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PATENT PROTECTION OF PHARMACOLOGICALLY ACTIVE METABOLITES: THEORETICAL AND TECHNOLOGICAL ANALYSIS ON THE JURISPRUDENCE OF FOUR REGIONS*

Richard Li-dar Wang[†] and Pei-Chen Huang^{††}

Abstract

Active metabolite patents have been instrumental for brand-name pharmaceutical companies to maintain their exclusivity even after the drug patents expire. This strategy obstructs market entry of generic medicine and reduces affordable drugs. The authors review jurisprudence from the United States, Europe, India, and Taiwan in search for practical solutions to confront this problem. Given the unique pharmacological value that active metabolites may possess, patent protection for those purified or synthesized in vitro should be preserved, but for those produced by metabolism should be declined. Except India, most countries under investigation comport with this dichotomy. Their jurisprudence may be subsumed into three possible solutions. The United States and the United Kingdom adopt the inherent anticipation doctrine; yet depriving artisan recognition of novelty analysis makes this doctrine highly controversial. The product of nature doctrine gravely suffers from incoherence and uncertainty in judging patentability. The non-practice theory, as articulated by Taiwan's Intellectual Property (IP) Court, avoids these shortcomings. The unambiguous and sound rationale further support this theory to be the preferable solution among the three.

* This article draws partially on Pei-Chen Huang's LL.M. thesis "Investigation of Patentability for Derived Pharmaceutical Inventions—Focusing on Derivatives of A Known Substance and Active Metabolites" (in Chinese). The authors considerably furthered the analyses and arguments that originate therein.

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I. INTRODUCTION

Considering the theoretical foundations of the patent system from a utilitarian perspective,¹ the basic rationale for the existence of patent rights is to trigger a series of economic activities that benefit society by providing inventors (or their successors) with the legal right to exclude others from practicing their inventions (right to exclude). Innovation and invention are sources of technological improvement for society. However, because innovations possess the characteristics of public goods, they are often appropriated by competitors, resulting in free riding.² Providing inventors with exclusive rights can prevent competitors from copying inventions without their permission and destroying the opportunity to recover their research and development costs from the market. In this

1. See generally Edwin C. Hettinger, *Justifying Intellectual Property*, 18 PHIL. & PUB. AFF. 31, 47-48 (1989).

2. WILLIAM M. LANDES & RICHARD A. POSNER, *THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW* 13-14 (2003); Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1024-26 (1989).

situation, patents act as incentives to invent. They encourage exploration of new inventions, and prevent free riding that may result in an insufficient investment of research and development.³

Additionally, when new inventions are developed, they must undergo a lengthy process of commercialization. Adequate product designs and efficient manufacturing processes must be instigated, which enable technological inventions to be actually applied to commercial commodities, thereby being employed in the market and benefiting the consuming public. Patents can provide incentives to commercialize as well. The protection of patent rights can attract necessary funding for supporting the expenditure of commercialization and market development. Furthermore, due to the fact that inventors have to disclose the technological content of their innovations when applying for patents, the exclusive patent terms induce inventors from keeping their innovations confidential.⁴ This is a major incentive to disclose new technical development, and an important method for encouraging public accumulation and exchange of state-of-the-art technological information.⁵

However, the awarding of exclusive patent terms creates conflicting interest between inventors and the public. This conflict occurs in the pharmaceutical field as well. Drug patents can satisfy the profit demands of pharmaceutical manufacturers, and assist with accumulating and sustaining research and development funding and capability. However, the fact that patent protection excludes unlicensed generic manufacturers from producing the same drug often runs contrary to the patient's need for affordable medicine. Additionally, pharmaceutical companies often prosecute and obtain secondary patents to further extend the exclusivity period of brand-name drugs, which usually comes from primary patents on active ingredients of the drugs, so as to block generic manufacturers even longer and pursue the brand-name manufacturers' own interests. This strategy creates the phenomenon of "patent evergreening."⁶ Medical products and pharmaceuticals are indispensable resources for saving human life and health. Extending brand-name exclusivity over time

3. See, e.g., Eisenberg, *supra* note 2, at 1024-28; Lara J. Glasgow, *Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?*, 41 IDEA 227, 229 (2001).

4. Eisenberg, *supra* note 2, at 1028-30.

5. *Id.*

6. See Alfred B. Engelberg, *Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness?*, 39 IDEA 389, 401 n.44 (1999); Robin Feldman, *Rethinking Rights in Biospace*, 79 S. CAL. L. REV. 1, 30 (2005).

through secondary patents not only runs counter to fairness and equality, but is also closely related to public health. Recently, this problem of drug patent evergreening has received significant international attention. That suggests this troublesome issue is gradually spreading throughout the world, and urgently requiring proper resolution.

The issue of evergreening drug patents is potentially resolvable from two angles: patentability and rights enforcement. Technically, secondary patents are normally derived from the active ingredient of the drug, including its enantiomers, position isomers, geometrical isomers, homologues, crystalline forms, and so on. The authors choose to focus on active metabolites, of which the patentability and infringement litigation have been controversial in recent years. In this study, they thoroughly investigate the jurisprudence of different countries, engaging in a technical and legal assessment of their approaches to this issue, and critically evaluating their advantages and disadvantages respectively.

This article begins with a brief introduction of pharmacologically active metabolites, the role they play in pharmaceutical treatment, and the controversies they may bring about in patent law. In Parts III through VI, the authors examine, respectively, how the United States, Europe, India, and Taiwan manage the patentability and enforcement issues arising from active metabolites. In Part VII, the authors introduce insightful theoretical perspectives and technological analysis, subsuming the jurisprudence of those four regions into three potential solution models. The article further addresses the questions whether these models are consistent with the role of active metabolites in pharmaceutical research, and whether patent law is aiming at encouraging valuable inventions instead of monetizing basic pharmaceutical principles that are not truly innovative. Finally, the conclusion of this study is summarized in Part VIII.

Pharmacologically active metabolites are produced by the human metabolism, which is purely a natural reaction of the human body, not subjectively known to or controlled by the patient who is taking the medicine. This reaction is not based on conscious behavior by humans, but instead constitutes an automatic biological mechanism that is part of the digestion system. Metabolites are therefore much closer to products of nature than to human inventions. It seems inadequate to grant patents on those substances. Nevertheless, the discovery and *in vitro* manufacturing of these substances has

considerable technological value in the pharmaceutical industry.⁷ Therefore, the awarding of patents to this type of metabolites should still be permitted. This study concludes that the product of nature doctrine⁸ and the non-practice theory⁹ can both yield the same end result. However, because the product of nature doctrine may present risks of excessively denying patents for other types of pharmaceutical research results, it would be more appropriate to adopt the non-practice theory articulated by Taiwan's Intellectual Property Court in their judgment.

II. ACTIVE METABOLITES AND PATENT LAW

When pharmacologically active ingredients are used in the body, some of the compounds are absorbed and directly produce physiological effects, whereas others must undergo a series of metabolic reactions to achieve the desired result. A number of cases have indicated that the metabolites of the original compounds are pharmacologically active as well. Additionally, studies have found that the pharmacological effect of some compounds originates entirely from their metabolites, meaning the administered compound is itself inactive. The desired pharmaceutical effect can be obtained only through the body's natural metabolism and the resulting metabolites.¹⁰ Because of the limited current knowledge into human physiology, pharmaceutical firms typically do not understand how a drug works on the pharmacological level when putting it on the market. It sometimes takes a number of years after launching the drug for those companies to figure out the pharmacokinetic mechanism of that drug and then apply for a patent on the active metabolite.

The chemical structure of pharmacologically active metabolites differs from the compounds originally administered. Theoretically, it is patentable if a metabolite is novel, non-obvious, and possess sufficient utility. However, granting patents on active metabolites has sparked significant controversies, the core issue of which is whether the intake or marketing of drugs known to generate specific active metabolites actually infringes patents covering the metabolites of those drugs. In practice, after drug patents have expired,

7. See *infra* Part VII.A for a specific example and further explanations.

8. See *infra* Part VII.C. See generally JANICE M. MUELLER, AN INTRODUCTION TO PATENT LAW 226-29 (2d ed. 2006).

9. See *infra* Part VII.D.

10. PHILIP W. GRUBB, PATENTS FOR CHEMICALS, PHARMACEUTICALS AND BIOTECHNOLOGY: FUNDAMENTALS OF GLOBAL LAW, PRACTICE AND STRATEGY 231 (4th ed. 2004).

pharmaceutical manufacturers alternatively assert active metabolite patents, if any, against those who manufacture and sell generics of the same drug, in an attempt to extend their market exclusivity in real terms. Consequently, active metabolites have become the subject of secondary pharmaceutical patents. Patents on active metabolites thus might delay the arrival of generic drugs on the market, which prevents the public from enjoying the benefit of more affordable medicine after the original patent has expired.

Since active metabolites are arguably just the flip side of the original pharmaceutical compounds, this type of extending brand-name exclusivity is somewhat frustrating in light of the basic rationale of the patent system, which is to promote innovation, commercialization and technology disclosure with only a limited period of exclusivity.¹¹ However, active metabolites are also just a type of chemical compounds, and denying patent protection for a new, useful and non-obvious metabolite would be contrary to the principles of modern patent laws. In the following chapters, the authors investigate the relevant jurisprudence of the United States, Europe, India, and Taiwan, with an aim of exploring and identifying feasible solutions to reconcile this dilemma.

III. ACTIVE METABOLITES IN U.S. LAW

The first U.S. case that deals with the issue of active metabolites is *Zenith v. Bristol-Meyers*,¹² where the Federal Circuit considers the patent claims might encompass active metabolites, yet reverses the ruling of induced infringement below for the reason that no evidence in the record rightly comparing the patent claims with the drug that allegedly formed the active metabolites after being ingested by patient.¹³ In a number of later cases, however, U.S. courts are inclined to hold that the sale or use of drugs known to produce specific active metabolites does not constitute an infringement of active metabolite patents. Those opinions include varying reasons to reach this conclusion.¹⁴

11. See *supra* text accompanying notes 1-5.

12. *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418 (Fed. Cir. 1994).

13. *Id.* at 1421-24.

14. For an overview of U.S. cases tackling the active metabolite issue, see Andrew W. Torrance, *Physiological Steps Doctrine*, 23 BERKELEY TECH. L.J. 1471, 1478-99 (2008).

A. Marion Merrell Dow Inc. v. Baker Norton Pharmaceuticals, Inc.

The court in *Marion Merrell Dow* uses claim construction to pass a judgment of non-infringement.¹⁵ Merrell Dow held the U.S. Patent No. 3,878,217 ('217) that claimed the compound terfenadine and its use as a treatment for human allergic reactions. The '217 patent expired in 1994, when Baker Norton submitted an Abbreviated New Drug Application (ANDA) to the U.S. Food and Drug Administration (FDA), hoping to manufacture and sell the corresponding generic drug after the patent expired. Merrell Dow initiated infringement litigation after learning of this submission, alleging that Baker Norton's manufacturing and selling of the generic terfenadine infringes the unexpired Patent No. 4,254,129 ('129), also held by Merrell Dow. The '129 patent covers terfenadine's active metabolite, terfenadine acid metabolite (TAM), and its use as a treatment for allergic reactions. Merrell Dow argued that Baker Norton's manufacture and sale of the generic drug would constitute active inducement of infringement because TAM would be produced in patients' livers after consuming Baker Norton's generic drug.¹⁶ Baker Norton subsequently filed a counterclaim, arguing that because patients were already using TAM prior to the application for the '129 patent, and TAM had already implicitly been disclosed in the '217 specification, TAM was anticipated by the '217 patent and thus lost its novelty.

In this case, the court focused on construing the claim terms of the '129 patent. The court indicated that its primary task for literal infringement analysis involves defining the meaning and scope of the claims at question. The court has the authority and obligation to interpret the textual meaning of the claims, taking into consideration the intrinsic evidence such as the specification and prosecution history.¹⁷ In this case, the claim term in dispute was the word "compound." Merrell Dow asserted that this term covers TAM produced *in vivo* through the liver's metabolism and those synthesized *in vitro* as well. Baker Norton countered that the same word represents only TAM that was synthesized *in vitro*.¹⁸ The court

15. *Marion Merrell Dow Inc. v. Baker Norton Pharm., Inc.*, 948 F. Supp. 1050 (S.D. Fla. 1996).

16. *Id.* at 1051-53.

17. See *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996).

18. *Marion Merrell Dow Inc.*, 948 F. Supp. at 1053-54.

pointed out in its ruling that although the claim did not clearly define the production method of the “compound,” it also contained nothing suggesting that TAM was generated through human metabolism. The court indicated that Claim 10 of the disputed patent recited the pharmaceutical composition of TAM in unit dosage form, which involved the combination of an effective amount of TAM with a “significant amount of a pharmaceutically acceptable carrier,” and hence the claim should rightly be restricted to TAM obtained from *in vitro* synthesis. On the other hand, if the claim included TAM both produced through *in vivo* metabolism and *in vitro* synthesis, as alleged by Merrell Dow, it could only cover the *in vivo* TAM that had been extracted from the human body, and combined with the pharmaceutical carrier after purification. However, this seemed unreasonable to the court and in pharmaceutical practice. Based on this construction, the court decided that the “compound” in the disputed patent should be restricted to TAM obtained from *in vitro* synthesis.¹⁹

The court further stated that patent specifications should be consulted when constructing claims. The specification of the disputed patent explained in detail TAM’s chemical formula, efficacy, and usage. However, it lacked the information that TAM could be produced by human metabolism. This implies that “compound” in the disputed patent claim should be restricted to *in vitro* synthesis. Additionally, the prosecution history of a patent constitutes other primary evidence that should be considered when constructing claims.²⁰ The court stated that Claims 1 and 2 of the disputed patent were virtually identical when initially presented by Merrell Dow. The only difference between Claims 1 and 2 was that Claim 2 specified the compound as “an essentially pure compound of TAM.” The patent examiners rejected the claims on the basis that “no appropriate distinction exist[ed] between these two claims in the specification.” Merrell Dow then withdrew Claim 2 to get Claim 1 allowed by the examiner. Furthermore, Merrell Dow acquiesced to the patent examiners’ interpretation that the term “compound” in Claim 1 is restricted to pure TAM by withdrawing Claim 2. The court pointed out that this type of behavior, where a patent applicant had restricted the range of her claims during patent prosecution and then later attempted during litigation to recover what she previously had

19. *Id.* at 1054.

20. *Phillips*, 415 F.3d at 1317.

forfeited, should be strictly prohibited.²¹ On this basis, the court held that “compound” in the disputed claim should be restricted to *in vitro* synthesis. Thus, the TAM produced by the metabolism of patients consuming terfenadine did not fall within the scope of the ’129 patent and did not constitute a direct infringement. As a result, Baker Norton’s manufacturing and selling of generic terfenadine did not constitute active inducement of infringement.²² Merrell Dow’s subsequent appeal to the U.S. Court of Appeals for the Federal Circuit (CAFC) was dismissed by the parties, ending litigation.²³

B. Schering Corp. v. Geneva Pharmaceuticals, Inc.

In this later case,²⁴ the U.S. court used the “inherent anticipation doctrine” to address the issue of whether selling and using the original drugs constituted an infringement of active metabolite patents. In this case, the plaintiff Schering Corp. held U.S. Patent Nos. 4,282,233 and 4,659,716. The ’233 patent claimed loratadine, an antihistamine substance, which was used to suppress allergic reactions without the side effect of drowsiness. Schering Corp. labeled loratadine as the active component of the drug bearing the brand name Claritin. The ’716 patent claimed descarboethoxyloratadine (DCL), another antihistamine compound and the active metabolite of loratadine, did not cause drowsiness either. The ’716 patent did not expire until April 2004, whereas the ’233 patent expired earlier in 2003. After the ’233 patent expired, a number of pharmaceutical companies intended to manufacture and sell the generic version of loratadine, which needed the FDA approval. Since the Schering Corp enlisted the ’716 patent in the Orange Book as patents protecting its Claritin product, generic producers in order to obtain FDA approval of their ANDA submissions asserted that the patent is invalid. In response, Schering Corp. initiated infringement litigations against Geneva and a number of other generic manufacturers.²⁵

While engaging in claim construction, the trial court held that the claim to DCL in the ’716 patent included both “production through metabolism” and “*in vitro* synthesis.” Both parties agreed to this interpretation. The trial court stated that the ’233 patent did not

21. *Marion Merrell Dow Inc.*, 948 F. Supp. at 1055-56.

22. *Id.* at 1057.

23. *Marion Merrell Dow, Inc. v. Baker Norton Pharm., Inc.*, 152 F.3d 941 (Fed. Cir. 1998) (unpublished table decision).

24. *Schering Corp. v. Geneva Pharm., Inc. (Schering Corp. II)*, 339 F.3d 1373 (Fed. Cir. 2003).

25. *Id.* at 1375-76.

explicitly disclose DCL or references to metabolites of loratadine. However, DCL is inevitably produced and present as a metabolite when following the method of administering loratadine as specified in the '233 patent. Applying this claim construction, the trial court determined that the DCL claim in the '716 patent is already inherently anticipated by the '233 patent. Thus, the claim failed the novelty requirement and was therefore invalid.²⁶

Schering Corp. appealed to the CAFC, and the appellate court passed a judgment substantially identical to the ruling of the trial court. The CAFC stated that when a single earlier reference had exposed all of the technological features of the claimed invention under dispute, the patent was invalid because the invention was anticipated and its novelty was thus lost. Furthermore, even if the piece of prior art did not disclose a certain technological feature of the disputed invention, if the omitted element is inherently implied or had to be present according to the disclosure of that reference, the disputed invention was anticipated as well.²⁷ The appellate court further suggested that according to previous case law, the application of the inherent anticipation doctrine did not demand that the person having ordinary skill in the art (PHOSITA) had to recognize the omitted element being inherent in the prior reference. If the technological feature that the reference failed to expressly describe had to be formed or was present when following the teaching of a single prior art, regardless of whether a PHOSITA could identify the omitted element or not, the inherent anticipation doctrine still applied, and the disputed claim was invalid due to a lack of novelty.²⁸

The court further explained that in the earlier *Continental Can* case,²⁹ the court's rationale did not demand that the PHOSITA having to recognize all omitted elements from a single prior art before the inherent anticipation doctrine could be applied. The *Continental Can* decision only stated that the court could consult with the PHOSITA to clarify the disclosure of specific former references, including the technological features that were missing but inherently implied. The CAFC did not accept the argument advocated by Schering Corp. that "the PHOSITA recognizing the omitted elements" is a necessary condition for inherent anticipation. Regardless of whether the

26. Schering Corp. v. Geneva Pharm., Inc. (*Schering Corp. I*), 275 F. Supp. 2d 534, 540-42 (D.N.J. 2002), *aff'd*, 339 F.3d 1373 (Fed. Cir. 2003).

27. *Schering Corp. II*, 339 F.3d at 1377.

28. *Id.*

29. *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991).

PHOSITA realized that the '233 patent inherently embraced the compound DCL at the filing date of the '716 patent, the inherent anticipation doctrine might still be applicable.³⁰

The CAFC noted that the facts of this case differed from previous ones, where the inherent anticipation doctrine was applied. In those cases, portions of technological features claimed in the disputed patent had already been explicitly disclosed in a prior reference, while only some features were inherently implied. In this case, however, the '233 patent failed to explicitly disclose any features of DCL. Thus, the focus of applying the inherent anticipation doctrine in this instance was not any specific omitted features but rather DCL as a whole.³¹ Nevertheless, the CAFC held that the main consideration for determining whether the claimed subject matter had been omitted yet was inherent in a prior reference was whether the cited reference had placed the subject matter in the public domain; that is, whether the general public had already freely made, used or sold the subject matter. Patents cannot be awarded to retrieve inventions from the public domain to the patentee's proprietary terrain. Therefore, "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."³² This basic principle persists regardless of whether the PHOSITA understands all of the configuration or underlying scientific knowledge of the prior art reference. Therefore, the court ruled that the inherent prior art anticipated the entire invention as well as single elements within an invention.³³ In this case, the scientific data showed that the use of loratadine necessarily resulted in the DCL compound through human metabolism. The court finally ruled that the '233 patent inherently anticipated the DCL claims in the '716 patent.³⁴

The CAFC further distinguished the conditions in this case with those in cases of accidental anticipation.³⁵ In the present case, DCL was not produced accidentally or under unusual situations, rather

30. *Schering Corp. II*, 339 F.3d at 1377-78.

31. *Id.* at 1378-79.

32. *Id.* at 1379-80 (quoting *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999)).

33. *Id.* at 1380.

34. *Id.*

35. See *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45 (1923); *Tilghman v. Proctor*, 102 U.S. 707 (1880). Cf. *Chem. Cleaning, Inc. v. Dow Chem. Co.*, 379 F.2d 294, 296-97 (5th Cir. 1967). Monomethylthiourea breaks down and produces thiourea as claimed in the patent when applied to industrial boilers. This conversion is intentional and does not happen in human bodies.

unavoidably generated when administering loratadine in ordinary circumstances. The formation of DCL was an intrinsic outcome of patients consuming loratadine.³⁶ Moreover, the CAFC pointed out that a qualified prior art reference capable of refuting a disputed invention's novelty must allow a PHOSITA to make or use the prior art accordingly. Although the '233 patent did not describe how to manufacture the isolated DCL compound, disclosure of "any" method capable of manufacturing DCL would have sufficed to satisfy the enablement requirement under the first paragraph of 35 U.S.C. § 112.³⁷ Since patients consuming loratadine had already been described in the '233 patent, and DCL will necessarily be generated in the human body, the court found that the '233 patent was an enabling prior art that inherently anticipated the DCL claims of the '716 patents.³⁸

C. Analysis

U.S. courts have so far adopted different approaches to reach the same conclusion of non-infringement on the issue whether the manufacturing, sale or consuming of drugs known to produce specific active metabolites infringes on patents claiming those metabolites. In the two sets of cases, the patents at bar were similarly drafted, both containing claims to the active metabolites, claims to the processes of synthesizing the active metabolites *in vitro*, claims to combinations of the active metabolites and drug carriers, and claims to the metabolites' methods of use. The court in *Merrell Dow* used claim construction as an instrument to resolve the dispute on active metabolites. In *Schering Corp.*, however, the CAFC eschewed claim construction and resorted to the inherent anticipation doctrine. The reason for this disparity might come from the fact that both parties in *Schering Corp.* conceded as to the interpretation of the key claim term "compound" to be limited.³⁹

More importantly, the way that the CAFC explains inherent anticipation in *Schering Corp.* has incited numerous theoretical and

36. *Schering Corp. II*, 339 F.3d at 1378.

37. Janice M. Mueller & Donald S. Chisum, *Enabling Patent Law's Inherent Anticipation Doctrine*, 45 HOUS. L. REV. 1101, 1144-54 (2008) (arguing for a heightened enablement requirement for patent-defeating prior art reference, in order to avoid using the inherent anticipation doctrine).

38. *Id.* at 1149.

39. A third approach that U.S. courts have ever used to address the issue of active metabolites is the doctrine of equivalents. *See, e.g.*, *Ortho Pharm. Corp. v. Smith*, No. 90-0242, 1990 WL 121353, at *11-14 (E.D. Pa. Aug. 17, 1990), *aff'd*, 959 F.2d 936 (Fed. Cir. 1992).

practical discussions.⁴⁰ After this decision, obtaining patents for active metabolites has increased in difficulty, because a patent claims an active metabolite only through its chemical formula, the inherent anticipation doctrine still applies, potentially anticipating such a claim. It is noteworthy, however, that the *Schering Corp.* decision did not totally deny any patent protection for active metabolites. The court indicated in this decision that patents can be granted on purified or isolated active metabolites, or on their methods of use or composition with other substances.⁴¹

IV. ACTIVE METABOLITES IN EUROPEAN LAW

In comparison, the European Patent Office (EPO) holds a conservative stance on the inherent anticipation doctrine. In light of controversies regarding this doctrine, the EPO has not adopted it so far, thus refrained from denying categorically the novelty of active metabolite inventions.⁴² However, does administering a drug infringe on its active metabolite patent, and consequently manufacturing generics of this drug constitute active inducement of infringement? The EPO's sole responsibility concerns patent examination and awarding, not handling patent infringement litigation. Thus, the courts of each European nation independently decide the controversy described above.

In the case of *Marion Merrell Dow Inc. v. Baker Norton Pharmaceuticals Inc.*, the plaintiff Merrell Dow used the same arguments to file infringement suits against the defendant Baker Norton in Germany, the United Kingdom, and the United States. The courts of the three countries all employed different reasoning to reach the same conclusion of non-infringement. In Germany, the Munich District Court dismissed the plaintiff's claim on the basis of equity. The court found the compound manufactured and marketed by the defendant to be identical to the terfenadine claimed in the plaintiff-owned expired patent. However, the court further reasoned that when

40. See, e.g., *Schering Corp. v. Geneva Pharm., Inc.* (*Schering Corp. III*), 348 F.3d 992, 993-96 (Fed. Cir. 2003); H. Sam Frost, *The Unique Problem of Inventions Which Are Fully Enabled and Fully Described, But Not Fully Understood (Merrell Dow's Terfenadine Revisited)*, 20 INTELL. PROP. J. 369 (2007), available at <http://www.bereskinparr.com/files/file/docs/PatentTerfenadineFrost.pdf>; Ben Herbert, Note, *When Nature's Anticipation Inherently Prevents Your Discovery: A New Look at an Overlooked Requirement of Patentability and Its Impact on Inherent Anticipation*, 50 JURIMETRICS 111 (2009). For further discussion of the inherent anticipation doctrine, see *infra* Part VII.B.

41. *Schering Corp. II*, 339 F.3d at 1381.

42. GRUBB, *supra* note 10, at 233.

the allegedly infringing behavior is entirely within the scope of exclusive rights of an expired patent, this behavior cannot infringe on any other valid patent. The plaintiff later appealed to the German Higher District Court, which agreed with the district court's judgment. It further elaborated that any person can freely use technologies from expired patents, since the patentees of those technologies have been amply rewarded during the earlier exclusivity period of the corresponding patents. Finally, Merrell Dow appealed to the German Federal Supreme Court, which denied review of its appeal, therefore finalizing the lower court's judgment.⁴³ In summary, both German and U.S. courts in this case did not invalidate the controversial claims of active metabolites, but merely maintained that the defendant's behavior was outside the scope of indirect infringement.

Conversely, the court in the United Kingdom invoked the inherent anticipation doctrine to address this infringement action. The court held the active metabolite claims at issue to be invalid, therefore finding no patent infringement by the defendant.⁴⁴ As part of the claim construction, the House of Lords⁴⁵ ruled that the disputed TAM compound claim encompasses both TAM produced through metabolism in the human body and synthesized *in vitro*. The court analyzed this dispute by differentiating two types of anticipation: anticipation by use and by disclosure. Specifically, Lord Hoffman discussed the novelty issue in the alternative by answering the following two questions: (1) Does patients' use of TAM prior to the filing date of the disputed patent constitute prior art to the claim in that patent, thus defeating its novelty? (2) Or does the disclosure of the earlier dated '217 patent similarly constitute prior art to the disputed patent's claim? The House of Lords then stated that although the EPO's decision is non-binding on the U.K. courts, since the European Patent Convention (EPC) shall be followed by all contracting countries with the EPO being an important agency in interpreting this convention, the EPO's opinions should be respected by the U.K. courts.

43. Frost, *supra* note 40, at 380-81.

44. Merrell Dow Pharm. Inc. v. H. N. Norton & Co., [1996] R.P.C. 76 (UKHL 1995).

45. Before the U.K. Supreme Court established operations in October 2009, the House of Lords was the highest judicial authority in the United Kingdom. Twelve Lords of Appeal in Ordinary (Law Lords) tried cases appealed from appellate courts. See *Introduction to the Justice System: The House of Lords*, JUDICIARY OF ENG. AND WALES, <http://www.judiciary.gov.uk/about-the-judiciary/introduction-to-justice-system/the-house-of-lords> (last visited Mar. 17, 2013).

Regarding the anticipation by patients' prior use of TAM, the court by referring to previous EPO cases,⁴⁶ held that only when prior usage provides the sufficient and necessary information of the disputed invention to enable a PHOSITA to practice it, does this usage defeat the novelty of the invention at issue. In the case of TAM, patients were entirely unaware that after administering terfenadine their bodies would automatically generate TAM to achieve the desired pharmaceutical effect. Thus, this use alone did not disclose any technological features of TAM, and neither did it enable the PHOSITA to practice the invention of the TAM compound. Consequently, the invention of the TAM compound maintained its novelty despite the patients' prior use of terfenadine.⁴⁷

Nevertheless, the House of Lords ruled that the technical disclosures in the '217 patent still defeated the novelty of the TAM claim. Their key point in determining this issue was whether the prior patent provided enough information to enable a PHOSITA to practice the disputed invention. The House of Lords states that although the '217 patent did not disclose how to manufacture pure TAM, it described how administering terfenadine will produce chemical reactions in the patient's body and thereby achieving antihistamine effects, which the House of Lords deemed sufficient to allow "any person" to produce TAM through metabolism. In other words, the technical disclosure in the '217 patent provided sufficient information to enable the PHOSITA to make TAM. Under the above premises, even if the prior art reference did not disclose all the technological features of TAM, TAM was still in the prior art, and therefore lacked novelty.⁴⁸

A number of commentators suggested that despite the U.K. decision of *Marion Merrell Dow Inc.* referencing earlier EPO cases, inconsistencies still remained between this decision and the EPO's conservative attitude toward applying inherent anticipation doctrine. In previous EPO cases, the boards of appeal held that a prior reference inherently disclosing the technological features of the disputed invention is insufficient to anticipate this invention and defeat its novelty. Prior art references must actually "convey" technological features to the public for the disputed invention to be found not novel. Thus, even if the implementations of technologies

46. Mobil Oil III / Friction-Reducing Additive, No. G 2/88, [1990] O.J. EPO 93 (Bd. App. Dec. 11, 1989).

47. *Merrell Dow Pharm. Inc.*, [1996] R.P.C. at 84.

48. *Id.* at 87.

from prior art references unavoidably allow people to practice later claimed inventions, those inventions should still be recognized as undisclosed as long as the references themselves do not explicitly convey any technological features of these inventions to a PHOSITA.⁴⁹ This position is contrary to the view expressed by the U.K. House of Lords in *Merrell Dow*. However, the decisions by the EPO have only referential value and are not mandatory for the courts in EPC member states. Given these contradictory stances by the EPO and U.K. House of Lords, it remains to be seen whether the EPC members would resolve this issue and develop a harmonized common approach.⁵⁰

In brief, the United States and various European countries have diverged in their solutions to the problem of active metabolite patents. After *Schering Corp.*, the U.K. and U.S. approaches appear to converge. Both countries adopted the inherent anticipation doctrine denying novelty to active metabolites on the basis of earlier technical disclosure of the drug that converts *in vivo* into the metabolite. Under this doctrine, patents are granted only for active metabolites that are purified or synthesized *in vitro*.⁵¹ Thus, the United Kingdom and the United States displayed a more narrow and restrictive attitude towards the patentability of active metabolites.

V. ACTIVE METABOLITES IN INDIAN LAW

Regarding active metabolite patents, Section 3(d) of India's 2005 Patents (Amendment) Act and the explanation passed together with the Amendment recognize metabolites as "new types of known substances", in principle considered identical to known substances and thus unpatentable. Only those metabolites that differ significantly in their characteristics regarding efficacy are deemed patentable.⁵²

49. Christopher Floyd, *Novelty under the Patents Act 1977: The State of the Art after Merrell Dow*, 18 EUR. INTELL. PROP. REV. 480, 483 (1996).

50. Similar to the United States, there is also a U.K. decision that held active metabolites infringing on the original compound claims under the doctrine of equivalents. *See, e.g., Beecham Grp. Ltd. v. Bristol Labs. Ltd.*, [1978] R.P.C. 153 (UKHL 1977).

51. For further discussion of the inherent anticipation doctrine, see *infra* Part VII.B.

52. Section 3 of the Indian Patents (Amendment) Act of 2005, No. 15, Acts of Parliament, 2005 (India) provides the following:

[T]he mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation.—For the purposes of this clause, salts, esters, ethers,

Furthermore, the Indian Patent Office and the High Courts have held that substantial increase in bioavailability, physical or chemical stability do not satisfy this exception of enhancement of the known efficacy.⁵³ Accordingly, obtaining patents for active metabolites in India is extraordinarily difficult.

The attitude of India is surely adverse and restrictive towards awarding metabolite patents. Typically, scholars in the developing world believe that active metabolites are “natural products” from known substances. They are not “creations” or “inventions,” and thus should not be patentable, regardless of whether they are formed through metabolism or synthesized *in vitro*.⁵⁴ Before the 2005 Amendment the India Patent Office originally adopted a similar position. In particular, the 2005 Draft Manual of Patent Practice and Procedure of the Office stipulated that active metabolites are not patentable, regardless of whether their efficacy differs from the original drugs.⁵⁵ Thus, scholars have speculated whether the addition of the enhanced efficacy exception to the 2005 Amendment was just to conform to Article 27.1 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (the TRIPS Agreement), which provides that inventions in any field of technology may apply for and equally enjoy patent protection without prejudice.⁵⁶

VI. NOTEWORTHY COURT DECISIONS IN TAIWAN

There is no provision in Taiwan’s patent law or patent examination guidelines to address the problem of active metabolites. As for court decisions, a 2008 case by the Intellectual Property Court

polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.

Id.

53. Susan Fyan, *Pharmaceutical Patent Protection and Section 3(D): A Comparative Look at India and the U.S.*, 15 VA. J.L. & TECH. 198, 210-11, 216-17 (2010).

54. See, e.g., Carlos Correa, *Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective* 18 (Univ. of Buenos Aires, Working Paper, 2007), available at http://www.iprsonline.org/resources/docs/Correa_Patentability%20Guidelines.pdf.

55. PATENT OFFICE, MANUAL OF PATENT PRACTICE AND PROCEDURE (DRAFT) app. I § 5.4, at 140 (2005) (India).

56. Linda L. Lee, Note, *Trials and TRIPS-ulations: Indian Patent Law and Novartis AG v. Union of India*, 23 BERKELEY TECH. L.J. 281, 282-85, 292-95 (2008); Tanuja V. Garde, *Circumventing the Debate over State Policy and Property Rights: Section 3(d) of the Indian Patents Act Law*, in PATENTS AND TECHNOLOGICAL PROGRESS IN A GLOBALIZED WORLD: LIBER AMICORUM JOSEPH STRAUS 243, 246-50 (Wolrad Prinz zu Waldeck und Pymont et al. eds., 2009).

(IP Court), a specialty court with priority jurisdiction over IP cases,⁵⁷ illustrated the attitude of Taiwanese judges towards this type of patents.⁵⁸ The plaintiff in this case was the Japanese Takeda Pharmaceutical Company that initially held a patent for the combination of an anti-diabetic drug, brand-named Actos, and other anti-diabetic drugs. Takeda later acquired Patent No. 63119 ('119 patent) for a tetrahydrothiazolyl-thione derivative, which is the metabolite of Actos' active ingredient, pioglitazone hydrochloride. Pioglitazone itself and the active metabolite were both responsible for causing the desired anti-diabetic effects in the human body. The defendant in this case was China Chemical & Pharmaceutical Co., Ltd. (CCPC), a Taiwanese pharmaceutical company, which intended to manufacture and sell a generic version of pioglitazone after the Actos patent expired. CCPC filed with the Taiwanese Food and Drug Administration (TFDA) and obtained a drug license on July 12, 2006. Takeda later filed an infringement suit against CCPC based on the '119 patent.⁵⁹

Takeda argued that patients necessarily produce the metabolite through metabolism after consuming the generic drug of pioglitazone. However, patients were unaware of this metabolic process, which occurred unconsciously, and in reality equated to a tool for CCPC to infringe the metabolite patent. Therefore, by manufacturing and selling this drug CCPC directly infringed Takeda's '119 patent of the pioglitazone metabolite. Alternatively, CCPC knowingly aided patients in infringing the '119 patent, resulting in indirect infringement of this patent by CCPC.⁶⁰ The defendant countered that the '119 patent lacked novelty and non-obviousness, and was thus invalid on grounds of the metabolite having previously been disclosed in the pertinent literature and pharmacopoeia. In light of this disclosure any person could have produced the metabolite by simply consuming pioglitazone, leading a PHOSITA to easily create the metabolite. In the alternative, CCPC argued that regardless of the

57. Taiwan's IP Court enjoys priority jurisdiction over civil and administrative IP litigations in the first and second instances, and criminal IP litigations only in the second instance.

58. Rishang Wutian Yaopin Gongye Gufen Youxian Gongsi, Zhongguo Huaxue Zhiyao Gufen Youxian Gongsi (日商武田藥品工業股份有限公司, 中國化學製藥股份有限公司) [Takeda Pharm. Co. v. China Chem. & Pharm. Co.], 97 Civil Patent Suit Judgment No. 5 (Intell. Prop. Ct., Oct. 28, 2008) (Taiwan), *aff'd in part, rev'd in part*, 97 Civil Patent Appeals Judgment No. 20 (Intell. Prop. Ct. Mar. 19, 2009) (Taiwan), available at <http://jirs.judicial.gov.tw/Index.htm>.

59. *Id.* Facts and Reasoning ¶¶ 1.1, 1.3.

60. *Id.* Facts and Reasoning ¶ 1.4.

'119 patent's validity it did not directly infringe the '119 patent, since it did not manufacture or sell the metabolite, but rather pioglitazone. Consequently, the defendant should not be responsible for inducement or contributory infringement of the patent.⁶¹

The IP Court's division of first instance ruled that the '119 patent is valid but that the defendant did not infringe it. In the judgment, the court did not expound on the patent's validity, but instead merely analyzed whether infringement had occurred. With regard to direct infringement, the court noted that the defendant produced generic drugs that only contained pioglitazone not the metabolite of the '119 patent. The active ingredient recorded in the defendant's instruction label also was pioglitazone that differed in its chemical structure from the claimed metabolite. The court held that the plaintiff could not expand the scope of the '119 patent scope to include pioglitazone. Furthermore, although pioglitazone converted into the claimed metabolite after natural metabolism in the human body, this was not the result of human controlled will or effort, nor it did involve any commercial sales or advertisement. Thus, the defendant's actions were not related to practicing the invention of the '119 patent. The plaintiff argued that consumption of pioglitazone by third parties (patients) with the drug's conversion into the '119 patent's metabolite within the human body constituted "direct manufacturing" and "use" by the defendant. The court explicitly rejected the plaintiff's inference of a third parties' acts being the deliberate consequence of the defendant's acts.⁶²

On indirect infringement, the court noted that "inducement" refers to the formation of intention after notification and encouragement by others, whereas "contributory infringement" referred to assisting the direct infringer to fulfill her existing intentions. However, indirect infringement still requires that direct infringers understand the consequences of their acts, which was not the case here. Moreover, the defendant only sold a generic drug containing pioglitazone without the instruction label notifying patients that digesting the drug would result in the metabolite of the '119 patent, and refrained from encouraging patients to "intentionally manufacture" this metabolite. As a result, the court found the defendant's acts to be inconsistent with the elements of inducement and contributory infringement.⁶³

61. *Id.* Facts and Reasoning ¶ 2.4.

62. *Id.* Facts and Reasoning ¶ 5.4.

63. *Id.* Facts and Reasoning ¶ 5.4.

Upon appeal the IP Court's appellate division agreed with the opinion from the division of first instance, holding that the disputed patent was valid, but that the defendant did not directly or indirectly infringe the '119 patent.⁶⁴ Regarding validity, the appellate court found the appellee's evidence only contained basic drug activity tests relating to pioglitazone and its analogs, but lacking the claimed metabolite, and therefore failed to prove lack of novelty of the '119 patent.⁶⁵ Concerning direct and joint infringement, the appellate court reasoned similarly to the division of first instance's opinion.

This case illustrates that Taiwan's patent law has not adopted the inherent anticipation doctrine to refute the novelty of active metabolite patents. Rather, according to the Taiwanese IP Court the metabolite production through unconscious human metabolism does not constitute practicing the invention of metabolite patents. The court found that there was no basis for finding for inducement and contributory infringement due to the lack of direct infringing practices. The ruling paved the way for generic drugs to the market despite patents covering the active metabolites of those generic drugs. Notably, Taiwan has not expressly codified indirect infringement in its patent law. Metabolite patent holders who wish to claim their rights from generic drug manufacturers in the name of inducement or contributory infringement can only resort to the joint infringement provision under the Taiwanese tort law, where the direct infringer's intention or negligence plays a potential role in determining indirect infringement. Thus, in terms of statutory provisions for indirect infringement, differences arise to other countries.

VII. THEORETICAL AND TECHNOLOGICAL ANALYSIS AND TRANSNATIONAL CATEGORIZATION

The countries discussed above demonstrate contradicting attitudes towards active metabolite patents. No consistent solution has emerged for those patents possibly preventing generic drugs from entering the market place even after patents for the generic drugs have expired. In this chapter, the authors introduce a technological analysis and insightful theoretical perspectives to rationally assess the various different approaches. Plausible solutions are then summarized for a

64. Rishang Wutian Yaopin Gongye Gufen Youxian Gongs, *Zhongguo Huaxue Zhiyao Gufen Youxian Gongs* (日商武田藥品工業股份有限公司, 中國化學製藥股份有限公司) [*Takeda Pharm. Co. v. China Chem. & Pharm. Co.*], 97 Civil Patent Appeals Judgment No. 20 (Intell. Prop. Ct. Mar. 19, 2009) (Taiwan), available at <http://jirs.judicial.gov.tw/Index.htm>.

65. *Id.* Facts and Reasoning ¶ 5.3.3.4-5.

separate and more focused investigation and deliberation.

A. A Portion of Active Metabolites Deserves Patent Protection

When considering how the patent law treats active metabolites, the focus of that task hinges on whether those metabolites deserve patent protection. Commentators have indicated that metabolites and original compounds before metabolism are just two forms of the same substance. Although their chemical structures differ, chemical formulae are only the “textual” manifestation for documenting chemical compounds. Although the external appearances of compounds prior to metabolism and their active metabolites differ, the two actually possess the same pharmacology, treating the same physiological effects. Thus, the differences between the two are insubstantial and negligible, existing only in the appearance and the “textual” form of documentation. In essence, they exert identical treatment results. Pursuant to this line of thought, active metabolites seem to lack the value for patent protection.⁶⁶

This article argues nonetheless that a portion of active metabolites may possess characteristics that differ from those of the compounds before metabolism. Those characteristics may cause the metabolites to have unique value and significance in pharmacological and medical practice, which makes them worthy of patent protection. Consider the case of diazepam and oxazepam as an example. Diazepam is a pre-metabolic compound, whereas oxazepam is an active metabolite of diazepam following metabolism. The two use the same pharmacological mechanism to sedate and relax the patient’s muscles. However, diazepam was later found to have a longer sedative effect than oxazepam. Thus, physicians typically prescribe diazepam as a sleep medication. By contrast, oxazepam has only a brief sedative effect. Thus, oxazepam is rather used as a tranquilizer not as a sleep medication. Additionally, because oxazepam does not require hepatic metabolism, it is less harmful to liver function than diazepam and more appropriate for older adults and patients with liver disease.⁶⁷

The diazepam-oxazepam example shows that active metabolites are not merely the flip side of pre-metabolic compounds. The

66. JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 386 (2005); Shayana Kadidal, *Digestion as Infringement: The Problem of Pro-Drugs*, 78 J. PAT. & TRADEMARK OFF. SOC’Y 241, 249 (1996).

67. N.A. Buckley et al., *Relative Toxicity of Benzodiazepines in Overdose*, 310 BRIT. MED. J. 219 (1995), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2548618/pdf/bmj00577-0021.pdf>.

differences between the two are not necessarily restricted to their chemical structure. In practice, many active metabolites differ from pre-metabolic compounds in their side effects, prolonged effectiveness, and mechanisms of action.⁶⁸ This proves that active metabolites are not merely another form of pre-metabolic compounds, but constitute at least in some instances new and unique substances. Therefore, active metabolites are potentially valuable and deserving of patent protection.

The patent law was established to award a period of exclusivity to encourage research and promote the accumulation and disclosure of technical knowledge. In contrast, the patent law also guarantees the public to freely utilize patented inventions, servicing public interest, after the patents to those inventions have expired. Considering active metabolite patents a restrictive attitude should be adopted if the goal is to guarantee the public's free use of medicines from expired patents. However, this runs contrary to the patent law's to encourage innovation and promote public disclosure. If active metabolites are deemed unpatentable, the patent law provides no incentive to the further study of unknown pharmacological metabolisms. It would also fail to provide incentives for inventors to disclose newly-found active metabolites. However, if the emphasis is to encourage research and disclosure of new and useful metabolic compounds and mechanisms, the public may be denied access to affordable generic drugs from expired patents.⁶⁹

Metabolic mechanisms and active metabolites have been identified as having potential value in pharmacological and medical practice as described above. How patent law should treat active metabolites in order to adequately satisfy its many policy objectives is a difficult but important task. Below, the authors put forward three possible solutions to address this issue based on various countries' jurisprudence, including comments on their usefulness and feasibility.

B. Possible Mode I: Inherent Anticipation Doctrine

The U.K. and the U.S. courts mainly employed the inherent anticipation doctrine to refute the patentability of active metabolites.⁷⁰ Under this doctrine, novelty is lost based on known pre-metabolic compounds, and patents cannot claim the scope of the invention to include active metabolites formed upon metabolizing those pre-

68. Correa, *supra* note 54, at 18.

69. Frost, *supra* note 40, at 369, 377-78.

70. See *supra* Part III.B; *supra* text accompanying notes 46-47.

metabolic compounds. Thus, this doctrine can effectively resolve problems with active metabolite patents, which otherwise would prevent generic drugs of those metabolites from entering the market place. However, when the scope of the claims is expressly limited to include only active metabolites that have been purified or were synthesized *in vitro*, those claims fall outside the realm of inherent anticipation. The latter case preserves the incentive to research and disclose new metabolic mechanisms and compounds. The inherent anticipation doctrine consequently appears to be a suitable model for addressing active metabolites in patent law.

On the other hand, over utilizing the inherent anticipation doctrine can lead to broadly expanding and distorting the doctrine itself. This doctrine bridges the gap between written technical features in a prior art reference and the genuine features of the referenced technology. Occasionally, prior art references do not disclose in writing all the technical features of an invention, but on the basis of their professional experience and knowledge, PHOSITAs can still realize the omitted, but implied features. This situation led to the rise of the inherent anticipation doctrine, which allowed judges and patent examiners to recite technical features that were not expressly written into the specification of a prior patent but could be discerned from it by the PHOSITA to refute novelty of later patents. This application of the doctrine avoids awarding or maintaining patents on inventions that appear novel on its face but have lacked novelty in substance from the PHOSITA's point of view.⁷¹

However, the doctrine originally was applied in a situation quite different from the active metabolite patents, where a PHOSITA could not necessarily discern the omitted but in-fact-present technical features from the prior art reference. The early leading case of the inherent anticipation doctrine, *Continental Can Co. v. Monsanto Co.*,⁷² amply demonstrates the doctrine's original meaning and function. Continental Can's patent covered a plastic can having hollow ribs. Continental Can sued Monsanto for infringing its patent. During litigation, Monsanto provided a prior art reference disclosing a container with hollow ribs.⁷³ However, the reference itself did not expressly disclose the ribs to be hollow, but instead that the ribs were manufactured according to conventional blow molding techniques.⁷⁴

71. Herbert, *supra* note 40, at 116-17.

72. *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991).

73. *Id.* at 1267-68.

74. *Id.*

In its decision, the CAFC noted that in determining novelty extrinsic evidence could complement a prior art reference that does not expressly disclose certain technological features. If the extrinsic evidence shows that common knowledge in the technical field could fill the gap, and thus enable the PHOSITA to recognize the omitted features from the reference, those absent features have actually been implicitly disclosed in the prior art. If all technological features of an invention are simultaneously disclosed in a single prior art reference, the invention lacks novelty and the patent should be invalidated. In this case, if extrinsic evidence demonstrates that blow molding techniques invariably generate hollow ribs, which is also recognized by the PHOSITA, then the prior art has implicitly disclosed the “hollow ribs” feature.⁷⁵ Consequently, the CAFC remanded the case for further proceeding to clarify this factual issue.

The *Continental Can* case showed that two conditions are necessary for applying the inherent anticipation doctrine: (1) the omitted technological features are inherently present as disclosed in the prior art reference; (2) a PHOSITA could recognize the omitted features on the basis of the prior art reference. In *Schering Corp.*, in sharp contrast, the CAFC changed the requirements for applying this doctrine, and now only the first condition has to be met. The second condition since then has been dropped from the inherency analysis.⁷⁶ This development has raised controversies and intense discussions regarding its fairness and the suitable criteria for the doctrine to apply.⁷⁷

For applying the inherent anticipation doctrine, the authors contend that the second condition in the *Continental Can* decision should still be maintained. Excluding the criterion that the PHOSITA is able to recognize the omitted features is contrary to the original purpose of the doctrine, which was based on the premises to have the PHOSITA’s general knowledge assist in interpreting the prior art reference. Furthermore, the doctrine will be inconsistent with the settled concepts of “prior arts” and “novelty” as used in patent law.

75. *Id.* at 1268-69. *See also* MUELLER, *supra* note 8, at 129-31.

76. The turning point of the U.S. case law concerning the inherent anticipation doctrine is *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999). *See also* Irving N. Feit & Christina L. Warrick, *Inherency in Patent Law*, 85 J. PAT. & TRADEMARK OFF. SOC’Y 5, 19-21 (2003); Todd R. Miller, *Patented Compounds Inherently Coproduced as Trace Impurities: Issues of Inherent Anticipation and Literal Infringement*, 32 AIPLA Q.J. 425, 452 (2004).

77. *See, e.g.*, Dan L. Burk & Mark A. Lemley, *Inherency*, 47 WM. & MARY L. REV. 371, 372-74 (2005); Steven C. Carlson, *Inherent Anticipation*, 40 IDEA 297, 306-18 (2000); Feit & Warrick, *supra* note 76, at 21; Herbert, *supra* note 40, at 113-14; Miller, *supra* note 76, at 442; Mueller & Chisum, *supra* note 37, at 1102-05.

Prior art refers to technical knowledge that already falls within the public domain, whereas novelty identifies new information that is still privately held outside of the public domain. If the requirement of PHOSITA's recognition were eliminated, technological features unknown to the PHOSITA would be deemed prior art that would defeat the novelty of these features. However, since these features have never been explicitly disclosed to the public or are known to the PHOSITA, the public will in all actuality be unable to use or share the technology associated with these features. The core quid pro quo in patent law rests on the public freely and openly learning, sharing, and utilizing these technologies and other types of information while granting a limited monopoly to the inventor. Thus, neglecting the PHOSITA recognition requirement will result in serious contradictions with the widely accepted notions of public domain and novelty.⁷⁸ Therefore, the authors conclude that PHOSITA's recognition should be required when applying the inherent anticipation doctrine.

Turning back to the issue of active metabolites, if the PHOSITA's recognition requirement is reinstated, metabolite patents may not be inherently anticipated by prior art disclosing their corresponding pre-metabolic drugs. Since the PHOSITA cannot identify any technological features of the active metabolites from the prior art reference, patents for those metabolites can still retain their novelty under this doctrine. The authors hence believe that the inherent anticipation doctrine, if applied in this manner, would not be a suitable model to resolve the controversies regarding active metabolite patents.

C. Possible Mode II: Product of Nature Doctrine

Turning to active metabolite patents and patent evergreening, a number of commentators suggested employing the product of nature doctrine to confront this problem.⁷⁹ For example, § 101 of the U.S. Patent Act (35 U.S.C. § 101 et seq.) specifies the scope of patentable

78. Herbert, *supra* note 40, at 123. *But see* Burk & Lemley, *supra* note 77, at 374.

79. EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp., 268 F.3d 1342, 1350-51 (Fed. Cir. 2001); ICN Pharm., Inc. v. Geneva Pharm. Tech. Corp., 272 F. Supp. 2d 1028, 1051 (C.D. Cal. 2003); Burk & Lemley, *supra* note 77, at 403-08; Cynthia Chen, Note, Schering Corp. v. Geneva Pharmaceuticals, Inc.: *Clarification of the Inherent Anticipation Doctrine and Its Implications*, 20 BERKELEY TECH. L.J. 95, 113 (2005); Herbert, *supra* note 40, at 143-45. *See also* Torrance, *supra* note 14, at 1500-05. Torrance puts forth a physiological steps doctrine, which considers products and processes of *in vivo* conversion are unpatentable subject matters. The essence of that doctrine and the natural product doctrine is quite similar, and from the authors' point of view could be effectively classified into the same category. *Id.*

subject matters to include any invention or discovery on a “process, machine, manufacture, or composition of matter.”⁸⁰ The term “discovery” in this section does not refer to the original meaning of the term, but instead constitutes a synonym for invention.⁸¹ Pure discovery of natural products or phenomena is still not an invention that is patentable under § 101.⁸² In *Gottschalk v. Benson*,⁸³ the U.S. Supreme Court set up the taxonomy of unpatentable subject matters to comprise laws of nature, physical phenomena, and abstract ideas. The court noted that those types of discoveries are the collective treasures of the human race, which should be shared by the general public without constraint, and thus may not be preempted by patent owners.⁸⁴ In the same vein, Taiwan’s patent examination guidelines espouse similar rules, stating that pure scientific discoveries of objects, phenomena, and laws that are inherent in the natural world are not patentable subject matters.⁸⁵

At the extreme end of the spectrum, India’s patent law adopts an entirely negative attitude toward active metabolite patents. It posits that active metabolites are fundamentally products of nature and should not be granted patents. The rationale of this position is that the identification of active metabolites is merely a discovery, not an invention, involving a level of technological innovation that is relatively low. Thus, awarding process patents with weaker exclusivity should be appropriate, whereas product patents granting stronger exclusivity in exchange for disclosure are deemed unnecessary and too restrictive.⁸⁶ On this basis, active metabolites are excluded from patent protection, regardless whether they are produced through metabolism or *in vitro*.

The authors propose that the product of nature doctrine may lend itself to mitigate the problems caused by active metabolite patents. Nevertheless, the doctrine does not necessarily refute patentability of

80. 35 U.S.C. § 101 (2011) (“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”).

81. ALBERT HENRY WALKER, TEXT-BOOK OF THE PATENT LAWS OF THE UNITED STATES OF AMERICA § 2, at 2 (2d ed. 1889).

82. See *Pyrene Mfg. Co. v. Boyce*, 292 F. 480, 481 (3d Cir. 1923); *Morton v. N.Y. Eye Infirmary*, 17 F. Cas. 879, 881-82 (S.D.N.Y. 1862) (No. 9,865).

83. *Gottschalk v. Benson*, 409 U.S. 63 (1972).

84. *Id.* at 71-72.

85. Faming Zhuanli Shiti Shencha (發明專利實體審查) [Patent Examination Guidelines] (promulgated by Intell. Prop. Office, Ministry of Econ. Affairs in 1994, effective on Nov. 27, 1994, as revised in 2004) tit. 2, ch. 2, sec. 1.3.2 (Taiwan).

86. Herbert, *supra* note 40, at 144-46.

natural substances that are purified or synthesized *in vitro*. The U.S. patent law, for instance, holds that if those substances were obtained by human intervention and differ sufficiently from products as found in their natural states, they can still meet the requirement under § 101 and thus are deemed patentable subject matters.⁸⁷ Currently, a number of judicial U.S. decisions held that natural products in their purified states are patentable.⁸⁸ This rule was first articulated in the *Parke-Davis* case.⁸⁹ Here, the disputed invention involved epinephrine in its purified state. Because epinephrine is an important hormone naturally secreted and formed in the human body, it is undoubtedly a “product of nature.” In this case, the inventor Takamine developed a method of separating epinephrine from glandular tissue, which resulted in epinephrine unadulterated by other organic matter. Takamine applied for patents of the separation method and purified epinephrine.⁹⁰ However, using epinephrine for treatment purposes was already established in the medical field prior to Takamine’s separation method. The traditional practice included air-drying and crushing animal adrenal glands prior to dissolving them into an organic solution. This solution, which comprised a number of organic residual substances, was then injected into the patient for treatment with some of these substances being harmful to the patient.⁹¹ With regard to the patentability of epinephrine in its purified state, the court stated that no regulations indicated that extracts of products of nature are unpatentable. The court further noted that Takamine was the first person to separate epinephrine from glandular tissue. As for its medical benefit, the unadulterated epinephrine was actually a brand new substance with substantial commercial and therapeutic value. Consequently, the court held epinephrine in its purified state to be worthy of patent protection.⁹²

In light of the tremendous value of purified or synthesized products of nature, as in the case of purified epinephrine, the product of nature doctrine under the U.S. law that distinguishes between *in vitro* and metabolically produced substances provides an excellent

87. MUELLER, *supra* note 8, at 226.

88. W. Lesser, *Nature or Nurture: Is There a Case Basis for a Judicially Created ‘Product of Nature’ Exclusion? Are Genes Somehow Different?*, 11 J. MARSHALL REV. INTELL. PROP. L. 318, 347-50 (2011).

89. *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95 (S.D.N.Y. 1911), *aff’d in part and rev’d in part*, 196 F. 496 (2d. Cir. 1912).

90. *Id.* at 97.

91. *Id.* at 106.

92. *Id.* at 103.

approach for assessing patentability of materials with natural origins. Regarding active metabolites, the example of diazepam and its metabolite, oxazepam, demonstrated that active metabolites might, too, possess unique pharmacological properties that are different from those of their original pre-metabolic compounds.⁹³ The discovery of unadulterated active metabolites and the process of *in vitro* production through isolation and purification or synthesis thus represent technological progress. The distinction between adulterated metabolites formed through natural metabolism and those that are purified or synthesized *in vitro* may strike a desirable balance between assuring affordable medicine and promoting pharmaceutical innovation. Declining patents for *in vivo* metabolites prevents patent evergreening and could accelerate the market entry of generic drugs. On the other hand, affording patent protection for purified or *in vitro* synthesized metabolites may provide a proper incentive for valuable pharmaceutical development. For these reasons, the authors believe that unadulterated active metabolites that are produced *in vitro* are worthy of the protection afforded under the patent system.

However, some shortcoming of product of nature doctrine may be fatal despite this doctrine trying to adequately address the issue of active metabolite patents. The most serious problem lies with this doctrine's unpredictability. What falls under products of nature is considerably ambiguous. There is no settled meaning or definite scope for this concept in patent law. The intuition of judges or examiners regarding the disputed subject matter may sometimes become a controlling factor. For instance, the patentability of DNA sequences had once been settled for more than ten years. But in recent years, it has been fiercely challenged in the *Association for Molecular Pathology* case in U.S. courtrooms. The district court found in 2010 that isolated DNA did not possess markedly different characteristics from those of natural DNA in human cells despite their structural and functional differences, and thus was unpatentable under the product of nature doctrine.⁹⁴ On appeal, the CAFC overturned the decision of the lower court,⁹⁵ which was in turn vacated by the Supreme Court and remanded for further consideration⁹⁶ in view of *Mayo Collaborative*

93. For detailed explanation of diazepam and oxazepam see *supra* Part VII.A.

94. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181, 227-32 (S.D.N.Y. 2010), *aff'd in part and rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011), *vacated*, 132 S. Ct. 1794 (2012).

95. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011), *vacated*, 132 S. Ct. 1794 (2012).

96. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012).

Services v. Prometheus Laboratories, Inc., where the Court recently held another type of subject matters unpatentable as a law of nature.⁹⁷ This contentious case illuminates the uncertainty and divergence about the character and scope of unpatentable natural products.

The situation is further exacerbated by mutual overlap between different types of unpatentable subject matters. New development in one category of unpatentable subject matters may create percussions for another. Before deciding on its merits, the Supreme Court remanded the *Mayo Collaborative Services* case,⁹⁸ requiring the Federal Circuit to reconsider it in light of *Bilski v. Kappos*,⁹⁹ a newly delivered Supreme Court decision concerning abstract ideas—a third category of unpatentable subject matters. The invention at issue in *Mayo Collaborative Services*—methods for measuring proper dosage of thiopurine to treat autoimmune diseases,¹⁰⁰ is quite dissimilar to the claimed invention in *Bilski*, where the applicant filed for patents on methods of hedging risk in energy trading market.¹⁰¹ The underlying rationales for the Supreme Court to rule the subject matter to be unpatentable in those two cases diverge considerably. However, the mutual impact and chain reaction among different types of unpatentable subject matters, as illustrated in *Bilski*, *Mayo Collaborative Services* and *Association for Molecular Pathology*, demonstrate instability spread from one group to another. This phenomenon significantly intensifies the uncertainty in securing patents and casts unnecessary doubts on products with natural origins. For these reasons elaborated above in this section, those that originate from human bodies yet purified or synthesized *in vitro* should be adequately awarded patent protection. In light of the serious shortcomings of instability and uncertainty, the product of nature doctrine would not be an appropriate solution to the issue of active metabolite patents.

D. Possible Mode III: Non-Practice Theory

Besides dealing with active metabolites through the principles of patentability, Taiwan's IP Court utilized an alternative approach by

97. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012) (holding that claims directed to the relationship between the concentrations of blood metabolites and response to a therapeutic drug are not eligible for a patent because they incorporate laws of nature).

98. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 130 S. Ct. 3543 (2010).

99. *Bilski v. Kappos*, 130 S. Ct. 3218 (2010).

100. *Mayo Collaborative Servs.*, 132 S. Ct. at 1295-96.

101. *Bilski*, 130 S. Ct. at 3223-24.

way of assessing infringement. In the *Takeda v. CCPC* case,¹⁰² the court found that although the generic version of pioglitazone produced the patented active metabolite through metabolism in humans, this *in vivo* production was entirely unknown to any patient taking pioglitazone. A patient was not capable of controlling the metabolic process by his or her own will or acts, nor did it involve any commercial sales of the claimed active metabolite. Thus, the court ruled that the metabolic production was unrelated to the practicing of the asserted metabolite patent, hence did not constitute patent infringement.¹⁰³

In its decision, the Taiwanese IP Court articulated a “non-practice theory” to confront the problem of market entry barrier that generic drugs suffer owing to active metabolite patents. As for patients that take generic drugs, patents on those drugs either expired or were ruled invalid. What patients consciously consume are medicines that are already beyond the term of patent exclusivity. Although active metabolites are in reality formed inside the patients’ bodies by taking these generics, these patients could hardly know about the metabolites being produced inside their bodies. They may not know that their metabolism produces these active metabolites, nor do they consciously force their bodies to manufacture or use these claimed metabolites. Given the fact that this unconscious metabolism is not self-inflicted by those patients, it may not be reasonably counted as a human act that could be culpable for legal liability and punishment.¹⁰⁴ Actually, metabolism is a chemical process that the patients cannot control or intervene by their own will. Thus, it would be absurd to hold these patients accountable for such unconscious and involuntary processes that quietly carry on in their bodies. From this point of view, under a non-practice theory *in vivo* metabolism should be excluded from the scope of infringing acts under the patent law.

The non-practice approach just exempts metabolic reactions in human bodies from infringement liability. It still maintains patent protection over active metabolites that are purified or synthesized *in*

102. See *supra* Part VI.

103. See *supra* text accompanying notes 57-61 for further details in this case.

104. See, e.g., *People v. Newton*, 87 Cal. Rptr. 394, 404-05 (Ct. App. 1970). The court stated that unconsciousness, when not self-induced (e.g., voluntary intoxication), is a complete defense to a criminal act. *Id.* Unconsciousness need not be confined to physical dimensions as commonly associated with the term; it can exist mentally as well, where the person in fact acts, but is not at the time conscious of her action. *Id.* at 405. See also *United States v. Gracidas-Ulibarry*, 231 F.3d 1188, 1196 n.11 (9th Cir. 2000) (stating that sleepwalking falls within the category of unconscious behavior and that the act a person commits during sleepwalking is not criminally culpable); MODEL PENAL CODE § 2.01(2)(b) (1962).

vitro. This distinction adequately controls the claim scope of active metabolite patents, striking a fine balance between protecting pharmaceutical inventions and making medicine more affordable. It also avoids the problems of patent evergreening and preventing market entry by generic pharmaceuticals, both caused by a proliferation of secondary patents.¹⁰⁵ Unlike the product of nature doctrine, whose basic rationale is rooted in the vague concept of a natural world without human intervention, this theory in particular is based on the concept of unconsciousness that is a unique characteristics of *in vivo* processes such as metabolism and digestion. This focused underlying rationale enables the theory to have an unambiguous connotation and clear scope of application, preventing the shortcomings of instability and uncertainty, from which the product of nature doctrine has suffered.

One of the main functions that the patent system performs is to provide incentive for inventors to improve upon existing technologies.¹⁰⁶ Some commentators have argued that inventing upon patents is socially wasteful in that it might attract investment to the task of finding redundant solutions to already solved problems.¹⁰⁷ It is undeniable, on the other hand, that designing around an invention is the most common and feasible method to mitigate blockages that patents bring about.¹⁰⁸ Relatively, compound patents are difficult to invent around due to their respective idiosyncrasies. A good approach that releases active metabolites generated *in vivo* from infringement liability, such as the non-practice theory, may provide a significant conduit for inventing around in the pharmaceutical field. When researchers successfully identify the pre-metabolic compound of a patented drug through endeavors, they may make use of the leeway for active metabolites as discussed above to compete with the drug on the market. Those pre-metabolic compounds are called “pro-drugs.” They can be induced to convert into the patented medicine through

105. See *supra* text accompanying notes 92-94 for further explanation.

106. *State Indus., Inc. v. A. O. Smith Corp.*, 751 F.2d 1226, 1236 (Fed. Cir. 1985); ROGER E. SCHECHTER & JOHN R. THOMAS, *INTELLECTUAL PROPERTY: THE LAW OF COPYRIGHTS, PATENTS AND TRADEMARKS* 289 (2003); Richard Li-dar Wang, *Biomedical Upstream Patenting and Scientific Research: The Case for Compulsory Licenses Bearing Reach-Through Royalties*, 10 YALE J.L. & TECH. 251, 265, 325 (2008).

107. E.g., SUBCOMM. ON PATENTS, TRADEMARKS, AND COPYRIGHTS OF THE S. COMM. ON THE JUDICIARY, 85TH CONG., *AN ECONOMIC REVIEW OF THE PATENT SYSTEM* 51 (Comm. Print 1958) (prepared by Fritz Machlup).

108. John M. Golden, *Injunctions as More (or Less) Than “Off Switches”*: *Patent-Infringement Injunctions’ Scope*, 90 TEX. L. REV. 1399, 1408-09 (2012).

metabolism inside of the patient's body.¹⁰⁹ If the patented drug and pro-drug accomplish substantially the same function and result in substantially the same way, the doctrine of equivalents becomes applicable and the pro-drug would still infringe on the drug patent. Otherwise, the non-practice theory could provide a feasible way for pharmaceutical inventing around, a common practice in other fields of technology.¹¹⁰

VIII. CONCLUSION

This article begins with an overview of transnational jurisprudence in tackling the problem of active metabolite patents, which may instigate drug patent evergreening and hence delaying the market entry of generic medicine. The United States and the United Kingdom adopt the inherent anticipation doctrine, considering active metabolites as inherent in prior art references concerning the corresponding pre-metabolic compounds, usually the active ingredients of the drug, and therefore refute novelty of those metabolite claims. The authors believe this approach removes the key component of PHOSITA recognition from the notion of prior arts, hence stretching the novelty analysis too thin. It runs against the settled meaning of the public domain as well.

India's patent law traces an extreme position in the aspect of the product of nature doctrine. Metabolites are by definition products of metabolism, a process of nature. Based on this reason, Indian law categorically treats metabolites as products of nature, one type of well-recognized unpatentable subject matters. There are also more modest versions of the product of nature doctrine, which still retain patent protection for metabolites purified or synthesized *in vitro*. No matter which version of the doctrine, however, they all suffer from instability and uncertainty with regard to patentability determination. The critical shortcoming makes this approach unadvisable.

Taiwan's IP Court suggests a third approach, the non-practice theory. In light of the unconsciousness of metabolism *in vivo*, this theory exempts the use and production of metabolites in human bodies from the scope of infringing practices under patent law. This

109. Kadidal, *supra* note 66, at 241-42.

110. *See id.* at 241-43 (noting that the practice of using pro-drugs to design around pharmaceutical patents has existed for decades, but the controversies concerning active metabolites are relatively new). The introduction of the non-practice theory would clear the blockage from metabolite patents and stabilize the original status of pro-drugs. Enormous expansion of inventing around and pro-drug competition, on the other hand, might not come into being eventually.

new approach distinguishes between metabolites unconsciously produced *in vivo* and those purified or synthesized *in vitro*, striking a right balance between encouraging pharmaceutical innovations and providing affordable medicine. Following the *in vivo-in vitro* distinction, the theory adequately curbs the claim scope of active metabolite patents, increasing affordable medicine by more market entry of generics and inventing around through pro-drugs. The article is confident that the non-practice theory should be a preferable approach to confronting the problems that patents for active metabolites may generate.