IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY LTD. and TAP PHARMACEUTICAL PRODUCTS INC.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 06-033-SLR
TEVA PHARMACEUTICALS USA INC.,	)	
Defendant.	)	

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OPINION

Dated: March 31, 2008
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA")[1] by Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively, "Teva") to market a generic version of the antibacterial drug PREVACID® proprietary to Takeda Pharmaceutical Company, Ltd. ("Takeda") and exclusive licensee TAP Pharmaceutical Products Inc. ("TAP") (collectively, "Takeda"). The active ingredient in PREVACID® is lansoprazole, which is protected by, inter alia, U.S. Patent Nos. 4,628,098 ("the '098 patent") and 5,045,321 ("the '321 patent"). Upon receiving notification of the filing of Teva's ANDA, Takeda brought this suit for infringement of the '098 and '321 patents pursuant to 35 U.S.C. § 271(e)(2)(A).[2] (D.I. 1)[3] Teva concedes that its generic drug infringes the '098 patent. (D.I. 146 at ¶ 31) The parties previously submitted their memoranda on claim construction to the court. From October 29 to November 6, 2007, a bench trial was held on Takeda's claim that Teva infringes the '321 patent, and Teva's defenses and counterclaims that the '098 and '321 patents are invalid and/or unenforceable due to obviousness and inequitable conduct. The issues were fully briefed post-trial. The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the

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[1]No. 77-255.

[2]"(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

[3]Suit was originally brought under five of Takeda's patents; only two remained at issue at the time of trial.

court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Parties

1. Takeda is a Japanese corporation with a principal place of business in Okasa, Japan. (D.I. 1 at ¶ 1) TAP is a Delaware corporation with a principal place of business in Lake Forest, Illinois. (Id. at ¶ 2) Takeda and TAP are involved in the research, development and marketing of pharmaceutical products. (Id. at ¶¶ 1,2)

2. Teva is a Delaware corporation having its principal place of business in North Wales, Pennsylvania. (Id. at ¶ 3) Teva is also involved in research, development and marketing of pharmaceutical drugs. (Id.)

B. The Patents and Technology at Issue

3. This case involves the proprietary compound lansoprazole, a particular benzimidazole, which is a member of a class of drugs known as proton-pump inhibitors, or "PPI"s. PPIs prevent parietal stomach cells from pumping acid into the gastrointestinal tract, and relieve symptoms of several common debilitating diseases such as duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome and erosive esophagitis.

4. Takeda's '098 patent, issued December 9, 1986, claims the lansoprazole compound itself. It expires on May 10, 2009.

5. Despite its pharmaceutical potential, lansoprazole is unstable under a variety of conditions, and degrades in the presence of acid, such as occurs naturally in the

stomach, other ingredients commonly used in pharmaceutical compositions, heat, moisture, and light. Takeda scientists solved these degradation problems by discovering that certain basic inorganic salts of magnesium and calcium, in particular, magnesium carbonate ($MgCo_3$), stabilize lansoprazole. Takeda was awarded the '321 patent claiming, inter alia, the combination of lansoprazole and magnesium carbonate, on September 3, 1991. The '321 patent is set to expire on September 3, 2008.

5. PREVACID® is Takeda's commercial lansoprazole product.

6. Teva's proposed generic drug product is a capsule containing multilayer enteric-coated granules. These granules are made of four layers, applied atop a sugar core. Each layer is applied by a separate manufacturing step via spraying on a dispersion. The first dispersion contains lansoprazole, talc, and hypromellose dispersed in a solution of water and ammonia. The second dispersion contains a small amount of hypromellose and talc dispersed in water. The third dispersion contains hypromellose and magnesium carbonate. The fourth dispersion contains the enteric coating agent. (DTX-056; PTX-445A at 6853) Each layer is dried before application of the next layer. (DTX-056 at 6856-99) Teva's ANDA requires that water make up no more than 5.0% of its final product; testing demonstrated that water comprises 1.1% of the final product. (PTX-445A at 7761; D.I. 168 at 465:3-11)

7. Claim 1 of the '321 patent reads as follows:

> 1. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of the anti-ulcer compound 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl]methylsulfinyl] benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate

> aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.
>
> Claim 2 depends from claim 1, and reads:
>
> 2. A pharmaceutical composition as claimed in claim 1, wherein the basic inorganic salt of magnesium is magnesium carbonate.

Takeda asserts that Teva's proposed generic drug product infringes claim 2 of the '321 patent.

C. '321 Patent: The Intrinsic Record

8. The '321 patent discloses a physically stable benzimidazole composition. The prior art recognized that benzimidazole compounds could be stabilized by converting benzimidazole into its salt form. (Col. 1, l. 60 - col. 2, l. 2) In contrast, the invention provides for the incorporation of a basic inorganic salt of magnesium or calcium with the benzimidazole. The specification provides that

> [t]he composition of the invention is prepared by **homogeneously admixing** the above benzimidazole compound, the basic inorganic salt of magnesium and/or basic inorganic salt of calcium, and the above additives.

(Col. 9, ll. 45-48) (emphasis added)

> The **method of admixing is optional** if the benzimidazole compound can finally be in contact with the basic inorganic salt of magnesium and/or of calcium **evenly**. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound and the basic inorganic salt of magnesium and/or calcium as prepared by preliminary admixing, or the basic inorganic salt of magnesium and/or of calcium may be added to a mixture of the benzimidazole compound and the additives as prepared by preliminary admixing.

(Col. 9, ll. 56-66) (emphasis added)

9. The specification further provides for a method by which tablets and granules

can be produced by a conventional method.

> [F]or example, tablets are produced by adding the basic inorganic salt of magnesium and/or of calcium to a mixture of the benzimidazole compound, vehicle and disintegrant, mixing, adding a binder, granulating the mixture, adding a lubricant etc. and tableting the resultant granular composition. Granules are produced by extrusion in approximately the same manner as in the production of tablets or by coating nonpareils, which contain sucrose and corn starch, with a mixture of benzimidazole compound, a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and additives (e.g. sucrose, corn starch, crystalline cellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone). Capsules are produced by mere mixing and filling.

(Col. 10, ll. 19-34)

10. Examples 1-4 describe compounds made whereby the components were "mixed together"; no specific time or provisions are provided regarding what may constitute "sufficient admixing." (Col. 12, l. 59 & ll. 61-61; col. 13, l. 27) Examples 5-7 describe compositions formed whereby the ingredients were "mixed well" (col. 13, l. 54); example 8 describes the ingredients being "thoroughly mixed together" (col. 14, l. 47).

11. The '321 patent was filed as application no. 14,303 ("the '303 application"). The '303 application was rejected by the examiner and ultimately allowed after an appeal to the commissioner.

12. Original claim 1 of the '303 application claimed a pharmaceutical composition comprising benzimidazole and a basic inorganic salt of magnesium and/or calcium. (PTX-4 at 739470) In response to the first office action, the applicants canceled claim 1 and inserted new claim 19 in its place; claim 19 required "the benzimidazole compound being in contact with the basic inorganic salt evenly." (Id. at 739670-71)

During prosecution, the '303 application was rejected as obvious in view of, inter alia, U.S. Patent No. 4,686,230 to Rainer et al. ("Rainer"). In response, the applicants admitted that Rainer disclosed the combination of benzimidazole compounds and magnesium carbonate, but argued that

> the reference makes no comment or suggestion on stabilization of the benzimidazole compounds by contacting with magnesium aluminate or any other basic inorganic salt of magnesium and calcium **evenly**. It should be noted that in Rainer et al., magnesium aluminate is contained in the pharmaceutical formulations as an antacid, and in such use as an antacid, the salt need not contact the benzimidazole compounds at all.

(Id. at 739674) (emphasis in original) The applicants explained that

> [t]he importance of the even distribution of the basic inorganic salt of the present compound is demonstrated by the experimental information presented herewith under 37 C.F.R. 1.132. The experiment follows the procedure of "Content Uniformity" as set forth by the United States Pharmacopeia, 21st revision, January 1, 1985. The criteria set forth in this standard reference demonstrates that an even or homogenous mixture is defined when each individual unit is within 6 percent of the relative standard deviation. In table 1 of the declaration, it is shown that when these guidelines are met, each individual unit will have an even contact between the benzimidazole compound and the included inorganic salt which leads to a stabilization not shown to be expected in the prior art.

(Id. at 739674-75) The applicants were not successful in obtaining allowance of the '303 application during regular prosecution, and appealed to the Commissioner. (Id. at 739711)

12. On appeal, the applicants again stressed that even distribution was a key distinguishing feature of their invention. (Id. at 739755) ("The present independent composition and method claims require that the benzimidazole derivatives be contacted **evenly** with a basic inorganic salt of magnesium or calcium. This serves to stabilize the benzimidazole derivatives and is not suggested by the combination of references relied on by the examiner.") (emphasis in original). The applicants again emphasized that

Rainer did not disclose such even contact, and that "[n]o evidence of record suggests why one of ordinary skill would infer that the Rainer et al. antacids should be mixed evenly with the benzimidazole derivatives." (Id.) The Commissioner disagreed, stating that applicants' "remarks regarding contact not being required in Rainer et al. do not obviate the rejection since components are routinely mixed in the art before tabletting." (Id. at 739776) On remand to the examiner (id. at 739823), the applicants characterized the question with respect to all of the cited prior art as not "whether the salts are known excipients, but rather whether it would have been obvious to mix the salt with the active ingredient so as to provide even contact with the active ingredient . . . [n]othing in [the prior art suggests] this claimed feature of even contact." (Id., ex. 13 at 739832) Following a hearing before the Board of Patent Appeals and Interferences, the examiner was reversed, and the '303 application issued as the '321 patent on September 3, 1991.

D. Claim Construction

13. The disputed claim language of the '321 patent, as identified by the above referenced parties, shall be construed consistent with the tenets of claim construction set forth by the Unites States Court of Appeals for the Federal Circuit in Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005), as follows:

a. "**A pharmaceutical composition**" means a medicinal drug product in a state suitable for administration to a patient.[4]

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[4]See Abbott Labs. v. Sandoz, Inc., No. Civ. A. 05-5373, 2007 WL 4287501, *5 (N.D. Ill. Dec. 4, 2007) (construing "pharmaceutical composition" in this manner consistent with its plain and ordinary meaning).

Teva's argument that the claimed "pharmaceutical composition" excludes any excipients used for coating the composition is an impermissable attempt to read process limitations into a product claim. See Vanguard Products Corp. v. Parker Hannifin Corp., 234 F.3d 1370, 1373 (Fed. Cir. 2000) ("The method of manufacture, even when cited as advantageous, does not of itself convert product claims into claims limited to a particular process."). Nowhere in the specification or the prosecution history was the term "pharmaceutical composition" expressly limited or redefined to mean something different from its ordinary meaning. That example 1 of the '321 patent describes mixing lansoprazole and magnesium in a separate manufacturing step, prior to formulation into a tablet or granule and the application of the excipient coating, is inconsequential absent such intrinsic evidence. See Teleflex, Inc. v. Ficosa North Am. Corp., 299 F.3d 1313, 1327 (Fed. Cir. 2002) ("[A]n accused infringer cannot overcome the "heavy presumption" that a claim term takes on its ordinary meaning simply by pointing to the preferred embodiment or other structures or steps disclosed in the specification or prosecution history.").

Teva notes that, during prosecution, claim 1 was amended from "a pharmaceutical composition, which comprises . . ." to "a pharmaceutical composition, wherein the composition is made up into tablets or granules and **then** coated by a coating agent, which comprises. . . ." (PTX-4 at 739684) (emphasis added) Just as "[t]he presence of acts recited in the claim does not transform a claim covering a thing . . . into one covering the process by which that thing is made,"[5] this recited sequence of

[5]In re Nuijten, 500 F.3d 1346, 1355 (Fed. Cir. 2007).

steps is, conversely, not properly interpreted as a narrowing limitation on the nature of the claimed product (described by the manufacturing steps) absent "words or expressions of manifest exclusion or restriction" indicating otherwise.[6] The claim at issue is a product-by-process claim. The "wherein" clause describes the pharmaceutical composition at least in part by the process in which it is made; the claim is, nevertheless, still directed to the ultimate product.[7] The court declines to limit the plain meaning of "pharmaceutical composition" absent more compelling intrinsic evidence.

b. A "**granule**" is a small pellet that is typically combined with other granules into a tablet or capsule.[8]

c. "**[C]oated by a coating agent**" means that the pharmaceutical composition has a pharmaceutically acceptable coating.

For the reasons discussed above, the court declines to read a sequential process limitation into claim 1, i.e., that a "pharmaceutical composition" must be made into tablets or granules before any coating occurs. In the context of the claim, "coated by a coating agent" describes a property of the claimed product, and does not limit the

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[6]Teleflex, 299 F.3d at 1327.

[7]SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, 1317 (Fed. Cir. 2006).

[8]Teva's proffered definition includes additional limitations regarding the shape of the granules and that they may also contain additives. (D.I. 132, ex. 2) (claim chart) Teva points to no intrinsic support for reading in such limitations. Teva concurrently states that the term "granule" does not require construction. (D.I. 140 at 8) The court construes "granule" in accordance with its plain and ordinary meaning.

scope of that claimed product to a process by which it is made.[9]

c. "**[T]he amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight**" refers to the total amounts of salt and benzimidazole in the pharmaceutical compound, without respect to whether these ingredients are in even contact. Claim 1 separately requires that the salt and benzimidazole are in contact evenly; importing this requirement here would render that limitation superfluous.

d. "**[T]he benzimidazole compound being in contact with the basic inorganic salt evenly**" means that the benzimidazole and inorganic salt are uniformly disbursed therein,[10] without respect to the actual proportion of the components.

The specification provides that the composition of the invention is "prepared by homogeneously admixing" the benzimidazole and inorganic salt, but that "[t]he method of admixing is optional" so long as the result is that the benzimidazole and inorganic salt is in contact "evenly." (col. 9, ll. 45-48, 56-59) Teva's proposed construction would require that the benzimidazole compound and inorganic salt be "mixed honogenously together." (D.I. 132, ex. 2) This construction impermissibly focuses on the process of

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[9]The specification provides that tablets and granules "may be" coated with a coating agent for the purpose of masking taste or providing enteric or sustained release properties. (Col. 10, ll. 3-6) This permissive, but not exclusive, language does not justify importing limitations that the coating material masks the taste or provides such properties, as Teva suggests. (D.I. 132, ex. 2 (claim chart))

[10]This construction is consistent with the applicants' statements during prosecution emphasizing the importance of the even distribution of the inorganic salt, with reference to the guidelines for "content uniformity" set forth in United States Pharmacopecia, 21st revision for achieving "even contact" between the two compounds. (PTX-4 at 739674-75)

admixing rather than the resultant mixture, i.e., impermissibly reads a process limitation into the claim.

The granules of Teva's proposed generic product are formulated by layering the lansoprazole and inorganic salt. Because these components are not admixed prior to being sprayed onto the granules in Teva's process, Takeda's proposed construction of "in contact . . . evenly" would require the mixture to be in "contact with the basic (i.e., alkaline) inorganic salt in a uniformly basic environment." (D.I. 132, ex. 2) Takeda's expert, Dr. Stephen R. Byrn, declares that "drug formulators in 1986 would have understood that 'contact' between two components in a formulation means that two solids are in close enough proximity to interact with each other." (D.I. 134 at ¶ 48) According to Dr. Byrn, skilled drugmakers would have connected this requirement of proximity, in addition to the disclosure that there is some water present in the composition of the invention (col. 9, ll. 54-56), to the concept that "the water is used as a vehicle for establishing a basic environment surrounding the lansoprazole." (D.I. 134 at ¶ 51) Takeda does not point to and, indeed, cannot point to any support in the specification or prosecution history for importing the requirement that the components exist in a "uniformly basic environment."[11] Accordingly, the court declines to permit the unjustified broadening of claim 1 as proposed by Takeda.

E. Infringement

1. "In contact . . . evenly"

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[11]Ironically, Takeda criticizes Teva's proposed construction on the ground that the claim term does not contain the words "mixed" or "homogenously," while their own proposed construction fares no better. (D.I. 141 at 4)

14. As discussed previously, Teva's manufacturing process involves spraying a series of four dispersions onto a sugar core. Each of the dispersions contains some amount of water. Takeda asserts that, because of this water, there is blending and intermixing of the components of each subcoat. In addition, the water and moisture retained by Teva's granules creates a uniformly basic environment, which effectuates "even" contact between the magnesium carbonate and lansoprazole. (D.I. 177 at 22)

15. Dr. Byrn asserts that the talc layer[12] of Teva's product granules does not keep the lansoprazole[13] and magnesium carbonate layers[14] separate, i.e., that the talc layer is permeable. (D.I. 166 at 137:0-139:12) In support, Dr. Byrn points to several Teva documents which acknowledge penetration of the talc layer. (Id. at 141:3-12; PTX-446B; PTX-446C) Dr. Byrn testified that he was unaware of a case where a subcoat of that thinness could be made to be impermeable. (D.I. 166 at 141:14-17; 143:10-18 (talc layer is "much too small, much too thin" to function as a subcoat))

16. Each party conducted its own testing of Teva's proposed product; the parties debate what was the more appropriate method. Both parties analyzed cross-sections of Teva's product granules in order to determine their composition. Takeda utilized Raman spectroscopy, a technique using unique vibrational signals to identify the type of molecules present in a sample. Teva utilized ToF-SIMS, short for "time of flight secondary ion mass spectrometry," where an ion beam is used to eject secondary ions

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[12]The second dispersion, also called the "Subcoat 1 Coating Dispersion."

[13]The first dispersion, also called the "Drug Coating Dispersion."

[14]The third dispersion, also called the "Subcoat 2 Coating Dispersion."

which are then used to identify the chemical composition of molecules. The Raman laser penetrated into Takeda's samples to a depth of 5.6 microns, and did not extend through the entire granule sample. (D.I. 172 at 1410:12-15)[15] Because ToF-SIMS has a greater spatial resolution than Raman (D.I. 167 at 254:11-12; 297:24-25), a smaller volume of sample was analyzed at one time; a penetration of only 0.001 microns was accomplished (D.I. 166 at 134:15). Takeda's expert, Dr. David Bugay, testified that a lansoprazole particle is about 10 microns in diameter, and magnesium carbonate ranges from 10-40 microns in diameter.[16] (Id. at 216:8-14) Therefore, under Takeda's characterization of the molecules, neither Raman nor ToF-SIMS can be used to identify molecules stacked atop one another; each can only detect the first molecule exposed by the cross-section.

17. Dr. Bugay collected Raman data from Teva's product granules using "line maps." The lines of analysis were divided into 12 separate "bins" that were 2 x 6 (x. 5.6) microns in size. (Id. at 210:11-211:1) Because the bin size is smaller than a lansoprazole or magnesium carbonate particle, the presence of both in the same bin indicates that the molecules are necessarily either touching or in extremely close proximity to each other. (Id. at 216:15-217:5) Dr. Bugay found the coexistence of lansoprazole and magnesium carbonate particles in several of the bins examined for

[15]Dr. Byrn testified that Raman penetrates into the granule "about 10 microns." (D.I. 166 at 126:11-12)

[16]Dr. Gerald Meyer, Teva's expert, testified that magnesium carbonate could be smaller. (D.I. 167 at 414:1-16)

each of five samples. (Id. at 217:6-23, PTX-408 (bins 1, 2, 3, 4, 5, 7, 10))[17] Takeda asserts that this touching and/or proximity constitutes "even contact" as per the claims due to the uniform basic environment in which the molecules are contained. (D.I. 163 at 34-35; D.I. 177 at 22)

18. Dr. Byrn testified regarding the amount of moisture and residual water present in Teva's product. Because the court does not adopt Takeda's claim construction, which would have incorporated a "uniform basic environment" limitation, it need not focus on this evidence. Rather, the court turns its attention to the evidence of record regarding the dispersion of lansoprazole and magnesium carbonate relative to each other.

19. Dr. Byrn did not opine that the lansoprazole and magnesium carbonate are distributed uniformly in Teva's product. (D.I. 166 at 168:18-21) Under his theory, there is a uniform basic environment throughout the granule, but he cannot quantify how much lansoprazole and magnesium carbonate are in any given location. (Id. at 168:22-169:2) Dr. Bugay confirmed that Takeda's techniques do not provide a quantification of how much mixing is present. (D.I. 167 at 256:10-257:17) The court agrees with Takeda that "in contact . . . evenly" does not include a quantitative requirement, though such quantitative evidence, in theory, could lend support to a theory of "even" distribution if accompanied by a relevant spacial analysis.

[17]Dr. Bugay testified that the results demonstrated in PTX-408 were consistent with those found in the other four series of experiments. (D.I. 166 at 217:8-23; see also PTX-413-14; PTX 433; PTX-926-27)

20. Teva's expert, Mr. Drew Hirt, utilized ToF-SIMS to analyze Teva's product.[18] A diamond knife was used to cross-section each pellet used for preparation, to help ensure that particles were not smeared between layers during cutting. (Id. at 309:4-15) ToF-SIMS is unable to distinguish between the magnesium present in talc and the magnesium present in magnesium carbonate. (Id. at 322:18-21) The presence of silicon, however, uniquely identifies the talc layer. (Id. at 322:25-323:2) A few of the ToF-SIMS images contained discrete smears of talc across the magnesium carbonate layer. (Id. at 338:19-339:4) Notwithstanding, Mr. Hirt opined that ToF-SIMS revealed distinct lansoprazole, talc and magnesium carbonate layers. (DTX-63-2; D.I. 167 at 321:17-323:20)

21. To further distinguish the magnesium present in the magnesium carbonate layer as compared to that present in talc, Mr. Hirt employed Raman spectroscopy,[19] which verified the existence of the magnesium carbonate layer. (Id. at 330:4-23) On cross-examination, Mr. Hirt acknowledged that several spectra contained some trace of both molecules. (e.g., id. at 351:12-352:7) Mr. Hirt testified that this was the result of the poor spacial resolution of Raman spectroscopy. (Id. at 358:9-15; 367:16-22 ("The fact that the species all are seen to be present in the same spectrum is not an indication of intermixing of layers, but a demonstration of the actual volume of sample that is being analyzed in Raman instruments."))

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[18]The ToF-SIMS analysis was performed at a third party laboratory, Evans Analytical Group, under Mr. Hirt's close supervision. (D.I. 167 at 311:2-312:10)

[19]Mr. Hirt designed the test, which was carried out by scientists at a third party laboratory, R.J. Lee Company. (D.I. 167 at 328:4-19)

22. Mr. Hirt also tested the samples using energy dispersive x-ray spectroscopy ("EDX" spectroscopy), which has a deep surface penetration, to verify the ToF-SIMS data. EDX also confirmed that Teva's product is layered. (DTX-63-4; DTX-63-5; D.I. 167 at 341:16-342:12) Because no smear lines were detected by EDX, Mr. Hirt opined that ToF-SIMS picked up on some particles loosened and distributed in the cutting process. (D.I. 167 at 338:21-341:14)

23. Dr. Bugay also performed EDX testing. He testified that the images created by Takeda's EDX show contact, physical touching and close proximity between the lansoprazole and magnesium carbonate in Teva's product, and that his results were consistent with Mr. Hirt's. (Id. at 232:8-23)

2. Discussion

24. The evidence demonstrates that, although Teva's product granules are layered,[20] lansoprazole and magnesium carbonate are touching in many areas, and are likely interspersed in some areas.[21] The presence of both molecules in the same region

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[20]The court notes that, with respect to Teva's evidence, Takeda's arguments that ToF-SIMS is an inappropriate testing method are not convincing. Dr. Bugay confirmed that ToF-SIMS is more precise than Raman spectroscopy, and is an appropriate technique for identifying the molecules on a surface sample. (D.I. 167 at 254:8-21; 264:24-265:3) This observation is confirmed by others in the art. (DTX-903 at 5626 ("Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is a powerful method for characterizing cross sections of drug dosage forms, allowing imaging with high spacial resolution and spectroscopy for molecular chemical identification."); DTX-904 at 252 ("The surface chemical imaging capabilities of ToF-SIMS provide new insight into drug distribution within solid dosage forms, offering significant improvements in spatial and elemental resolution over existing technologies. . . . ToF-SIMS provides an invaluable tool for formulation scientists, providing significant insight into drug and excipient distribution within a matrix."))

[21]Teva's expert, Dr. Walter Chambliss, stated on cross that "there may be some contact between the two ingredients." (D.I. 168 at 533:13-21) Dr. Meyer testified

of space is not dispositive, however, as to whether this proximity (or touching) constitutes "even" contact as per the claims. Contact, even where "substantial,"[22] is not necessarily even. On the present record, the court finds that it is at least as likely that the distribution of lansoprazole and magnesium carbonate in Teva's granules is not uniform; Takeda has not proven infringement by a preponderance of the evidence.

25. Takeda argues that, even under Teva's claim construction, Teva's product is a "homogenous mixture" as defined by the Content Uniformity Standard referenced in the prosecution history ("an even or homogenous mixture is defined when each individual unit is within 6 percent of the relative standard deviation"). (D.I. 177 at 23) Dr. Byrn testified that, according to Teva's ANDA, the amount of drug in each capsule averaged 99.3%, with a 1.7% relative standard deviation. (D.I. 166 at 145:6-146:10) The overall content of each drug capsule, however, does not bear on the question of whether the distribution of lansoprazole and magnesium carbonate is "even" as the claims require, especially in view of the fact that Teva's product granules are undisputably prepared by a series of dispersions rather than the pre-mixing of components.

26. Takeda's evidence consists of its Raman and EDX spectra. As discussed previously, Dr. Bugay found both lansoprazole and magnesium carbonate particles in several of the bins examined by Raman spectroscopy. Mr. Hirt had comparable

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similarly on cross. (D.I. 167 at 434:13-15 (there was "some section where there was magnesium carbonate, talc and lansoprazole seen in the same spectrum")).

[22]For example, Dr. Bugay stated that close proximity existed "substantially along the various areas that were tested." (D.I. 167 at 229:10-19)

findings. (D.I. 167 at 221:9-223:14 (Bugay); 411:23-412:3, 430:6-9 (Meyer)) Dr. Byrn confirmed that Mr. Hirt's data indicates a "significant portion" of the layers overlap, referencing line maps between 20 and 42 microns. (D.I.166 at 127 at 10:22) Takeda's experts, however, did not present testimony or other evidence tending to demonstrate that the molecules have an even, or uniform, distribution in the granule. Mr. Hirt offered a credible cross-contamination explanation for why both lansoprazole and magnesium carbonate were found in many of the same areas.

27. Takeda also asserts that the EDX data demonstrates even contact (D.I. 163 at 35) but, again, points to no testimony of record supporting the proposition that the molecules have an even, or uniform, distribution in the granule. Takeda attempts to bridge this gap with their "uniformly basic environment" theory, which focuses not on the spatial relationship of the lansoprazole and magnesium carbonate, but on the pH of the granule. While the court does not hold that all of the lansoprazole and magnesium carbonate must be touching for there to be even contact, more was required in this case to demonstrate infringement by a preponderance of the evidence.[23]

3. Other claim limitations

28. Under the court's adopted claim constructions, Teva's generic product is a "pharmaceutical composition" (D.I. 166 at 111:17-112:17 (Dr. Byrn); D.I. 168 at 518:15-17 (Dr. Chambliss)) which contains "granules" (D.I. 166 at 112:18:113:23 (Dr. Byrn)) as

[23]Takeda argues that "[t]he only explanation for the stability of Teva's product is contact between the lansoprazole and magnesium carbonate as described and claimed in the '321 patent." (D.I. 177 at 14) Teva was not required to affirmatively demonstrate that the stability of its product is caused by something other than the components being mixed evenly.

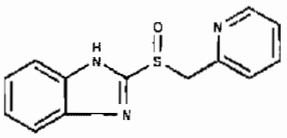
required by claim 2. It is also "coated by a coating agent." (D.I. 168 at 462:18-463:2; 518:21-24 (Dr. Chambliss)) Teva does not argue that its product does not meet the weight ratio limitation absent the additional "even contact" limitation it advocates. (D.I. 174 at 55) For these reasons, Teva's product meets the additional limitations of claim 2. Because Takeda has not proven, by a preponderance of the evidence, that the lansoprazole and magnesium carbonate are "in contact . . . evenly," a finding of noninfringement is proper in this case.

F. Validity

29. As discussed supra, lansoprazole is a member of a class of drugs known as proton pump inhibitors, or PPIs, which prevent stomach cells from pumping acid into the gastrointestinal tract. An enzyme found in the pareital stomach cells in the stomach walls is responsible for pushing hydrogen (H+) ions into the stomach to form gastric acid. This enzyme is called H+/K+–ATPase, or the "proton pump." Under normal conditions, a mucous layer protects the stomach wall from the hydrochloric (HCl) gastric acid. Where ulceration has occurred and this layer is damaged or eroded, gastric acid erodes the stomach wall and produces ulcers. Controlling acidity, by controlling the amount of gastric acid produced in the stomach, is a method of treating and curing ulcers. PPIs act directly on the proton pump, causing an inhibition on the release of hydrogen from the pareital cells. Once administered, PPIs become converted into an intermediate that becomes trapped and accumulates in the strongly acid environment of the parietal cells.

1. Prior art relating to the validity of the '098 patent[24]

30. The first PPI was timoprazole. Timoprazole was disclosed and claimed in U.S. Patent No. 4,045,563 ("the '563 patent") which was published in 1977, and assigned to the Swedish company Aktiebolaget Hassle ("Hassle"). Timoprazole is regarded as a "skeleton key"; it is the basic molecular skeleton upon which every subsequent successful PPI has been based. The timoprazole molecule has three sections: a benzimidazole double ring, methylsulfinyl bridge, and pyridine ring, as pictured below (sequentially):

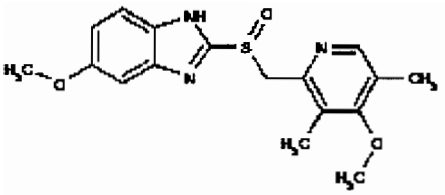


Timoprazole has no substituents on either the benzimidazole double ring or pyridine rings.

31. Omeprazole, another PPI, was subsequently discovered by inventors at Hassle; it is the subject of U.S. Patent No. 4,255,431 ("the '431 patent") (DTX-5), issued on March 10, 1981. Omeprazole contains the same backbone as timoprazole, but has three substituents: (1) a methoxy (alkoxy) ($O\text{-}CH_3$) substituent on the benzimidazole ring; (2) a methyl (CH_3) substituent at the 3-position and the 5-position of the pyridine ring; and (3) a methoxy substituent at the 4-position of the pyridine ring, as pictured below:

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[24]The relevant time for the obviousness analysis with respect to the '098 patent is August 16, 1984, the date of filing of the Japanese patent application to which the '098 patent claims priority. The '321 patent claims priority to two Japanese patent applications, filed February 13, 1986 and February 26, 1986.



Omeprazole has a greater inhibitory effect than timoprazole. (DTX-5 at col. 1, ll. 54-56)

32. On March 22, 1984, the New England Journal of Medicine and Surgery published an article by pharmacologist Dr. George Sachs entitled "Pump Blockers and Ulcer Disease" (hereinafter, the "Sachs article"). (DTX-13) The Sachs article disclosed that, given the acidic environment of the parietal cell, a PPI should have a pKa[25] of about 4.0:

> Consideration of the properties of the parietal cell suggests some design features for a selective inhibitor of gastric ATPase. The secretory canaliculus, into which acid is secreted by the ATPase, can be regarded as a membrane-bound region of low pH. Such a space should accumulate weak bases with a pKa higher than the pH of the compartment. Various cellular organelles, such as lysosomes, secretory granules, and perhaps Golgi, have a pH of about 5, whereas the parietal cell when stimulated should have a pH of about 1. Thus, a weak base with a pKa of about 4 should accumulate exclusively in the secretory canaliculus.

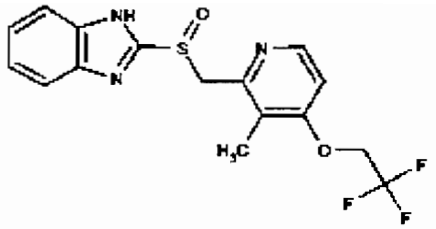
(DTX-13 at 786). Sachs states that omeprazole has a pKa of about 4, and its potency is "rather convincing evidence that omeprazole is rapidly accumulated in the parietal cell" due to its acidity level. (Id.) The pyridine ring is the portion of the omeprazole skeleton that provides the pKa of approximately 4. (D.I. 169 at 750:12-15; 751:23-752:20) More specifically, the methoxy group at the 4-position of the pyridine ring is the major influence on the pKa of omeprazole. (Id. at 754:2-9)

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[25]The pKa (or dissociation constant) measures the relative strength of an acid.

33. Other PPIs were subsequently developed in the industry. Byk Gulden Lomberg Chemische Fabrik Gesellschaft mit beschrankter Haftung ("Byk Gulden"), a German company, is the assignee of U.S. Patent Nos. 4,472,409 ("the '409 patent") and 4,555,518 ("the '518 patent") (collectively, the "Byk Gulden patents"), which issued in September 1984 and November 1985, respectively. The '409 and '518 patents disclose compounds having the timoprazole skeletal structure, a methyl group at the 3-position, plus a methoxy group at the 4-position of the pyridine ring. In addition, the PPIs of the Byk Gulden patents have fluorinated substituents, i.e., substituent molecules containing fluorine atoms. The '409 patent discloses the use of a trifluoromethyl group (CF_3) on the benzimidazole ring. (DTX-7 at col. 1, l. 53-col. 2, l. 4) The '518 patent discloses a 2,2,2-trifluoroethoxy fluorinated substituent ($O\text{-}CH_2\text{-}CF_3$) on the benzimidazole ring. (DTX-9 at col. 1, ll. 29-52)

34. Lansoprazole, discovered by Takeda scientists in 1984, does not have a substituted benzimidazole ring. Like omeprazole and the Byk Gulden compounds, lansoprazole has a methyl group at the 3-position of the pyridine ring. In contrast to omeprazole, lansoprazole does not have a substituent at the 5-position of the pyridine ring. Lansoprazole does, however, contain a trifluoroethoxy fluorinated substituent – the same disclosed for the benzimidazole ring in the '518 patent – for the 4-position of the pyridine ring. ('098 patent, col. 2, ll. 5-9) The structure of lansoprazole is reproduced below.



2. Additional prior art relevant to the validity of the '321 patent

35. In January 1985, the journal "Gastroenterology" published an article entitled "Omeprazole: A Study of its Inhibition of Gastric pH and Oral Pharmacokinetics After Morning or Evening Dosage" by Peter J. Prichard et al. (the "Prichard article"). (DTX-33) In the Prichard article, the authors disclose that "[o]meprazole is a crystalline solid that is chemically labile and rapidly degraded in acidic media. It was therefore administered as an encapsulated, enteric-coated granulate (each capsule containing 20 mg of omeprazole)."[26] (Id. at TVL065993)

36. On January 31, 1985, the Japanese Patent Office published publication no. S60-19716, corresponding to a Japanese patent application (no. 19715/85) to inventors Maseo Ueno and Hirotake Kubota ("the Ueno application"). (DTX-18) The Ueno application was directed to the stabilization of an isocarbostyril pharmaceutical preparation, which was achieved with a magnesium silicate or magnesium oxide stabilizing agent. (Id. at 681589) The reference discloses results for sodium salt

[26]Another 1985 article, entitled "Development of an Oral Formulation of Omeprazole," by A. Pilbrant and C. Cederberg, describes the administration of an enteric coated granule of omeprazole in a critical study. (DTX-42 at TVL059554)

stabilizers in addition to the magnesium salts.[27] (Id. at 681593, table 1) The Ueno application discloses that "[t]he amounts in which these stabilizing agents are used range[s] between 0.5-20 fold, preferably 1-3 fold, in relation to the active ingredient." (Id. at 681589) "To obtain the pharmaceutical preparation according to this invention, excipients, . . . binders, . . . lubricants, . . . and wetting agents . . . are suitably used together with the active ingredient, stabilizing agent, and excipients. First the powder can be obtained through being uniformly mixed in a mixer together with the active ingredient, stabilizing agent, and excipients." (Id. at 681590) The Ueno application provides additional detail on how to formulate granules, tablets, and hard capsules utilizing this powder. (Id.)

37. U.S. Patent No. 4,686,230 ("the '230 patent"), issued on August 11, 1987, discloses benzimidazole derivatives useful as PPIs. (DTX-16) The '230 patent discloses that the benzimidazoles described can be part of pharmaceutical formulations, which "can also contain one or more pharmaceutically active substituents from other groups of medicaments, such as antacids, for example aluminum hydroxide and magnesium aluminate . . . ." (Id. at col. 40, ll. 22-34)

3. Obviousness standard

38. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which

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[27]The parties' experts disagree on whether the Ueno application teaches that the magnesium salts were more effective stabilizers.

depends on several underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)). "Because patents are presumed to be valid, see 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted).

39. With respect to the '098 patent, Teva asserts that the timoprazole backbone, methyl and trifluoroethoxy fluorinated substituents were disclosed by the prior art. With respect to the '321 patent, Teva asserts that each component of the claimed pharmaceutical composition was disclosed by the prior art. In each context, therefore, Teva must identify some "reason that would have prompted a person of ordinary skill in the relevant field to combine the[se] elements" to yield the claimed compounds. KSR, 127 S.Ct. at 1741. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition, Teva must demonstrate that such a person "would have had a reasonable expectation of success in doing so." PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007).

4. Discussion

40. Claim 10 of the '098 patent discloses the lansoprazole compound. Claim 2 of the '321 patent discloses a pharmaceutical composition containing a benzimidazole compound (such as lansoprazole) and a basic inorganic salt of magnesium or calcium, formulated into tablets or granules and then coated with a coating agent. The obviousness of each claim will be addressed in turn.

a. Lansoprazole

41. Teva's obviousness theory is that a person of ordinary skill in the art would undergo a series of steps in order to arrive at the lansoprazole compound. According to Teva, such a person of ordinary skill would have: (1) started with the timoprazole "skeleton key"; (2) focused on the pyridine ring in order to keep the pKa about 4.0 according to Sachs; (3) focused on the 4-position of the pyridine ring, which Sachs disclosed was responsible for the pKa of omeprazole; (4) made a short list of possible substitutions for the benzimidazole ring, 3-position and 5-position of the pyridine ring; and (5) arrived logically at lansoprazole. (D.I. 179 at 15-16) The court agrees with Teva that the evidence indicates that a person of ordinary skill in the art, seeking to make an improved PPI, would have started with a timoprazole skeleton and focused on the four key locations on the skeleton, as evidenced by the success of other analogs such as omeprazole and the Byk Gulden compounds. What is lacking, however, is an indication that such a person would have been motivated to substitute the trifluoroethoxy substituent, found previously on the benzimidazole ring in the compounds of the '518 patent, onto the 4-position of the pyridine ring to form lansoprazole (while leaving the benzimidazole ring and 5-position of the pyridine ring substituent-free), or would have had any reasonable expectation of success in doing

so.[28]

42. Teva points to the '431 patent, which shows alkoxy substituents such as an ethoxy substituent (table 2, ex. 15) and an ethoxy-methoxy group (ex. 27) at the 4-position, and emphasizes that the '518 patent claims any "alkoxy radical" at the 4-position, not only a methoxy group. (D.I. 179 at 18) While it is true that a trifluoroethoxy group is an alkoxy radical, of the ethoxy variety, the presence of the fluorinated 4-position substituent differentiates lansoprazole from the prior art Byk Gulden compounds. Teva's theory is that the '563 patent demonstrates that the Hassle scientists started with substitutions on the benzimidazole ring, before moving its substitutions strategy to the pyridine ring. (D.I. 165 at 32-33, D.I. 169 at 739:16-740:11) Teva applies this pattern to the prior art Byk Gulden compounds:

> Whereas Hassle started with the benzimidazole substitutions and proceeded to use the same substituents on the pyridine ring, Byk Gulden substituted the benzimidazole ring and stopped there. Takeda then took the next logical step of synthesizing the same fluorinated alkoxy substituents on the pyridine ring.

(D.I. 165 at 42) Teva's expert, Dr. George Lenz, did not point to any evidence tending to validate his theory regarding the Hassle scientists' methodology. (D.I. 169 at 765:2-769:23)

43. The testimony highlighted by Teva demonstrates that potential benefits of fluorinated substituents were known, but largely unexplored. (e.g., D.I. 161 at 1502:23-1504:16; D.I. 171 at 1144:7-1147:13, cited at D.I. 179 at 19) If fluorinated substituents were an "obvious choice to use [as] substituents on PPIs" (D.I. 179 at 19), in contrast to

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[28]The parties' dispute regarding the definition of a person of ordinary skill in the art has no bearing on the court's conclusion, as the court has determined that even someone of the skill level of the parties' experts would not find lansoprazole obvious.

merely obvious-to-try, it is telling that Teva has not identified any other prior art PPIs, other than the Byk Gulden compounds, utilizing fluorinated substituents as of 1984.[29] These Byk Gulden compounds had a methoxy group at the 4-position, signifying that this group was favored at the 4-position. (D.I. 171 at 1200:18-1201:1) As Dr. Lipinski testified, "the fluorine in one position could have a very, very different solubility than a fluorine in another."[30] (Id. at 1272:13-15) Further, not all fluorinated substituents function in the same way. (Id. at 1188:17-1189:6) Teva itself admits, "[m]olecules are not like Legos® in which we pop off one substituent and snap on another."[31] (D.I. 179 at 19)

44. In short, Teva has not identified a sufficient suggestion in the art for moving the 2,2,2-trifluoroethoxy group to the pyridine ring. See Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) (the prior art must "suggest[ ] making the specific molecular modifications necessary to achieve the

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[29]Takeda's expert, Dr. Christopher Lipinski, did a search of all compounds containing a pyridine ring as of 1984, and discovered only two examples of existing compounds having a trifluoroethoxy group at the 4-position. One was an herbicide and the other an antimalarial drug. Only four drug compounds were found to have a trifluoroethoxy group anywhere in the molecule also containing a pyridine ring; none of these were gastrointestinal drugs. (D.I. 169 at 802:5-13; D.I. 171 at 1189:22-1191:1)

[30]Dr. Lenz also admitted that substituent changes can have significant effects. (D.I. 169 at 781:11-13; 785:3-15)

[31]If Teva's theory were correct, and the use of fluorininated substituents was straightforward in view of fluorine's small molecular size and similarity to hydrogen in this respect, the '409 and '518 patents would likely be obvious in view of the '431 patent, or the omeprazole prior art. Indeed, the differences between omeprazole and the Byk Gulden compounds is less than that present in the case at bar; the distinguishing characteristic between them, aside from omeprazole's methyl group at the 5-position of the pyridine ring, is the choice of substituent on the benzimidazole ring (non-fluorinated alkoxy or fluorinated/fluorinated alkoxy).

claimed invention," such as may be the case where "close or established structural relationships" exist between the compounds) (citing In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995)). Because each substituent is critical, and there are three differing substituents between lansoprazole and the prior art, the difference between lansoprazole and the prior art is not insubstantial. Even assuming that a person of skill in the art would have been motivated to move substituents from the benzimidazole ring to the 4-position, an assumption not justified on the present record, Teva has not proffered clear and convincing evidence that such a person would have been motivated to relocate the 2,2,2-trifluoroethoxy substituent to this specific location with a reasonable expectation of success. Teva has not demonstrated that the claimed combination was a predictable solution for a stable PPI. See KSR, 127 S.Ct. at 1732 ("obvious to try" may satisfy the "obviousness" standard in cases where "a design need or market pressure to solve a problem and . . . a finite number of identified, predictable solutions" within the technical grasp of a person of skill in the art exist).

45. Finally, Takeda has put forward evidence of secondary considerations that buttresses the court's finding of non-obviousness. Lansoprazole has made over $35 billion since its launch and has annual sales of over $1 billion. (D.I. 170 at 1056:24-1058:7) Teva asserts that the success of PREVACID® is not attributable to its properties as a drug, rather, to Takeda's aggressive marketing. Even if half of this success is attributable to marketing, Teva's expert agreed that Prevacid® would still be a "good product." (Id. at 1030:16-20) Teva also asserts that lansoprazole met no long-felt need that was not already met by omeprazole in 1984. When PRILOSEC® (commercial omeprazole) was released in 1989, however, it carried a black-box warning

about potential toxicity issues. (D.I. 171 at 1207:5-11) Takeda introduced evidence that lansoprazole had superior properties to omeprazole in several respects, for example, superior chemical stability (id. at 1206:3-10), better bioavailability (D.I. 169 at 831:25-832:15), and a faster onset of action (id. at 836:12-20). Out of dozens who tried, only four companies succeeded in producing a viable PPI. (D.I. 171 at 1208:4-13) The court finds Takeda's evidence evidence of non-obviousness convincing.

b. Pharmaceutical composition

46. Teva asserts that each of the limitations of claim 2 of the '321 patent is disclosed in the prior art. The '098 patent, which is prior art to the '321 patent, teaches that lansoprazole can be "administered orally in a dosage form of capsules, tablets, granules, etc. by formulating with a pharmacologically acceptable carrier, excipient, diluent, etc." ('098 patent, col. 6, ll. 55-59) The '230 patent teaches the combination of benzimidazoles with antacids such as magnesium aluminate;[32] magnesium carbonate is a comparable basic inorganic salt. The Pilbrant article discloses the administration of a coated granule formulation of omeprazole in a clinical study. The Ueno reference discloses preparing an isocarbostyril pharmaceutical compound by uniformly mixing with a stabilizing agent and excipient, using the stabilizer in an amount from 0.5-20 parts by weight, and formulating the product into granules.

47. Teva argues that, "given that the Ueno Japanese patent prevents the exact same type of degradation as experienced by lansoprazole, namely content decrease and significant color change in the presence of acid, a person of ordinary skill in the art

[32]As noted previously, the '230 patent generally discloses formulating benzimidazole compounds with excipients in tablet form.

seeking to stabilize lansoprazole would have considered the teachings in the Ueno Japanese patent to be relevant." (D.I. 165 at 55-56) According to Teva, "ample motivation to combine exists" because "the Ueno Japanese patent and the Pilbrant reference both teach the use of basic inorganic salts to stabilize acid-labile compounds" and "both the '230 patent and the Pilbrant reference teach the combination of a benzimidazole compound with an antacid." (Id. at 56)

48. Although Dr. Chambliss generally testified that the sum of these references renders the '321 patent invalid for obviousness (D.I. 168 at 515:22-516:23), Teva points to no testimony regarding a motivation to combine, or a reasonable expectation of success. Absent more, Teva has not met its burden to demonstrate invalidity by clear and convincing evidence.

49. This conclusion is bolstered by several facts tending to indicate that there was no motivation to combine the references cited by Teva to solve the lansoprazole stabilization problem. The '230 patent discloses that its compounds have high storage stability (DTX-16 at col. 39, ll. 40-43); its mention of antacids such as magnesium aluminate, therefore, was not clearly connected to the concept of imparting stability (D.I.168 at 557:10-16). The '431 patent also does not discuss stabilization. (Id. at 559:8-10) The Pilbrant article does not mention magnesium carbonate or the use of a stabilizer. (Id. at 561:20-562:5)

50. The Ueno reference (and its equivalent U.S. Patent No. 4,666,919) were before the examiner during prosecution of the '321 patent. See Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1467 (Fed. Cir. 1990) (the challenger's "burden is especially difficult when the prior art was before the PTO examiner during prosecution

of the application."). In addition, there are structural differences between the isocarbostyril pharmaceutical preparation disclosed in Ueno and lansoprazole which impart differences in functionality. (D.I. 170 at 1091:2-9) Notwithstanding, Ueno does not mention lansoprazole or magnesium carbonate. For the aforementioned reasons, the record does not support a conclusion that a person of skill in the art would look to combine the references presented by Teva to make the claimed combination, and would have a reasonable expectation of success in doing so.

G. Inequitable Conduct

51. Teva argues that the '098 patent is unenforceable for inequitable conduct committed when Takeda withheld highly material data during prosecution. The '098 patent was filed as U.S. Patent Application No. 760,568 ("the '568 application") on July 29, 2005. The specification discloses that "the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5-20 times or more." ('098 patent, col. 6, ll. 30-32) Takeda provided data showing that the "ID_{50}"[33] for lansoprazole was less than 1.0 mg/kg, while the ID_{50} for omeprazole was 21.0 mg/kg. ('098 patent, col. 6, ll. 15-23) After the '568 application was filed, an Information Disclosure Statement ("IDS") was filed by the applicants on July 29, 1985. (PTX-2) This IDS cited three references, one of which was the '431 omeprazole patent. (Id.) The application was thereafter allowed without any objections or rejections, and issued as the '098 patent on December 9, 1986. (Id.) Teva asserts that only one set of data supported Takeda's "20 times or more" assertion, and that Takeda was in possession

[33]This measurement correlates to the dose at which there is a 50% inhibition of ulcer activity.

of data that directly contradicted its assertion but withheld such data from the examiner.

52. Of critical importance on this issue is Takeda's internal document entitled "Planning and Development Head Office Interim Research Meeting (125th) Document – AG-1749"[34] (the "Head Office report"). (DTX-705) The Head Office report discloses the results of two sets of tests done in 1984 on the anti-ulcer effect of lansoprazole. The first was a water immersion immobilization stress test, which resulted in an ID_{50} value of 2.0 mg/kg for lansoprazole and 8.2 mg/kg for omeprazole, or a four-fold increase in anti-ulcer effect for lansoprazole. (DTX-705 at 44327) The second test was the indomethacin-induced ulcer ("IMAU") test, which resulted in ID_{50} values of 1 and 21 mg/kg for lansoprazole and omeprazole – the 20-fold increase in anti-ulcer effect mirrored in the '098 specification. (Id. at 44329) There are no other comparable results within the Home Office report with respect to the anti-ulcer effect of lansoprazole; the Home Office report contains data for the supression of gastric acid secretion, taken from studies in rats and dogs. (Id. at 44311, 44313) The ID_{50} values for lansoprazole and omeprazole were comparable in these tests.[35]

53. Takeda submitted a pharmacological profile for lansoprazole to the FDA in September 1986 ("the FDA report"). (DTX-120) The FDA report stated that, in rats, lansoprazole was "2-10 times as potent as omeprazole" for the inhibition of the formation of gastric ulcers, and was "2-3 times as potent as omeprazole" for

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[34]AG-1749 denotes lansoprazole.

[35]Regarding the acid secretion in canine gastric parietal cells (in vitro), Takeda's results indicated that lansoprazole was about 2-3 times more effective; results regarding histamine-induced acid secretion were comparable between the two (0.28 and 0.2 mg/kg; 0.14 and 0.15 mg/kg). (DTX-705 at 44311 & 44313)

accelerating the healing of ulcers.[36] (DTX-120 at 571238) For acute gastric ulcers in rats, Takeda reported that lansoprazole had ID_{50} values of 2.5, 0.7, and 8.5 mg/kg (compared to 7.0, 3.1, and 15.3 mg/kg for omeprazole, respectively). For acute duodenal lesions in rats, Takeda reported ID_{50} values of 1.1 and 0.3 mg/kg for lansoprazole (compared to 5.7 and 3.0 mg/kg for omeparazole). (Id. at 517239) Takeda also reported better healing rates for lansoprazole. (Id. at 517240)

54. In 1988, '098 patent inventors Akira Nohara and Yoshitaka Maki, in addition to Dr. Hiroshi Satoh, were among the named authors of a paper in the Journal of Pharmacology and Experimental Therapeutics entitled "Antisecretory and Antiulcer Activities of a Novel Proton Pump Inhibitor AG-1749 in Dogs and Rats" (the "JPET paper"). (DTX-595) The abstract of the JPET paper states that

> the inhibitory potency of AG-1749 in dogs was much the same as that of omeprazole and about half that of ranitidine. However, it was about 2 to 10 times more potent than omeprazole and 4 to 34 times more potent than ranitidine in rats. These results suggest that AG-1749 exerts prominent antiulcer activities mainly by suppressing acid secretion via an inhibition of a proton pump in gastric parietal cells and partly by protecting the gastrointestinal mucosa against various ulcerative stimuli.

(Id. at 59746)

55. In 1990, Drs. Satohs and Nohara were among the authors of a paper published in the Chemical Pharmaceutical Bulletin entitled "Synthesis of 2-[[(4-Fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazoles as Antiulcer Agents" (the "CPB paper"). (DTX-82) Dr. Keiji Kubo, a Takeda scientist, testified that the CPB

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[36]In contrast, "[t]he inhibitory potency of AG-1749 was almost equal to that of omeprazole" with respect to inhibition of (H+/K+)-ATPase, acid formation, and gastric acid secretion. (DTX-120 at 571237-38)

paper describes the results of three types of biological testing performed on lansoprazole (pylorus ligation, water immersion stress test, and the ethanol lesion or erosion test), but that the IMAU test cited in the Home Office report was not included. (D.I. 171 at 1148:6-17)

56. Teva introduced portions of Takeda's laboratory notebooks at trial.[37] (DTX-122) Dr. Esam Dajani, a pharmacologist, reviewed Takeda's data. Dr. Dajani testified for Teva that the notebook data indicates that lansoprazole and omeprazole are "essentially equally active in [the] inhibition of stress ulcers in rats given by the oral administration." (D.I. 168 at 693:25-697:5) In other words, the compounds are "indistinguishable from each other." (Id. at 698:5-12) Dr. Dajani also reviewed the report and findings of Teva's statistician, Dr. Robert Hirsch, who calculated ID_{50} values based on Takeda's laboratory notebook data.[38] Dr. Dajani testified that Dr. Hirsch's calculations also supported his conclusion that the compounds were equally effective. (Id. at 701:19-705:14)

1. Standards

57. Applicants for patents and their legal representatives have a duty of candor, good faith, and honesty in their dealings with the PTO. Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995); 37 C.F.R. § 1.56(a). This duty is predicated on the fact that "a patent is an exception to the general rule against monopolies and to the right of access to a free and open market." Precision Instrument Mfg. Co. v. Auto.

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[37]The dates of the entries referenced by Teva are unclear.

[38]Takeda objected at trial to the admission of the entirety of Dr. Hirsch's report; the court admitted tables 2 and 5 admitted as DTX-218.1.

Maint. Mach. Co., 324 U.S. 806, 816 (1945). The duty of candor, good faith, and honesty includes the duty to submit truthful information and the duty to disclose to the PTO information known to patent applicants or their attorneys which is material to the examination of a patent application. Elk Corp. of Dallas v. GAF Bldg. Materials Corp., 168 F.3d 28, 30 (Fed. Cir. 1999). A breach of this duty constitutes inequitable conduct. Molins, 48 F.3d at 1178.

58. If it is established that a patent applicant engaged in inequitable conduct with respect to one claim, then the entire patent application is rendered unenforceable. Kingsdown Med. Consultants v. Hollister Inc., 863 F.2d 867, 877 (Fed. Cir. 1988). Additionally, "[a] breach of the duty of candor early in the prosecution may render unenforceable all claims which eventually issue from the same or a related application." Fox Indus., Inc. v. Structural Pres. Sys., Inc., 922 F.2d 801, 803-04 (Fed. Cir. 1990).

59. A finding of inequitable conduct is "an equitable determination" and, therefore, "is committed to the discretion of the trial court." Monon Corp. v. Stoughton Trailers, Inc., 239 F.3d 1253, 1261 (Fed. Cir. 2001).

60. In order to establish unenforceability based on inequitable conduct, a defendant must establish by clear and convincing evidence that: (1) the omitted or false information was material to patentability of the invention; (2) the applicant had knowledge of the existence and materiality of the information; and (3) the applicant intended to deceive the PTO. Molins, 48 F.3d at 1178.

61. A determination of inequitable conduct follows a two-step analysis. The withholding of information must first meet threshold findings of materiality and intent. Id.

62. The Federal Circuit has recently stated that, prior to 1992, two standards for materiality were in effect: (1) the materiality standard set forth in the present version of PTO Rule 56, 37 C.F.R. § 1.56(b); and (2) the previous version of that rule. See Digital Control Inc. v. Charles Machine Works, 437 F.3d 1309, 1314 (Fed. Cir. 2006). The Court in Digital Control held that the new 1992 iteration of Rule 56 was not intended to replace the broader old Rule 56, and "merely provides an additional test of materiality." Id. at 1316. Therefore, "if a misstatement or omission is material under the new Rule 56 standard, it is material. Similarly, if a misstatement or omission is material under the 'reasonable examiner' standard or under the older three tests, it is also material." Impax Labs., Inc. v. Aventis Pharm. Inc., 468 F.3d 1366, 1374 (Fed. Cir. 2006) (quoting Digital Control, 437 F.3d at 1316)).

63. Rule 56 formerly provided that "information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." 37 C.F.R. § 1.56 (1990).

64. Currently, Rule 56 is narrower in scope:

> Information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
>
> (2) It refutes, or is inconsistent with, a position the applicant takes in:
> (i) Opposing an argument of unpatentability relied on by the Office, or
> (ii) Asserting an argument of patentability.

37 C.F.R. § 1.56(b) (2007).[39]

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[39]"A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of

65. The inquiry presented under the prior "reasonable examiner" standard is whether "a reasonable examiner would have considered such [omitted] prior art important in deciding whether to allow the patent application." Impax Labs., 468 F.3d at 1374 (quoting Digital Control, 437 F.3d at 1314)).

66. The applicable "older three tests" referenced in Digital Control include: (1) the objective "but-for" standard, in other words, "where the misrepresentation was so material that the patent should not have issued;" (2) the subjective "but-for" test, in other words, "where the misrepresentation actually caused the examiner to approve the patent application when he would not otherwise have done so;" and (3) the "but it may have" standard, "where the misrepresentation may have influenced the patent examiner in the course of prosecution." See Impax Labs., 468 F.3d at 1374, n.5 (quoting Digital Control, 437 F.3d at 1315)).

67. After determining that the applicant withheld material information, the court must decide whether the applicant acted with the requisite level of intent to mislead the PTO. See Baxter Int'l, Inc. v. McGaw Inc., 149 F.3d 1321, 1327 (Fed. Cir. 1998). "Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for finding a deceptive intent." Hebert v. Lisle Corp., 99 F.3d 1109, 1116 (Fed. Cir. 1996). That is, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Kingsdown, 863 F.2d at

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evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability." 37 C.F.R. § 1.56(b) (2007).

876. A "smoking gun" is not required in order to establish an intent to deceive. See Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1422 (Fed. Cir. 1989). An inference of intent, nevertheless, is warranted where a patent applicant knew or should have known that the withheld information would be material to the PTO's consideration of the patent application. See Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1256 (Fed. Cir. 1997).

68. Once materiality and intent to deceive have been established, the trial court must weigh them to determine whether the balance tips in favor of a conclusion of inequitable conduct. N.V. Akzo v. E.I. DuPont de Nemours, 810 F.2d 1148, 1153 (Fed. Cir. 1987). The showing of intent can be proportionally less when balanced against high materiality. Id. In contrast, the showing of intent must be proportionally greater when balanced against low materiality. Id.

69. Because a patent is presumed valid under 35 U.S.C. § 282, inequitable conduct requires proof by clear and convincing evidence. Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 551 (Fed. Cir. 1990).

2. Materiality

70. The specification discloses that lansoprazole has "superior anti-ulcer action as compared with known compounds by about 1.5-20 times or more." This representation is not only limited to anti-ulcer activity, as compared to antisecretory or gastroptorective activity,[40] but includes the broad range of about 1.5 to about 20 times

[40]The fact that the '098 patent is not limited to a compound with anti-ulcer activity (as per the claims) does not change, as Teva asserts, the plain import of this statement in the specification. Nor does the applicants' criticism of prior art compounds for having insufficient cytoprotective activity. (D.I. 179 at 9, citing '098 patent, col. 1, ll. 13-16

effectiveness. Teva asserts that Takeda's failure to disclose to the examiner that it posessed additional data that did not support this claim regarding the superiority of lansoprazole constitutes inequitable conduct. (D.I. 165 at 14) Teva does not argue that the IMAU data, supporting the greatest (20-fold) ratio of this range, was inaccurate. Rather, the crux of its complaint is that the available data as a whole did not support the uppermost of this disclosed range.

71. Of the purportedly omitted data cited by Teva, only the Head Office report and the 1986 FDA report include data that is contemporaneous with the period of time the '098 patent was pending before the Examiner.[41]

72. As discussed previously, the Head Office report contains two sets of data regarding anti-ulcer activity generated through different testing methods. The Head Office report contains what appears to be the only IMAU data of record; this data supports the 20-fold ratio disclosed to the PTO. It also includes data obtained by water immersion testing indicating a 4-fold ratio in improvement for anti-ulcer activities. The FDA report disclosed that lansoprazole was 2-10 times as potent for anti-ulcer activity;

("[W]hile these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents."))

[41]The FDA submission was dated September 1986. (DTX-120) The '098 patent was allowed on May 12, 1986, but did not issue until December 9, 1986. (PTX-2)

Teva points out that, on direct examination, Dr. Brendan Whittle, a pharmacologist testifying for Takeda, stated that there were some additional studies on lansoprazole conducted by Takeda using the IMAU test method that were not included in the chart in the '098 patent specification. (D.I. 165 at 9-10, citing D.I. 172 at 1338:3-7) It is unclear what data this entails. (D.I. 179 at 2-4) Because there is no indication that any of the data cited by Teva, aside from the FDA report data, was in Takeda's possession during the pendency of the '098 patent, the court does need not address the materiality of these references.

this testing involved methods other than IMAU testing, such as water immersion and acetic acid injection. (DTX-120)

73. The '568 application was not rejected prior to its issuance as the '098 patent. Thus, there is no specific indication that the examiner relied upon the "about 1.5-20" range as evidence of patentability (non-obviousness due to unexpected results) over the prior art.[42] Had the withheld data been disclosed to the PTO, it would have fallen squarely within the "about 1.5-20" range disclosed and the results tabulated in the specification for the IMAU tests ('098 patent, col. 6, ll. 5-32),[43] but would possibly have highlighted a narrower sub-range, despite the fact that the results were derived from different testing models.[44] Takeda itself indicates that the IMAU data was disclosed to the PTO because it considered that to be the "more valued" and "best model," necessarily implying a comparison to, and the relevancy of, alternate models. (D.I. 173 at 36, citing D.I. 161 at 1482:12-14; 1570:21-1571:1) Drs. Dajani and Whittle both testified that all models are, to some degree, useful. (D.I. 168 at 665:3-12; D.I. 172 at 1364:20-21) In view of the foregoing, the court declines to find that the additional test data in Takeda's possession would **not** have been deemed important under the reasonable examiner standard. Takeda had actual knowledge of the withheld data, and the court finds that it should have known of its materiality. For purposes of the court's

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[42]Notably, as Teva points out, the examiner of the '568 application was the same examiner for the Byk Gulden '409 and '518 patents, yet no obviousness rejection based upon either compound was ever made.

[43]The court declines to find the data "inconsistent" with an assertion made in favor of patentability.

[44]For this reason, the data is not cumulative.

balancing test, however, the court assigns this data a low level of materiality.[45]

3. Intent

74. The justification offered by Takeda for not including non-IMAU test data in the '098 patent specification, and not providing such data to the PTO, is that the IMAU data is more reliable (it "more closely mimics the development of ulcers in man"[46]) and Takeda, therefore, placed greatest reliance on this data. (D.I. 173 at 33-36)

75. Takeda has presented evidence that placed a heavy reliance on the IMAU testing, as compared to other testing methods. For example, a Takeda internal report indicates that AG-1760 was selected for further study based on the results generated by IMAU testing. (PTX-132) While in vitro antisecretary and gastroprotective assays indicated a separate compound, AG-1710, had more favorable results (PTX-133), Takeda developed lansoprazole.[47] (D.I. 172 at 1318:16-1322:23) Dr. Whittle opined that it "[the IMAU testing] model must have been the model which swung the balance of which compound [Takeda] put into the patent and which they didn't, from a biological perspective." (D.I. 172 at 1374:7-25) Takeda asserts that other test data was sent to

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[45]Teva has not pointed to any particular evidence or made any argument that would compel a finding of "high" materiality.

[46](D.I. 173 at 34, citing D.I. 172 at 1303:16-24)

[47]Teva cites some of this same evidence in support of its argument that the evidence demonstrates that Takeda relied equally on all testing methods. (D.I. 179 at 14, citing PTX-131-134). With respect to the additional evidence, it is unclear what testing methods were referenced in an internal July 1984 monthly report detailing "relatively strong activity" for AG-1760 (PTX-131). A September 1984 monthly report included data obtained from other test methods. (PTX-134) None of these exhibits demonstrate how Takeda weighed the applicable testing methods or results vis-a-vis IMAU testing; Teva points to no trial testimony on this point.

the FDA because "[t]he IMAU test did not exist or was too new when other companies filed IND applications for omeprazole, ranitidine, or other prior art anti-ulcer agents," and "the regulatory agencies would expect comparative data with the prior art anti-ulcer agent, ranitidine," which is inactive in the IMAU model. (D.I. 173 at 39, citing 927:8-11; 1350:11-16; 1350:17-1351:8)

76. Teva's arguments regarding Takeda's intent to deceive rests primarily on the trial testimony of Dr. Satoh, who testified that the "results from th[e IMAU test] model were more important as compared to other test results . . . and that was the reason that we put the data or the result of indomethacin-induced an[ti-]ulcer model in the patent[.]" (D.I. 161 at 1569:11-16) Teva asserts that Dr. Satoh's testimony indicates that IMAU testing is not a superior method, and that the "about 1.5-20" data was selected for disclosure only because of the superiority of the result. (D.I. 165 at 4) As noted previously, Dr. Whittle agreed that every model has some utility, otherwise practitioners would not utilize the model. (D.I. 171 at 1295:3-8 (stating that the model used "is very much up to the program, the therapeutic target that you identify")) Dr. Dasani testified that, in 1984, no one test methodology was superior to others. (D.I. 168 at 665:3-12)

77. Teva argues that the court should infer intent to deceive in this case; its factual basis for such a finding, however, is lacking for several reasons. First, as noted previously, the court does not find the omitted data highly material, such as would support an inference of an intent to deceive. Compare Bruno Ind. Living Aids, Inc. v. Acorn Mobility Scvs., Ltd., 394 F.3d 1348, 1354 (Fed. Cir. 2005) (affirming judgment of unenforceability in view of the "high materiality" of the omitted prior art concurrently submitted to the FDA and absence of a credible explanation for the nondisclosure)

(cited by Teva at D.I. 179 at 5-6). There is evidence that Takeda itself viewed the IMAU results as the best evidence of the activity of lansoprazole. See Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F.Supp.2d 341, 390-92 (S.D.N.Y. 2006) (stating that it is appropriate to apply professional judgment in selecting which test results were most reliable; applicant's "only obligation [is] to present its results as of that time honestly."). Takeda identified the relevant prior art (omeprazole and the '431 patent) to the PTO, and did not manipulate the data it reported to the PTO. See id. (finding no inequitable conduct in view of several indicia of Takeda's good faith, including these factors). Teva does not dispute that the data Takeda submitted in its application is correct, only that additional data possibly would have brought the patentability of the claims into question. Takeda did not overcome any rejections posed by the examiner based on the data it included in the application, or in reliance on any absence of additional data; in short, it made no misrepresentations to the PTO. Compare Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359, 1365 (Fed. Cir. 2007) (affirming judgment of unenforceability where undisclosed documents contained test data demonstrating a similar oxidative stability to a prior art compound, "a crucial issue during prosecution") (cited by Teva at D.I. 179 at 5); Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1420 (Fed. Cir. 1989) (affirming finding of inequitable conduct based on disparity in PTO and FDA submissions, where applicant "argued over and over" during prosecution that its drug was free of side effects such as drowsiness, but its FDA submissions indicated that it was aware of exactly such side effect). The court recognizes that Takeda's disclosure of the most favorable of its test data to the PTO was self-serving; however, absent any indication that the IMAU data was false, manipulated, the focus of the examiner in any

manner, the court declines to find a high level of intent on this record such as would tip the balance in favor of inequitable conduct in this case.

III. CONCLUSION

For the reasons discussed above, the court concludes that Takeda has failed to prove, by a preponderance of the evidence, that Teva infringes the '321 patent. The court also finds that Teva has failed to prove, by clear and convincing evidence, that: (1) the '098 or '312 patents are invalid for obviousness; or (2) the '098 patent is unenforceable due to inequitable conduct.