

PHYSIOLOGICAL STEPS DOCTRINE¹

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I. INTRODUCTION

Most inventions exist in the world outside the human body. For these, the usual legal rules of the patent statute and interpreting case law apply. Inventions ranging from

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bicycles, barometric chambers, and bobby socks to tumbling mats, toasters, and toenail clippers fall squarely within patentable subject matter. And, since *Diamond v. Chakrabarty*, the potentially patentable has extended almost to the limits of the human imagination.³ There are specifically recognized exceptions to patentable subject matter: “The laws of nature, physical phenomena, and abstract ideas have been held not patentable.”⁴ However, there are also unrecognized exceptions, and this paper argues that these include the metabolic products of *in vivo* conversion.

Patent claims that require the participation of a human being fit uneasily into patent law. Inventions carried out using human thought have been subject to such limitations as mental steps doctrine. The United States Patent and Trademark Office (“USPTO”) has declared inventions consisting of a human being to be unpatentable subject matter despite the lack of any statutory prohibition.⁵ Though the law has yet to speak clearly on the matter, inventions that include a human being as part of their structure or operation generally sit towards the nonpatentable end of the patentability spectrum.

One class of inventions that have a significant human component involve *in vivo* conversion. *In vivo* conversion is a process, usually metabolic in nature, wherein one substance, usually a chemical compound, is altered significantly by physiological pathways in the body to be transformed into a different substance or substances.⁶ For

³ *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)

⁴ *Id.* at 309.

⁵ Statement of Commissioner of Patents, United States Patent and Trademark Office (1987).

⁶ If the process of *in vivo* conversion transforms a precursor chemical into a second chemical that has therapeutic efficacy, precursor is sometimes called a “prodrug”, and the resulting therapeutic chemical a “drug”.

example, when a patient ingests a therapeutic drug, that drug is often converted by the natural chemistry of the digestive system into a distinctly different metabolite.

Sometimes the metabolites produced by *in vivo* conversion possess therapeutic efficacy. Such metabolites have been claimed in numerous patent applications, either as compositions *per se* or as parts of methods of treatment. Although the USPTO has granted patents claiming products generated by *in vivo* conversion of ingested drugs, no such claims to products *in vivo* conversion products have been found valid and enforceable against alleged infringers by the highest court to consider the issue.⁷

This paper reviews the judicial decisions considering infringement by *in vivo* conversion, including a forerunner of *in vivo* conversion cases involving “natural conversion”. It then considers several possible explanations for these decisions’ unanimity in finding *in vivo* conversion claims invalid or unenforceable. Finally, it suggests a novel doctrinal framework to explain the invalidity or unenforceability of *in vivo* conversion claims: “physiological steps doctrine”.

II. “NATURAL CONVERSION” PATENTS

Prior to the first *in vivo* conversion case, a dispute between two agricultural feed companies considered the issue of whether a claim to a specific mixture of ingredients could be infringed by a mixture initially lacking a claim element, but then subsequently generating that element by a natural process (in this case, fermentation) occurring within the initial mixture. Although the district court found infringement, the appeals court disagreed.

⁷ I would like to thank Jonathan Singer, a distinguish patent attorney at Fish & Richardson LLC, very much for bringing this striking pattern of judicial decisions to my attention, and for encouraging me to explore the issues this pattern raises.

Feed Service Corporation (“Feed Service”), an agricultural feed company that made feed for livestock, owned United States Patent No. 2,808,332 (“’332 patent”).⁸ The ‘332 patent had 21 claims divided between feeds of specified formulations and methods of using such feeds to improve rates of growth in cattle.⁹ According to the specification of the patent, improvement in rates of cattle growth was achieved by including synthetic urea and ethanol as ingredients.¹⁰ The ‘332 patent discloses that ethyl alcohol (also known as ethanol) had been previously mentioned in association with feeding animals, but never to achieve improved growth in ruminants; in fact, ethanol was usually identified as an ingredient to avoid.¹¹ Feed Service marketed its feed under the trade name “Morea”, and its product was a commercial success.¹²

Kent Feeds, Inc. (“Kent Feeds”) developed and sold competing feeds, trade named “Bovino” and, later, “Bovino-Lac”.¹³ Feed Service sued Kent Feeds for infringing claims of the ‘332 patent, alleging that “Bovino-Lac” contained each and every claimed ingredient.¹⁴ Kent Feeds disputed infringement on the ground that their product lacked ethanol, pointing out that its products included fermented molasses instead of ethanol.¹⁵ In response, Feed Service argued that there was, in fact, infringement because “the fermentation process of the blackstrap molasses converts virtually all of the sugar in the molasses to alcohol”.¹⁶

⁸ Feed Service v. Kent Feeds, 528 F.2d 756, 757 (7th Cir. 1976); writ of certiorari denied, Feed Service Corp. v. Kent Feeds, Inc., 429 U.S. 870 (1976).

⁹ United States Patent No. 2,808,332.

¹⁰ Feed Service v. Kent Feeds, 528 F.2d 756, 757 (7th Cir. 1976).

¹¹ United States Patent No. 2,808,332, column 2, lines 19-30.

¹² Feed Service v. Kent Feeds, 528 F.2d 756, 757 (7th Cir. 1976).

¹³ Id. at 763.

¹⁴ Id. 758-759.

¹⁵ Id. at 763.

¹⁶ Id. at 763.

The district court sided with Feed Services, finding that Kent Feeds' product contained ethanol in the amounts specified by the claims,¹⁷ and thus infringed all of the claims of the '332 patent.¹⁸ The district court appears to have been untroubled by the provenance of ethanol in feed: direct addition of ethanol to feed versus ethanol produced by fermentation of molasses within the feed mixture itself.

Kent Feeds appealed, alleging that the claims of the '332 patent were invalid, unenforceable, and not infringed by its feed product.¹⁹ Unlike the district court, the Seventh Circuit Court of Appeals, relying on the prosecution history of the '332 patent, considered the provenance of ethanol in the feed to be an decisive issue:

We do not read the claims in suit to be broad enough to cover all feed supplements containing urea and ethanol no matter how the alcohol is obtained. We read the claims to teach the use of alcohol in its liquid form and not the use of alcohol derived in a fermentation process of molasses or from other fermented sources. Although plaintiff strenuously argues to the contrary, we incline to the more narrow view that the '332 patent in suit covers the *addition* of alcohol as such to its claimed combination. We cannot say that its monopoly extends to the mere presence of alcohol resulting from a molasses fermentation process.²⁰

Furthermore, the Court of Appeals appeared to make a distinction between claimed ingredients added to feed by conscious human agency and claimed ingredients that arise *in situ*:

Certain things have become crystal clear to us at this time. In our considered judgment the plaintiff is limited to a narrow construction of the patent in suit. Defendants do not *add* alcohol to their feed supplements

¹⁷ Feed Service v. Kent Feeds, 185 U.S.P.Q. 745, 18 (N.D.Ill. 1975).

¹⁸ Id. at 32.

¹⁹ Feed Service v. Kent Feeds, 528 F.2d 756, 757 (7th Cir. 1976).

²⁰ Id. at 763.

and plaintiff does not charge them with that. The charge of infringement is based on the use by defendants of fermented molasses which provides the alcohol in question as a natural occurring event. We have concluded that the patent in suit is limited to the teaching of the *addition* of alcohol in feed supplements. The fact that the defendants' Bovino product may reach the same result as plaintiff's Morea is not conclusive of the determination of infringement.²¹ [Underline added for emphasis.] Accordingly, the Court of Appeals reversed the district court's finding of infringement, though it did affirm the lower court's finding of validity.²²

In his dissent, Judge Stevens disputed the majority's interpretation of "addition":

I agree with Judge Hastings' conclusions that the patent is valid and that the claims only cover the addition of alcohol in feed supplements, but it seems to me that the incorporation of fermented molasses is a method of adding ethanol.²³

In addition, some commentators have suggested that the Court of Appeals wrongly imported a claim element (that is, "incorporating") from the process claims into the product claims.²⁴ However, as claims 11 and 16, both product claims to feed mixtures, are the only claims the Court of Appeals reproduces in its opinion, and are both product claims,²⁵ Court appears to have been aware that its interpretation included product claims.

²¹ Id. at 764.

²² Id.. Significantly, the court interpreted not just the process claims, but also the product claims covering the feed itself, to involve ethanol that had been added or incorporated as ethanol *per se*.

²³ Id. at 764.

²⁴ See, e.g., Patent Law Perspectives § 3.2 ("In *Feed Service Corp. v. Kent Feeds, Inc.*, the Seventh Circuit appears to have committed serious error in reversing the lower court's holding of infringement of composition of matter claims to a cattle feed supplement "comprising urea and ethanol. One can find no warrant whatsoever, in fact or in law, for such a construction of these patent claims. The invention of these claims was a feed supplement comprising ethyl alcohol and urea--not how to make such a supplement. This is confirmed by the court's observation that "[T]he novelty of the patent in suit was the conception of the idea of incorporating ethyl alcohol and a synthetic nitrogen source in feed supplements. This led to the formulation of feed supplements containing ethyl alcohol and urea as the source of synthetic nitrogen." This opinion indicates either a failure on the part of the court adequately to comprehend patent law or an inability on the part of the court adequately to express its reasons for deciding as it did."").

²⁵ *Feed Service v. Kent Feeds*, 528 F.2d 756, 758 (7th Cir. 1976).

Furthermore, the United States Supreme Court denied Feed Service's request for certiorari.²⁶

Although the Court of Appeals did not offer a clear rationale for its decision, it consider the "natural" origin of an ingredient in the feed mixture to be significant, and, perhaps, even decisive. By doing so, *Feed Service v. Kent Feeds* set the stage for later *in vivo* conversion cases by suggesting that claims to products generated by natural processes may be less patentable than claims to identical products made artificially.

III. *IN VIVO* CONVERSION PATENTS

A. OVERVIEW OF *IN VIVO* CONVERSION LITIGATION

Since *Feed Service v. Kent Feeds* was decided in 1976, there have been ten litigations involving allegations of infringement of products generated by *in vivo* conversion of known drugs that have led to recorded judicial decisions. Though these cases display a variety of facts and rationales, their results agree in one significant respect: none of the claims to products of *in vivo* conversion in dispute were found to be infringed.²⁷

B. *IN VIVO* CONVERSION CASELAW

1. *ORTHO V. SMITH*

Ortho Pharmaceutical Corporation ("Ortho") sued for declaratory judgment against American Home Products, the exclusive licensee of United States Patent

²⁶ *Feed Service Corp. v. Kent Feeds, Inc.*, 429 U.S. 870 (1976) (Writ of certiorari denied).

²⁷ At first glance, *Ortho Pharmaceutical Corporation v. Herchel Smith*, 959 F.2d 936, 939 (Fed. Cir. 1992), would seem to be an exception. However, here infringement was found to lie under the doctrine of equivalents.

No. 3,959,322 (“‘322 patent”), Dr. Herchel Smith, and Wyeth-Ayerst Laboratories (collectively “AHP”), asking the district court for a declaration of invalidity of claims of the ‘322 patent.²⁸

Ortho marketed norgestimate, an oral contraceptive, a steroid it had developed by modifying norgestrel, a chemical covered by claims 5 and 19 of the ‘322 patent:

Norgestimate was initially ‘made from norgestrel by Dr. Arvin Shroff of Ortho, who was identified as the inventor of norgestimate. (Exh. D-25, 29; Exh. P-239). Dr. Shroff did not know how to make norgestrel; he used a bottle of norgestrel he had obtained from his stockroom. He used basic laboratory techniques known to undergraduate students in the 1950s, and the whole process took less than a day. (Dep. Shroff 30-33, 101; Exh. D-19 at 89-91; Tr. Rorig 602-604; Tr. Doorenbos 238-39).²⁹

When ingested, norgestimate is transformed by *in vivo* conversion into norgestrel.³⁰ The district court found that:

claims 5 and 19 infringed under the doctrine of equivalents because Ortho’s norgestimate had been shown to break down in the body to, among other things, norgestrel (the product of claim 5) and norgestrel acetate (the product of claim 19), and those two breakdown products are primarily responsible for the biological activity of norgestimate.³¹

Although it did appeal on other grounds, including invalidity of the ‘322 patent, Ortho did not appeal the finding of patent infringement itself.³²

Despite the fact that this case did, indeed, involve one compound (that is, norgestimate) that is transformed by *in vivo* conversion into a different infringing compound (that is, norgestrel), it is conceptually distinct from the other *in vivo*

²⁸ Ortho Pharmaceutical v. American Home Products, 959 F.2d 936, 937-938 (Fed. Cir. 1992).

²⁹ Ortho Pharmaceutical Corporation v. Herchel Smith, 18 U.S.P.Q.2d 1977, 30? (E.D. Penn. 1990).

³⁰ Ortho Pharmaceutical Corporation v. Herchel Smith, 959 F.2d 936, 939 (Fed. Cir. 1992).

³¹ Id..

³² Id. at 940.

infringement cases because the basis for the district court's decision was the doctrine of equivalents. Under the court's application of the doctrine of equivalents, both norgestimate and its *in vivo* product, norgestrel, were found independently to infringe claims 5 and 19 of the '332 patent. In other words, the court did not find that infringement was triggered by *in vivo* conversion. By contrast, all of the cases considered below involve the issue of whether infringement can be triggered by *in vivo* conversion.

2. *ZENITH V. BRISTOL-MYERS SQUIBB*

Bristol-Myers Squibb ("BMS") developed an antibiotic, cefadroxil, and a novel, crystalline form of cefadroxil, named the "Bouzard monohydrate", that possessed significant advantages over other forms of cefadroxil in terms of its manufacture and therapeutic administration.³³ BMS owned United States Patent No. 3,489,752 ("752 patent"), which claimed all forms of cefadroxil, and United States Patent No. 4,504,657 ("657 patent"), which contained a single claim to the Bouzard monohydrate using a chemical formula and 37 specific x-ray diffraction properties.³⁴

Zenith Laboratories ("Zenith") planned to market a form of cefadroxil, Cefadroxil DC, that differed structurally from the Bouzard monohydrate.³⁵ After BMS alleged that Cefadroxil DC infringed the claim of the '657 patent, Zenith sued in district court for a declaratory judgment against BMS, alleging, among other things, that Cefadroxil DC did not infringe the claim of the '657 patent.³⁶ After agreeing that Cefadroxil DC did not

³³ *Zenith Laboratories v. Bristol-Myers Squibb*, 19 F.3d 1418, 1419 (Fed. Cir. 1994); rehearing, *en banc*, denied by *Zenith Lab. v. Bristol-Myers Squibb Co.*, 1994 U.S. App. LEXIS 14626 (Fed. Cir. May 26, 1994); writ of certiorari denied by *Bristol-Myers Squibb Co. v. Zenith Lab.*, 513 U.S. 995 (1994).

³⁴ *Zenith Laboratories v. Bristol-Myers Squibb*, 19 F.3d 1418, 1419-1420 (Fed. Cir. 1994).

³⁵ *Id.* at 1420.

³⁶ *Id.*

literally infringe, BMS adjusted its theory of infringement to (1) infringement under the doctrine of equivalents and (2) infringement because “Zenith’s product converted into the patented compound in the patient’s stomach, and thus the sale of cefadroxil DC would induce infringement of the ‘657 patent under 35 U.S.C. §271(b)(1988).”³⁷

Initially, the court granted Zenith’s motion for summary judgment of no infringement.³⁸ But later, the court vacated its first decision, citing new evidence that “had demonstrated a genuine dispute on the *in vivo* conversion issue”.³⁹ After a bench trial, the court found no infringement under the doctrine of equivalents, but

the court found that cefadroxil DC converts to Bouzard monohydrate in the patient's stomach. Since an act of literal infringement thus occurs in the patient's stomach as a result of ingestion of cefadroxil DC, the court concluded that Zenith's sale of cefadroxil DC would induce infringement of the '657 patent.⁴⁰

Zenith appealed.⁴¹

The Court of Appeals for the Federal Circuit had never before considered a case involving infringement triggered by *in vivo* conversion. The Federal Circuit rejected Zenith’s proposed interpretation limiting the claim of the ‘657 patent to a pre-ingested form of the Bouzard monohydrate.⁴² And, in a footnote, the Federal Circuit implied that a product of *in vivo* conversion could trigger infringement:

The trial court apparently reached the same conclusion: "use of converted Bouzard monohydrate by a patient who ingests cefadroxil DC is an

³⁷ Id..

³⁸ Id..

³⁹ Id. at 1421.

⁴⁰ Id..

⁴¹ Id..

⁴² Id. at 1422.

infringing use." (But see note 6 regarding the significance of the term 'use.')

⁴³

However, the reference to “note 6”, and that footnote’s discussion of the word “use” render this implication ambiguous:

As noted previously, Zenith offered three other grounds on which the judgment of the trial court could be reversed: an incidental conversion to Bouzard crystals does not "use" the claimed compound; the reverse doctrine of equivalents forecloses literal infringement by conversion; and equitable estoppel. In view of our disposition of the appeal we need not address these other grounds for reversal.⁴⁴

Though the Federal Circuit did not reach this issue, the suggestion that *in vivo* conversion producing Bouzard crystals might not constitute “use” of the claimed compound vitiates the Federal Circuit’s otherwise strong statement in Footnote 4.

Indeed, the Federal Circuit reversed the district court’s finding of infringement under the doctrine of equivalents.⁴⁵ The grounds it employed to justify reversal were evidentiary. First,

[the] district court, instead of requiring the comparison of the accused compound following conversion to be made with the lines specified in the claim, allowed Bristol to make the comparison with the diffraction pattern exhibited by a sample (the reference pattern) of a material considered by Bristol to be the patented compound.⁴⁶

In addition, the Federal Circuit considered the district court’s infringement analysis insufficiently thorough:

The x--ray diffraction pattern exhibited by Bristol's sample (the reference pattern) consisted of a table of only 30 lines of relative intensities. Of this

⁴³ Id..

⁴⁴ Id. at 1424.

⁴⁵ Id. at 1426.

⁴⁶ Id. at 1423.

total, the court only compared 22 lines to corresponding lines recited in the claim. Zenith II, 24 U.S.P.Q.2D (BNA) at 1665. Based on its comparison, the court concluded the two were sufficiently similar to permit Bristol to use the reference pattern in its infringement analysis. In fact, the number of lines recited in the claim is 37. Thus, 15 of the lines recited in the claim (representing about 40% of the total) were not considered by the court in its comparison. Although the term "essentially" recited in the claim permits some leeway in the exactness of the comparison with the specified 37 lines of the claim, it does not permit ignoring a substantial number of lines altogether. It is the claim that sets the metes and bounds of the invention entitled to the protection of the patent system. On the basis of this evidence the trial court concluded that when cefadroxil DC is ingested Bouzard monohydrate is created in a patient's stomach, that that constitutes an infringing use, and that therefore the sale of cefadroxil DC by Zenith would constitute inducement of infringement under 35 U.S.C. § 271(b). Since the finding of infringement was based on testimony which incorporated an improper comparison, and since that comparison was an essential element in the conclusion that infringement occurred, the conclusion that Zenith by selling cefadroxil DC would engage in inducement of infringement is insupportable. Zenith is correct that there was a failure of proof as to whether any crystals, assumed to form in the stomach from ingested cefadroxil DC, literally infringe the '657 claim. In the absence of evidence comparing, the '657 claim with the cefadroxil DC after ingestion Bristol has failed to establish any infringing use and therefore we must reverse the district court's conclusion that Zenith's sale of cefadroxil DC induces infringement of the '657 patent.⁴⁷

Given the Federal Circuit's finding of no infringement by the product of *in vivo* conversion, as well as the ambiguity latent in Footnotes 4 and 6, it might seem odd that

⁴⁷ Id. at 1423-1424.

dicta in *Zenith v. Bristol-Myers Squibb* would be cited for the proposition that products of *in vivo* conversion can indeed trigger infringement. However, almost all subsequent decisions in patent infringement suits involving *in vivo* conversion have done precisely that, citing *Zenith v. Bristol-Myers Squibb* for a proposition whose validity it never had formally to test as if that proposition were an authoritative legal rule.⁴⁸

3. *MARION MERRELL V. GENEVA*

Marion Merrell Dow, Inc. (“MMD”) developed terfenadine, an antihistamine drug with the advantageous property of not causing drowsiness, and marketed it under the trade name of Seldane®.⁴⁹ MMD owned United States Patent No. 3,818,217 (“’217 patent”), claiming administration of terfenadine and other piperidine derivatives.⁵⁰ MMD’s subsequent research on terfenadine yielded terfenadine acid metabolite (“TAM”), a product produced by *in vivo* conversion after ingestion of terfenadine, and obtained United States Patent No. 4,254,129 (“’129 patent”) to cover both TAM itself and methods of administering a therapeutically effective amount of TAM.⁵¹

Geneva Pharmaceuticals, Inc. (“Geneva”) applied to the FDA for regulatory approval to market a generic version of terfenadine once the ‘217 patent expired, and, as part of the regulatory certification process stated that its generic product would not infringe claims of the ‘129 patent.⁵² In response, MMD sued Geneva, and Geneva

⁴⁸ See, e.g., *Hoechst v. Lehman* (Fed. Cir. 1997) and *Novartis v. Eon* (Fed. Cir. 2004).

⁴⁹ *Marion Merrell v. Geneva Pharmaceuticals*, 877 F.Supp. 531, 533 (D.Col. 1994).

⁵⁰ *Id.*.

⁵¹ *Id.* at 534.

⁵² *Id.*.

requested summary judgment that the asserted claims of the ‘129 patent were invalid as inherently anticipated.⁵³

MMD alleged infringement based on a theory of *in vivo* conversion: “because the product to be marketed by Geneva converts after being ingested by a patient into a compound whose use, inter alia, is claimed in the ‘129 patent.” (Pl.’s Resp., Introduction).⁵⁴ The district court pointed out “that infringement may result from the *in vivo* conversion of one product or compound into another”, citing *Zenith v. Bristol-Myers Squibb*, 19 F.3d 1418, 1423-1424 (Fed. Cir. 1994), for support.

Geneva argued that claims of the ‘129 patent were anticipated by the disclosure of the prior ‘217 patent and by a scientific article, which had been issued and published, respectively, more than a year prior to the priority date of the ‘129 patent.⁵⁵ Geneva contended that both of these pieces of prior art disclosed preparation and administration of terfenadine, not TAM, but that, after ingestion, terfenadine was necessarily transformed via *in vivo* conversion into metabolic products, including TAM.⁵⁶ In other words, claims to the use of TAM in the ‘129 patent were allegedly inherently anticipated by the teachings of the prior art.⁵⁷

The district court denied Geneva’s motion for summary judgment because “[it] is unclear to me where, scientifically, all the elements regarding terfenadine and its administration, as claimed in the 217 [sic] patent, are identical to the elements regarding TAM and its administration as claimed in the 129 [sic] patent. Although I express no opinion concerning the

⁵³ Id..

⁵⁴ Id..

⁵⁵ Id. at 536.

⁵⁶ Id..

⁵⁷ Id..

ultimate merit of Geneva's ability to establish such facts at trial, I find that such determination cannot be made based upon the record before me.”⁵⁸ Litigation over terfenadine and its metabolite, terfenadine acid metabolite (TAM),⁵⁹ continued a few years later in *Marion Merrell Dow et al. v. Baker Norton Pharmaceuticals*, 948 F.Supp. 1050 (S.D.Fla. 1996).

4. *MARION MERRELL V. BAKER NORTON*

Baker Norton Pharmaceuticals (“Baker Norton”) manufactured a generic version of terfenadine (sold by Marion Merrell Dow, Inc., and Merrell Dow Pharmaceuticals, Inc. (collectively “MMD”) as Seldane®), a drug described and previously protected by claims in Marion Merrell’s now expired ‘217 patent.⁶⁰ In response to an Abbreviated New Drug Application (ANDA) filed by Baker Norton to cover its generic terfenadine, MMD filed a lawsuit alleging that selling or manufacturing terfenadine would infringe the unexpired ‘129 patent owned by MMD. MMD moved for summary judgment that “Baker Norton [would] infringe the ‘129 Patent as a matter of law by its planned manufacture and sale of terfenadine to treat allergic reactions.”⁶¹ Because terfenadine was not claimed in the ‘129 patent, MMD’s theory of infringement depended on the physiological transformation of terfenadine into TAM within the body of a human who ingested generic terfenadine: infringement triggered by *in vivo* conversion.

⁵⁸ Id. at 537.

⁵⁹ *Marion Merrell Dow Inc., and Merrell Dow Pharmaceuticals, Inc. v. Baker Norton Pharmaceuticals, Inc.*, 948 F.Supp. 1050, 1051 (S.D.Fla. 1996) (“Generally speaking, TAM is created as a result of the metabolism of terfenadine in the liver”); dismissed without opinion in *Marion Merrell Dow, Inc. v. Baker Norton Pharms., Inc.*, 152 F.3d 941 (Fed. Cir. 1998).

⁶⁰ *Marion Merrell Dow Inc., and Merrell Dow Pharmaceuticals, Inc. v. Baker Norton Pharmaceuticals, Inc.*, 948 F.Supp. 1050, 1051 (S.D.Fla. 1996).

⁶¹ Id. at 1052.

During claim construction, the court focused its analysis on the meaning of the claim element “compound”.⁶² MMD argued for an expansive interpretation by which “compound” “refers to the compound TAM regardless of whether it is created by the liver’s metabolism of terfenadine (inter vivo conversion) or by synthetic means.”⁶³ Thus, under this construction, TAM produced in the patient’s body by *in vivo* conversion would fall within claim 1 of the ‘129 patent, and infringement would lie. By contrast, Baker Norton urged the court to adopt a much narrower interpretation of “compound” that included “only synthetically produced TAM”.⁶⁴ Drawing on evidence from the organization of the claims themselves, discussion of TAM in the specification, and the prosecution history of the ‘217 patent, the court sided with Baker Norton’s interpretation, construing the word “compound” to mean only synthetic TAM, and not TAM produced by *in vivo* conversion.⁶⁵

Given the narrow interpretation of “compound” as covering only *synthetic* TAM, the court found no literal infringement by TAM *naturally* produced in a patient’s body by *in vivo* conversion.⁶⁶ Furthermore, the court declined to find infringement under the doctrine of equivalents.⁶⁷ However, in its analysis under the doctrine of equivalents, the court provided only an opaque rationale for its decision not to find infringement,

⁶² Id. at 1054.

⁶³ Id..

⁶⁴ Id..

⁶⁵ Id. at 1053-1054 (Especially devastating to Marion Merrell’s chosen interpretation of “compound” was testimony from its former head of clinical pharmacology, Murray Weiner, M.D.: “in my wildest dreams I wouldn’t think of [contemplating that the claims of the ‘129 Patent application could cover the swallowing of terfenadine and the subsequent conversion to TAM] because I was aware that terfenadine has been swallowed for many, many years and that its action was known . . . There was nothing I could see invented of utility. . . . And for that reason I didn’t conceive that the well--known product terfenadine could come under a patent for something into which it is converted in the body...”).

⁶⁶ Marion Merrell Dow Inc., and Merrell Dow Pharmaceuticals, Inc. v. Baker Norton Pharmaceuticals, Inc., 948 F.Supp. 1050, 1056-1057 (S.D.Fla. 1996).

⁶⁷ Id. at 1057.

ostensibly relying on the discretion allowed it by the equitable nature of that doctrine.⁶⁸

Consequently, the court granted Baker Norton's motion for summary judgment of noninfringement of claims of the '129 patent by generic terfenadine.⁶⁹

Nowhere in its published opinion did the court directly comment on the issue of whether or not a product of *in vivo* conversion could trigger infringement. And, given the narrow claim construction of the word "compound" to cover only synthetic TAM, it was unnecessary for the court to explore this issue.

5. *HOECHST-ROUSSEL V. LEHMAN*

After the FDA granted Warner-Lambert Company ("Warner-Lambert") approval in 1993 to market its drug, COGNEX®, a treatment for Alzheimer's disease containing tacrine hydrochloride, Hoechst-Roussel Pharmaceuticals, Inc. ("Hoechst"), filed a lawsuit against Warner-Lambert alleging that COGNEX® infringed their United States Patent No. 4,461,286 ("286 patent").⁷⁰ While the '286 patent included claims to 1-hydroxy-tacrine as a composition and methods of administering the compound to treat memory loss in a patient, it did not claim tacrine hydrochloride, the active ingredient in COGNEX®.⁷¹ Hoechst contended that Warner-Lambert infringed claims in the '286 patent because, once ingested by a human, tacrine hydrochloride is converted by *in vivo* conversion into 1-hydroxy-tacrine and other metabolites.⁷² Litigation concluded with a

⁶⁸ Id..

⁶⁹ Id..

⁷⁰ Hoechst-Roussel Pharmaceuticals Inc. v. Bruce A. Lehman and William K. Summers, 109 F.3d 756, 757 (Fed. Cir. 1997); rehearing denied by, en banc, Hoechst-Roussel Pharms. v. Lehman, 1997 U.S. App. LEXIS 15064 (Fed. Cir. June 5, 1997).

⁷¹ Hoechst-Roussel Pharmaceuticals Inc. v. Bruce A. Lehman and William K. Summers, 109 F.3d 756, 757 (Fed. Cir. 1997).

⁷² Id..

consent judgment by the district court “in which Warner-Lambert admitted that tacrine hydrochloride infringes certain claims of the ‘286 patent”.⁷³

Based upon the regulatory review period for FDA market approval of COGNEX®, Hoechst applied to the USPTO for a patent term extension for its ‘286 patent. Under 35 U.S.C. §156(a), a patent owner may request that

[the] term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended...from the original expiration date of the patent if...the product has been subject to a regulatory review period before its commercial marketing or use.⁷⁴

Hoechst contended that “a patent “claims” an FDA-approved product, within the meaning of that term as employed in the statute, if the FDA-approved product would infringe a claim of that patent.”⁷⁵ Furthermore, “[because] use of tacrine hydrochloride allegedly [infringed] its claim to a method of using 1-hydroxy-tacrine, Hoechst [contended] that the ‘286 patent “claims” a method of using tacrine hydrochloride.”⁷⁶ The USPTO denied this application because “Hoechst was not a proper applicant for term extension because Hoechst was not involved, either directly or indirectly, in the regulatory approval process for tacrine hydrochloride” and the ‘286 patent “does not claim tacrine hydrochloride, as required by the statute.”⁷⁷ The district court granted the USPTO’s motion for summary judgment, finding that Hoechst was not an eligible applicant for term extension of the ‘286 patent.⁷⁸ Hoechst appealed to the Court of Appeals for the Federal Circuit.

⁷³ Id..

⁷⁴ Id..

⁷⁵ Id. at 758.

⁷⁶ Id..

⁷⁷ Id. at 757-758.

⁷⁸ Id. at 758.

The Federal Circuit affirmed the judgment of the district court “on the basis that Hoechst’s patent does not claim either the drug product [tacrine hydrochloride] which received regulatory approval or its use.”⁷⁹

However, in its decision the Federal Circuit discussed how infringement via *in vivo* conversion might occur:

Admittedly, Hoechst may be entitled to exclude others from administering tacrine hydrochloride to patients. But this right to exclude would not arise from the fact that Hoechst has claimed tacrine hydrochloride; nor would it arise from the fact that COGNEX(R) contains the product claimed by Hoechst, 1--hydroxy--tacrine. Instead, the right to exclude may arise from the fact that when administered, tacrine hydrochloride metabolizes into another product, 1--hydroxy--tacrine, which Hoechst has claimed.⁸⁰

The Federal Circuit cited *Zenith v. Bristol-Myers Squibb* for the proposition that “infringement may occur if the administered product is converted in vivo into the claimed product”.⁸¹ However, it failed to point out that the basis for this statement was *dicta* because there was no actual finding of infringement in *Zenith v. Bristol-Myers Squibb*. Though disagreeing on some issues, the concurrence by Judge Newman agreed that *Zenith v. Bristol-Myers Squibb* stands for the proposition that “in vivo conversion into the drug named in the claims is direct infringement.”⁸²

⁷⁹ Hoechst-Roussel Pharmaceuticals Inc. v. Bruce A. Lehman and William K. Summers, 109 F.3d 756, 757 (Fed. Cir. 1997). For qualified support of the decision, see Matthew Hinsch, Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman, 13 Berkeley Tech. L.J. 163, 173 (“Unfortunately, the court in Hoechst came to the correct decision, but for the wrong reasons. Those wrong reasons are now precedent and undermine the Hatch/Waxman Act’s public policy goals of rewarding pharmaceutical innovators.”).

⁸⁰ Hoechst-Roussel Pharmaceuticals Inc. v. Bruce A. Lehman and William K. Summers, 109 F.3d 756, 757 (Fed. Cir. 1997).

⁸¹ Hoechst-Roussel Pharmaceuticals Inc. v. Bruce A. Lehman and William K. Summers, 109 F.3d 756, 757 (Fed. Cir. 1997) *citing* Zenith Labs. v. Bristol-Myers Squibb, 19 F.3d 1418, 1422, 30 U.S.P.Q.2D (BNA) 1285, 1288 (Fed. Cir. 1994).

⁸² Hoechst-Roussel Pharmaceuticals Inc. v. Bruce A. Lehman and William K. Summers, 109 F.3d 756, 757 (Fed. Cir. 1997) *citing* Zenith Labs. v. Bristol-Myers Squibb, 19 F.3d 1418, 1422, 30 U.S.P.Q.2D (BNA) 1285, 1288 (Fed. Cir. 1994).

6. *MYLAN V. THOMPSON*

In 1998 Mylan Pharmaceuticals, Inc. (“Mylan”), a manufacturer of generic drugs, submitted an abbreviated new drug application (“ANDA”) with the FDA, hoping to market a generic version of BuSpar®, BMS’ brand name for a drug containing the active ingredient buspirone hydrochloride (“buspirone”).⁸³ BMS owned United States Patent No. 4,182,763 (“‘763 patent”), which claimed methods of using buspirone to treat patients with generalized anxiety disorder.⁸⁴ The ‘763 patent expired on November 22, 2000, and Mylan planned to place its own generic version of buspirone on the market that same day.⁸⁵ However, the day before the ‘763 patent expired the USPTO issued United States Patent No. 6,150,365 (“‘365 patent”), which includes a claim to a method of treating anxiety in a patient by administering 6-hydroxy-busprione, a metabolite of buspirone produced by *in vivo* conversion.⁸⁶ In light of the issuance of the ‘365 patent, and of a declaration from BMS asserting that the ‘365 patent claimed the use of buspirone, the FDA declined to grant Mylan final approval for its ANDA covering generic buspirone.⁸⁷ Mylan and several other generic drug companies filed lawsuits on

⁸³ Mylan Pharmaceuticals, Inc. v. Tommy G. Thompson and Bristol-Myers Squibb Co., 139 F.Supp.2d 1, 14 (D.D.C. 2001); reversed by Mylan Pharms., Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001); rehearing, en banc, denied by Mylan Pharms., Inc. v. Thompson, 2002 U.S. App. LEXIS 2624 (Fed. Cir. Jan. 9, 2002); writ of certiorari denied, Mylan Pharms., Inc. v. Thompson, 537 U.S. 941 (Fed. Cir. 2001) (Claim construction by district court not addressed on the merits).

⁸⁴ Mylan Pharmaceuticals, Inc. v. Tommy G. Thompson and Bristol-Myers Squibb Co., 139 F.Supp.2d 1, 14 (D.D.C. 2001).

⁸⁵ Id. at 15-16.

⁸⁶ Id. at 22.

⁸⁷ Id. at 16-17.

November 30, 2000, seeking a preliminary injunction to have the ‘365 patent delisted from the FDA’s “Orange Book”⁸⁸, thus freeing the path to approval of Mylan’s ANDA.⁸⁹

A threshold consideration for the court was whether or not the claim of the ‘365 patent covered use of buspirone in addition to use of its metabolite, 6-hydroxy-busprione. If use of buspirone was not within the claim, Bristol-Myers’ declaration to the FDA would be inaccurate. The court interpreted the meaning of “claim a method of using [a drug]” in 21 U.S.C. §355(c)(2) as equivalent to the meaning of “claims...a method using [a drug]” in 35 U.S.C. §156(a).⁹⁰ Then, it concluded that, just as for the ‘286 patent in *Hoechst-Roussel v. Lehman*, “so too is the ‘365 patent limited to the use of the [6-hydroxy-busprione] metabolite, and therefore the ‘365 patent cannot claim title administration of buspirone”.⁹¹ This conclusion foreclosed the argument that administration of buspirone could trigger infringement by *in vivo* conversion into the 6-hydroxy-busprione metabolite.⁹² The court then acceded to Mylan’s request for a

⁸⁸ See *Mylan Pharmaceuticals, Inc. v. Tommy G. Thompson and Bristol-Myers Squibb Co.*, 139 F.Supp.2d 1, 5 (D.D.C. 2001) (“Upon approval of the NDA [New Drug Application], the FDA publishes any claimed patents for the approved drug in “Approved Drug Products with Therapeutic Equivalence Evaluations,” also known as the “Orange Book.” See 21 U.S.C. §355(j)(7)(A)(iii).”)

⁸⁹ *Mylan Pharmaceuticals, Inc. v. Tommy G. Thompson and Bristol-Myers Squibb Co.*, 139 F.Supp.2d 1, 23 (D.D.C. 2001).

⁹⁰ *Id.* at 56-57.

⁹¹ *Id.* at 58.

⁹² To demonstrate that Bristol-Myers’ ‘365 patent disclaims claim coverage of oral administration, Mylan offered the following analogy to illustrate *in vivo* conversion:

Let’s assume that a Bristol scientist had found ... that a particular chemical compound in an apple was metabolized in the human body into a compound we will call “Apple--A” and that when you administer Apple--A it improve[s] health... They file a patent application and get a patent on the systemic administration of Apple--A... They make tablets with Apple----A. They sell those tablets. They want to stop other people from making tablets with Apple--A in them. That is fine. That is a complicated case involving issues of inherency. This is not a complicated case because what they have done here is they have tried to use this patent to stop people from selling and eating apples by arguing that when you eat an apple, it is metabolized in the human body into the equivalent of the Bristol metabolite, the equivalent of Apple--A.

preliminary injunction, which required that (1) Bristol-Myers request the FDA to delist the '365 patent from the Orange Book and (2) the FDA grant immediate approval of Mylan's ANDA.⁹³

7. *IN RE BUSPIRONE*

Litigation involving the '365 patent continued,⁹⁴ with the district court rejecting infringement by Mylan's generic buspirone of the '365 patent.⁹⁵ The court based its finding on three different lines of analysis. First, the court construed the claim language "systemic administration to the mammal of an effective but non-toxic anxiolytic dose of the 6-hydroxy-metabolite" to mean

the administration of an externally-measured quantity of the metabolite into the body, and not to the administration of a dose of buspirone into the body, which, in turn, produces variable and changing levels (not doses) of the metabolite in the bloodstream. See 365 Patent, at col. 16.⁹⁶

Next, after reviewing the prosecution history of the '365 patent, the court decisively rejected Bristol-Myers' assertion that the patent claim covered buspirone:

Mylan Pharmaceuticals, Inc. v. Tommy G. Thompson and Bristol-Myers Squibb Co., 139 F.Supp.2d 1, 65 (D.D.C. 2001).

⁹³ On appeal, the Court of Appeals for the Federal Circuit reversed the grant of preliminary injunction, Mylan Pharmaceutical, Inc. v. Thompson, 268 F.3d 1323, 1329-1333 (Fed. Cir. 2001).

⁹⁴ The *In re Busiprone* litigation also involved significant questions of antitrust law centering around Bristol-Myers alleged attempts impermissibly to extend their patent monopoly by seeking patent protection for metabolites of busiprone. See generally, Tim Meade, *In re Busiprone* patent and antitrust litigation, 9 Rich. J.L. & Tech. 1 (2002). For a general discussion of the antitrust issues implicated by patents claiming metabolites, see Christine S. Paine, Brand-name drug manufacturers risk antitrust violations by slowing generic production through patent layering, 33 Seton hall L. Rev. 479 (2003).

⁹⁵ *In re Busiprone*, 185 F.Supp. 2d 340, 363 (S.D.N.Y. 2002); claim dismissed by *In re Busiprone* Patent & Antitrust Litig., 185 F. Supp. 2d 363 (S.D.N.Y. 2002); motion denied by, motion granted by *In re Busiprone* Antitrust Litig., 208 F.R.D. 516 (S.D.N.Y. 2002); motion denied by, objection denied by, class certification granted by *In re Busiprone* Patent & Antitrust Litig., 210 F.R.D. 43 (S.D.N.Y. 2002); motion denied by *In re Busiprone* Antitrust Litig., 211 F.R.D. 249 (S.D.N.Y. 2002); motion denied by *In re Busiprone* Antitrust Litig., 2002 U.S. Dist. LEXIS 23463 (S.D.N.Y. Dec. 10, 2002); judgment entered by La. Wholesale Drug Co. v. Bristol-Meyers Squibb Co. (*In re Busiprone* Antitrust Litig.), 2003 U.S. Dist. LEXIS 26538 (S.D.N.Y. Apr. 11, 2003).

⁹⁶ *In re Busiprone*, 185 F.Supp. 2d 340, 353 (S.D.N.Y. 2002).

In sum, every time Bristol--Myers explicitly claimed a use of "buspirone" or a "prodrug" of the 6--hydroxy--metabolite, the application was rejected. Bristol—Myers only obtained the 365 Patent after omitting all references in the claim to "buspirone" and any "prodrug," and after making express declarations that the amendments acted to exclude uses of buspirone. Viewed in its totality, this is a case where the prosecution history establishes beyond doubt that Bristol--Myers gave up a claim covering the use of buspirone in order to obtain a patent covering a method of using the 6--hydroxy--metabolite, and where, accordingly, Bristol--Myers cannot now reasonably assert a claim for the use of buspirone. See, e.g., *Rheox*, 276 F.3d at 1325; *Spectrum Int'l*, 164 F.3d at 1378--79; *Ahlstrom Machinery, Inc. v. Clement*, 13 F. Supp. 2d 45, 48 n.2 (D.D.C. 1998), *aff'd* sub nom. *Kamyr, Inc. v. Clement*, 217 F.3d 860 (Fed. Cir. 1999) (*per curiam*). Hence, the 365 Patent does not cover any uses of buspirone.⁹⁷

Finally, the court held that, if the '365 patent claim were construed to cover the use of buspirone, as Bristol-Myers urged, then the claim would be anticipated based on 35 U.S.C. §102(b) because buspirone had been sold as a treatment for anxiety, its use for treating anxiety had been published, and its use had been public, all at least one year prior to the earliest priority date of the '365 patent.⁹⁸ Furthermore, the court rejected BMS' proposed claim construction because, if 6-hydroxy-busprione were reliably produced by administration of busiprone, then the claim of the '365 patent would be inherently anticipated by *in vivo* conversion of busiprone into its 6-hydroxy-busprione metabolite. Thus, the court concluded that a narrow claim construction that included use of 6-hydroxy-busprione *per se*, but excluded use of busiprone, would be required to avoid invalidity of the claim.⁹⁹

⁹⁷ Id. at 359.

⁹⁸ Id. at 359-363.

⁹⁹ Id. at 362.

8. *SCHERING V. GENEVA*

Schering Corporation (“Schering”) owned two patents with claims covering antihistamines: United States Patent No. 4,282,233 (“‘233 patent”) claimed loratadine, an active ingredient of the brand-name antihistamine CLARATIN® marketed by Schering; United States Patent No. 4,659,716 (“‘716 patent”) claimed descarboethoxyloratadine (DCL), a metabolite resulting from *in vivo* conversion of loratadine ingested by a human.¹⁰⁰ Upon expiration of the ‘233 patent, Geneva Pharmaceuticals, Inc. and other generic drug manufacturers (“Geneva *et al.*”) sought to bring generic drugs containing loratadine to market.¹⁰¹ As part of the process of applying for regulatory approval from the FDA, Geneva *et al.* certified that claims of the ‘716 patent were invalid.¹⁰² In response, Schering filed a lawsuit against Geneva *et al.* alleging that these generic drugs containing loratadine infringed claims of the ‘716 patent that ostensibly covered DCL, but not loratadine.

The district court construed claims 1 and 3 of the ‘716 patent broadly, concluding that they covered all forms of DCL, including both synthetic DCL and DCL produced by *in vivo* conversion of loratadine.¹⁰³ Both Schering and Geneva *et al.* agreed to this interpretation.¹⁰⁴ Then, the court used the claim construction “[to find] that the ‘233 patent did not expressly disclose DCL”.¹⁰⁵ However, because “DCL was necessarily formed as a metabolite by carrying out the process disclosed in the ‘233 patent”, and the

¹⁰⁰ Schering Corporation v. Geneva Pharmaceuticals, Inc. et al., 339 F.3d 1373, 1374-1375 (Fed. Cir. 2003); rehearing, en banc, denied by Schering Corp. v. Geneva Pharms., Inc., 348 F.3d 992 (Fed. Cir. 2003).

¹⁰¹ Schering Corporation v. Geneva Pharmaceuticals, Inc. et al., 339 F.3d 1373, 1376 (Fed. Cir. 2003).

¹⁰² Id..

¹⁰³ Id..

¹⁰⁴ Id..

¹⁰⁵ Id..

‘233 patent had expired more than a year prior to earliest priority date of the ‘716 patent, the court granted summary judgment in favor of Geneva *et al.*, finding that the ‘233 patent “anticipated claims 1 and 3 of the ‘716 patent under 35 U.S.C. §102(b)” by inherent anticipation.¹⁰⁶

Schering appealed this grant of summary judgment to the Federal Circuit.¹⁰⁷ The Federal Circuit recognized that this issue “may be a case of first impression, because the prior art supplies no express description of any part of the claimed subject matter.”¹⁰⁸ In fact, the panel noted that

In these prior cases, however, inherency was only necessary to supply a single missing limitation that was not expressly disclosed in the prior art.

This case, as explained before, asks this court to find anticipation when the entire structure of the claimed subject matter is inherent in the prior art.¹⁰⁹

Nevertheless, the panel affirmed the district court’s decision regarding inherent anticipation, rejecting Schering’s contention that DCL is formed accidentally:

The record shows that DCL necessarily and inevitably forms from loratadine under normal conditions. DCL is a necessary consequence of administering loratadine to patients.¹¹⁰

Based on these findings, the panel concluded that human ingestion of loratadine would infringe claims 1 and 3 of the ‘716 patent because the loratadine would be transformed by *in vivo* conversion into the DCL metabolite.¹¹¹ Consequently these same claims must be

¹⁰⁶ Id..

¹⁰⁷ Id..

¹⁰⁸ Id. at 1377.

¹⁰⁹ Id. at 1379.

¹¹⁰ Id..

¹¹¹ Id. at 1380.

invalid in light of the ‘233 patent because “[an] identical metabolite must then anticipate if earlier in time than the claimed compound.”¹¹²

In *dicta* the panel supported the proposition that a metabolite produced within the body by *in vivo* conversion can indeed trigger infringement of a claim covering that metabolite itself or its use:

This court has recognized that [HN9] a person may infringe a claim to a metabolite if the person ingests a compound that metabolizes to form the metabolite. See *Hoechst--Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997) ("The right to exclude may arise from the fact that when administered, [the accused product] metabolizes into another product . . . which Hoechst has claimed."); see also *Zenith Lab., Inc. v. Bristol--Myers Squibb Co.*, 19 F.3d 1418, 1421--22 (Fed. Cir. 1994) (stating that a compound claim could cover a compound formed upon ingestion).¹¹³

The Federal Circuit later stressed that their finding of inherent anticipation in this case would not “preclude patent protection for metabolites of known drugs.”¹¹⁴ In fact, “[with] proper claiming, patent protection is available for metabolites of known drugs. [Citations omitted.]”¹¹⁵ However, the Federal Circuit considered such “proper claiming” to be restricted to purified metabolites not found in nature in purified form, citing *In re Kratz*, 592 F.2d 1169, 1174 (CCPA 1979) (claims to substantially pure compounds may be patentable), and *In re Bergstrom*, 427 F.2d 1394, 1401-1402 (CCPA 1970) (claims to pure substances may be patentable), as illustrations. And such *in vivo* conversion metabolites, including those recited in claims 1 and 3 or the ‘716 patent, “may not receive protection via compound claims...[because such] bare compound claims include within

¹¹² Id..

¹¹³ Id..

¹¹⁴ Id. at 1381.

¹¹⁵ Id.

their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug.”¹¹⁶ The Federal Circuit stated a general rule as follows: “these broad compound claims are inherently anticipated by a prior art disclosure of a drug that metabolizes into the claimed compound.”¹¹⁷ A patent applicant wishing to claim a metabolite would have to settle for claims reciting a pure and isolated metabolite, a pharmaceutical composition containing not only the metabolite but other ingredients as well, or a method of administering the metabolite or pharmaceutical composition thereof.¹¹⁸

9. *IN RE OMEPRAZOLE*

Astra Aktiebolag and related companies (“Astra”) marketed a gastric acid inhibiting drug brand-named PRILOSEC®, whose active ingredient was omeprazole.¹¹⁹ Several generic drug companies, Genpharm, Inc., Cheminor Drugs Ltd., Reddy-Cheminor, Inc., and Schein Pharmaceutical, Inc. (collectively “Genpharm *et al.*”) applied for ANDAs to market generic versions of omeprazole.¹²⁰ Astra had listed two of its patents in the FDA Orange Book: United States Patent No. 4,255,431 (“‘431 patent”), which includes claims to omeprazole as a compound and to its oral administration for gastric acid inhibition and United States Patent No. 4,636,499 (“‘499 patent”), which includes compound claims to a class of metabolites of omeprazole, called sulphenamides, as well as method claims on administration of sulphenamides to treat gastroinflammatory

¹¹⁶ Id..

¹¹⁷ Id..

¹¹⁸ Id..

¹¹⁹ *In re Omeprazole Patent Litigation*, 2001 WL 585534, 1 (S.D.N.Y. 2001).

¹²⁰ Id..

diseases.¹²¹ Because the ‘431 patent was close to expiration, Genpharm *et al.* had applied for ANDAs in anticipation of marketing generic omeprazole. Astra sued Genpharm *et al.* for infringement of the ‘499 patent based on 35 U.S.C. §271(e)(2)(A) because Genpharm *et al.*’s ANDAs included paragraph IV certifications specifically challenging the validity of the ‘499 patent.

Astra sued for infringement on the theory that “oral administration of omeprazole...[would] infringe the ‘499 patent because when a patient takes the Genpharm...products, sulphenamides will form in the patient’s body”, citing *Zenith v. Bristol-Myers Squibb* in support of their position.¹²² Genpharm *et al.* disputed Astra’s interpretation of *Zenith v. Bristol-Myers Squibb*, and cited *Marion Merrell Dow v. Baker Norton*, 948 F.Supp. 1050, 1054 (S.D.Fla. 1996), for the proposition that *Zenith v. Bristol-Myers Squibb* did not articulate a *per se* rule that claims to compounds covered both those made synthetically and those produced by *in vivo* conversion.¹²³ The district court decided this issue in favor of Genpharm *et al.* stating that:

It cannot be that a claim to a “compound” covers the compound whether it is made synthetically or produced *in vivo*, regardless of whether such a construction is supported by the evidence intrinsic to the patent.¹²⁴ And, after construing the claims the district court decided that they should be interpreted to cover only synthetic sulphenamides, not metabolite sulphenamides resulting from the *in vivo* conversion of omeprazole.¹²⁵ Based on this claim construction, the court then granted Genpharm *et al.* summary judgment of invalidity of the ‘499 patent’s claims

¹²¹ Id. at 1-2.

¹²² Id. at 3.

¹²³ Id..

¹²⁴ Id. at 4.

¹²⁵ Id. at 7.

based on inherent anticipation by prior art teaching administration of omeprazole to inhibit gastric acid.¹²⁶

10. *NOVARTIS V. EON*

Novartis Pharmaceuticals Corporation and allied companies (“Novartis”) owned United States Patent No. 5,389,382 (“‘382 patent”), which included claims directed to a hydrosol encapsulating the immunosuppressant drug cyclosporin.¹²⁷ Cyclosporin is difficult to administer to a patient because it is fairly insoluble in water, a problematic characteristic within the wet interior of the human digestive system.¹²⁸ The ‘382 patent disclosed and claimed increasing the effective solubility of cyclosporin by dissolving it “in a water-miscible solvent and then adding a comparatively large amount of water to that solution.”¹²⁹ The result was a mixture of water and tiny particles containing cyclosporin that can be absorbed more easily from a patient’s digestive system.¹³⁰

Novartis sued Eon Labs Manufacturing, Inc. (“Eon”) in district court for infringing claims of the ‘382 patent, despite the fact that Eon’s product was a capsule containing cyclosporin, ethanol, and no water.¹³¹ Novartis advanced an *in vivo* conversion theory of infringement, contending that “when one of Eon’s capsules is ingested an infringing hydrosol is formed when the capsule mixes with the aqueous environment of the user’s stomach.”¹³² The district court granted Eon summary judgment of no infringement, either literally or under the doctrine of equivalents, based

¹²⁶ Id. at 12.

¹²⁷ Novartis Pharmaceuticals Corporation et al. v. Eon Labs Manufacturing, Inc., 363 F.3d 1306, 1307 (Fed. Cir. 2004).

¹²⁸ Id..

¹²⁹ Id..

¹³⁰ Id..

¹³¹ Id..

¹³² Id..

on the court’s construction of the claim element “hydrosol” as including only synthetic mixtures, and excluding those produced by *in vivo* conversion in a patient’s stomach.¹³³

Novartis appealed to the Federal Circuit.

The majority of the Federal Circuit panel hearing the appeal affirmed the district court’s claim construction, and agreed that ““hydrosol” as used in the ‘382 patent was limited to an aqueous medicinal preparation prepared outside the body”.¹³⁴ The panel majority also affirmed the grant of summary judgment of no infringement, either literally or under the doctrine of equivalents.¹³⁵

In arriving at its decision, the panel majority distinguished two previous decisions of the Federal Circuit involving *in vivo* conversion. It pointed out that the facts of *Zenith v. Bristol-Myers* differed from the instant case because the claim at issue in the former involved a “specific chemical compound”, cefadroxil monohydrate, and the plain language of the claim was clear and unambiguous.¹³⁶ Furthermore, the claim contained “no express or implied pre-ingestion limitation”, unlike claims of the ‘382 patent.¹³⁷ Next, the panel majority contrasted *Schering v. Geneva* as involving inherent anticipation, by a drug, of a claim covering a metabolite that the parties agreed was produced by *in vivo* conversion of that drug within a human, whereas, in the instant case the parties disagreed about whether the product of *in vivo* conversion – the hydrosol – was covered by a claim of the ‘382 patent.¹³⁸

¹³³ Id. at 1308.

¹³⁴ Id. at 1312.

¹³⁵ Id..

¹³⁶ Id. at 1311.

¹³⁷ Id..

¹³⁸ Id. at 1311-1312.

Judge Clevenger dissented from the panel majority's decision, and would have defined "hydrosol" broadly enough to place a hydrosol of cyclosporin within the scope of the '382 patent's claims. He also disagreed with the panel majority's interpretation of "medicines" as "things made outside the body".¹³⁹ Rather, Judge Clevenger characterized "medicines" as much broader:

Our case law has long recognized that medicines claimed in patents can be made inside or outside the body, and that infringement will lie in either case if the proper proofs are made. These cases are no less concerned with patient treatment than the instant case. In all of them, we have a "medicine" whose ordinary meaning carries no manufacturing site limitations. See *Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373 (Fed. Cir. 2003); *Hoechst--Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997); *Zenith Labs.*, 19 F.3d at 1421--22. Each of these precedents involved medical preparations. But until this case, no one had suggested that a suspect dictionary definition of the term "medicine" should be used to deny a patentee the right to prove infringement when the claimed composition is formed as a medicine in the body following the ingestion of a different composition that was manufactured outside the body.¹⁴⁰

This reasoning stands in clear contrast to the position of the panel majority, where "medicine" was limited to "a preexisting product that is administered to treat disease and therefore must necessarily be prepared outside the body."¹⁴¹

IV. INFRINGEMENT OF *IN VIVO* CONVERSION CLAIMS

A. *IN VIVO* CONVERSION DOES NOT TRIGGER INFRINGEMENT

¹³⁹ Id. at 1315.

¹⁴⁰ Id. at 1316. Interestingly, none of the three cases cited here by Judge Clevenger did the Federal Circuit find infringement.

¹⁴¹ Id. at 1309.

As reviewed above, federal courts in the United States have repeatedly considered whether transformation of a drug via *in vivo* conversion into a metabolite can trigger infringement claims covering the metabolite or methods of using the metabolite. A growing number of such infringement disputes have reached the courts. However, in none of these disputes has the highest court to rule on the issue yet found that a claimed product produced by *in vivo* conversion of an existing drug triggered infringement.¹⁴²

Courts have employed diverse rationales to avoid finding infringement in *in vivo* conversion cases. Some courts have pointed to difficulties of obtaining sufficient evidence of infringing products from within the human body. Others have relied upon anticipation, finding inherency where there has been previous use, public knowledge, or sale of a precursor compound that is necessarily transformed by *in vivo* conversion into a claimed product. Still other courts have offered ambiguous reasoning for their rulings of no infringement. Underlying this variety of rationales, but unanimity of findings of no infringement, lies a discomfort with very idea that a product arising naturally within the body can infringe, let alone be the subject of a valid and enforceable patent claim. This paper suggests such discomfort can be explained by a novel theory that can be named physiological steps doctrine.

B. PROBLEMS OF EVIDENCE

Zenith v. Bristol-Myers Squibb is perhaps the most influential case considering the issue of whether a product of *in vivo* conversion can trigger infringement of a patent

¹⁴² In *Ortho Pharmaceutical Corporation v. Herchel Smith*, 959 F.2d 936, 939 (Fed. Cir. 1992), both norgestimate and its *in vivo* product, norgestrel, independently infringed claims to the '332 patent under the doctrine of equivalents. Thus, though it did involve a product of *in vivo* conversion, it did not base its finding on infringement triggered by *in vivo* conversion of a product claimed in a patent.

claim to that product. Every subsequent case addressing the issue of infringement by *in vivo* conversion, with the exception of *In re Buspirone* and *In re Omeprazole*, cited *Zenith v. Bristol-Myers Squibb* for the proposition that such infringement can occur. Ironically, the poster child of infringement by *in vivo* conversion found no infringement due to lack of evidence,¹⁴³ rendering its oft-cited statement of support *dicta*.

In *Zenith v. Bristol-Myers Squibb* the Federal Circuit never squarely considered the principle of law for which it is usually cited. Instead, the court found that BMS had presented insufficient evidence that Zenith's generic cefadroxil would meet each and every element of the claim of BMS' '657 patent.¹⁴⁴ Of particular significance to the court was that fact that BMS had presented evidence of only 30 lines of x-ray diffraction relative intensities, of which the district court had compared only 22 lines, whereas the claim itself recited 37 lines.¹⁴⁵

Obtaining evidence of an *in vivo* conversion product is difficult. The challenges include obtaining a specific biological sample from a specific location at a specific time with a living human body. In fact, as the Federal Circuit explained, the samples used as evidence in *Zenith v. Bristol-Myers Squibb* were created *in vitro*, were not biological in origin, and did not come from a human who had ingested cefadroxil DC:

[The] scientific fact appears to be that there is no known way to actually sample the contents of patients' stomachs at the precise moment and conduct the x-ray diffraction analyses required to ascertain if all 37 lines described in the patent are present.¹⁴⁶

¹⁴³ *Zenith Laboratories v. Bristol-Myers Squibb*, 19 F.3d 1418, 1423-1424 (Fed. Cir. 1994).

¹⁴⁴ Eitan A. Ogen, Assembling a theory of infringement: third party liability based on *in vivo* production of patented pharmaceuticals, 17 *Cardozo L. Rev.* 117, 139 ("The Zenith facts present an array of legal issues... These issues were left unresolved because the CAFC decided the case on an evidentiary basis.")

¹⁴⁵ *Zenith Laboratories v. Bristol-Myers Squibb*, 19 F.3d 1418, 1423-1424 (Fed. Cir. 1994).

¹⁴⁶ *Id.* at 1422.

Obviously, any process of gathering evidence that depends on so many contingencies, not to mention practical difficulties, is bound to yield a low rate of success. In addition, there are issues of informed consent and privacy that may prevent even an attempt at obtaining a sample. It is hard to imagine a court successfully ordering a patient who has ingested a drug to submit to such an invasive procedure in the civil context of a patent trial. Consequently, lack of evidence is likely to remain a significant hurdle to proving infringement by *in vivo* conversion.¹⁴⁷

Although evidentiary challenges do make findings of infringement by *in vivo* conversion less likely, only the outcome of *Zenith v. Bristol-Myers Squibb* can be explained on these grounds.

C. INHERENCY

A patent claim is invalid for anticipation under 35 U.S.C. §102 if each and every element of that claim is disclosed by a single prior art reference.¹⁴⁸ Even if each and every element of a patent claim is not explicitly disclosed in a single prior art reference, a patent claim may still be anticipated if those claim elements not explicitly disclosed are disclosed inherently by the prior art reference.¹⁴⁹

Inherent anticipation has played a significant role in findings of no infringement of patent claims to products of *in vivo* conversion in four cases.¹⁵⁰

¹⁴⁷ The only practical way to sidestep this obstacle is for all parties to a litigation to stipulate

¹⁴⁸ See, e.g., *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987)

¹⁴⁹ See, e.g., *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (“[A] prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it.”).

¹⁵⁰ In a fourth case, *Mylan v. Thompson*, inherent anticipation is mentioned in passing in discussion of an analogy. See note 92.

In *Marion Merrell v. Geneva*, Geneva moved for summary judgment that patent claims to the metabolite, TAM, was invalid as inherently anticipated by a previous patent claiming therapeutic administration of terfenadine.¹⁵¹ Geneva did not dispute that terfenadine was converted *in vivo* into TAM, or that such *in vivo* conversion would trigger infringement of MMD's '129 patent were the patent valid.¹⁵² In fact, Geneva argued that such conversion into TAM, in conjunction with the '217 patent and the Huther article, inherently anticipated the asserted claims of the '129 patent.¹⁵³ However, the district court decided that the scientific issues underpinning the case were too uncertain to warrant summary judgment because there remained "genuine issues of fact."¹⁵⁴

In *In re Omeprazole*, the court decided that any claim in the '499 patent construed to cover metabolites of omeprazole generated *in vivo* would be invalid as anticipated by claims of the prior art '431 patent that had claims covering omeprazole itself.¹⁵⁵ The court then construed the claims narrowly, so as to avoid their inherent anticipation, and consequently granted summary judgment of no infringement by *in vivo* metabolites of omeprazole.¹⁵⁶

The district court in *In re Buspirone* noted that "[this] case is...similar to [*In re Omeprazole*]"¹⁵⁷ Instead of omeprazole and its metabolites, *In re Buspirone* involved the drug buspirone and its *in vivo* conversion products, including 6-hydroxy-busprione.¹⁵⁸ Just as in *In re Omeprazole*, the district court in *In re Buspirone* construed patent claims

¹⁵¹ *Marion Merrell v. Geneva Pharmaceuticals*, 877 F.Supp. 531, 533 (D.Col. 1994).

¹⁵² *Id.* at 536.

¹⁵³ *Id.*

¹⁵⁴ *Id.* at 537.

¹⁵⁵ *In re Omeprazole Patent Litigation*, 2001 WL 585534, 12 (S.D.N.Y. 2001).

¹⁵⁶ *Id.*

¹⁵⁷ *In re Buspirone Patent Litigation*, 185 F.Supp. 2d 340, 362 (S.D.N.Y. 2002).

¹⁵⁸ *Id.*

to the metabolite narrowly, with the consequence that generic buspirone was found not to trigger infringement.¹⁵⁹

In a case of first impression,¹⁶⁰ the Federal Circuit in *Schering v. Geneva* ruled on the issue of whether there can be inherent anticipation “when the entire structure of the claimed subject matter is inherent in the prior art.”¹⁶¹ *Schering v. Geneva* was the first reported Federal Circuit case “[that] considered invalidating a patent claim on the basis that the entire anticipatory disclosure was inherently disclosed in a prior-art reference.”¹⁶² The court found that each and every element of claims 1 and 3 of the ‘716 patent, covering a metabolite, DCL, produced by *in vivo* conversion of the antihistamine loratadine, were inherently disclosed by the prior art ‘233 patent claiming loratadine.¹⁶³ This case provides strong support for the proposition that a metabolite necessarily produced by *in vivo* conversion after ingestion of known precursor drug is inherently anticipated by a prior art disclosure of that drug.

The courts in a sizable minority of *in vivo* conversion cases have cited inherency as a ground for finding no infringement. In addition, one *in vivo* conversion case,

¹⁵⁹ *Id.*

¹⁶⁰ *Schering Corporation v. Geneva Pharmaceuticals, Inc. et al.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003). This decision has attracted a large amount of commentary. See, e.g., Randy P. Boyer, *Schering Corporation v. Geneva Pharmaceuticals, Inc.: Requiem for the recognition requirement in the law of inherent anticipation*, 14 Fed. Cir. B.J. 677 (2004); Anne Brown & Mark Polyakov, *The accidental and inherent anticipation doctrines: where do we stand and where are we going?*, 4 J. Marshall Rev. Intell. Prop. L. 63 (2004). Some commentary has suggested that the effect of this decision on the drug industry, at least, will be minimal. See, e.g., Cynthia Chen, *Schering Corp. v. Geneva Pharmaceuticals, Inc.: Clarification of the inherent anticipation doctrine and its implications*, 20 Berkeley Tech. L.J. 95, 121 (2005). Some have expressed support for the outcome of this case. See, e.g., Dan L. Burk & Mark A. Lemley, *Inherency*, 47 William and Mary Law Review 371, 381 (2005) (“*Schering* and the rejection of *Elan* seem to have set the Federal Circuit on the right course, recognizing that knowledge is not required for inherency”). Others maintain that inherent anticipation should be interpreted as having a knowledge requirement. See, e.g., Peter D. Smith, Note: *Anticipating too much: Why the court should avoid expanding the doctrine of inherent anticipation*, 61 N.Y.U. Ann. Surv. Am. L. 823, 853-854 (2006).

¹⁶¹ *Schering Corporation v. Geneva Pharmaceuticals, Inc. et al.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

¹⁶² Robert A Matthews, Jr., & Louis M. Troilo, *Schering Corp. v. Geneva Pharmaceuticals, Inc.: Just how far can inherent anticipation extend?*, 20 Santa Clara Computer & High Tech L.J. 779, 781 (2004).

¹⁶³ *Schering Corporation v. Geneva Pharmaceuticals, Inc. et al.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003).

Schering v. Geneva, has significantly expanded the scope of inherency doctrine. Yet, as with evidentiary problems, inherency does not explain the result in even a bare majority of *in vivo* conversion cases, let alone all of them. Another, more universal rationale is required to explain the striking unanimity of results.

V. PHYSIOLOGICAL STEPS DOCTRINE

Identifying a theory that can explain why the highest court to rule on the issue has never found infringement of a patent claiming a product to be triggered by *in vivo* conversion into the product. Based on such stark math, it would appear that courts are reluctant to allow the involuntary activity of a human body trigger patent infringement. This implies an unrecognized legal principle that underlies *in vivo* conversion court decisions.

During the middle of the 20th Century the courts and the USPTO developed a legal doctrine governing the patentability of claims involving “mental steps”.¹⁶⁴ “Mental steps doctrine” rendered unpatentable any patent claim to a process made up of “purely mental steps”.¹⁶⁵ In a famous statement of this rule, the court in *In re Abrams*, 188 F.2d 165, 168 (C.C.P.A. 1951), declared that “[it] is self-evident that thought is not patentable.”¹⁶⁶

Human thought itself should not be patentable subject matter for at least two reasons. Natural phenomena, such as “laws of nature, physical phenomena, and abstract ideas are not patentable”.¹⁶⁷ Human thought falls within at least two of these specific

¹⁶⁴ 1 D. CHISUM, PATENTS, § 1.03[6] (2002).

¹⁶⁵ *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

¹⁶⁶ *In re Abrams*, 188 F.2d 165, 168 (C.C.P.A. 1951).

¹⁶⁷ *Diamond v. Chakrabarty*, 447 U.S. 303, 303 (1980).

categories of unpatentable subject matter: thoughts themselves surely qualify as “abstract ideas”; and, the physiological processes involving neurons, neural networks, and electrical and neurochemical signals by which thoughts are generated within the brain are “physical phenomena”.

Just as thoughts are the results of human physiology, so are metabolites produced by *in vivo* conversion of precursor chemicals. Thus, in humans neither thoughts themselves nor products of *in vivo* conversion themselves should qualify as patentable subject matter. In fact, “mental steps doctrine” can be viewed as merely a subset of a broader “physiological steps doctrine” that precludes patentability of claims covering products of human physiological processes.

There are intimations of this physiological steps doctrine in the judicial decisions involving *in vivo* conversion. Prior to *in vivo* conversion cases involving therapeutic drugs, the court in *Feed Service v. Kent Feeds* noted a crucial distinction between deliberate addition of a chemical compound and generation of that same chemical compound through a natural process. As the court explained:

Certain things have become crystal clear to us at this time. In our considered judgment the plaintiff is limited to a narrow construction of the patent in suit. Defendants do not add alcohol to their feed supplements and plaintiff does not charge them with that. The charge of infringement is based on the use by defendants of fermented molasses which provides the alcohol in question as a natural occurring event. We have concluded that the patent in suit is limited to the teaching of the *addition* of alcohol in feed supplements. The fact that the defendants’ Bovino product may reach the same result as plaintiff’s Morea is not conclusive of the determination of infringement.¹⁶⁸ [Underline added for emphasis.]

¹⁶⁸ *Feed Service v. Kent Feeds*, 528 F.2d 756, 764 (7th Cir. 1976).

What makes the distinction between addition of ethanol and generation of ethanol via “a natural occurring event” particularly striking is the fact that the court appears to have imputed an element recited only in process claims 1-7 of the ‘332 patent (that is, “incorporating...ethanol”)¹⁶⁹ to product claims 8-21 lacking that element¹⁷⁰. The rationale explaining the result of this case is the distinction between ethanol deliberately added to feed and ethanol generated in the feed *in situ* by a “natural occurring event”. Similarly, on several occasions courts in *in vivo* conversion cases have employed claim construction to limit the scope of claims to synthetic versions of metabolites, thus excluding coverage of the same metabolites produced within the human body by *in vivo* conversion.

The court in *Marion Merrell v. Baker Norton* used various strands of evidence, including the specification’s silence on *in vivo* conversion¹⁷¹ and the absurd implications of construing claims to cover products of *in vivo* conversion,¹⁷² to support its conclusion that only “synthetically produced TAM” was covered by claims of the ‘129 patent, and, therefore, that terfenadine would not infringe.¹⁷³

Similarly, the court in *In re Mylan* interpreted the claim of the ‘365 patent, covering administration of 6-hydroxy-busprione, as likely to exclude 6-hydroxy-busprione produced as a metabolite by *in vivo* conversion of its precursor drug,

¹⁶⁹ United States Patent No. 2,808,332, Column 7, Lines 32-65.

¹⁷⁰ *Id.* at Column 7, Line 66 to Column 8, Lines 1-62.

¹⁷¹ See *Marion Merrell Dow Inc., and Merrell Dow Pharmaceuticals, Inc. v. Baker Norton Pharmaceuticals, Inc.*, 948 F.Supp. 1050, 1055 (S.D.Fla. 1996).

¹⁷² See *Marion Merrell Dow Inc., and Merrell Dow Pharmaceuticals, Inc. v. Baker Norton Pharmaceuticals, Inc.*, 948 F.Supp. 1050, 1054 (S.D.Fla. 1996) (“Baker Norton persuasively points out that if as MMD suggests the term “compound” refers to impure TAM created in the body by metabolism, claim 10 could be construed as the removal of impure TAM from human bodies to be combined pharmaceutically with a synthetic, or pure, carrier, which as a practical matter the Court finds to be a tenuous assertion leading to an absurd result.”).

¹⁷³ *Marion Merrell Dow Inc., and Merrell Dow Pharmaceuticals, Inc. v. Baker Norton Pharmaceuticals, Inc.*, 948 F.Supp. 1050, 1057 (S.D.Fla. 1996).

buspirone.¹⁷⁴ Instead, the court considered it likely that the claim covered only direct administration of 6-hydroxy-buspirone.¹⁷⁵ During its discussion of claim construction, the court quoted a revealing analogy that had been offered by Mylan:

Let's assume that a Bristol scientist had found ... that a particular chemical compound in an apple was metabolized in the human body into a compound we will call "Apple--A" and that when you administer Apple--A it improve[s] health... They file a patent application and get a patent on the systemic administration of Apple--A... They make tablets with Apple--A. They sell those tablets. They want to stop other people from making tablets with Apple--A in them. That is fine. That is a complicated case involving issues of inherency. This is not a complicated case because what they have done here is they have tried to use this patent to stop people from selling and eating apples by arguing that when you eat an apple, it is metabolized in the human body into the equivalent of the Bristol metabolite, the equivalent of Apple--A.¹⁷⁶

By quoting this example of eating apples, the court emphasized the implications of the natural character of the health benefits flowing from the apple: what human physiology does to the apple once ingested to produce those health benefits constitutes unpatentable subject matter. Given the result at which the court arrived – construing the claim of the ‘365 patent to exclude metabolites produced naturally by *in vivo* conversion – one can infer that the court approved of the reasoning in the analogy.

In later litigation over busiprone and its 6-hydroxy-busprione metabolite, the court in *In re Busiprone* construed the word “dose” in the claim of the ‘365 patent to exclude metabolites produced by *in vivo* conversion:

¹⁷⁴ Mylan Pharmaceuticals, Inc. v. Tommy G. Thompson and Bristol-Myers Squibb Co., 139 F.Supp.2d 1, 75 (D.D.C. 2001).

¹⁷⁵ Id. at 69.

¹⁷⁶ Id. at 65.

The idea of a "dose" as a quantity that is "taken at one time" has a clear meaning in reference to an externally—measured amount of a substance that is to be ingested or administered into the body all at once, but would have no precise meaning if used to refer to *in vivo* levels in the bloodstream, which are constantly changing.¹⁷⁷

Again, claim construction was used to exclude from patent claims products of *in vivo* conversion that arose within the human body.

The opinion of the court in *In re Omeprazole* included a statement that lends a more direct form of support for physiological steps doctrine. In this case, the ‘499 patent included claims purporting to cover sulphenamides, metabolites produced by *in vivo* conversion of the drug omeprazole.¹⁷⁸ In explaining why claims to sulphenamides themselves would be invalid, the court stated that “[by] claiming patent protection for sulphenamides formed *in vivo* after the oral administration of omeprazole, Astra has merely attempted to patent the unpatentable – “a scientific explanation for the prior art’s functioning.”[internal citation omitted]”¹⁷⁹ Despite the formal use of inherency doctrine as the rationale for its decision, here the court classifies metabolites produced by *in vivo* conversion within the category of natural phenomena. Once a patient has ingested a drug, metabolites of that drug produced within the human body through the processes of human physiology may provide “a scientific explanation of [the drug’s] functioning”, but they are unpatentable subject matter.

After finding invalid claims 1 and 3 of the ‘233 patent, which covered products of *in vivo* conversion, the Federal Circuit in *Schering v. Geneva* stated that its conclusion

¹⁷⁷ *In re Busiprone Patent Litigation*, 185 F.Supp. 2d 340, 353 (S.D.N.Y. 2002).

¹⁷⁸ *In re Omeprazole Patent Litigation*, 2001 WL 585534, 1-2 (S.D.N.Y. 2001).

¹⁷⁹ *In re Omeprazole Patent Litigation*, 2001 WL 585534, 12 (S.D.N.Y. 2001) *quoting* *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

“does not preclude patent protection for metabolites of known drugs.”¹⁸⁰ However, the Federal Circuit then outlined a very strict standard governing how patent protection for products of *in vivo* conversion might be attained through “proper claiming”.¹⁸¹

“[Naturally occurring] metabolites may not receive [patent] protection via compound claims...[because] such bare compound claims include within their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug.”¹⁸² Instead,

the metabolite may be claimed in its pure and isolated form...or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition.¹⁸³

However, according to this unanimous opinion of the Federal Circuit, one cannot obtain patent protection for a metabolite produced by *in vivo* conversion of a precursor drug. This provides more strong support for physiological steps doctrine.

In *Novartis v. Eon*, the majority opinion construed the “hydrosol” in claims of the ‘382 patent to be “medicinal” in nature.¹⁸⁴ Consequently, the claims were interpreted to be limited to “a preexisting product that is administered to treat disease and therefore must necessarily be prepared outside the body.”¹⁸⁵ Again, construction was employed to avoid a finding of infringement triggered by *in vivo* conversion. This too is consistent with physiological steps doctrine.

¹⁸⁰ Schering Corporation v. Geneva Pharmaceuticals, Inc. et al., 339 F.3d 1373, 1381 (Fed. Cir. 2003).

¹⁸¹ Id..

¹⁸² Id..

¹⁸³ Id..

¹⁸⁴ Novartis Pharmaceuticals Corporation et al. v. Eon Labs Manufacturing, Inc., 363 F.3d 1306, 1309 (Fed. Cir. 2004).

¹⁸⁵ Id..

Thus, whether a court employs evidentiary rationales, inherency doctrine, or claim construction, the result is always the same: patent claims purporting to cover products of *in vivo* conversion are either invalid, unenforceable, or are construed not to cover these products. Physiological steps doctrine is consistent with all final court decisions involving allegations that known drugs transformed by *in vivo* conversion into products can trigger infringement. Moreover, physiological steps doctrine provides the best explanation of this striking pattern of judicial decisions.

VI. CONCLUSION

Recognition of physiological steps doctrine has several advantages. It provides a theoretical underpinning to explain the results in cases involving products of *in vivo* conversion. This theoretical underpinning not only has explanatory power for interpreting previous case law, but is also useful in predicting the outcome of future patent prosecution and litigation. In addition, physiological steps doctrine adds a new element to the debate about where inventions involving human beings fit within the spectrum of patentable subject matter.