

PHYSIOLOGICAL STEPS DOCTRINE

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TABLE OF CONTENTS

I. INTRODUCTION	1472
II. “NATURAL CONVERSION” PATENTS	1474
III. <i>IN VIVO</i> CONVERSION PATENTS.....	1478
A. INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS	1478
1. Ortho Pharmaceutical v. Smith.....	1478
B. PROBLEMS OF EVIDENCE	1479
1. Zenith Labs. v. Bristol-Myers Squibb.....	1479
C. INHERENCY	1482
1. Marion Merrell Dow, Inc. v. Geneva Pharms, Inc.....	1482
2. Schering Corp. v. Geneva Pharms., Inc.	1484
3. In re Omeprazole.....	1486
4. <i>Discussion</i>	1487
D. CLAIM CONSTRUCTION.....	1489
1. Marion Merrell Dow Inc v. Baker Norton Pharms., Inc.	1489
2. Hoechst-Roussel Pharms, Inc. v. Lehman	1491
3. Mylan Pharms, Inc. v. Thompson.....	1493
4. In re Buspirone.....	1495
5. Novartis Pharmaceuticals Corp. v. Eon Labs Manufacturing Inc.....	1496
6. <i>Discussion</i>	1498
IV. THE PHYSIOLOGICAL STEPS DOCTRINE.....	1500
A. THE EUROPEAN EQUIVALENT.....	1501
B. WITHIN THE UNITED STATES.....	1502

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V. CONCLUSION1505

I call on Congress to pass legislation that bans unethical practices such as the . . . patenting . . . of human life.

—George W. Bush¹

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 bicycles, barometric chambers, and bobby socks to tumbling mats, toasters, and toenail clippers all fall squarely within patentable subject matter. Moreover, since *Diamond v. Chakrabarty*, the potentially patentable subject matter has extended almost to the limits of the human imagination.² However, the bounds are not limitless. There exist specifically recognized exceptions to patentable subject matter; for instance, “[t]he laws of nature, physical phenomena, and abstract ideas have been held not patentable.”³ However, there may also be exceptions yet unrecognized. This Article argues that the metabolic products of *in vivo* conversion by and within the human body fall within one of these unrecognized categories of unpatentable subject matter.

Patent claims whose elements involve the physiological functions inside a human being fit uneasily into patent law. The patent laws of the United States already include explicit limits on patent claims as they relate to humans and human bodies. Inventions carried out using human thought have long been subject to limitations such as the Mental Steps Doctrine.⁴ Further restrictions include limits on inventions related to surgery and medicine, limiting liability for patent infringement by medical personnel and medical facilities, and the unpatentability of human-nonhuman genetic hybrids, or chimaeras.⁵ Specifically, the “Weldon Amendment” rider, which has been renewed since 2004, states that “[n]one of the funds ap-

1. State of the Union 2008 (January 28, 2008), in 44 WEEKLY COMP. PRES. DOC. 117 at 120.

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

3. *Id.* at 309.

4. See, e.g., *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) (“Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.”).

5. 35 U.S.C. § 287(c) (2000); Patent Application Is Disallowed as “Embracing” Human Being, 58 PAT. TRADEMARK & COPYRIGHT J. (BNA) 203 (June 17, 1999).

propriated or otherwise made available under this Act may be used to issue patents on claims directed to or encompassing a human organism.”⁶ Similarly, it has been the stated policy of the USPTO since 1987 that “[a] claim directed to or including within its scope a human being will not be considered to be patentable subject matter.”⁷ President William J. Clinton has publicly opposed patents on human clones,⁸ and President George W. Bush has urged Congress “to pass legislation that bans unethical practices, such as the . . . patenting . . . of human life.”⁹ Notwithstanding USPTO policy and the unambiguous exhortations of Presidents Clinton and Bush, there is no clear statutory prohibition against human beings, or properties thereof, being patentable subject matter. Though the law has yet to speak clearly on the matter, this Article suggests that inventions that include a human being as part of their structure or operation generally sit towards the unpatentable end of the spectrum.

Such classes of potentially unpatentable inventions involving significant human participation include products of *in vivo* conversion. *In vivo* conversion is a process, often metabolic in nature, wherein one substance, usually a chemical compound, is altered significantly by physiological pathways in the body into one or more different substances.¹⁰ For example, when a patient ingests a therapeutic drug, that drug is often converted by the natural physiology of the digestive system into one or more chemically different metabolites. The end products of *in vivo* conversion sometimes possess therapeutic efficacy.

Many patent applications have claimed such therapeutic metabolites, either as compositions *per se* or as parts of methods of treatment. Although the USPTO has granted patent claims to such products generated by *in vivo* conversion of ingested drugs, and courts have noted the eligibility of such products as patentable subject matter, never has a United States court of final appeal upheld such a patent claim as valid, enforceable, and infringed.¹¹

This Article reviews the judicial decisions that considered infringement by *in vivo* conversion, including the forerunners of *in vivo* conver-

6. Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 3, 101 (2004).

7. Animals—Patentability, 1077 OFF. GAZ. PAT. OFFICE 24 (Apr. 21, 1987).

8. Eliot Marshall, *Clinton Urges Outlawing Human Cloning*, 276 SCI. 1640 (1997).

9. State of the Union 2008, (January 28, 2008), in 44 WEEKLY COMP. PRES. DOC. 117.

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

11. See discussion *infra* Part III.

sion cases: those involving “natural conversion.” It then considers several possible explanations for these decisions’ unanimity in never finding *in vivo* conversion claims valid, enforceable, and infringed. Finally, it proposes a novel doctrinal framework that can explain the consistent outcome of *in vivo* conversion cases: the Physiological Steps Doctrine.

II. “NATURAL CONVERSION” PATENTS

Long before they began to grapple with patentability and infringement issues surrounding *in vivo* conversion, courts considered an analogous phenomenon: “natural conversion.” Natural conversion involves the transformation of one or more starting substances into one or more product substances without direct human intervention to cause the transformation. The fermentation of alcohol provides a simple example. The carbohydrates in an initial mixture of grape juice and yeast, if maintained at an appropriate temperature and exposed to a minimal concentration of oxygen, will be chemically transformed into an ethanol mixture otherwise known as wine. Though wines are usually produced with careful human oversight, fermentation also commonly occurs in nature without human involvement.

When one or more noninfringing chemical reactants are converted into one or more different chemical products, and at least one of these products falls within a patent claim, the usual result is patent infringement. For example, in *Chemical Cleaning v. Dow Chemical*, Chemical Cleaning, Inc. (CCI) was found to have infringed a patent by selling a cleaning product, Sequestrol 60, that, upon decomposition, produced a chemical, thiourea, claimed in Dow Chemical’s patent.¹² The Fifth Circuit Court of Appeals affirmed the district court’s finding that CCI was liable for patent infringement under the doctrine of equivalents.¹³ Similarly, in *Broadview Chemical v. Loctite*, Broadview Chemical Corporation tried to avoid infringement of a patent claim whose elements included the chemical quinone by substituting the chemical hydroquinone into its product instead.¹⁴ The court, however, found that Broadview Chemical Corporation did infringe that claim because upon use of the product the hydroquinone un-

12. *Chem. Cleaning, Inc. v. Dow Chem. Co.*, 379 F.2d 294, 296-97 (5th Cir. 1967) (“Sequestrol 60 is prepared by compounding thiourea and formaldehyde under alkaline conditions. The process is reversible, and the trial court found that under the boiler treating conditions employed by CCI, Sequestrol 60 disassociates to produce about 90% by weight of thiourea in the free or uncombined form, and some formaldehyde.”).

13. *Id.* at 297.

14. *Broadview Chem. Corp. v. Loctite Corp.*, 159 U.S.P.Q. 80, 85 (D. Conn. 1968).

derwent a chemical reaction and released quinone.¹⁵ Thus, in nonbiological chemical contexts, there is strict liability for patent infringement both in situations where the allegedly infringing chemical is initially present in a product and where the allegedly infringing chemical arises in the product by means of chemical reaction. However, involvement by an organism in the production of the infringing chemical appears to alter this result.

Prior to the first *in vivo* conversion case, *Feed Service Corp. v. Kent Feeds, Inc.*, involving a dispute between two agricultural feed companies, considered 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.¹⁶ Although the district court found infringement, the Court of Appeals disagreed, ultimately laying the groundwork for later *in vivo* conversion cases.¹⁷

Feed Service Corporation, an agricultural feed company that made feed for livestock, owned U.S. Patent No. 2,808,332 ('332 patent).¹⁸ The '332 patent had twenty-one claims for feeds of specified formulations and methods of using such feeds to improve rates of growth in cattle that according to the specifications was achieved by adding synthetic urea and ethyl alcohol (also known as ethanol) as ingredients.¹⁹ The '332 patent disclosed that 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.²⁰ Feed Service marketed its feed under the trade name "Morea," and its product was a commercial success.²¹

Kent Feeds, Inc. developed and sold competing feeds, trade named "Bovino" and, later, "Bovino-Lac."²² Feed Service sued Kent Feeds for infringing claims of the '332 patent, alleging that "Bovino-Lac" contained each and every claimed ingredient.²³ Kent Feeds disputed infringement on the ground that their product included fermented molasses and not etha-

15. *Id.*

16. *Feed Serv. Corp. v. Kent Feeds, Inc.*, 528 F.2d 756, 763 (7th Cir.), *cert. denied*, 429 U.S. 870 (1976).

17. *Id.* at 763-64.

18. *Id.* at 757.

19. U.S. Patent No. 2,808,332 (filed Feb. 17, 1955); *Feed Serv. Corp.*, 528 F.2d at 758.

20. '332 Patent, col. 2 l.19-30.

21. *Feed Serv. Corp.*, 528 F.2d at 759.

22. *Id.* at 763.

23. *Id.* at 759.

nol.²⁴ 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. . . .”²⁵

The district court agreed with Feed Services, finding that Kent Feeds’s product contained ethanol in the amounts specified by the claims,²⁶ and thus infringed all of the claims of the ’332 patent.²⁷ Just as in the three nonbiological chemical cases noted above, the district court appears to have been untroubled by the provenance of the patented chemical, drawing no distinction between the direct addition of ethanol to feed and ethanol produced by fermentation of molasses within the feed mixture itself.

Kent Feeds appealed, alleging that the claims of the ’332 patent claims were invalid, unenforceable, and not infringed by Feed Services’s feed product.²⁸ 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 a decisive issue, and refused to construe the patent claims as covering any and all feed supplements containing ethanol, regardless of how the ethanol was 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. . . . We cannot say that its monopoly extends to the mere presence of alcohol resulting from a molasses fermentation process.²⁹

Furthermore, the Court of Appeals distinguished between claimed ingredients added to feed by conscious human agency and claimed ingredients arising *in situ*:

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*. . . . The fact that the defendants’ Bovino product may reach the same result as plaintiff’s Morea is not conclusive of the determination of infringement.³⁰

24. *Id.* at 763.

25. *Id.*

26. Feed Serv. Corp. v. Kent Feeds, Inc., 185 U.S.P.Q. 745, 750 (N.D. Ill. 1975).

27. *Id.* at 753.

28. Feed Serv. Corp. v. Kent Feeds, Inc., 528 F.2d 756, 757 (7th Cir. 1976).

29. *Id.* at 763.

30. *Id.* at 764 (emphasis added).

Accordingly, the Court of Appeals reversed the district court's finding of infringement, though it did affirm the lower court's finding of validity.³¹

In his dissent, Judge Stevens disputed the majority's interpretation of "addition," noting "that the incorporation of fermented molasses is a method of adding ethanol."³² In addition, some commentators have suggested that the Court of Appeals wrongly imported the claim element of "incorporating" from process claims into product claims.³³ However, as claims 11 and 16, both product claims to feed mixtures, are the only claims the Court of Appeals reproduces in its opinion,³⁴ the court appears to have been aware that its interpretation included product claims.

Although the Court of Appeals did not offer a clear rationale for its decision, it appears to have considered the "natural" origin of an ingredient in the feed mixture to be significant—perhaps even decisive.³⁵ 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 *biological* processes may be less patentable than claims to identical products made synthetically or artificially.

31. *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*. *See id.* (noting that defendant's actions were "a far cry from plaintiff's overzealous charge of blatant infringement, literal piracy and outright duplication.").

32. *Id.* at 764.

33. *See, e.g.*, 3 MARTIN J. ADELMAN ET AL., PATENT LAW PERSPECTIVES § 3.2 (2d ed. 2006)

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.

Id.

34. *Feed Serv. Corp. v. Kent Feeds, Inc.*, 528 F.2d 756, 758 (7th Cir. 1976).

35. *Id.* at 764.

III. *IN VIVO* CONVERSION PATENTS

Since the 1976 *Feed Service* opinion, there have been ten recorded judicial decisions of cases involving allegations of infringement of products generated by *in vivo* conversion of known drugs. These decisions were decided on different grounds: the doctrine of equivalents, evidentiary insufficiency, inherent anticipation, and claim construction. Though these cases display a variety of facts and rationales, their results agree in one significant respect: no appeals court ever found a claim on a product of *in vivo* conversion to be valid and infringed.³⁶

A. Infringement Under the Doctrine of Equivalents

1. *Ortho Pharmaceutical v. Smith*

Ortho Pharmaceutical Corporation (Ortho) sued for declaratory judgment against American Home Products, the exclusive licensee of U.S. Patent No. 3,959,322 ('322 patent), Dr. Herchel Smith, and Wyeth-Ayerst Laboratories (collectively American Home Products, or AHP), asking the district court for a declaration of invalidity of claims of the '322 patent.³⁷

Ortho marketed norgestimate, a steroid oral contraceptive that it had developed by modifying norgestrel, a chemical covered by claims 5 and 19 of the '322 patent.³⁸ When ingested, norgestimate is transformed by *in vivo* conversion into norgestrel, one of two "products [that] are primarily responsible for the biological activity of norgestimate."³⁹ Thus, the district court found infringement under the doctrine of equivalents.⁴⁰ Although it did appeal on other grounds, including invalidity of the '322 patent, Ortho did not appeal the finding of patent infringement itself.⁴¹

Despite the fact that this case involved one compound, norgestimate, that is transformed by *in vivo* conversion into a different infringing compound, norgestrel, it is conceptually distinct from the other *in vivo* infringement cases because the district court based its decision on the doctrine of equivalents. Under the court's application of the doctrine of equivalents, both norgestimate and its *in vivo* product, norgestrel, were found

36. At first glance, *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 939 (Fed. Cir. 1992), would seem to be an exception. However, here the court found infringement under the doctrine of equivalents.

37. *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 937-38 (Fed. Cir. 1992).

38. *Ortho Pharm. Corp. v. Smith*, 18 U.S.P.Q.2d 1977, 31 (E.D. Pa. 1990).

39. *Ortho Pharm. Corp.*, 959 F.2d at 939.

40. *Id.*

41. *Id.* at 940.

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.

B. Problems of Evidence

1. *Zenith Labs. 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.⁴² BMS owned U.S. Patent No. 4,504,657 ('657 patent), which contained a single claim to the Bouzard monohydrate specifying a chemical formula and thirty-seven specific x-ray diffraction properties.⁴³

Zenith Laboratories planned to market a form of cefadroxil, Cefadroxil DC, that differed structurally from the Bouzard monohydrate, but converted into the Bouzard monohydrate through *in vivo* conversion.⁴⁴ After BMS alleged that Cefadroxil DC infringed the '657 patent claim, 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.⁴⁵ After agreeing that Cefadroxil DC did not 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)."⁴⁶

Initially, the court granted Zenith's motion for summary judgment of noninfringement.⁴⁷ But later, the court vacated its first decision, citing new evidence that "had demonstrated a genuine dispute on the *in vivo* conversion issue."⁴⁸ After a bench trial, the court found no infringement under the doctrine of equivalents, but "[s]ince 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

42. *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1419 (Fed. Cir. 1994).

43. *Id.* at 1419-20.

44. *Id.* at 1420.

45. *Id.*

46. *Id.*

47. *Id.*

48. *Id.* at 1421.

would induce infringement of the 657 patent.”⁴⁹ Zenith subsequently appealed.⁵⁰

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.⁵¹ Further, in Footnote 4, the Federal Circuit implied that a product of *in vivo* conversion could, in theory, trigger infringement: “The trial court apparently reached the same conclusion: ‘use of converted Bouzard monohydrate by a patient who ingests cefadroxil DC is an infringing use.’ (But see note 6 regarding the significance of the term ‘use.’)”⁵² However, the parenthetical statement that ends Footnote 4 vitiates the possibility of finding infringement via *in vivo* conversion by employing the contrasting word “But” to signal that Footnote 6 (a recitation of arguments offered by Zenith, but not relied upon by the Federal Circuit) offers an interpretation of the word “use” that would require non-incidental *in vivo* conversion:

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.⁵³

Because the Federal Circuit disposed of the case on evidentiary grounds, the court noted that “we need not address these other grounds for reversal.”⁵⁴ Nevertheless, the Federal Circuit’s decision to temper Footnote 4 by pointing out, but not disposing of, the interpretation of “use” in Footnote 6 suggests that *in vivo* conversion producing Bouzard crystals might not constitute infringement.

Indeed, the Federal Circuit reversed the district court’s finding of infringement under the doctrine of equivalents on evidentiary grounds.⁵⁵ First,

[the] district court, instead of requiring the comparison of the accused compound following conversion to be made with the lines

49. *Id.*

50. *Id.*

51. *Id.* at 1422.

52. *Id.* at 1422 n.4.

53. *Id.* at 1424 n.6.

54. *Id.*

55. *Id.* at 1426.

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.⁵⁶

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

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.⁵⁷

Thus, "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."⁵⁸

Given the Federal Circuit's finding of noninfringement by the product of *in vivo* conversion, as well as the ambiguity latent in Footnotes 4 and 6, it might seem odd that *dicta* in *Zenith v. Bristol-Myers Squibb* would be cited for the proposition that products of *in vivo* conversion can indeed trigger infringement. Despite this, *Zenith* is perhaps the most influential case to consider the issue of whether a product of *in vivo* conversion can trigger infringement. Every subsequent case addressing the issue of infringement by *in vivo* conversion, with the exception of *In re Buspirone* and *In re Omeprazole*, has cited *Zenith* for the proposition that such infringement can occur. Ironically, though this case is invoked as the poster child of infringement via *in vivo* conversion, the court in *Zenith* did not find infringement due to lack of evidence.⁵⁹ Consequently, its oft-cited statements of support of infringement via *in vivo* conversion are *dicta*. Nevertheless, a close look at these subsequent *in vivo* conversion cases dispels some of this incongruity: while cases do cite *Zenith v. Bristol-Myers Squibb* on the issue of infringement via *in vivo* conversion, no judicial opinion has found it solely controlling on the issue of infringement.

In *Zenith*, 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

56. *Id.* at 1423.

57. *Id.* at 1424.

58. *Id.*

59. *Id.* at 1423-24.

meet each and every element of the claim of BMS's patent.⁶⁰ Of particular significance to the court was that fact that BMS had presented evidence of only thirty lines of x-ray diffraction relative intensities, of which the district court had compared only twenty-two lines, whereas the claim itself recited thirty-seven lines.⁶¹

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 within a living human body. In fact, as the Federal Circuit explained, "[S]cientific 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."⁶² As a result, the samples used as evidence in *Zenith* were created *in vitro*, were not biological in origin and did not come from a human who had ingested cefadroxil DC. 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, a lack of evidence is likely to remain a significant hurdle to proving infringement by *in vivo* conversion. Nevertheless, *Zenith* is the only *in vivo* conversion case thus far whose outcome regarding infringement can be attributed to evidentiary grounds.

C. Inherency

1. *Marion Merrell Dow, Inc. v. Geneva Pharms, Inc.*

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®.⁶³ MMD owned U.S. Patent No. 3,878,217 ('217 patent), claiming administration of terfenadine and other piperidine derivatives.⁶⁴ MMD's subsequent research on ter-

60. Eitan Alexander Ogen, *Assembling a Theory of Infringement: Third Party Liability Based on In Vivo Production of Patented Pharmaceuticals*, 17 CARDOZO L. REV. 117, 139 (1995) ("The *Zenith* facts present an array of legal issues. . . . These issues were left unresolved because the CAFC decided the case on an evidentiary basis.").

61. *Zenith Labs.*, 19 F.3d at 1423-24.

62. *Id.* at 1422-23.

63. *Marion Merrell Dow, Inc. v. Geneva Pharms., Inc.*, 877 F. Supp. 531, 533 (D. Colo. 1994).

64. *Id.*

fenadine yielded terfenadine acid metabolite (TAM), a product produced by *in vivo* conversion after ingestion of terfenadine, and obtained U.S. Patent No. 4,254,129 ('129 patent) to cover both TAM itself and methods of administering a therapeutically effective amount of TAM.⁶⁵

Geneva Pharmaceuticals, Inc. applied to the FDA for regulatory approval to market a generic version of terfenadine once the '217 patent expired, and stated, as part of the regulatory certification process, that its generic product would not infringe claims of the '129 patent.⁶⁶ In response, MMD sued Geneva, and Geneva requested summary judgment on the grounds that the asserted claims of the '129 patent were invalid as inherently anticipated.⁶⁷

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 [sic] patent."⁶⁸ The district court pointed out "that infringement may result from the *in vivo* conversion of one product or compound into another," citing *Zenith* for support.⁶⁹

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 more than a year prior to the priority date of the '129 patent.⁷⁰ Geneva acknowledged 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.⁷¹ In other words, claims to the use of TAM in the '129 patent were allegedly inherently anticipated by the teachings of the prior art.⁷²

The district court denied Geneva's motion for summary judgment because it was "unclear . . . whether, 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."⁷³

65. *Id.*

66. *Id.* at 534.

67. *Id.* at 534-37.

68. *Id.* at 535 (quoting Pl.'s Resp., Introduction).

69. *Id.*

70. *Id.* at 536.

71. *Id.*

72. *Id.*

73. *Id.* at 537.

2. *Schering Corp. v. Geneva Pharms., Inc.*

Schering Corporation owned two patents with claims covering antihistamines: U.S. Patent No. 4,282,233 ('233 patent) claimed loratadine, an active ingredient of the brand-name antihistamine CLARITIN® marketed by Schering; and U.S. Patent No. 4,659,716 ('716 patent) claimed descarboethoxyloratadine (DCL), a metabolite resulting from *in vivo* conversion of loratadine.⁷⁴ 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.⁷⁵ 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.⁷⁶ 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.⁷⁷ Both Schering and *Geneva et al.* agreed to this interpretation.⁷⁸ Then, the court used the claim construction to find "that the '233 patent did not expressly disclose DCL."⁷⁹ However, because "DCL was necessarily formed as a metabolite by carrying out the process disclosed in the '233 patent," and the '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.⁸⁰

Schering appealed this grant of summary judgment.⁸¹ 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."⁸² In fact, the panel noted that

[i]n these prior cases, however, inherency was only necessary to supply a single missing limitation that was not expressly dis-

74. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1374-75 (Fed. Cir. 2003).

75. *Id.* at 1376.

76. *Id.*

77. *Id.*

78. *Id.*

79. *Id.*

80. *Id.*

81. *Id.*

82. *Id.* at 1378.

closed 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.⁸³

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."⁸⁴ 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.⁸⁵ Consequently, these same claims must be invalid in light of the '233 patent because "[a]n identical metabolite must then anticipate if earlier in time than the claimed compound."⁸⁶

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 a person may infringe a claim to a metabolite if the person ingests a compound that metabolizes to form the metabolite."⁸⁷ The Federal Circuit later stressed that their finding of inherent anticipation in this case would not "preclude patent protection for metabolites of known drugs."⁸⁸ In fact, "[w]ith proper claiming, patent protection is available for metabolites of known drugs."⁸⁹

The Federal Circuit, however, considered such "proper claiming" to be restricted to purified metabolites not found in nature in purified form, citing *In re Kratz*⁹⁰ and *In re Bergstrom*⁹¹ as illustrations.⁹² And such *in vivo* conversion metabolites, including those recited in claims 1 and 3 of the '716 patent, "may not receive protection via compound claims . . . [be-

83. *Id.* at 1379.

84. *Id.* at 1378.

85. *Id.* at 1380.

86. *Id.*

87. *Id.* (citing *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997) and *Zenith Lab., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1421-22 (Fed. Cir. 1994)).

88. *Id.* at 1381.

89. *Id.* (internal citations omitted).

90. *In re Kratz*, 592 F.2d 1169 (C.C.P.A. 1979) (claims to substantially pure compounds may be patentable).

91. *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970) (claims to pure substances may be patentable).

92. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003).

cause 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.”⁹³ 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.”⁹⁴ 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.⁹⁵

3. *In re Omeprazole*

Astra Aktiebolag and related companies (Astra) marketed a gastric acid inhibiting drug brand-named PRILOSEC®, whose active ingredient was omeprazole.⁹⁶ Astra had listed two of its patents in the FDA Orange Book: U.S. Patent No. 4,255,431 (’431 patent), which includes claims to omeprazole as a compound and to the oral administration of omeprazole for gastric acid inhibition and U.S. 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 diseases.⁹⁷ Because the ’431 patent was close to expiration, several generic drug companies, Genpharm, Inc., Cheminor Drugs Ltd., Reddy-Cheminor, Inc., and Schein Pharmaceutical, Inc. (collectively Genpharm *et al.*) applied for an Abbreviated New Drug Application (ANDA) to market generic versions of omeprazole.⁹⁸ Astra sued Genpharm *et al.* for infringement of the ’499 patent, which was not close to expiration, 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 argued 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* in support of their position.⁹⁹ Genpharm *et al.* disputed Astra’s interpretation

93. *Id.*

94. *Id.*

95. *Id.*

96. *In re Omeprazole Patent Litig.*, No. MDL 1291, 2001 WL 585534, at *1 (S.D.N.Y. May 31, 2001).

97. *Id.* at 1-2.

98. *Id.*

99. *Id.* at 3.

of *Zenith*, and cited *Marion Merrell Dow, Inc. v. Baker Norton*,¹⁰⁰ for the proposition that *Zenith* did not articulate a *per se* rule that claims to compounds covered both those made synthetically and those produced by *in vivo* conversion.¹⁰¹

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.”¹⁰² It thus construed the claims as only covering synthetic sulphenamides, not metabolite sulphenamides resulting from the *in vivo* conversion of omeprazole.¹⁰³ The court then granted Genpharm *et al.* summary judgment of invalidity of the ’499 patent’s claims based on inherent anticipation by prior art teaching administration of omeprazole to inhibit gastric acid.¹⁰⁴

4. Discussion

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.¹⁰⁵ Even if 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.¹⁰⁶ Inherency includes both inherent anticipation and inherent obviousness.

Inherent anticipation has played a significant role in findings of noninfringement in three of the *in vivo* conversion cases discussed above.¹⁰⁷

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

101. *In re Omeprazole*, 2001 WL 585534, at *3.

102. *Id.* at 4.

103. *Id.* at 7.

104. *Id.* at 12-13.

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

106. *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.”).

107. In a fourth case, *Mylan Pharms., Inc. v. Thompson*, 139 F. Supp. 2d 1 (D.D.C. 2001), inherent anticipation is mentioned in passing in discussion of an analogy. *See infra* note 153.

In a case of first impression,¹⁰⁸ the Federal Circuit in *Schering v. Geneva* ruled on whether there can be inherent anticipation “when the entire structure of the claimed subject matter is inherent in the prior art.”¹⁰⁹ *Schering* 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.”¹¹⁰ 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.¹¹¹ 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.

In *Marion Merrell v. Geneva*, Geneva moved for summary judgment, arguing that patent claims to the metabolite, TAM, were invalid due to inherent anticipation by a previous patent claiming therapeutic administration of terfenadine.¹¹² 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 if that patent was valid.¹¹³ In fact, Ge-

108. *Schering Corp. v. Geneva Pharms., Inc.*, 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 (2005); 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 WM. & MARY L. REV. 371, 381 (2005) (“Schering and the rejection of *Elan* seem to have set the Federal Circuit firmly 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, 853-54 (2006).

109. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

110. 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).

111. *Schering Corp.*, 339 F.3d at 1381.

112. *Marion Merrell, Inc. v. Geneva Pharms., Inc.*, 877 F. Supp. 531, 533, 535 (D. Colo. 1994).

113. *Id.* at 536.

neva argued that such conversion into TAM, in conjunction with the '217 patent and the Huther article, inherently anticipated the asserted '129 patent claims.¹¹⁴ But the district court decided that the scientific issues and evidence underpinning the case were too uncertain to warrant summary judgment.¹¹⁵

The court in *In re Omeprazole* decided that any claim language in the patents that could be construed to cover metabolites generated *in vivo* would be invalid. Such a construction would be anticipated by the prior art patent containing claims covering the original product itself.¹¹⁶ The court then construed the claims narrowly, avoiding their inherent anticipation, and consequently granted summary judgment of noninfringement by *in vivo* metabolites of omeprazole.¹¹⁷

In a sizable minority of *in vivo* conversion cases, courts have cited inherency as a ground for finding noninfringement. In fact, one, *Schering*, significantly expanded the scope of the inherency doctrine. Yet, as with evidentiary problems, inherency does not satisfactorily explain the outcomes 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.

D. Claim Construction

1. *Marion Merrell Dow Inc v. Baker Norton Pharms., Inc.*

Baker Norton Pharmaceuticals manufactured a generic version of terfenadine, a drug described and previously protected by claims in MMD's now expired '217 patent.¹¹⁸ In response to an 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 and moved for summary judgment.¹¹⁹ Because the '129 patent did not claim terfenadine, MMD's theory of infringement depended on the physiological transformation of terfenadine into TAM

114. *Id.*

115. *Id.* at 537.

116. *In re Omeprazole Patent Litig.*, No. MDL 1291, 2001 WL 585534, at *12 (S.D.N.Y. May 31, 2001).

117. *Id.* at *12-13.

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

119. *Id.* at 1051-52.

within the body of a human who ingested generic terfenadine: infringement triggered by *in vivo* conversion.¹²⁰

During claim construction, the court focused its analysis on the meaning of the claim element “compound.”¹²¹ 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.”¹²² Under this construction, TAM produced in the patient’s body by *in vivo* conversion would fall within claim 1 of the ’129 patent, and thus, infringement would lie. By contrast, Baker Norton urged the court to adopt a much narrower interpretation of “compound” that included “only synthetically produced TAM.”¹²³ 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.¹²⁴

Given the narrow interpretation of “compound,” the court found no literal infringement by TAM *naturally* produced in a patient’s body by *in vivo* conversion.¹²⁵ Furthermore, the court declined to find infringement under the doctrine of equivalents.¹²⁶ However, in its analysis under the doctrine of equivalents, the court provided only an opaque rationale for its decision not to find infringement, ostensibly relying on the discretion al-

120. *Id.* at 1053 (“MMD argues that Baker Norton's proposed practice of the expired '217 Patent covering terfenadine and its administration will literally infringe the '129 Patent because when a patient takes the Baker Norton product, his or her liver will necessarily produce TAM.”).

121. *Id.* at 1054.

122. *Id.*

123. *Id.*

124. *Id.* at 1053-56. Especially devastating to MMD’s chosen interpretation of “compound” was testimony from its former head of clinical pharmacology, Murray Weiner, M.D.:

[i]n 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.*

Id. at 1056.

125. *Id.* at 1056-57.

126. *Id.* at 1057.

lowed it by the equitable nature of that doctrine.¹²⁷ Consequently, the court granted Baker Norton's motion for summary judgment of noninfringement of claims of the '129 patent by generic terfenadine.¹²⁸

Since the court construed the word "compound" as covering only synthetic TAM, it was unnecessary for the court to consider TAM produced naturally in the body. Therefore, nowhere did the court directly comment on the issue of whether or not a product of *in vivo* conversion could trigger infringement.¹²⁹

2. *Hoechst-Roussel Pharms, Inc. v. Lehman*

After the FDA granted Warner-Lambert Company 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 alleging that COGNEX® infringed their U.S. Patent No. 4,631,286 ('286 patent).¹³⁰ 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®.¹³¹ Litigation concluded with a consent judgment by the district court "in which Warner-Lambert admitted that tacrine hydrochloride infringe[d] certain claims of the '286 patent."¹³²

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.¹³³ 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 ex-

127. *Id.*

128. *Id.*

129. The court, however, did address *Zenith*:

The Court declines to find a *per se* rule in *Zenith* which requires that all claims which describe a compound be construed as covering both the metabolically produced and synthetic produced forms of the compound, without regard to the language of the claims, the specification of the patent or the prosecution history. Instead, the Court will conduct the construction pursuant to *Markman*, and as will be demonstrated *infra*, the reference points for construction in this case are much more replete with evidence that a different interpretation of the term "compound" is appropriate here than was the case in *Zenith*.

Id. at 1054 n.4.

130. *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 757 (Fed. Cir. 1997).

131. *Id.*

132. *Id.*

133. *Id.*

tended . . . 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.”¹³⁴ 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.”¹³⁵ Furthermore, “[b]ecause use of tacrine hydrochloride allegedly infringe[d] its claim to a method of using 1-hydroxy-tacrine, Hoechst contende[d] that the ’286 patent ‘claims’ a method of using tacrine hydrochloride.”¹³⁶ The USPTO denied this application for two reasons. First, Hoechst was an improper applicant and, second, the ’286 patent “does not claim tacrine hydrochloride, as required by the statute.”¹³⁷ The district court agreed with the USPTO’s findings and granted the USPTO’s motion for summary judgment.¹³⁸ Hoechst appealed to the Court of Appeals for the Federal Circuit.¹³⁹

The Federal Circuit affirmed the district court’s judgment “on the basis that Hoechst’s patent does not claim either the drug product [tacrine hydrochloride] which received regulatory approval or its use.”¹⁴⁰

However, in *dicta* 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® 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.¹⁴¹

134. *Id.* at 758.

135. *Id.*

136. *Id.*

137. *Id.* at 757-58.

138. *Id.* at 758.

139. *Id.*

140. *Id.* at 757. For qualified support of the decision, see Matthew Hirsch, Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman, 13 BERKELEY TECH. L.J. 163, 173 (1998) (“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.”).

141. Hoechst-Roussel Pharms., 109 F.3d at 759.

The Federal Circuit cited *Zenith* for the proposition that “infringement may occur if the administered product is converted *in vivo* into the claimed product.”¹⁴² However, it failed to point out that the basis for this statement from *Zenith* did not represent the rule of the case, but, instead, was *dicta*, because the Federal Circuit made no actual finding of infringement in *Zenith*. Though disagreeing on some issues, the concurrence by Judge Newman compounded the majority’s misinterpretation, agreeing that *Zenith* stands for the proposition that “*in vivo* conversion into the drug named in the claims is direct infringement.”¹⁴³

3. *Mylan Pharms, Inc. v. Thompson*

In 1998 Mylan Pharmaceuticals, Inc. submitted an 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).¹⁴⁴ BMS owned U.S. Patent No. 4,182,763 (’763 patent), which claimed methods of using buspirone to treat patients with generalized anxiety disorder.¹⁴⁵ 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.¹⁴⁶ However, the day before the ’763 patent expired, the USPTO issued BMS U.S. Patent No. 6,150,365 (’365 patent), which includes a claim to a method of treating anxiety in a patient by administering 6-hydroxy-buspirone, a metabolite of buspirone produced by *in vivo* conversion.¹⁴⁷

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.¹⁴⁸ Mylan and one other generic drug company filed lawsuits on November 30, 2000, seeking a preliminary injunction to have the ’365

142. *Id.* (citing *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1422 (Fed. Cir. 1994)).

143. *Id.* at 764 (citing *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1422 (Fed. Cir. 1994)).

144. *Mylan Pharms., Inc. v. Thompson*, 139 F. Supp. 2d 1 (D.D.C. 2001) (Claim construction by district court not addressed on the merits), *rev’d*, *Mylan Pharms., Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001).

145. *Id.* at 7-9.

146. *Id.* at 9.

147. *Id.*

148. *Id.* at 9-10.

patent delisted from the FDA's "Orange Book,"¹⁴⁹ freeing the path to approval of Mylan's ANDA.¹⁵⁰

A threshold consideration for the court was whether the claim of the '365 patent covered use of buspirone in addition to use of its metabolite, 6-hydroxy-buspirone. If use of buspirone fell outside 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).¹⁵¹ Then, it concluded that, just as for the '286 patent in *Hoechst-Roussel*, "so too is the '365 patent limited to the use of the [6-hydroxy-buspirone] metabolite . . . , and therefore the '365 patent cannot claim the administration of buspirone."¹⁵² This foreclosed the argument that administration of buspirone could trigger infringement by *in vivo* conversion into the 6-hydroxy-buspirone metabolite.¹⁵³ As a result, the court acceded to Mylan's request for a preliminary injunction, which required that (1) Bristol-Myers request the FDA to delist the '365

149. *Id.* at 4 ("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.'" (citing 21 U.S.C. § 355(j)(7)(A)(iii) (2000))).

150. *Id.* at 9-10.

151. *Id.* at 19-21.

152. *Id.* at 21.

153. *Id.* at 24. 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.

Id. at 23 n.16. By making an analogy to 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.

patent from the Orange Book and (2) the FDA grant immediate approval of Mylan's ANDA.¹⁵⁴

4. *In re Buspirone*

On the heels of *Mylan v. Thompson*, a growing number of patent lawsuits involving Bristol-Myers's '365 patent prompted the Judicial Panel on Multidistrict Litigation to consolidate four separate lawsuits into a single case in the District Court for the Southern District of New York.¹⁵⁵ There, litigation involving the '365 patent continued,¹⁵⁶ with the district court rejecting infringement by Mylan's generic buspirone of the '365 patent.¹⁵⁷ 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."¹⁵⁸ Next, after reviewing the prosecution history of the '365 patent, the court decisively rejected Bristol-Myers' assertion that the patent claim covered buspirone:

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. . . . [A]ccordingly, Bristol-Myers cannot now reasonably assert a claim for

154. *Id.* at 29. On appeal, the Court of Appeals for the Federal Circuit reversed the grant of preliminary injunction on grounds unrelated to claim construction or patent infringement. *Mylan Pharms., Inc. v. Thompson*, 268 F.3d 1323, 1329-33 (Fed. Cir. 2001).

155. *In re Buspirone Patent Litig.*, 185 F. Supp. 2d 340 (S.D.N.Y. 2002), *judgment entered*, No. MDL 1413, 2003 U.S. Dist. LEXIS 26538 (S.D.N.Y. April 11, 2003).

156. The *In re Buspirone* 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 buspirone. *See generally*, Tim Meade, *In re Buspirone 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, Comment, *Brand-Name Drug Manufacturers Risk Antitrust Violations by Slowing Generic Production Through Patent Layering*, 33 SETON HALL L. REV. 479 (2003).

157. *In re Buspirone*, 185 F. Supp. 2d at 363.

158. *Id.* at 353 (citing U.S. Patent No. 6,150,365 col. 16 (filed June 6, 2000)).

the use of buspirone. Hence, the '365 Patent does not cover any uses of buspirone.¹⁵⁹

Finally, the court held that if the '365 patent claim were construed to cover the use of busiprone, as Bristol-Myers urged, then the claim would be anticipated based on 35 U.S.C. § 102(b) because busiprone had been sold as a treatment for anxiety and its use for treating anxiety had been both published and public at least one year prior to the earliest priority date of the '365 patent.¹⁶⁰ Furthermore, the court rejected BMS's proposed claim construction because if 6-hydroxy-busiprone 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-busiprone metabolite.¹⁶¹ Thus, the court concluded that a narrow claim construction, which included use of 6-hydroxy-busiprone *per se* but excluded use of busiprone, would be required to avoid invalidity of the claim.¹⁶²

5. *Novartis Pharmaceuticals Corp. v. Eon Labs Manufacturing Inc.*

Novartis Pharmaceuticals Corporation and allied companies owned U.S. Patent No. 5,389,382 ('382 patent), which included claims directed to a hydrosol encapsulating the immunosuppressant drug cyclosporin.¹⁶³ 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.¹⁶⁴ 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."¹⁶⁵ The result was a mixture of water and tiny particles containing cyclosporin that can be absorbed more easily from a patient's digestive system.¹⁶⁶

Novartis sued Eon Labs Manufacturing, Inc. (Eon) in district court for infringing '382 patent claims, despite the fact that Eon's product was a capsule containing cyclosporin, ethanol, and no water.¹⁶⁷ Novartis ad-

159. *Id.* at 359 (internal citations omitted).

160. *Id.* at 359-63.

161. *Id.* at 362.

162. *Id.*

163. *Novartis Pharms. Corp. v. Eon Labs Mfg., Inc.*, 363 F.3d 1306, 1307 (Fed. Cir. 2004).

164. *Id.*

165. *Id.*

166. *Id.*

167. *Id.*

vanced 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.”¹⁶⁸ The district court granted Eon summary judgment of noninfringement, both literally or under the doctrine of equivalents, based 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.¹⁶⁹ Novartis appealed to the Federal Circuit.

A split Federal Circuit panel 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.”¹⁷⁰ The majority affirmed the grant of summary judgment of noninfringement.¹⁷¹

In arriving at its decision, the panel majority distinguished two previous decisions of the Federal Circuit involving *in vivo* conversion.¹⁷² It distinguished *Zenith* because the claim there involved a “specific chemical compound,” cefadroxil monohydrate, and the plain language of the claim

168. *Id.*

169. *Id.* at 1308.

170. *Id.* at 1312.

171. *Id.*

172. 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. *Novartis*, 363 F.3d at 1313–14. He also disagreed with the panel majority’s interpretation of “medicine” as “things made outside the body.” *Id.* at 1315. 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. . . . 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.

Id. at 1316. Interestingly, in none of the three cases cited here by Judge Clevenger did the Federal Circuit find infringement. 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.” *Id.* at 1309.

was clear and unambiguous.¹⁷³ Furthermore, the claim contained “no express or implied pre-ingestion limitation,” unlike the ’382 patent claims.¹⁷⁴ Next, the panel majority distinguished *Schering Corp. v. Geneva Pharmaceuticals, Inc.*¹⁷⁵ by noting that *Schering* involved inherent anticipation of a claim covering a metabolite that the parties specifically agreed was produced by *in vivo* conversion. Here, the majority noted, the parties disagreed about whether the product of *in vivo* conversion—the hydrosol—was covered by a ’382 patent claim.¹⁷⁶

6. Discussion

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:

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.¹⁷⁷

The distinction between addition of ethanol and generation of ethanol via “a natural occurring event” is particularly striking because the court imputed an element recited only in process claims 1-7 of the ’332 patent (that is, “incorporating . . . ethanol”)¹⁷⁸ to product claims 8–21 lacking that element.¹⁷⁹ It is this distinction between ethanol deliberately added to feed and ethanol generated in the feed *in situ* by a “natural occurring event” that determines the results of this case. 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 ex-

173. *Id.* at 1311.

174. *Id.*

175. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373 (Fed. Cir. 2003).

176. *Novartis*, 363 F.3d at 1311-12.

177. *Feed Serv. Corp. v. Kent Feeds, Inc.*, 528 F.2d 756, 764 (7th Cir. 1976) (emphasis added).

178. U.S. Patent No. 2,808,332 col.7 l.32-65 (filed Feb. 17, 1955).

179. ’332 Patent col.7 l.66, col.8 l.1-62.

cluding coverage of the same metabolites produced within the human body by *in vivo* conversion.

The courts in both *Marion Merrell v. Baker Norton* and *Mylan v. Thomas* found noninfringement based on a distinction between naturally occurring (by *in vivo* conversion) and synthetically produced metabolites. The court in *Marion Merrell v. Baker Norton* used various strands of evidence, including the specification's silence on *in vivo* conversion and the absurd implications of construing claims to cover products of *in vivo* conversion,¹⁸⁰ to support its conclusion that only "synthetically produced TAM" was covered by claims of the '129 patent, and, therefore, that terfenadine would not infringe.¹⁸¹ Similarly, the court in *In re Mylan* interpreted the '365 patent claim, covering administration of 6-hydroxy-buspirone, as likely to exclude 6-hydroxy-buspirone produced as a metabolite by *in vivo* conversion of its precursor drug, buspirone, and instead likely to cover only direct administration of the product.¹⁸²

In at least two separate cases, the courts have construed words or phrases narrowly to avoid a finding of infringement triggered by *in vitro* conversion. 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:

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.¹⁸³

180. *See Marion Merrell Dow Inc. v. Baker Norton Pharms., Inc.*, 948 F. Supp. 1050 at 1054. The court stated:

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 then 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.

Id.

181. *See Marion Merrell Dow Inc. v. Baker Norton Pharms., Inc.*, 948 F. Supp. 1050, 1054-55, 1057 (S.D. Fla. 1996).

182. *Mylan Pharms., Inc. v. Thompson*, 139 F. Supp. 2d 1, 22-26 (D.D.C. 2001).

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

In comparison, the majority in *Novartis v. Eon* construed the “hydro-sol” in claims of the ’382 patent to be “medicinal” in nature.¹⁸⁴ Consequently, the claims were interpreted to be “limited to a medicinal preparation consisting of a dispersion of solid particles in a liquid colloidal solution prepared outside the body.”¹⁸⁵ Thus, claim construction has been employed repeatedly to exclude from patent claims products of *in vivo* conversion that arise within the human body.

IV. THE PHYSIOLOGICAL STEPS DOCTRINE

Courts in the United States have repeatedly considered whether transformation of a drug via *in vivo* conversion into a metabolite can trigger infringement of patent claims covering the metabolite or methods of using the metabolite. A growing number of such infringement disputes have yielded final judgments, but not one of them found infringement.¹⁸⁶

Courts have employed diverse rationales to avoid finding infringement in *in vivo* conversion cases. At least one court has pointed to difficulties of obtaining sufficient evidence of infringing products from within the human body. Others have relied upon inherency (*i.e.*, inherent anticipation) 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. Other courts have interpreted as meaningful difference between “synthetic” and “natural” biochemicals. Still others have attributed significance to whether claimed medicinal substances are located inside or outside the body. The most parsimonious explanation for this diversity of rationales, but unanimity of findings of noninfringement, is a discomfort with the very idea that a product arising naturally within the body, or the activity of the body itself, can infringe, let alone be the sub-

184. *Novartis Pharms. Corp. v. Eon Labs Mfg., Inc.*, 363 F.3d 1306, 1310-11 (Fed. Cir. 2004).

185. *Id.* (defining medicinal preparation as “a preexisting product that is administered to treat disease and therefore must necessarily be prepared outside the body”).

186. In *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936 (Fed. Cir. 1992), two of norgestrel’s *in vivo* products, norgestrel and norgestrel acetate, 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 of infringement triggered by *in vivo* conversion of a product claimed in a patent. For expanded explanation see *supra* Section III.A.I.I.A.1. Another case, *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713 (N.D.W. Va. 2004), found infringement of a claim covering the antimicrobial compound levofloxacin; however, levofloxacin is the levorotatory enantiomer of a racemic mixture, and, once it enters the human body, though it is possible that it undergoes a physical separation from the dextrorotatory enantiomer, it does not undergo any change in chemical form.

ject matter of, a valid and enforceable patent claim. This Article offers a name for this explanation: the Physiological Steps Doctrine.

A. The European Equivalent

Europe endorses explicitly what American courts appear to endorse implicitly. European patent law expressly limits the patentability of inventions relating to the human body, including methods of medical surgery, therapy, and diagnosis. The European Patent Convention (EPC) Article 53(c) places limits on patentable subject matter related to biological entities, stating that “European patents shall not be granted in respect of: . . . methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body,” though it does add that “this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.”¹⁸⁷ EPC Article 52(4), which was replaced by Article 53(c), declares that such subject matter “shall not be regarded as inventions which are susceptible of industrial application.”¹⁸⁸ More specifically, section (1) of Rule 29 (“The human body and its elements”) of the Implementing Regulations to the Convention on the Grant of European Patents declares that “[t]he human body, at the various stages of its formation and development, and the simple discovery of one of its elements . . . cannot constitute patentable inventions.”¹⁸⁹

On the other hand, Rule 29(2) allows that “[a]n element isolated from the human body or otherwise produced by means of a technical process . . . may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.”¹⁹⁰ The Guidelines for Examination in the European Patent Office clarifies that “[s]uch an element is not a priori excluded from patentability since it is, for example, the result of technical processes used to identify, purify and classify it and to produce it outside the human body, techniques which human beings alone are capable of putting into practice and which nature is incapable of ac-

187. Convention on the Grant of European Patents, art. 53(c), Nov. 29, 2000, 2001 O.J.E.P.O. SPEC. ED. NO. 1 38 [hereinafter EPC 2000].

188. Convention on the Grant of European Patents, art. 52(4), Oct. 5, 1973, 1065 U.N.T.S. 255 [hereinafter EPC 1973].

189. Implementing Regulations to the Convention on the Grant of European Patents, pt. II, ch. V, R29 § 1 (Dec. 13, 2006), available at <http://www.epo.org/patents/law/legal-texts/html/epc/1973/e/ma2.html> [hereinafter Implementing Regulations].

190. *Id.* at § 2.

complishing itself.”¹⁹¹ Thus, the EPC recognizes a distinction between the patentability of chemical inventions practiced outside and inside the human body. An “element isolated from the human body”¹⁹² or “produce[d] . . . outside the human body”¹⁹³ may constitute patentable subject matter, but, by implication, an element not isolated from, or produced inside, the human body is unpatentable. Similarly, the World Trade Organization Agreement on Trade-Related Aspect of Intellectual Property offers very comparable provisions in Articles 27(2) and (3).¹⁹⁴

This patentability criterion is consistent with the Physiological Steps Doctrine, and with the *in vivo* conversion cases discussed above. It would thus appear that European patent law definitively encompasses a Physiological Steps Doctrine, in contrast with the implicit Physiological Steps Doctrine of U.S. patent law.

B. Within the United States

U.S. law offers no existing theory that can explain why no court has ultimately found infringement of a patent claim by a product or process of *in vivo* conversion. It is highly improbable that such a one-sided outcome has occurred merely by chance. If the odds of a patent owner obtaining a finding of infringement in an *in vivo* conversion case were even (that is, 50%), the unanimous result of *in vivo* conversion cases in failing to find infringement would be equivalent to flipping a coin ten times in a row, and getting heads every single time, a result whose odds are less than 0.01%. Based on such stark math, it would appear that courts are reluctant to allow the involuntary activity of a human body to trigger patent infringement. This suggests an unrecognized explanation 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.”¹⁹⁵ The Mental Steps Doctrine rendered unpatentable any patent claim to a process made up of purely mental steps.¹⁹⁶ In a famous

191. European Patent Office, *Guidelines for Examination in the EPO*, pt. C, ch. IV, § 3.2, available at http://www.epo.org/patents/law/legal-texts/html/guix/e/c_iv_3_2.htm (last updated Dec. 13, 2007) [hereinafter EPO Guidelines].

192. Implementing Regulations, *supra* note 189, at § 2.

193. EPO Guidelines, *supra* note 191.

194. Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C art. 27(2)-(3), 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) [hereinafter TRIPs Agreement].

195. 1 DONALD S. CHISUM, CHISUM ON PATENTS § 1.03[6] (2007).

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

statement of this rule, the court in *In re Abrams*, declared that “[i]t is self-evident that thought is not patentable.”¹⁹⁷

Patent law itself strongly suggests that 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, have been held not patentable.”¹⁹⁸ Human thought falls within at least two of these specific 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 result from natural human physiology, so are metabolites produced by the natural *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, the 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 particular intimations of this Physiological Steps Doctrine in the judicial decisions involving *in vivo* conversion.¹⁹⁹ The court’s opinion 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.²⁰⁰ In explaining why claims to sulphenamides themselves would be invalid, the court stated that “[b]y 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.’ ”²⁰¹ Despite the formal use of inherency doctrine as the rationale for its decision, the court classified 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 ex-

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

198. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

199. *See supra* Part III.

200. *In re Omeprazole Patent Litig.*, No. MDL 1291, 2001 WL 585534, at *1-2 (S.D.N.Y. May 31, 2001).

201. *Id.* at 12 (quoting *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999)).

planation of [the drug's] functioning," but they are unpatentable subject matter.

After finding claims 1 and 3 of the '233 patent invalid, the Federal Circuit in *Schering v. Geneva* stated that its conclusion on inherent anticipation "does not preclude patent protection for metabolites of known drugs."²⁰² 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."²⁰³ "[Naturally occurring] metabolites may not receive [patent] protection via compound claims . . . [because] [s]uch 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."²⁰⁴ 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."²⁰⁵ 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, adding further support for the existence of an unarticulated Physiological Steps Doctrine.

Thus, whether a court employs evidentiary rationales, inherency doctrine, or claim construction, the result is consistently and predictably the same: patent claims purporting to cover products of *in vivo* conversion are either invalid, unenforceable, or not infringing. Unlike explanations involving lack of evidence and inherency, the Physiological Steps Doctrine is consistent with the ultimate decisions in all conversion cases. The "natural occurring event" of *Feed Service v. Kent Feeds*,²⁰⁶ the "synthetically produced TAM" of *Marion Merrell v. Baker Norton*,²⁰⁷ the direct administration of 6-hydroxy-buspirone in *Mylan Pharms., Inc v. Thompson*,²⁰⁸ the externally administered "dose" in *In re Buspirone*,²⁰⁹ the unpatentability of metabolites produced within the human body by *in vivo* conversion

202. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003).

203. *Id.*

204. *Id.*

205. *Id.*

206. *Feed Serv. Corp. v. Kent Feeds, Inc.*, 528 F.2d 756, 764 (7th Cir. 1976).

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

208. *Mylan Pharms., Inc. v. Thompson*, 139 F. Supp. 2d 1, 23 (D.D.C. 2001).

209. *In re Buspirone Patent Litig.*, 185 F. Supp. 2d 340, 353 (S.D.N.Y. 2002).

of *In re Omeprazole*,²¹⁰ *Schering v. Geneva*'s rule that "[naturally occurring] metabolites may not receive [patent] protection via compound claims[.]"²¹¹ and *Novartis v. Eon*'s "limit[] to a medicinal preparation . . . outside the body"²¹² all suggest the existence of an implicit Physiological Steps Doctrine in U.S. patent law. Unlike explanations involving lack of evidence and inherency, the Physiological Steps Doctrine is consistent with the ultimate decisions in all *in vivo* conversion cases.²¹³

V. CONCLUSION

The unanimity of results in cases involving patent infringement triggered by *in vivo* conversion is striking. In fact, its very improbability suggests a common underlying explanation for why *in vivo* conversion does not ever seem to trigger patent infringement. Explanations based on inherency or a lack of evidence provide a satisfactory explanation for only a minority of *in vivo* cases. The Physiological Steps Doctrine, which suggests that products and processes of *in vivo* conversion are unpatentable subject matter under U.S. patent law, offers an explanation that spans all *in vivo* conversion cases. Though the rationales offered to explain the results in a number of *in vivo* conversion cases are suggestive, there are several advantages for a more explicit recognition of the Physiological Steps Doctrine. Consistent with much international, European, and U.S. patent law, the Physiological Steps Doctrine provides a theoretical underpinning to explain the results in cases involving products and processes 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 *in vivo* conversion cases. In addition, the Physiological Steps Doctrine increases the understanding of where inventions involving human beings, and the biological products and processes thereof, fit within the spectrum of patentable subject matter.

210. *In re Omeprazole Patent Litig.*, No. MDL 1291, 2001 WL 585534, at *12 (S.D.N.Y. May 31, 2001).

211. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003).

212. *Novartis Pharms. Corp. v. Eon Labs Mfg., Inc.*, 363 F.3d 1306, 1309-10 (Fed. Cir. 2004) (defining medicinal preparation as "a preexisting product that is administered to treat disease and therefore must necessarily be prepared outside the body").

213. Furthermore, an article by Prof. Dan Burk, entitled *Patenting Speech*, may even suggest a Constitutional justification for a Physiological Steps Doctrine. Burk writes that "there would seem to be profound First Amendment implications to the concept of infringement by 'thinking patented thoughts.'" Dan L. Burk, *Patenting Speech*, 79 TEX. L. REV. 99, 140 (2000). If thinking patented thoughts implicates the First Amendment, then surely involuntarily engaging in physiological processes, such as *in vivo* conversion, that trigger infringement would have equally profound Thirteenth Amendment implications.