fail to meet the inventive step standard unless evidence is provided that it overcomes pharmaceutical or pharmacokinetically based problems of the parent drug in a non-evident manner."[82]

Although the improved efficacy of prodrugs in overcoming the barriers in parent drug delivery can be disputed, the standards applicable to these bio-reversible derivatives of drug molecules consider the technical side of claimed inventions. A key consideration under patent law is whether the development of a new prodrug is the outcome of an inventive activity or of routine research and experimentation. The first question that was addressed in these article was the extent of disclosure in second-generation patent applications concerning prodrugs. The second question, which is closely connected to the first one, is the validity of the prodrug patents in the light of fulfillment of novelty and inventive step requirements. To analyze these issues, this article provided an overview about the scientific notion of prodrugs and active metabolites explaining that because of structural similarities with the parent drug, prodrugs and active metabolites face challenges in overcoming the patentability criteria pertaining in the European Patent Convention. This article further analyzed the understanding of the term "disclosure" in European patent applications arguing that the scientific disclosure should be separated from the practical disclosure as they are targeted to judging different criteria of patentability. The extent of disclosure has a direct impact on the assessment of novelty and the inventive step requirements in European patent application. As analyzed in *Merrell Dow* the scientific disclosure relates to the novelty criteria. Deduced from the analysis in *Merrell Dow*, it was concluded that although novelty is generally assessed based on the information made available to the public, in cases involving subject matter targeting prodrugs and metabolites, it is possible that the scientific disclosure that sets the basis for the assessment of novelty, falls within the scientific "gap" meaning that it may not even be communicated to the public to be considered as prior art. Thus, although novelty contains the element of anticipation, one should distinguish between anticipation by "use" and by (scientific) "disclosure." When this discussion is applied to the assessment of novelty for prodrugs and metabolite patents,

81. *Id*. at 4755.

82. Carlos M. Correa, *Guidelines for Pharmaceutical Patent Applications: Examining Pharmaceutical Patents from Public Health Perspective*, UNDP, at 10 (2015), https://www.undp.org/content/dam/undp/library/HIV-AIDS/UNDP_patents_final_web_2.pdf.

the disclosure, even if not directly stated in the application of the parent drug, would inevitably infringe that patent if the second invention was performed. Thus, the prodrug/metabolite should (from the scientific perspective) be expected to contain the parent drug already.

The article also dealt with the legal analysis concerning the assessment of the inventive step arguing that the disclosure should be based strictly on the information made available the prior art. Differently, from the scientific disclosure that is a passive notion, the disclosure involving enablement requires active performance from the examiner to conduct tests with the subject matter. To destroy the inventive step requirement, enablement should be based on the information available in the prior art and the examiner should be capable of performing the invention as disclosed.