United States District Court,
S.D. New York.

In re OMEPRAZOLE PATENT LITIGATION.

July 6, 2001.

Generic drug manufacturer moved for summary judgment of invalidity and non-infringement of certain patents for drugs for treatment of gastritis and peptic ulcer. The District Court, Jones, J., held that: (1) abstract of a small drug study not subject to peer review, presented at a symposium not open to the public, was not a "printed publication" which qualified as anticipating prior art invalidating patent claiming process for administration of omeprazole for the express purpose of treating helicobacter pylori (HP) infection; (2) certain claims for drug combination for the treatment of gastritis and peptic ulcer were invalid as anticipated; (3) because the sequence of administration of drug combination was an element of certain patent claims and was not revealed in the prior art, those claims were not anticipated; and (4) genuine issue of material fact existed as to whether generic drug manufacturer, which filed abbreviated new drug application (ANDA), intended to induce infringement of patented branded drug.

Motion granted in part and denied in part.

5,599,794, 5,629,305. Invalid.

ORDER

JONES**, District Judge.**

Pending before the Court is the motion of defendant Genpharm, Inc. ("Genpharm") pursuant to Fed.R.Civ.P. 56 for summary judgment of invalidity and non-infringement of U.S. Patent Nos. 5,599,794 ("the '794 patent"), 5,629,305 ("the '305 patent") and 5,093,342 ("the '342 patent").

Pursuant to 28 U.S.C. s. 1407, the Judicial Panel on Multidistrict Litigation consolidated for pre-trial purposes before this Court the patent infringement suits filed by Astra Aktiebolag, Aktiebolaget Hassle, KBI-E, Inc., KBI, Inc. and Astrazeneca, L.P. (collectively "Astra") in response to various pharmaceutical companies' requests for permission from the Food and Drug Administration (FDA) to market generic versions of Prilosec, Astra's highly profitable gastric acid inhibiting drug.

The infringement actions arise out of Abbreviated New Drug Applications ("ANDAs") filed by the defendants. The Drug Price Competition and Patent Term Restoration Act, Pub.L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. s. 355 and 35 U.S.C. s. 271(e) (1994)), also known as the Hatch-Waxman Act, amended the Federal Food, Drug, and Cosmetic Act ("FDCA"), Pub.L. No. 52-675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. s.s. 301-397 (1994)), to permit filing of an ANDA to expedite FDA approval of a generic version of a drug previously approved by the FDA. *See Bayer* AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1244 (Fed.Cir.2000). Under the Hatch-Waxman Act, an applicant may seek FDA approval to market a generic drug without undergoing the same expensive and time-consuming FDA approval process undergone by the maker of the branded version of the drug, often called the pioneer drug, by 1) demonstrating that the generic drug is the bioequivalent of the branded drug

and 2) certifying that manufacturing, marketing and selling the drug will not infringe the patent rights held by the patentee of the pioneer drug.

The holder of the New Drug Application for the pioneer drug lists all of its patents that claim the drug or a use of the drug in the book "New Drug Products With Therapeutic Equivalence Evaluations" (referred to as "the Orange Book") published by the FDA. In its ANDA, the generic applicant must certify one of the following four statements with respect to the patents listed under the pioneer drug in the Orange Book: no patent information has been filed (paragraph I certification), the patent has expired (paragraph II certification), the patent soon will expire on a specified date (paragraph III certification), or the patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug" covered by the ANDA (paragraph IV certification). *See* 21 U.S.C. s. 355(j)(2)(A)(vii)(I)-(IV).

The term of Astra's basic omeprazole patent covering the chemical formula for omeprazole and its administration for gastric acid inhibition, U.S. Patent No. 4,255,431 ("the '431 patent"), will expire on October 5, 2001. FN1 The '431 patent is not, however, the only patent Astra has listed for omeprazole in the Orange Book. The patents at issue on this motion were also listed, and have been referred to by the parties as the "method of treatment" patents. The '342 patent, which will expire in 2010, claims the use of omeprazole as an antimicrobial agent against H. Pylori bacteria. The '794 and '305 patents, which will expire in 2014, claim the use of omeprazole in combination with an antibiotic to treat H. Pylori infections.

FN1. U.S. Patent No. 4,255,431 expired on April 5, 2001. However, the FDA granted Astra a six-month pediatric exclusivity extension of the patent term pursuant to 21 U.S.C. s. 355a.

[1] Although no actual infringement has taken place because the defendants' omeprazole product has not been released in the market, 35 U.S.C. s. 271(e)(2)(A) "define[s] a new (and somewhat artificial) act of infringement for a very limited and technical purpose that relates only to certain drug applications." Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676, 110 S.Ct. 2683, 110 L.Ed.2d 605 (1990). Section 271(e)(2)(A) provides a patentee with a cause of action for patent infringement based solely upon the filing of an ANDA containing a paragraph IV certification implicating the plaintiff's patent rights. The artificial infringement arising by operation of law is an integral part of a statutory scheme designed to allow pharmaceutical manufacturers to market, and the public to purchase, generic drugs as soon as possible after the expiration of patents covering the pioneer drug. The infringement suit under s. 271(e)(2) permits the patentee, in this case Astra, "to challenge the certification-i.e. to assert inter alia that the commercial manufacture, use or sale of the new drug *would infringe* its patent." Glaxo, Inc. v. Boehringer Ingelheim Corp., 954 F.Supp. 469, 473 (D.Conn.1996) (emphasis added). The patentee's challenge to the certification provides the Court with a justiciable controversy, permitting it to efficiently resolve patent issues in advance of the generic drug's release.

Genpharm certified in its ANDA for generic omeprazole that the method of treatmentpatents are "invalid or will not be infringed by the manufacture, use, or sale" of its generic omeprazole. *See* 21 U.S.C. s. 355(j)(2)(A)(vii)(IV). Based on Genpharm's ANDA filing, Astra filed a patent infringement suit pursuant to 35 U.S.C. s. 271(e)(2)(A), alleging that the generic omeprazole for which Genpharm seeks approval would induce infringement of the method of treatment patents because it would be used by doctors and patients, both alone or in combination with an antibiotic, to treat infections of H. Pylori bacteria. At the close of consolidated discovery Genpharm filed the instant motion for summary judgment.

I.

Summary judgment may not be granted unless "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c); *see also*

Celotex Corp. v. Catrett, 477 U.S. 317, 322, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986); Gallo v. Prudential Residential Servs., Ltd. Partnership, 22 F.3d 1219, 1223 (2d Cir.1994). In determining whether summary judgment is appropriate, a court must resolve all ambiguities and draw all reasonable inferences against the moving party. *See* Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp., 475 U.S. 574, 587, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986) (citing United States v. Diebold, Inc., 369 U.S. 654, 655, 82 S.Ct. 993, 8 L.Ed.2d 176 (1962)). Summary judgment is improper if there is any evidence in the record from any source from which a reasonable inference could be drawn in favor of the nonmoving party. *See* Chambers v. TRM Copy Ctrs. Corp., 43 F.3d 29, 37 (2d Cir.1994). Because each claim of a patent is presumed valid, in considering a motion for summary judgment of invalidity the Court must consider the facts in view of the clear and convincing evidentiary burden placed on the moving party to demonstrate invalidity. *See* Monarch Knitting Machinery Corp. v. Sulzer Morat Gmbh, 139 F.3d 877, 880 (Fed.Cir.1998).

II.

Astra was granted U.S. Patent No. 4,255,431 in 1981. The patent claims a chemical compound called omeprazole and its administration for inhibiting gastric acid secretion. Astra's scientists had found that when a human ingested omeprazole, the enzyme responsible for gastric acid secretion in the stomach, H^+K^+ ATPase, was inhibited and gastric acid was reduced. Japanese scientists working with Astra in a joint research and development venture later discovered that omeprazole had not only antisecretory properties useful in reducing gastric acid, but also antimicrobial properties useful in suppressing H. Pylori, the bacteria associated with the development of most cases of gastritis and peptic ulcer. Astra sought and received patent protection for this claimed discovery in the form of the '342 patent.

Building on the '342 patent, Astra scientists in Sweden found that combining omeprazole with an acid-degradable antibiotic such as clarithromycin or erythromycin increased the bioavailability FN2 of those antibiotics, thereby increasing their effectiveness in suppressing H. Pylori. Astra sought and received patent protection in the form of the '794 and '305 patents for these combination therapies for treating H. Pylori. The '794 patent claims a combination of clarithromycin and omeprazole for the treatment of gastritis and peptic ulcer. The '305 patent's 19 claims cover more broadly the combination of a class of proton pump inhibitors, which includes but is not limited to omeprazole, and a class of acid-degradable antibacterial compounds, which includes but is not limited to clarythromycin. Although the '305 patent's claims are broader, the '305 and '794 patents share the same patent specification.

FN2. Increased bioavailability is characterized by a greater concentration of the drug in the body's blood plasma, making the drug more "available" to exert its intended effect.

[2] Genpharm seeks summary judgment declaring the '342, '794 and '305 patents invalid under 35 U.S.C. s. 102(b) as anticipated by prior art. The anticipation analysis comprises two steps. In the first step, the Court construes the content and scope of the claims of the patent at issue. In the second step, the Court compares the properly construed claims to the allegedly anticipating prior art. *See* Helifix Ltd. v. Blok-Lok, Ltd., 208 F.3d 1339, 1346 (Fed.Cir.2000). When a single prior art publication, published more than one year before the date a patent application was filed, discloses each and every element of the patent claim, either expressly or inherently, the claim is invalid. *See* In re Schreiber, 128 F.3d 1473, 1477 (Fed.Cir.1997); Verdegaal Bros. Inc. v. Union Oil Co., 814 F.2d 628, 631 (Fed.Cir.1987).

A. *Claim Construction and Validity of* the '342 Patent

The Court construes the claims of the patent according to the hierarchy of evidence articulated in Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed.Cir.1995), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996), looking first to the intrinsic evidence of the patent:

[T]he court has the power and obligation to construe as a matter of law the meaning of language used in the patent claim. As such, "[a] patent covers the invention or inventions which the court, in construing its provisions, decides that it describes and claims." ... "To ascertain the meaning of claims, we consider three sources: The claims, the specification, and the prosecution history."

52 F.3d at 979 (citations omitted). The '342 patent has only one claim:

1. A method for the treatment of Campylobacter infections comprising administering to a patient suffering therefrom an amount of [omeprazole] or a pharmaceutically acceptable salt thereof sufficient for the treatment of said infection.

U.S. Patent No. 5,093,342, col. 4. lines 63-67. The defendants argue that the preamble of the claim, "A method for the treatment of Campylobacter infections" is not a material claim limitation because it merely expresses the purpose of the invention. This argument misreads the Federal Circuit's holding in Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368 (Fed.Cir.2001), which the defendants cite to support their position. In that case, the Federal Circuit acknowledged that claim language reciting the purpose of a process can constitute a material limitation where the process is directed to a new use, but discarded the purpose language at issue as immaterial because the process was not directed to a new use. *See* id. at 1376 ("Bristol is correct that new uses of old processes may be patentable.... However, the claimed process here is not directed to a new use; it is the same use"). In this case, the '342 patent's claim and specification demonstrate that while the invention is comprised entirely of an old process, the administration of omeprazole, the old process is directed to a new use, the treatment of Campylobacter FN3 infections. If the Court were to read the preamble out of the claim, as the defendants urge, the remaining claim language "suffering therefrom" and "said infection" would have no referent and thus no meaning. The preamble language "A method for the treatment of Campylobacter infections" is therefore necessary to give "life, meaning and vitality" to the claim and constitutes a material limitation. *See* id. at 1373-74 (citing Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed.Cir.1999)).

FN3. Campylobacter is the name scientists formerly used to describe H. Pylori.

The parties also dispute the proper construction of the term "treatment." Astra argues that the term "treatment" of H. Pylori infection means "medical efforts undertaken to provide a health benefit" to persons with H. Pylori. Specifically, it argues that "treatment" does not require cure or eradication of H. Pylori, but it does require that the omeprazole be administered for the purpose of having some antimicrobial effect on an H. Pylori condition. The defendants dismiss this construction as an untenable "subjective intent" requirement, and argue that "treatment" means merely an antimicrobial effect resulting from the administration of omeprazole to an H. Pylori-infected person.

Defendants' proposed construction is too broad in light of the invention claimed by the patent.FN4 It is clear from all of the intrinsic evidence of the '342 patent that the claimed purpose of the administration of omeprazole, to treat H. Pylori infection, is the primary distinction over the prior art, and thus a material claim limitation. Within this context, the term "treatment" must be construed to reflect the purpose that animates the claim, and must therefore contain a limitation of purposeful directedness toward H. Pylori or an H. Pylori-associated condition. This limitation is essential to distinguish uses of omeprazole that are directed to a different purpose (and that are subject to prior patents, such as the '431 patent) but that would nonetheless have an incidental effect on any H. Pylori condition existing in the patient.

FN4. Presumably in an effort to invalidate the claim as anticipated by prior art, the defendants have offered a construction of the term "treatment" that is unwittingly self-defeating in the event the defendants, upon the imminent expiration of the '431 patent, intend to offer generic omeprazole for the purpose of suppressing gastric acid secretion. When omeprazole is administered for a purpose other than combatting H. Pylori, such

as inhibiting gastric acid secretion, the omeprazole still exerts an antimicrobial effect against H. Pylori in patients infected by the bacteria. If the Court were to accept the defendants' construction, one of the primary uses of omeprazole would be foreclosed because it would infringe the '342 patent.

Properly construed then, the '342 patent claims 1) the administration of omeprazole alone 2) for the express purpose of treating H. Pylori.

[3] In the second step of the anticipation analysis, the Court compares the properly construed claims against the allegedly anticipating prior art. However, the parties dispute whether the allegedly anticipating publication cited by Genpharm, Unge ISOP 1988, qualifies as prior art under s. 102(b), because they dispute whether it is a "printed publication" under the statutory definition of that term. The question of whether a document is a "printed publication" is a legal determination based on underlying issues of fact, and must be decided on a case-by-case basis. *See* In re Hall, 781 F.2d 897, 899 (Fed.Cir.1986). A document may be deemed a printed publication

upon a satisfactory showing that it has been disseminated or otherwise made available to the extent that persons interested and of ordinary skill in the subject matter or art, exercising reasonable diligence can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation.

In re Wyer, 655 F.2d 221, 226 (C.C.P.A.1981).

[4] [5] Astra notes that the document is an abstract of a small study not subject to peer review, was presented at a symposium not open to the public, and that "[t]he majority of such abstracts are never published as full manuscripts in reputable journals." Astra Opp. Memo. at 38; Astra Counterstmt. of Material Facts para.para. 341-342. Neither the document itself nor Genpharm's submissions on this motion reveal anything about the extent to which it was disseminated, either at the symposium or thereafter-Genpharm simply cites the standard for publication, without demonstrating how the Unge article satisfies it. *See* Genpharm Reply Memo. at 17. In light of Astra's direct challenge on the subject and Genpharm's burden of demonstrating anticipation by clear and convincing evidence, Genpharm's response is inadequate. Because the Court on the present factual record cannot say that the Unge article qualifies as anticipating prior art under s. 102(b), and the Unge article is the only allegedly invalidating prior art cited by Genpharm, its motion for summary judgment of invalidity of the '342 patent is denied. Further, should it ultimately be determined that the Unge abstract constitutes a publication under s. 102(b), genuine issues of material fact precluding summary judgment remain as to whether, among other things, the article would have disclosed to a practitioner skilled in the relevant art that omeprazole could have an antibacterial effect against H. Pylori.

B. ***Claim Construction and Validity of the '305 and*** '794 Patents

Genpharm argues that every limitation of the claims in the '794 patent and every limitation of the allegedly infringed claims FN5 in the '305 patent was expressly disclosed in two prior art publications published more than a year before Astra filed its applications for those patents: Petrino, et al., Omeprazole + *Claritromicin Treatment of Helicobacter Pylori Associated* Duodenal Ulcer, Gastroenterology, Vol. 100, No. 5 Part 2 May 1991, and Di Napoli, et al., *Antral* Gastritis *Improvement After Therapy of* Helicobacter Pylori Infection *with Omeprazole and Claritromicin,* The Italian Journal of Gastroenterology, Vol. 23 (supp.2) November 1991. Each article, Genpharm argues, discloses the combination of omeprazole, a proton pump inhibitor, with an acid degradable antibacterial compound, clarythromycin, to treat H. Pylori associated with duodenal ulcer and gastritis.FN6

FN5. Astra alleges that Genpharm will infringe claims 8, 9, and 16-18 of the '305 patent.

FN6. Astra argues that neither Petrino nor Di Napoli reveals anything beyond what was disclosed in the prior art source Astra presented to the patent examiner-Logan, et al., The Lancet, Vol. 340, 239 (1992), and that Genpharm's expert admits as much. *See* Astra Opp. Memo. at 43; Shelton Decl. Exh. 23 at 246:13-247:18. Astra then stresses that because it presented the Logan prior art to the patent examiner during the prosecution of the '794 and '305 patents and it is identical to the prior art cited by Genpharm, Genpharm bears an even heavier burden to demonstrate the invalidity of the patents because a patent examiner is regarded as skilled in the art and is presumed to do her job properly. *See* Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 447 (Fed.Cir.1986) ("when the prior art before the Court is the same as the prior art before the PTO, the burden on the party asserting invalidity is more difficult to meet.").

However, even without comparing the similarity of the publications, Genpharm correctly points out that little, if any, conclusion can be drawn from the examiner's consideration of the Logan publication. The Logan article was published on July 25, 1992, less than one year from the filing date of Astra's patent application on April 22, 1993, and therefore does not qualify as s. 102(b) prior art. *See* 35 U.S.C. s. 102(b). Accordingly, Astra cannot demonstrate, without engaging in unacceptable speculation, that the examiner even treated the Logan article as relevant prior art. The Court does not therefore impose a heavier burden on Genpharm to demonstrate the invalidity of the patents.
Astra argues that the Petrino and Di Napoli publications do not disclose two essential elements of the '305 and '794 patent claims: 1) stable eradication FN7 of H. Pylori bacteria and 2) increased bioavailability of the antibiotic. Genpharm does not dispute the meaning Astra ascribes to these patent terms, but argues that neither stable eradication nor increased bioavailability is a material limitation to the patents' claims or practice.

FN7. In its opposition brief, Astra argues that the Petrino and Di Napoli studies "[b]oth concern the use of omeprazole and clarithromycin, but neither showed much in the way of stable eradication," meaning neither article focused on the combination's efficacy rate for suppressing H. Pylori. Astra Opp. Memo. at 41.

The '794 patent's two claims are as follows:

1. A synergistic combination comprising from about 1-200 mg omeprazole or a pharmaceutically acceptable salt thereof and from about 250 mg to 10 g FN8 clarithromycin for the treatment of gastritis and peptic ulcer.

FN8. Although the original patent reads "10 mg," it was corrected on June 3, 1997 to read "10 g." *See* Shelton Decl. Exh. 9.

2. A method of orally administering an acid degradable antibiotic so as to increase its bioavailability comprising an effective amount of the synergistic combination of claim 1 to a human.
U.S. Patent No. 5,599,794, col. 14 lines 7-15.
[6] The Court agrees that "stable eradication" is not a material limitation. Nothing in the patents' claims or in any other source, intrinsic or extrinsic, demonstrates that "stable eradication" is an element of any of the '794 and '305 patent claims. Furthermore, even if stable eradication appeared expressly or implicitly in the patent's intrinsic or extrinsic evidence, the Court would not construe it as a material claim limitation. An expression of efficacy and intended result such as "stable eradication" does not constitute a material claim limitation where, as in this case, the expression does not result in a manipulative difference in the steps of the claimed practice. *See* Bristol-Myers Squibb Co., 246 F.3d at 1375-76 (construing "reducing hematologic toxicity" as expression of purpose or intended result immaterial to patent claim).

[7] Astra next argues that "the synergistic potentiation of the bioavailability of an acid degradable antibiotic"

is a limitation found in claims 1 and 2 of the '794 patent and claims 8 and 9 of the '305 patent. *See* Pl.'s Opp. Memo. at 43. Genpharm agrees that the term "synergistic" in those claims refers to the increased bioavailability of the antibiotic, but argues that "synergistic" is an expression of purpose or of intended result which is inherent in the patent practice, rather than a material claim limitation:

these terms simply describe a property of the combinations: that administration of the combinations at the recited dosages of omeprazole and an acid-degradable antibiotic will result in synergy, which in the context of these patents is an increased bioavailability of the antibiotic.

Defs.' Joint Claim Cnstr. Memo. at 16. Genpharm argues that the face of claim 2 of the '794 patent provides the strongest intrinsic evidence that increased bioavailability is an immaterial expression of intended result, because it reads "[a] method of orally administering an acid degradable antibiotic *so as to increase its bioavailability*." U.S. Patent No. 5,599,794, at col. 14 lines 12-16 (emphasis added). This statement in the preamble of claim 2 clearly supports Genpharm's position that "synergism" is simply the effect of combining omeprazole and clarithromycin. Furthermore, the only time "synergism" is expressly used in the shared patent specification, it refers to an improvement in results: "Thus, by combining the components of the present invention synergism of the antibacterial effect of antibiotic compounds is achieved resulting in an improved therapeutic efficiency." Id., at col. 2 lines 13-16 (emphasis added).

Astra's arguments for the materiality of the increased bioavailability limitation focus on the patents' prosecution histories, rather than on their claims or specification. Astra contends that the increased bioavailability limitation must be material to the claims because it was essential to the patent examiner's allowance of the claims. When the initial '794 patent application was filed, none of the claims expressly cited synergy or increased bioavailability. *See* Hovden Decl. Exh. 17, '794 patent file history at 29-30. In August of 1993, the Examiner rejected the application's 13 claims as unpatentable over the '342 patent and other background prior art. *See* id. at 64-66. Astra responded by explaining to the Examiner that none of the allegedly anticipating references disclosed the combination therapies claimed and the resulting increased bioavailability of the antibitiotic. *See* id. at 81, 86. The Examiner required Astra to select one omeprazole-antibiotic combination for prosecution of the '794 patent; Astra chose the combination of omeprazole and clarithromycin, eventually renumbered as claim 1 of the '794 patent. *See* id. at 141-43. The Examiner then set forth prior art separately disclosing omeprazole therapy for treating H. Pylori and erythromycin therapy for treating H. Pylori, and concluded that it would have been obvious to one skilled in the art to combine the two therapies to exploit their additive effect. *See* id. at 149-50. However, the Examiner noted "[a] showing of greater than additive effect would overcome this rejection." Id. at 150. Astra subsequently submitted test data and a declaration from Dr. Jan-Peter Idstrom detailing Astra's findings of a synergistic increase in the bioavailability of clarithromycin when co-administered with omeprazole. *See* id. at 154-183. Based on that submission, the Examiner allowed the '794 patent's two claims and the patent subsequently issued.

Astra prosecuted the '305 patent in similar fashion, filing it as a continuation of the '794 patent in order to seek coverage for other synergistic combination therapies. In the Examiner's Statement of Reasons for Allowance, he specifically noted:

The Declaration by Dr. Idstrom received July 15, 1996 demonstrates synergism between the proton pump inhibitor lansoprazole and the acid degradable macrolide antibiotic erythromycin in increasing the bioavailability of erythromycin and the treatment of gastritis and peptic ulcer caused by microbes such as H. Pylori.

Hovden Decl. Exh. 19, '305 Patent file history at 144.

Astra argues that the file history demonstrates that the increased bioavailability evidence was essential to establishing that the claimed combination therapies were patentable over the prior art and that therefore increased bioavailability necessarily constitutes a material claim limitation in the '794 and '305 patents.

Astra distinguishes *Bristol-Myers Squibb Co.,* arguing that in that case, the language construed as immaterial by the Court was voluntarily added by the patentee after the examiner allowed the claims, whereas in this case the examiner informed Astra that the demonstration of synergistic effect was a necessary precondition to allowance of the claims. *See* Astra Claim Constr. Memo. at 8-9, Bristol-Myers Squibb, 246 F.3d at 1374.

However, in response to the Examiner's challenge Astra added not only the synergy language, but also specific dosage ranges for the combinations, based on the bioavailability study described in the Idstrom declaration. *See* Hovden Decl. Exh. 17, '794 file history at 157. Genpharm argues, and the Court agrees, that the dosage ranges, rather than any language describing their intended effect, were necessary to the allowance of the claims. *See* Defs.' Claim Cnstr. Memo. at 19-20. Merely inserting the word "synergistic" without substantiating the description would be insufficient to distinguish the prior art; the Court therefore presumes that the demonstrated synergistic effect of combinations in the claimed dosage ranges constituted the material addition to the patent claim traversing the Examiner's obviousness rejection. It follows that while the dosage ranges are a material element of the claim, any language explicitly expressing the synergism inherent in the combinations at those dosage ranges is not material or limiting, because the expressions "synergistic" and "increased bioavailability" "[do] not result in a manipulative difference in the steps of the claim." Bristol-Myers Squibb, 246 F.3d at 1376.

As a result, the combinations, the dosage ranges and the uses of the inventions are the only material limitations of the allegedly infringed claims of the '794 and '305 patents. The '794 patent thus claims 1) the combination of omeprazole and clarithromycin 2) within the claimed dosage ranges 3) administered to a human to combat gastritis and peptic ulcer.

1. *Comparison of* the '794 Patent ***and Prior Art***

Petrino described the aim of his research as "to test a new drug association [omeprazole + clarithromycin] for the treatment of Helicobacter Pylori (HP) Infection," the same combination therapy claimed in claim 1 of the '794 patent. Astra's expert testified that the dosages given to the patients in the Petrino study were within the dosage ranges claimed in the '794 patent. *See* Shelton Decl. Exh. 42, Czinn Depo. Tr. at 160-171. The use in the Petrino study, combatting H. Pylori, is the same as that claimed by the '342 patent. *See* U.S. Patent No. 5,093,342 at col. 1 lines 22-23 "[t]his application is specifically directed to the treatment of infections caused by Campylobacter Pylori." Petrino concluded "[t]hese results suggest that Omeprazole and Claritromicin can be an effective and well tolerated therapy against HP infection."

[8] [9] Astra argues that the most significant distinction between the '794 patent and the Petrino study is that Petrino did not explicitly demonstrate increased bioavailability. While Astra may be correct,FN9 the assertion is irrelevant. Newly discovered results of known processes directed to the same purpose are inherent and unpatentable. *See* Bristol-Myers Squibb Co. 246 F.3d at 1376 (citing In re May, 574 F.2d 1082, 1090 (C.C.P.A.1978)). In the '794 patent, Astra has attempted to patent an old process disclosed by Petrino-the combination of omeprazole and clarithromycin-applied to the same use as Petrino-the suppression of H. Pylori infections. As such, any newly discovered synergy or increased bioavailability resultingfrom the application of that combination for that purpose is inherent FN10 in the Petrino art and does not render Astra's claims patentably distinguishable over Petrino. Every element of the claims of the '794 patent is therefore disclosed in the Petrino prior art and the patent is invalid under 35 U.S.C. s. 102(b) as anticipated.FN11

FN9. Genpharm's expert witness, as well as expert witnesses for Cheminor and Andrx, defendants whose cases were also consolidated before this Court, testified that the Petrino and Di Napoli prior art does not expressly disclose increased bioavailability of antibiotics when used in combination with omeprazole. *See* Shelton Decl. Exh. 18 at 201:18-202:10; *id.,* Exh. 19 at 189:16-19; *id.,* Exh. 41 at 150:4-21.

FN10. There is no genuine dispute that increased antibiotic bioavailability has been documented and is expected when the antibiotic is used in combination therapy with omeprazole. For example, one of Astra's research scientists, Hans Christer Cederberg, testified as follows:
Q: ... was it always the case that omeprazole administered together with clarithromycin led to an increased plasma concentration of clarithromycin?
A: As I can recall it, yes.

Decl. of Christian Smolizza, Exh. 16 at 215:4-18. Astra's expert gastroenterologist, Stephen Czinn, testified that combinations within the ranges of 1 to 200 milligrams of omeprazole and 250 milligrams and 10 grams of clarithromycin would produce a synergistic effect. *See* Hovden Decl. Exh. 21 at 163:19-24; *see also id*. at 164:7-16 ("[t]he data there does show increased bioavailability, and again, it's reasonable to assume that the combinations within those ranges will also give that increased bioavailability."); Hovden Decl. Exh. 40 at 383:16-25 ("[o]ne of skill in the art would understand ... that the combination results in increased bioavailability of the acid degradable antibiotic.").
FN11. Astra argues at length that the Petrino article did not address bioavailability at all, let alone disclose a synergistic increase in bioavailability. To the extent that Astra is arguing that the Petrino prior art was not sufficiently enabling to anticipate, the argument is rejected. Although Petrino did not observe a synergistic increase in bioavailability, the Court has determined that the claims only require the administration of specific amounts of omeprazole and clarithromycin. Petrino performed all of the claimed steps at dosage levels that anticipate those in the claims. Petrino thus enabled the performance of those steps, even if he did not observe a synergistic outcome. *See* Bristol-Myers Squibb, 246 F.3d at 1380.

2. *Comparison of* the '305 Patent ***and Prior Art***

Astra alleges that Genpharm will infringe claims 8, 9, and 16-18 of the '305 Patent. Claim 8 of the '305 Patent claims

8. A synergistic pharmaceutical combination of a therapeutic amount ranging from about 1-200 mg of proton pump inhibiting compound or salt thereof, which increases intragastric pH; and a therapeutic amount ranging from about 250 mg to 10 g of an acid degradable antibacterial compound for the treatment of gastritis and peptic ulcer.

U.S. Patent No. 5,629,305 at col. 14 lines 3-8. Petrino discloses the combination of 20 mg of omeprazole with 250mg clarithromycin, dosages within the ranges described in claim 8. As discussed above, the fact that Petrino did not expressly disclose the synergistic effect of the combination is irrelevant because the synergy claimed by Astra is inherent in the combination at the claimed dosage ranges. Astra's expert Dr. Czinn testified that omeprazole is a proton pump inhibitor and that clarithromycin is an acid degradable antibacterial compound. *See* Hovden Decl. Exh. 21, Czinn Depo. Tr. at 169:4-170:18. Petrino noted that duodenal ulcer was healed in all cases; Czinn testified that duodenal ulcer is a peptic ulcer. *See* id. at 167:16-22. DiNapoli combined clarithromycin and omeprazole at the same dosages and found "significant improvement of associated gastritis, cured in our eradicated cases." Therefore all of the material limitations of claim 8 are contained in each prior art source, and the claim is invalid as anticipated.

[10] Claim 9 claims "[t]he synergistic pharmaceutical combination according to claim 8 wherein the acid degradable antibacterial compound is selected from the group consisting of a penicillin and a macrolide."*See* U.S. Patent no. 5,629,305 at col. 14 lines 8-11. Petrino and DiNapoli both disclose clarithromycin, which Dr. Czinn testified is a macrolide. *See* Czinn Expert Rpt. at 22. All of the material limitations of claim 9 are therefore contained in each prior art source, and the claim is therefore anticipated.

[11] Claims 16 through 18 claim a method of administration of a proton pump inhibitor before or

concomitantly with an acid degradable antibacterial compound. Astra argues that even if Petrino and DiNapoli disclose the relevant combination, neither discloses the sequence of administration. Genpharm does not argue on reply either that the sequence of administration is disclosed in Petrino and DiNapoli or that the sequence of administration is not a material limitation in the claim. Becuase the sequence of administration is an element of claims 16-18 and is not revealed in the prior art, those claims are not anticipated.

Accordingly, Genpharm's motion for summary judgment of invalidity of claims 1 and 2 of the '794 patent and claims 8 and 9 of the '305 patent is granted; its motion for summary of invalidity of claim 1 of the '342 patent and claims 16-18 of the '305 patent is denied.

III.

Genpharm has also moved for summary judgment on Astra's claims that Genpharm will induce and contribute to the infringement of the method of treatment patents. Astra contends that Genpharm's generic omeprazole will be substituted freely by doctors and patients for Astra's Prilosec for the treatment of H. Pylori both alone as a monotherapy and in combination therapy with acid-degradable antibiotics.

[12] "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. s. 271(b). In order to demonstrate inducement of infringement under s. 271(b), the patent holder must demonstrate 1) direct infringement of the patent and 2) proof of the defendant's actual intent to cause the acts which constitute the infringement. *See* Met-Coil Systems Corp. v. Korners Unlimited, Inc., 803 F.2d 684, 687 (Fed.Cir.1986); Water Technologies v. Calco, Ltd., 850 F.2d 660, 668 (Fed.Cir.1988).

[13] Genpharm first argues that since there has been no direct infringement in this case, there can be no claim for inducement of infringement. While Genpharm is correct that there has been no conventional infringement in this case, the inquiry in an infringement claim brought in response to an ANDA filing is properly directed not to what has happened, but rather to what will happen, that is, whether "the commercial manufacture, use or sale of the new drug *would infringe*" the plaintiff's patent. Glaxo, Inc. v. Boehringer Ingelheim Corp., 954 F.Supp. at 473 (emphasis added). As with the direct infringement inquiry under s. 271(e)(2), the inquiry in an indirect infringement claim such as induced infringement brought in response to an ANDA filing is also properly directed to what will happen, rather than to what has happened. *See* Warner-Lambert Co. v. Apotex, Corp., No. 98-4293, 1999 WL 259946, at (N.D.Ill. April 8, 1999) ("in support of a suit brought under section 271(e)(2), a patent owner may rely on the theory that the commercial manufacture, use, or sale of a drug claimed in a patent or the use of which is claimed in a patent *will actively induce the infringement* of the owner's patent.") (emphasis added); Marion Merrell Dow Inc. v. Baker Norton Pharmaceuticals, Inc., 948 F.Supp. 1050, 1053 (S.D.Fl.1996) ("MMD argues that ... when a patient takes the Baker Norton product, his or her liver will necessarily produce TAM. Therefore, Baker Norton *will induce infringement* in patients taking its product") (emphasis added).

Astra has presented evidence tending to show the following: 1) almost all patients with gastritis or peptic ulcer disease are infected with H. Pylori; 2) medical experts agree that H. Pylori should be treated, and 3) omeprazole is widely used today in treating H. Pylori infections associated with gastrointestinal disorders, particularly in combination therapy with antibiotics such as clarithromycin. *See* Astra Opp. Memo. at 11-13 and Exhs. thereto. Genpharm's own experts admitted that they have used Astra's Prilosec in combination with clarithromycin to treat H. Pylori. *See* Shaw Depo. Tr. at 83:11-84:15; Kornbluth Depo. Tr. at 112:9-113:3. When asked whether Genpharm's generic omeprazole, if approved, would be used to treat H. Pylori infections, Dr. Robert Shaw, one of Genpharm's experts testified "I think it's reasonable to speculate that it could be used for that and it may be used for that." Shelton Decl. Exh. 23, Shaw Depo. Tr. at 318:10-318:15. When asked if omeprazole would be so used in combination with clarithromycin, he testified "I once again say that it is the same functional entity and it's plausible someone could use it in that way." *Id.* at 319:3-319:13. Arthur Kornbluth, another of Genpharm's experts, testified:

Q: If Genpharm's generic omeprazole product is approved, will it be used to treat H. Pylori?

A: It might be part of a multi-drug regimen to treat H. Pylori. That would be my assumption.

Q: You would expect that to happen?

A: Yes.

Q: Will it be used to treat H. Pylori-associated gastritis?

A: I imagine that would be among the many indications whereby it would be used.

Q: And will it be used to treat H. Pylori-associated peptic ulcer disease?

A: I would assume it would be, yes.

Id., Exh. 17, Kornbluth Depo. Tr. at 111:18-112:8.

Astra has also noted that the substitution of an FDA-approved generic drug for its more expensive branded counterpart is not only common, but is in some circumstances mandated by state law. *See* Shelton Decl. Exh. 22 (surveying relevant state laws). Accordingly, Astra has presented circumstantial evidence that Genpharm's generic omeprazole will be used to infringe the method of treatment patents, while Genpharm has offered little in opposition except simple denials. Astra's circumstantial showing of direct infringement is sufficient to survive Genpharm's motion for summary judgment. *See, e.g.,* Snuba Int'l, Inc. v. Dolphin World, Inc., No. 99-1357, 2000 WL 961363, at (Fed.Cir. July 11, 2000) ("[a]lthough Snuba's evidence regarding actual use by Dolphin World's customers is entirely circumstantial, Dolphin World offered no evidence to contradict the only reasonable conclusion to be drawn therefrom").

However, in order to survive summary judgment, Astra must not only demonstrate that direct infringement of the method of treatment patents will occur, but also proof of actual intent on the part of Genpharm to induce infringement. *See* Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1469 (Fed.Cir.1990). Because it is rarely possible to present direct evidence of a party's intent, intent may be proved by circumstantial evidence. *See* Drexelbrook Controls, Inc. v. Magnetrol Int'l, Inc., 720 F.Supp. 397, 407 (D.Del.1989) ("[t]he requisite intent may be inferred from all the circumstances."), *aff'd,* 904 F.2d 45 (Fed.Cir.1990).

[14] The spectrum of acts potentially demonstrating the requisite intent for inducinginfringement is broad. Many courts agree that designing a product to infringe and advertising and providing instructions for use of a device in an infringing manner may also constitute sufficient circumstantial evidence to establish actual intent for an inducement claim. *See, e.g.,* Applied Biosystems, Inc. v. Cruachem, Ltd., 772 F.Supp. 1458, 1466-67 (D.Del.1991) ("[A] cause of action for inducing patent infringement arises out of advertising."). However, advertising and instructions to customers are not a prerequisite to establish intent. *See* Mendenhall v. Astec Indus., Inc., 887 F.2d 1094 (Fed.Cir.1989) (absence of direct instruction on infringement to customers, even if proved, does not foreclose finding of active inducement where the intended use of products would be readily apparent to the customer).

[15] Although both parties have offered conclusions from the circumstantial evidence presented, intent is a fact question particularly appropriate for resolution by a jury. *See* Oak Indus., Inc. v. Zenith Electronics Corp., 726 F.Supp. 1525, 1543 (N.D.Ill.1989) ("The determination of intent is a question of fact which should be decided by a jury."); Water Techs. Corp. v. Calco, Ltd., 850 F.2d 660, 669 (Fed.Cir.1998) ("[i]ntent is a factual determination particularly within the province of the trier of fact."). Genpharm has not

established on the present record that no reasonable juror could conclude that Genpharm intends to induce its customers to infringe Astra's patents. Genpharm's motion for summary judgment on Astra's claim that Genpharm's generic omeprazole will induce infringement of the method of treatment patents is therefore denied.

Astra also argues that Genpharm's generic omeprazole will contribute to the infringement of the method of treatment patents in violation of 35 U.S.C. s. 271(c). Section 271(c) provides that:

Whoever sells a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

35 U.S.C. s. 271(c).

However, Astra did not plead the elements of contributory infringement in the method of treatment claims of either of the complaints filed against Genpharm, while it did specifically plead them in the other patent claims. *Compare* Astra Cmplt. para.para. 18, 28, 39 and 74 *with id*. para.para. 47, 55, and 63. Astra used the same language in its Complaint against Cheminor, another generic manufacturer, and answered in a contention interrogatory that it was not alleging contributory infringement against Cheminor. *See* Decl. of Christian Smolizza, Exh. 8 at 35.

Astra's pleadings did not therefore put Genpharm on notice that Astra sought to assert a contributory infringement claim with respect to the method of treatment patents. Permitting Astra to add such a claim in its reply brief at this stage of the proceedings would unduly prejudice Genpharm in violation of Fed.R.Civ.P. 15, and the Court declines to so amend Astra's pleading.

Conclusion

Genpharm's motion for summary judgment of invalidity is granted as to claims 1 and 2 of the '794 patent and claim 8 and 9 of the '305 patent and is otherwise denied. Genpharm's motion for summary judgment on Astra's claim for inducement of infringement is denied.

SO ORDERED.

S.D.N.Y.,2001.
In re Omeprazole Patent litigation

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