IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY, LTD., and TAP PHARMACEUTICAL PRODUCTS INC.,	)	
Plaintiffs and Counterclaim-Defendants,	)	
v.	)	C.A. No. 06-033-SLR
TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.,	)	
Defendants and Counterclaim-Plaintiffs.	)	

REPLY POST-TRIAL BRIEF OF DEFENDANTS TEVA PHARMACEUTICALS USA AND TEVA PHARMACEUTICALS INDUSTRIES LTD. REGARDING UNENFORCEABILITY AND INVALIDITY OF THE '098 PATENT, AND INVALIDITY OF THE '321 PATENT

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INTRODUCTION

Takeda committed inequitable conduct in 1984 to secure a patent on the "me-too" compound it calls lansoprazole. (D.I. 165 at 2-19.) Takeda pursued that me-too compound to further Plaintiffs' business strategy of getting into a nascent but potentially lucrative PPI market as fast as possible. In trying to establish the patentability of lansoprazole over the "benchmark" industry standard compound omeprazole, Takeda disclosed a single piece of favorable IMAU data that showed lansoprazole was "20-times superior" to omeprazole. Takeda made the 20-times superior argument because it knew that it could avoid an obviousness rejection if it asserted (as had Byk Gulden before) that its me-too compound was vastly superior to omeprazole. (D.I. 165 at 19-50.) The evidence of record, however, shows that Takeda had, but failed to disclose to the PTO, a wide range of other test results that contradicted the claim that lansoprazole is 20-times superior. The fact that Takeda disclosed all of these other test results to the FDA underscores their materiality.

Further, a person of ordinary skill in the art would have developed lansoprazole by starting with the benchmark compound omeprazole and applying the clear teachings in the prior art. A person of ordinary skill had more than a reasonable expectation that he/she would succeed in developing a me-too compound. This expectation of success renders the '098 patent invalid.

Plaintiffs' Answering Brief raises a series of red-herring arguments. In the very first paragraph, Plaintiffs smear Teva by suggesting that it routinely asserts invalidity and unenforceability arguments without basis. This is false. Teva never challenged the '431 patent on omeprazole; Plaintiffs, on the other hand, exploited the teachings of that patent to develop a me-too drug to compete with omeprazole. Further, Teva did not assert its inequitable conduct claim until Plaintiffs produced the documents that contained the contradictory data that Plaintiffs withheld from the PTO. Plaintiffs did not oppose the addition of that inequitable conduct claim.

The equities are with Teva. Teva did not seek to compete in this marketplace until the '431 omeprazole patent expired in October 2001, whereas Plaintiffs introduced their me-too omeprazole analog in 1995. Now, more than seven years after the '431 patent expired, Plaintiffs seek to enjoy their ill-gotten monopoly and monopolistic drug prices for years to come, and prevent Teva from introducing a generic version of lansoprazole that will benefit the public with reduced prices.

Equity also abhors dereliction of the duty of candor. Candor means painting a fair picture of test results, not only submitting favorable data that serves one's interest. Candor means fairly presenting the body of data so the patent examiner can make an informed decision.

Teva respectfully submits that the Court should enter judgment that the '098 patent is invalid and unenforceable, and that the '321 patent is invalid and not infringed.[1]

I. TAKEDA COMMITTED INEQUITABLE CONDUCT BY SELECTIVELY DISCLOSING ONLY A SINGLE PIECE OF ITS TEST DATA

The key question underlying the inequitable conduct claim is whether a reasonable patent examiner would have wanted to consider the data that Takeda withheld from the PTO. Because that data contradicts Takeda's assertion that lansoprazole was greater than 20 times superior to omeprazole, the answer is "yes." Takeda has failed to point to any evidence to the contrary.

A. It Is Undisputed That Takeda Held, But Failed to Disclose to the PTO, Data Comparing Omeprazole and Lansoprazole, and That Data Was Inconsistent With Takeda's Claim of 20 Times Superiority.

Column six of the '098 patent discloses ID_{50} data from the IMAU anti-ulcer model. That data compares seven Takeda compounds, the second of which is lansoprazole, to two prior art compounds: omeprazole and a Byk Gulden compound. (PTX1, col.6, ll.5-28.) The ratio of the

[1] Teva set forth its invalidity position on the '321 patent in its Opening Post-Trial Brief (D.I. 165 at 50-56), and its non-infringement position on the '321 patent in its Answering Post-Trial Brief. (D.I. 174.) Teva relies on those filings.

ID_{50} values for those compounds indicates their relative potency. The table in column six indicates that lansoprazole has an ID_{50} of "<1.0" and that omeprazole has an ID_{50} of "21.0." (Id.) The other claimed compounds have a range of ID_{50} values between "<1.0" through "3.7." The other "known compound," the Byk Gulden compound listed last on the table, has an ID_{50} value of "5.5." Thus, the inventors asserted, "the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5-20 times or more." (Id. col.6, ll.30-32.)

There can be no doubt that Plaintiffs represented to the PTO and the world specifically that lansoprazole was 20 times more potent than omeprazole, and Plaintiffs' suggestion that Teva unfairly avoids the "about 1.5" end of the range is disingenuous in the extreme. The only data in the patent that compares lansoprazole with omeprazole – as opposed to comparing, generally, the "compounds of this invention" with "known compounds" – are results that purport to establish a 20-fold advantage for lansoprazole – "<1.0" versus "21.0." It is that data that a reasonable examiner would have considered in making his/her patentability decision on lansoprazole. It is also that data that is contradicted by every remaining piece of data in Plaintiffs' hands.[2]

Plaintiffs do not, and cannot, dispute that they withheld all other test results comparing omeprazole and lansoprazole. Those tests (which included data from antisecretory models, cytoprotective models, in vitro assays, other anti-ulcer models, and even data taken from further IMAU testing) are shown in a number of documents produced from Takeda's files, including the 1984 Head Office Report and the 1986 FDA IND submission. (DTX705 and DTX120.) The 1984 Head Office Report was submitted to Takeda's Central Research Division, which oversees The Chemical Research Institute that employed named inventor Dr. Nohara and the Biological

[2] None of Takeda's withheld data, including even other IMAU data and data taken from other assays, supports an ID_{50} for lansoprazole of less than 1.0 or an ID_{50} for omeprazole of 21.0 or greater. All of the withheld data requires a less favorable comparison.

Research Institute that employed the other named inventor Dr. Maki. (DTX705.) In fact, the 1986 FDA IND submission was signed by inventor Dr. Maki.[3] (DTX120.)

Plaintiffs also cannot dispute that these not-disclosed results failed to support the claims that lansoprazole is 20 times superior to omeprazole. Indeed, results from some models showed omeprazole was superior. (See, e.g., DTX705 at TAKEDA-0044310 & TAKEDA-0044313-16.)

Plaintiffs instead defend the selective disclosure of data by arguing that the contradictory results were not material and there was no intent to deceive. The evidence belies those defenses.

B. Materiality: A Reasonable Patent Examiner Would Have Wanted to Consider the Full Range of Comparative Data Held By Takeda.

(1) A Reasonable Examiner Would Have Considered Contradictory Data.

(a) An Examiner Would Consider Contradictory Data Disclosed to the FDA.

Plaintiffs spend little space addressing the legal standard for materiality: whether a reasonable examiner would have considered the information important to the question of patentability. McKesson Information Solutions, Inc. v. Bridge Med., Inc., 487 F.3d 897, 913, 925 (Fed. Cir. 2007); Akron Polymer Container Corp. v. Exxel Container, Inc., 148 F.3d 1380, 1382 (Fed. Cir. 1998). Plaintiffs proffer, at trial and in briefs, arguments that the not-disclosed data was not material. (See D.I. 173 at 40-46.) This misses the point. These arguments should have been made during prosecution of the '098 patent. Plaintiffs deprived the examiner of the opportunity to consider the data and weigh the arguments. Hindsight assertions cannot fix this.

Plaintiffs claim that a reasonable examiner would not have considered even the disclosed IMAU data – or, presumably, the claims of "20 times" superiority – in evaluating the patentability

[3] Plaintiffs claim that the data in the 1986 FDA IND submission was selected by Takeda's Regulatory Authority, but cite no support for that claim. (D.I. 173 at 39.) In fact, it was Dr. Maki who signed the 1986 FDA IND submission. (DTX120 at Takeda–571236.)

of lansoprazole. (D.I. 173 at 47-78.) This new argument is speculation. A reasonable patent examiner would find undisclosed data or prior art that contradicts assertions made during prosecution important to patentability, particularly when that data is relied upon by the patentee in FDA submissions. See Monsanto Co. v. Bayer Bioscience N.V., No. 2007-1109, 2008 WL 200027 at *4, 7-9 (Fed. Cir. Jan. 25, 2008) (affirming finding of inequitable conduct arising from failure to disclose employee's notes about a prior art reference that contradict assertions made during prosecution); McKesson, 487 F.3d 897; Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359 (Fed. Cir. 2007); Bruno Independent Living Aids v. Acorn Mobility Services, 394 F.3d 1348 (Fed. Cir. 2005); Merck & Co. v. Danbury Pharmacal, Inc., 694 F. Supp. 1 (D. Del. 1988), aff'd, 873 F.2d 1418 (Fed. Cir. 1989).

Takeda's failure to disclose material data to the PTO is strikingly similar to the facts in Cargill on which the Federal Circuit affirmed a finding of inequitable conduct. Just as in Cargill, Plaintiffs disclosed certain data to the examiner, but withheld other data which the examiner would have wanted to see before deciding patentability. See 476 F.3d at 1366. And just as in Cargill, the withheld data was material, despite the fact that the data was from different test models and could not directly be compared to the data that was disclosed. Id. at 1365-66.[4]

Bruno compels the same result. In Bruno, the patentee claimed a stairlift; the patentee failed to disclose to the PTO several prior art stairlifts but, in a letter to the FDA seeking approval to sell the invention, it claimed that its stairlift was "similar in design and function" to those prior art stairlifts. This supported a finding of inequitable conduct. Bruno, 394 F. 3d at 1351-53 ("Had

[4] Plaintiffs attempt to distinguish Cargill on the grounds that the data was a "crucial issue" during prosecution and came from the same models as the data disclosed to the PTO, whereas in this case the data was not addressed by the examiner and came from different models. (D.I. 173 at 51.) The point in both cases, however, is that the patentee deprived the examiner of the opportunity to base the patentability decision on a complete understanding of the patentee's data.

the examiner known about the prior art, the patentee could not have touted the front offset swivel as a point of novelty.").

Similarly, the Merck & Co. court found inequitable conduct based on the patentee's failure to disclose lab results and prior art. 694 F. Supp. at 34-35. Merck filed a patent application claiming use of cyclobenzaprine to treat certain types of skeletal muscle disorders. Merck disputed the materiality of the lab results showing that amitripyline and cyclobenzaprine share similar chemical structure and pharmacological properties. The district court disagreed, noting that the reasons the data was relevant to the FDA applied equally to the PTO. Id. at 33-34. It may have been important for the FDA to see a comparison of the chemical analogs to show there was a unique difference between the drugs, but such an argument may be made "just as plausibly in the context of a patent prosecution." Id. at 34.[5]

Plaintiffs rely heavily on Takeda Chem. Indus. v. Mylan Labs., Inc., 417 F. Supp. 2d 341 (S.D.N.Y. 2006) (see D.I. 173 at 50-51), but that is a dramatically different case. There, the withheld data was cumulative. Takeda, 417 F. Supp. 2d at 390. Here, all of the withheld data contradicts the assertions of 20-fold superiority. Further, in Takeda, the patentee relied upon the data disclosed to the PTO to make "critical business decisions" about which compounds would be selected for further research and development. Takeda, 417 F. Supp. 2d at 390. Here, there is no contemporaneous evidence that the IMAU data was relied upon more than any other model to make "critical business decisions" about lansoprazole. In addition, there was evidence that the

[5] See also Ranbaxy Labs. Ltd. v. Abbott Labs., No. 04-C-8078, 2005 WL 3050608 (N.D. Ill. Nov. 10, 2005) (unpublished) ("[I]t may be that Abbott's patent prosecuting attorneys had no duty to investigate the prior art, but it does not follow that there was no duty to disclose information that Abbot itself had generated, especially where Abbott selectively disclosed other information from the same study. If accepted, Abbott's argument would permit a company to conduct sweeping studies of an invention, compartmentalize the results in separate divisions, and then submit only discrete portions to the PTO in support of specific claims while claming ignorance of other, potentially highly material information.") (emphasis added).

patentee in Takeda considered the disclosed data to be the "most reliable" data in its possession. Id. at 390. No such evidence exists about the IMAU data in this situation.[6]

Finally, in trying to avoid a finding of materiality, Plaintiffs assert that "[i]t is the inventors' role as scientists to select what data is relevant." (D.I. 173 at 42.) Plaintiffs' inventors took this role, but it was not theirs. The inventors' duty as patentees is to provide the candid, truthful information that a reasonable examiner would consider when determining whether a patent should issue. See Cargill, 476 F.3d at 1366 ("[M]ateriality is determined from the viewpoint of a reasonable patent examiner, and not the subjective beliefs of the patentee."). In this case, the examiner would have wanted to know that both the 1984 Head Office Report and the 1986 FDA IND submission include (1) dog models showing omeprazole to be superior in potency to lansoprazole; (2) dog and rat models showing omeprazole and lansoprazole to be equipotent; and (3) in vitro assays showing omeprazole to be superior to lansoprazole in inhibiting the proton pump. (DTX705 & DTX120; see also Whittle Tr. 1360:23-1361:12, 1373:12-16, 1374:1-6, 1376:6-12, & 1377:7-14.)

(b) The Examiner of the '098 Patent Considered Evidence of Potency During Examination of Previous PPI Patents.

Moreover, there is evidence that this examiner would have found the not-disclosed test data material. The examiner of the '098 patent, Jane T. Fan, also was the examiner of the prior art

[6] Plaintiffs' other citations likewise fail to support their argument. (D.I. 173 at 49 & 51–52.) For instance, in Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D. W.Va. 2004), the court held that the oral toxicity tests were not material because they were a poor measure of toxicity and there was no showing that the oral tests would have been relevant to the examiner's patentability determination. Id. at 742. In Eisai Co. v. Dr. Reddy's Labs., Ltd., the facts are quite distinguishable, including an express statement by the examiner that she was not interested in comparisons to the prior art compound. 472 F. Supp. 2d 493, 524 (S.D.N.Y. 2006).

Byk Gulden '409 and '518 patents.[7] (See DTX7 & DTX9.) Examiner Fan rejected the claims submitted in the applications for the '409 and '518 patents as prima facie obvious in view of, among others, the '431 omeprazole patent. In response, Byk Gulden proffered data showing the claimed compounds to be superior to omeprazole. (DTX7, col.13-16; DTX9, col.25, ll.1-31.) Examiner Fan ultimately accepted these arguments of superiority and issued both Byk Gulden patents – the '409 patent issued nine months before the '098 patent was filed in the United States and the '518 patent issued four months after the '098 patent was filed. Thus, data showing a potency advantage was important to Examiner Fan when making the patentability determination. See Tenneco Auto. Operating Co. v. Visteon Corp., 375 F. Supp. 2d 366, 375 n.12 (D. Del. 2005) (Robinson, J.) ("[T]he court finds the views of the particular examiner in this case to be probative of what reasonable examiners would consider important.").

(2) The '098 Patent Claims a Drug With Antisecretory and Cytoprotective Activity, Not Merely Anti-Ulcer Activity.

Plaintiffs attempt to argue that the bulk of the not-disclosed tests are immaterial because they do not relate to anti-ulcer activity, and the '098 patent relates only to anti-ulcer activity. (D.I. 173 at 40-42.) However, the '098 patent is not limited to a compound with anti-ulcer activity. To the contrary, the patent establishes that antisecretory, cytoprotective and anti-ulcer activities are entirely interrelated, and the claimed compound exhibits all three. The patent states:

> It is considered that gastrointestinal ulcer is induced by unbalance between aggressive factors, e.g. hydrochloric acid, pepsin, and defensive factors, e.g. mucus secretion and mucosal blood flow. Therefore, a medicine having both an action of inhibiting gastric acid secretion and action of enhancing protection of gastric mucosa has been desired.

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[7] Plaintiffs assert for the first time in their Answering Brief that "A Reasonable Examiner Would Not Rely On The IMAU Results In Evaluating The Prima Facie Obviousness Case." (D.I. 173 at 46–48.) Plaintiffs proffer no evidence, but do cite to the MPEP, which was not introduced at trial. (Id. at 47, n.12.) Teva respectfully submits that, if the Court entertains this argument, the Court should consider Examiner Fan's actions during prosecution of the Byk Gulden patents.

> The present inventors diligently studied with the purpose of preparing an anti-ulcer agent having excellent actions of inhibiting gastric acid secretion, of protecting gastric mucosa and of antagonizing ulceration. They found that a certain type of pyridine derivatives meets the said purpose, and they conducted further study to accomplish the said invention.

(PTX1, col.1, ll.20-33 (emphasis added); see Whittle Tr. 1325:13-1326:5 & 1326:19-1327:4.)

Further, the '098 patent discloses a range of tests that model gastrointestinal ulcers, including the cytoprotective model known as the ethanol-induced gastric lesion model. (Id., col.5, ll.33-36 ("As the models of gastrointestinal ulcers, restraint and water immersion stress-induced ulcer, indomethacin induced ulcer and ethanol induced gastric mucosal lesions have been used."). The inventors also made clear that antisecretory and cytoprotective activities were important properties of the claimed inventions, and that the claimed compounds are better:

> [T]he compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5-20 times or more. Besides, the compound (I) of the invention shows excellent actions of inhibiting gastric acid secretion, protecting gastric mucosa membrane and preventing ulceration.

(PTX1, col.6, ll.30-36 (emphasis added).)

In fact, and perhaps most tellingly, Takeda criticized prior art compounds, including omeprazole, because they did not exhibit sufficient cytoprotective activity, which Takeda noted was required for a "satisfactory" anti-ulcer agent. (PTX1, col.1, ll.13-16.) Thus, Takeda claimed that lansoprazole enjoyed a 20-times advantage in potency while withholding data that established a vastly lower advantage, and other data establishing that omeprazole was more potent. And Takeda criticized omeprazole for its lack of cytoprotective activity, asserting it was therefore not a "satisfactory" anti-ulcer agent, all while withholding data that established omeprazole did have cytoprotective activity, and that lansoprazole was not even twice as potent a cytoprotective agent as omeprazole. (DTX705 at TAKEDA-044325-26.)

(3) Takeda's Disclosure of Data Regarding Byk Gulden Compounds Does Not Exclude Selective Disclosure of Omeprazole Data.

Plaintiffs argue that the withheld data was not material because the examiner, cognizant of non-omeprazole data that showed less than 20 times superiority of lansoprazole, allowed the patent. (D.I. 173 at 42-44.) This argument fails for a number of reasons. First, Teva's claim to inequitable conduct relates specifically to the disclosure of one data point suggesting that lansoprazole was more than 20 times superior to omeprazole. This was a key, if not the key, comparison – Plaintiffs admit that omeprazole was a "benchmark." (Id. at 9.) Second, while Plaintiffs did disclose data regarding a Byk Gulden compound purporting to show a greater than 5-times potency advantage, that data was not complete, either. Further, the omeprazole patent was one of only eight patents Takeda disclosed to the examiner, and Jane T. Fan (and certainly any person skilled in this art) would have looked to omeprazole when weighing validity.[8]

(4) Takeda's Reliance on the Withheld Data Further Establishes Its Materiality.

The question at issue, as noted above, is objective: "What would a reasonable examiner have wanted to consider?" Plaintiffs attempt to confuse the issue by arguing that the inventors considered the IMAU test to be the best, and that Takeda management made decisions based on the IMAU data. (D.I. 173 at 34-35.) This is irrelevant, and incorrect. The contemporaneous evidence plainly establishes that Takeda considered all of the test data to be important.

The not-disclosed data was derived from models that test the antisecretory, cytoprotective, in vitro and anti-ulcer activity of a drug. No single model establishes the

[8] This argument also ignores the legal standard. Maybe a reasonable examiner would have allowed the patent with all of the omeprazole comparison data before it – although that is very unlikely, given the Byk Gulden rejections, see supra section I.B.1.b. This is doubly true in light of Dr. Dajani's testimony that as a pharmacologist he did not consider a compound patentable unless it had a minimum of 10-times superiority over the prior art. (Dajani Tr. 975:24–976:21.) Takeda deprived Examiner Fan of this opportunity.

clinical profile of a compound; all of these models are needed. (Whittle Tr. 1297:6-12.) Antisecretory, cytoprotective, in vitro and anti-ulcer models are related but independent and provide different types of information. (Whittle Tr. 1347:9-14.) All of these models contribute to an understanding of the pharmacological profile of lansoprazole – which is unquestionably why Takeda engaged in the expense of conducting them. (Whittle Tr. 1356:16-24; see also Dajani Tr. 665:3-12.) Further, each of the not-disclosed data models was well-established and accepted as an industry standard. (Whittle Tr. 1299:15-1300:16 & 1349:6-13.) In fact, the only model at issue that was not well-established at the time the '098 patent was filed was the IMAU model, which had been described only recently and which Plaintiffs' expert Dr. Whittle never adopted. (Whittle Tr. 1308:7-23.)

Plaintiffs' scientists relied on all of these models, including the data withheld from the PTO, to evaluate the relevant potency of omeprazole and lansoprazole – and none of Takeda's records support the assertion that the IMAU test was considered superior to other models. For example, as noted in the Opening Brief, the Table of Contents for the 1984 Head Office Report lists Takeda models relating (1) in vitro tests on (H^++K^+) inhibition, (2) suppression of gastric acid secretion, (3) defense of gastric mucosa (i.e., cytoprotection), and (4) anti-ulcer effect. (DTX 705 at TAKEDA-044307; see also D.I. 165 at 6-8.) The IMAU test is listed last, in Section 4.2, and it is the only listed test reported to the PTO. Dr. Whittle acknowledged that it appeared to him that Takeda considered all of the models in the 1984 Head Office Report – not only the IMAU data – when it decided to develop lansoprazole in late 1984. (Whittle Tr. 1357:21-1358:10; see also Dajani Tr. 662-667.)[9]

[9] The Table of Contents from the 1984 Head Office Report demonstrates how easily Takeda could have disclosed this data and given the Examiner a full picture of lansoprazole's activity. Plaintiffs ignore the Table of Contents in their Answering Brief.

Even the Takeda internal reports cited by Plaintiffs establish that other models were considered important (material) to determine lansoprazole's properties, not only the IMAU model. (See D.I. 173 at 35, discussing PTX131-134.) For instance, PTX133 contains a grid on TAKEDA-436726 that was cited by Dr. Whittle as containing data relied upon by Takeda scientists. (Whittle Tr. 1317:9-1318:15.) That data includes antisecretory models in dogs and rats (denoted "gastric secretion (his.)"), cytoprotective models (ethanol model denoted as "EtOH"), and anti-ulcer models (denoted "IMAU"). (See also Whittle Tr. 1309:10-1311:5; PTX 131 at TAKEDA-040942; PTX132 at TAKEDA-040950; and PTX134 at TAKEDA-040957.)

(5) Plaintiffs Fail to Provide Any Credible Explanation for the Selective Disclosure of Contradictory Data to the FDA.

Dr. Maki, a named inventor, personally signed the 1986 FDA IND submission. As mentioned in Teva's Opening Brief, the IND also contains data concerning (1) the inhibition of $(H^+ + K^+)$-ATPase, (2) the inhibition of acid formation, (3) antisecretory activity, and (4) anti-ulcer activity. (DTX120; see also Dajani Tr. 668-683.) The IND does not include or rely upon the IMAU data, the only data disclosed in the '098 patent. (DTX120.)

Plaintiffs attempt to excuse this selective disclosure by claiming that Plaintiffs took a "conservative" approach with the FDA. (D.I. 173 at 39.) This is exactly Teva's point. If these other tests were more conservative – i.e., better established, more accepted, material – a reasonable patent examiner would have wanted to consider them.

C. Direct and Circumstantial Evidence Establishes That Plaintiffs Intended to Deceive the PTO: Plaintiffs Have Failed to Provide Any Plausible Good Faith Explanation for Their Selective Disclosure of Data.

"Intent is easily inferred when, as here, an applicant makes arguments to the PTO that it knows, or obviously should have known, are false in light of information not before the examiner and the applicant knowingly withheld the additional information." Monsanto, 2008 WL 200027, at *20 (citing Cargill) (emphasis added). The Court should infer intent here.

Takeda brought no scientists to trial to explain their decision to withhold the contradictory data. The data that was disclosed supported the asserted 20-times potency advantage of lansoprazole; all of the withheld data contradicted this assertion. Dr. Satoh testified that he chose to disclose the IMAU data when he drafted the patent application because lansoprazole "showed strong activities" in this model. (Satoh Tr. 1569, l. 9-19.) The inventors certainly knew of the withheld data; Dr. Maki signed the IND in which the withheld data (but not the IMAU data) was submitted to the FDA. When publishing their work, the inventors relied on the withheld data (but not the IMAU data). (DTX82 & DTX595.)

On this record, and in light of Plaintiffs' failure to explain why it withheld contradictory data, the Court should find that the Plaintiffs intended to deceive the PTO. This is the paradigm case of "selective disclosure" – in which an inventor discloses some data to one agency but not another – that the Court described in Praxair. See Praxair, Inc. v. ATMI, Inc., 489 F. Supp. 2d 387, 395 n.9 (D. Del. 2007). The incentive is palpable: the economic benefit that Takeda sought, and its fall back to a me-too drug in light of its failure to develop a non-obvious, New Chemical Entity. (See D.I. 165 at 18-19.)

In response, Plaintiffs contend that Takeda had no intent to deceive because Takeda believed the IMAU model to be superior to other gastrointestinal models. The only support is the speculation of Plaintiffs' witness Dr. Whittle, who drew an "inference" that Takeda believed the IMAU data to be superior to all other data. Where is the evidence underlying this inference? Dr. Whittle was not involved in the decision to withhold data from the PTO; he did not talk to the inventors to hear their explanation; and he admits that he does not know what Takeda's employees were thinking. (Whittle Tr. 1358:17-1359:2.) Moreover, this inference is undermined by Dr. Whittle's admission that he heard about the IMAU model in the early 1980s but did not adopt the model in his own work. (Whittle Tr. 1308:7-23 & 1365:13-15.)

Dr. Whittle's inference is further undermined by Dr. Satoh's deposition testimony. Contrary to Plaintiffs' characterizations (D.I. 173 at 36), Dr. Satoh did not claim that he believed the IMAU model to be more important than other models. Rather, Dr. Satoh testified that the IMAU model "showed strong activities" in the IMAU model so he decided that "the results from this model were more important as compared to other test models." (Satoh Tr. 1569:9-19; D.I. 165 at 12.)

Plaintiffs cite the litigation-oriented deposition testimony of Dr. Maki about the importance of the IMAU assay (see D.I. 173 at 36), but none of the contemporaneous documents support that assertion. To the contrary, those documents – including documents signed by Dr. Maki himself while prosecution of the '098 Patent was ongoing – show that Takeda relied equally on all test models. (DTX120 & PTX131-134.)

Perhaps realizing that their other inequitable conduct defenses are untenable, Plaintiffs rationalize their selective disclosure by complaining that full disclosure would require submission of every "stray bit" of data, and that any disclosure is "inherently selective." (D.I. 173 at 49.) Not true. Takeda was not required to submit any data at all. But once it characterized its test results and the relative potency of lansoprazole, it was obliged to characterize those results fairly. Takeda had in hand the 1984 Head Office Report, which contained a high level summary of its test results. It could have disclosed the 1986 FDA IND submission, which Dr. Maki himself signed. Both documents contained fair, complete summaries of Takeda's test results and disclosure of either would have met the duty of candor. That is what Takeda did when it submitted its IND to the FDA – it provided a fair and complete description of those results, and the FDA would have investigated any failure to do so. Its submission to the PTO should have been just as candid.

This is not a case of failure to disclose one piece of cumulative data; this is a case in which reams of contradictory data were withheld from the PTO, but selectively disclosed to FDA. This

is the paradigm case described in Bruno, Merck, Praxair and the other cases cited by Teva, and this selective disclosure renders the '098 patent unenforceable.

II. THE PRIOR ART TEACHES DIRECTLY TOWARDS A SMALL NUMBER OF COMPOUNDS, ONE OF WHICH IS LANSOPRAZOLE

A. One of Skill in the Art Would Recognize That Lansoprazole Is an Obvious, "Me-too" Variation on the Timoprazole Skeleton.

This case is unlike almost any other. The obviousness inquiry for chemicals and drugs usually turns on the chance that a change to the structure might work. What would happen if I changed this substitution, or add that one? Would the "new" compound still work? That is not the case here. By August 1984, one of ordinary skill would have expected to succeed using a me-too approach to PPIs. Some compounds might be a bit more or less potent, and a very few might raise minor toxicity concerns, but virtually all would stop the proton pump. With the chances of success nearly 100%, the motivation to take the me-too approach is clear and strong.

One of skill in the art at the time would have known that the timoprazole "skeleton key" structure resulted in PPI activity. (Lenz Tr. 744:10-745:2; Kubo Tr. 1119:16-21.) In addition to the skeleton key, the art published by Dr. Sachs taught that the pKa of those compounds should be "near 4.0" to allow the drug to accumulate in the proton pump. (DTX13, Lenz Tr. 748:1-25; Lipinski Tr. 1174:12-1175:6.) This guiding principle taught anyone of skill in the art to focus his/her "substitution strategy" on the pyridine ring. (Lenz Tr. 751:23-753:1 & 761:15-762:5; see also Lipinski Tr. 1260:17-1261:8 (Takeda considered the pKa of these compounds).) One of skill also knew that putting an alkoxy at the 4 position on the pyridine ring would keep the pKa near 4.0. (Lenz Tr. 746:15-751:22 & 760:14-762:1.)

After focusing on the 4 position, one of skill would make a short list of substitutions at the three other positions (the 3 and 5 positions on the pyridine, and the benzimidazole ring) to determine the effect on the compound's activity, a process that Dr. Lipinski described as

"peppering" or "probing" the compound. (Lipinski Tr. 1231:18-1232:3, 1269:16-1271:5; see also Lenz Tr. 767:12-768:7.) The result would be a set of me-too compounds to test: "maybe it's 15, 20 compounds, in that set, that will contain lansoprazole." (Lenz Tr. 768:11-12, 761:15-762:5 & 763:8-765:13.) Each such compound would have the "skeleton key" structure and a pKa near 4.0; one would expect that each would have activity. (Lenz Tr. 773:21-774:12.) Whether one started with omeprazole or timoprazole, the endpoint is lansoprazole. (Lenz Tr. 766:24-768:7.)

As much as Plaintiffs disavow this road map for developing a me-too PPI compound, there is no doubt that Takeda followed it to the letter. Takeda first made timoprazole. They then made omeprazole and used it as a "benchmark" or lead compound. They settled on an alkoxy (but not only a methoxy) substitution at the 4 position. They followed exactly the substitution strategy described by Dr. Lenz and taught by Hässle and Byk Gulden. And they arrived, logically and inevitably, at lansoprazole and "maybe . . . 15, 20" identical me-too compounds.

Plaintiffs present essentially four arguments that this me-too compound is not obvious: (1) the prior art taught away from lansoprazole, (2) there were "hurdles" to the development of a PPI that one of skill in the art would not have understood, (3) Takeda's gastrointestinal program lasted 28 months overall, and (4) secondary indicia rebut a prima facie showing of obviousness. (D.I. 173 at 7-32.) None of these assertions save the '098 patent.

B. The Prior Art Teaches Directly Towards Lansoprazole and Related Compounds.

(1) The Timoprazole "Skeleton Key" Stops the Proton Pump.

The prior art taught how to analog a successful PPI. Indeed, one of ordinary skill benefited from a surprisingly robust amount of information about a surprisingly robust class of compounds. Plaintiffs' Dr. Kubo admits that it was known that the timoprazole "skeleton key" structure was necessary for PPI activity; that is why Takeda used that skeleton in its me-too development. (Kubo Tr. 1119:16-21.) Omeprazole, itself sharing that skeleton, was the lead compound because

it was already in clinical trials in Europe and the United States, and doctors "eagerly awaited" this "miracle drug." (Fennerty Tr. 829:21-831:1; Lenz Tr. 766:10-21 & 1430:27-1431:7.)

As of August 1984, at least four patents already claimed me-too analogs, and each taught a substitution strategy focused on four key locations on the skeleton. (D.I. 165 at 30-39.) Every prior art patent, including the Hässle and Byk Gulden patents, disclosed the same systematic, step-wise substitution strategy. (See DTX5, DTX7 & DTX9.) The Hässle scientists used a short list of substituents (methyls, ethyls, alkoxies, and halogens such as fluorine), each only one or two carbons long, and pursued a logical, methodical approach, placing the components at four key positions (the benzimidazole, and at the 3, 4 and 5 positions on the pyridine) and virtually all worked. (D.I. 165 at 34-35; Lenz Tr. 744:10-745:2.) Byk Gulden introduced a small class of fluorinated substitutions, and they worked. (D.I. 165at 38-39.) By August 1984, over seventy me-too compounds were synthesized using this strategy; they inhibited the proton pump. (D.I. 165 at 30-39.)

These lessons were clearly taught by the art, but were not necessary. "Keeping one set of substitutions the same while changing others is a common approach to substitution oriented drug discovery[.]" (Lipinski Tr. 1223:10-13.)

(2) Omeprazole Was the "Benchmark."

Takeda was aware of timoprazole, omeprazole, and the '431 omeprazole patent when it adopted a me-too substitution approach. (Kubo Tr. 1121:2-6.) Takeda used omeprazole as the "benchmark" or "starting point" for research because omeprazole was already in clinics. (Kubo Tr. 1138:11-13; Lipinski Tr. 1227:24-1228:4, 1230:19-22 & 1254:17-25.)

(3) A Chemist Would Have Identified a Number of Obvious Alkoxies.

One of skill in the art in August 1984 knew that putting an alkoxy at the 4 position on the pyridine ring would keep the pKa near 4.0. Plaintiffs admit they were well aware of this fact.

(Lipinski Tr. at 1174:12-1175:6.) Plaintiffs assert, however, that a chemist would have considered only a particular type of alkoxy, methoxy, at the 4 position. (D.I. 173 at 16-17.)

Plaintiffs cannot deny that many alkoxy substitutions would work. The '431 omeprazole patent itself shows other alkoxies, not just methoxy, were successful. For instance, example 15 in Table 2 of the '431 omeprazole patent shows an ethoxy substituent (OC_2H_5) at the 4 position, and example 27 shows an ethoxy-methoxy group ($OC_2H_4OCH_3$) at the 4 position. (See DTX5, col.11-12, ll.1-40.) Both of those compounds showed PPI activity.

In support of this assertion, Plaintiffs point to the one fluorinated alkoxy that would not work: trifluoromethoxy. But both parties' chemistry experts testified that a chemist would have known to avoid that substituent. (Lipinski Tr. 1229:7-23; Lenz Tr. 815:4-816:2.)

Plaintiffs now also argue that the Byk Gulden patents only teach the use of a methoxy substitution at the 4 position. Hardly; claim 1 of the Byk Gulden '518 patent claims an "alkoxy radical" at the 4 position, not only a methoxy. (See DTX 9, col.26, ll.26-27 wherein "R3" refers to the 4 position of the pyridine ring.) Of course, ethoxy substitutions, including trifluoroethoxy substitutions, employ alkoxy radicals.

(4) One of Skill Would "Pepper" or "Probe" the Other Three Positions on the Pyridine and Benzimidazole Rings.

Plaintiffs further argue that the '431 omeprazole patent teaches away from the methyl substitution pattern and unsubstituted benzimidazole ring in lansoprazole. This argument ignores the road map provided by the prior art. In order to reach the "sweet spot" for PPIs (a pKa near 4.0), one of skill would begin with an alkoxy at the 4 position of the pyridine ring. After the alkoxy was set at the 4 position, one of skill would compose a list of the five or so common substituents (methyls, ethyls, alkoxies, halogens, etc.) to put at these positions on the pyridine and benzimidazole rings, and synthesize 15 or 20 compounds to test. (D.I. 165 at 43-45.)

(5) The Byk Gulden Patents Taught Fluorinated Alkoxy Substituents.

The Byk Gulden patents underscored the importance of the skeleton key structure and an alkoxy substituent at the 4 position of the pyridine ring. (D.I. 165 at 38-39.) Byk Gulden also suggested the use of fluorinated alkoxy substituents, such as trifluoroethoxy, in PPIs.

Dr. Lenz further testified that trifluoroethanol, the precursor to trifluoroethoxy, was readily available in August 1984. (Lenz Tr. 814:7-23.) Thus, Takeda would have been able to mass-produce compounds using trifluoroethoxy as a substituent, something Dr. Lipinski referred to as "synthetic doability." (Lipinski Tr. 1234:12-1235:10.)

In addition, well-known properties of fluorine, such as its ability to increase lipophilicity (and therefore bio-availability), make it an obvious choice to use in substituents on PPIs. (D.I. 165 at 39-40; DTX82; Nohara Tr. 1502:23-1504:16 & 1506:16-1507:17; Kubo Tr. 1144:7-20, 1146: 9-19 & 1147:10-13.) A fluorinated substituent will effect lipophilicity, regardless of where you substitute it on the PPI. (Lipinski Tr. 1272:16-21.)

(6) It Is Not Relevant That Omeprazole Cannot Be Converted to Lansoprazole.

Plaintiffs' claim that it is not possible to convert omeprazole into lansoprazole is irrelevant. One of skill in the art does not take one compound and convert it to another any more than a locksmith takes one key and converts it to another, or a chef uses steak au poivre to make steak tartare. Molecules are not like Legos® in which we pop off one substituent and snap on another. Rather, as Dr. Kubo testified, a lab maintains precursors and assembles molecules from them. (Kubo Tr. 1131:10-24.)

The point is what the development of the prior art compounds taught:

- Hässle introduced the skeleton key structure.
- Hässle synthesized fundamental substituents on the benzimidazole ring.
- Hässle moved those substituents to the pyridine ring to develop omeprazole.

- Byk Gulden then introduced fluorinated alkoxy substituents, including trifluoroethoxy, on the benzimidazole ring and proved they worked.

(D.I. 165 at 30-39.) The next logical step was to put the fluorinated alkoxy substituents, including trifluoroethoxy, at the 4 position of the pyridine ring, especially given that the benzimidazole ring was so thoroughly explored and patented that there was no chance left for novelty. (Lenz Tr. 773:2-774:1 & 1437:18-1439:11.)

(7) Prior Courts Have Found Obviousness Under Similar Facts.

This Court's holding in Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F.Supp. 330 (D. Del. 1991), aff'd, 972 F.2d 1354 (Fed. Cir. 1992) is instructive. The Imperial Chem. court held a claim covering the compound atenolol, one of a class of drugs known as beta-blockers used to treat hypertension, obvious in light of a prior art beta-blocker possessing a similar skeleton structure. See 777 F.Supp. at 373. There, "the prior art suggests not only the requisite structure necessary for beta-blocking activity but the portions of this structure which can tolerate modification without a resultant loss of beta-blocking activity." Id. at 369-370 (emphasis added); see also In re Merck & Co., 800 F.2d 1091, 1096 (Fed. Cir. 1986) ("Structural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties."). "Further, the prior art indicates that quite diverse modifications can be tolerated in the modifiable portions without a loss of either beta-blocking activity or usefulness in the treatment of hypertension." See 777 F. Supp at 370 (emphasis added).

The Hässle and Byk Gulden patents and the Sachs reference disclosed to one of skill in the art that the requisite structure for PPI activity was the timoprazole skelton with an alkoxy substituted at the 4 position of the pyridine ring to keep the pKa of the compound "near 4.0." (See supra section II.B; see also D.I. 165 at 28-45.) As long as that core structure was maintained, substitutions to the compound reasonably could be expected to show PPI activity.

Plaintiffs rely on Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007) and Bayer AG v. Dr. Reddy's Labs., Ltd., C.A. No. 04-179-SLR, 2007 WL 3120794 (D. Del. Oct. 25, 2007). (D.I. 173 at 25-26.) The holding in Takeda v. Alphapharm turned on the fact that the defendant selected an incorrect lead compound that had toxicity concerns and there was no reasonable expectation that making a change to the prior art would reduce or eliminate the toxicity concern. See 492 F3d at 1357-1360. In Bayer, this court likewise held that the defendant identified the wrong lead compound and failed to suggest a motivation to modify the incorrect lead compounds with any reasonable expectation of success.

This case is different. So long as the lead compound has the timoprazole skeleton key structure, it does not matter which you choose; using the obvious me-too substitution strategy, whether the chemist started with timoprazole or omeprazole they would arrive at lansoprazole. (Lenz Tr. 766:24-768:7.) Further, there would be much more than a reasonable expectation of success. And toxicity concerns that may have arisen with the discovery of timoprazole were settled by the development of omeprazole, and virtually no other PPIs showed toxicity at all.

C. Dr. Lipinski's "Hurdles" Did Not Play a Role in Lansoprazole's Development.

Plaintiffs essentially contend that no PPI patent could ever be obvious because medicinal chemists would not have understood how a PPI: (1) accumulates in the parietal cell, (2) remains stable in the blood, (3) converts to an active species, or (4) fits into the Proton Pump (Dr. Lipinski's so-called "hurdles" to development). (D.I. 173 at 12-14.) These arguments defy common sense. If Plaintiffs are correct that no one understood these "hurdles," then they would play no role in the development process.

Dr. Lipinski acknowledges that one of skill in the art does not have to understand how a new compound works to design it. (Lipinski Tr. 1229:24-1230:4.) Instead, one of skill would look to what was known from the prior art, identify a limited set of compounds to synthesize, and

test those compounds for activity. That's exactly what happened here. When Takeda went to a substitution approach, it started with the skeleton key, used the teachings of the '431 omeprazole patent and the Byk Gulden patents to identify new substituents to place on the skeleton key, and tested the synthesized compounds for activity. All of this occurred without Takeda having any knowledge about the final three of Dr. Lipinski's four hurdles.[10] Indeed, Takeda did not report on testing of the stability of lansoprazole (Hurdle No. 2) until September 1984 – after the priority application for the '098 patent had been filed and when Takeda was working on the lansoprazole formulation. (See PTX134 at Takeda-040957.)

D. Lansoprazole Was Developed in Less Than Twelve Months, Not 28 Months.

(1) In 1982, Takeda Began Work to Develop a "New Chemical Entity."

Plaintiffs claim that it took Takeda 28 months to develop lansoprazole. (D.I. 173 at 11.) This is misleading. Before beginning the me-too strategy, Takeda's first employed two other parallel approaches to development, neither of which was successful. First, Takeda engaged in what they termed "random screening," in which they screened whatever compounds they had in storage. (Kubo Tr. 1109:7-15.)[11] The random screening approach did not succeed. Second, Takeda broke down the known PPI compound timoprazole (the skeleton key structure) by separating it into its three components and replacing one or more of the components in an attempt to develop a truly new compound – a so-called "New Chemical Entity." (Kubo Tr. 1143:1-17;

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[10] As Teva explained in its Opening Brief, Takeda would have understood from the Sachs reference that a pKa of approximately 4.0 would result in proper accumulation of a PPI in the parietal cell. (D.I. 165 at 36-37, discussing DTX13.) The teachings of the '431 omeprazole patent further would instruct one of skill that a pKa of 4.0 resulted from the alkoxy at the 4 position of the pyridine ring. (Lenz Tr. 772:11–773:8.)

[11] When Dr. Lipinski arrived at his opinions concerning the amount of time and number of compounds that it took for Takeda to synthesize lansoprazole, he did not know that Plaintiffs used this "random screening" approach to development; he learned that only at trial. (Lipinski Tr. 1235:20-1236:1, 1236:12-1237:7 & 1237:21-1238:10.)

Lenz Tr. 729:5-15 & 1433:5-1434:2.) Takeda spent 18 months working on an NCE compound, but that also failed. (Lipinski Tr. 1239:18-21; Kubo Tr. 1137:16-18 .)

Both of these approaches were long shots or "high risk" strategies. (Lenz Tr. 729:16-730:2.) If they succeeded, however, Plaintiffs were virtually assured of patent protection.

(2) Takeda Switched to a Me-Too Substitution Approach and Synthesized Lansoprazole Ten Months Later.

In May 1983, having failed in its two initial approaches, Takeda switched to a me-too substitution approach when it synthesized omeprazole (AG-1414) and began working on omeprazole analogs. (Lipinski Tr. 1216:19-1217:8 & 1218:13-24; Lenz Tr. 1435:16-1436:6.) Until then, Takeda had not attempted a subsitution strategy. (Kubo Tr. 1143:1-7.) In the me-too approach, Takeda kept the known timoprazole skeleton intact and made minor changes using the same substitutions (methyls, ethyls, alkoxies and halogens, see Appendix A) taught by the inventors of omeprazole and the Byk Gulden patents. Nearly every one of those variations worked. (DTX59.) Only one or two raised any toxicity concerns. Nothing else – none of Takeda's New Chemical Entities – worked at all.

The motivation to take this me-too approach was strong. The potential market was enormous, and Plaintiffs wanted in as fast as possible. (Lenz Tr. 762:12-23.) The result was just what Takeda wanted. It took only one year to synthesize the lansoprazole – a time frame that Dr. Lipinski acknowledges is far shorter than normal. (Lipinski Tr. 1273:22-1274:18.)

Working from omeprazole, Takeda synthesized different kinds of alkoxy groups at the 4 position of the pyridine ring, while keeping in mind that the compound needed to stay within "a range of pKa values" near 4.0. (Lipinski Tr. 1174:22-1175:6 & 1264:11-15.) Dr. Kubo testified that the first thing that Takeda did was set this alkoxy at the 4 position. (Kubo Tr. 1139:4-1140:2.) In July 1983, only two months after synthesizing omeprazole, Takeda synthesized AG-1511. (Kubo Tr. 1124:12-16.) AG-1511 served as a turning point in Takeda's development because, like

omeprazole, AG-1511 had an alkoxy at the 4 position of the pyridine ring. (Lipinski Tr. 1265:2-5.) Interestingly, only two analog compounds were made in the 18 months between timoprazole (AG-879) and AG-1511 – omeprazole and one other. (Kubo Tr. 1140:19-23.) This is a sure sign that the me-too approach did not start until omeprazole was synthesized.

Shortly thereafter, Takeda began to rely on knowledge concerning fluorinated substituents that it had obtained from the Byk Gulden patents, including the use of trifluoroethoxy.[12] In fact, Takeda first used fluorinated substituents in its me-too development program just five weeks after the Byk Gulden '409 patent issued – a fact that Dr. Lipinski admitted he did not know until his cross-examination at trial. (Lipinski Tr. 1263:7-15.) Armed with this knowledge, Takeda took less than four months (July 1983-October 1983), and only eleven synthesized analog compounds, to go from alkoxy substituent at the 4 position in AG-1511 to a trifluoroethoxy substituent at the 4 position in AG-1598. (Kubo Tr. 1126:8-1127:9; Lenz Tr. 1435:20-1436:10 & 1438:7-1439:11.)

After AG-1598 showed activity as a PPI, Takeda began "peppering" or "probing" the pyridine and benzimidazole rings with various substituents, including various methyl substituents. (Lipinski Tr. 1225, l. 24-1225, l. 5; 1269, 1. 16-1270, l. 9.) The purpose was to see if these other substituents enhanced the activity of AG-1598.[13] (Kubo Tr. 1125:9-14.) As a result, lansoprazole was synthesized on May 24, 1984 – only seven months and 27 analog compounds after AG-1598 was synthesized. (Kubo Tr. 1127:20-22 & 1128:8-10.) In the end, Plaintiffs synthesized only 38

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[12] Takeda learned of the Byk Gulden patents in early 1983 and adopted a strategy of using the fluorinated substituents, including trifluoroethoxy, taught by Byk Gulden on the timoprazole skeleton. (Kubo Tr. 1143:14-17 & 1144:7-12.) There were two reasons for Takeda to focus on trifluoroethoxy: (1) it had not been used a lot before, and (2) it looked different if used on the pyridine ring, such Takeda could argue for a patent. (Lenz Tr. 1438:20–1439:8.)

[13] Indeed, Takeda continued to synthesize different methyl substituent combinations after lansoprazole was synthesized. (Lenz Tr. 1444:6-16.) Takeda likewise continued to synthesize compounds with both substituted and unsubstituted benzimidazole rings after lansoprazole was synthesized. (Lenz Tr. 1443:22–1444:5.) Thus, Takeda continued to follow the step-wise, substitution methodology made obvious by the prior art.

analog compounds between omeprazole (AG-1414) and lansoprazole (AG-1749).[14] Notably, Takeda never abandoned the "random screening" and "NCE" strategies, but continued to devote time and resources to them even after making lansoprazole.

A timeline of Takeda's actual development of lansoprazole is attached in Appendix A.

E. Plaintiffs Then Believed Lansoprazole Was "Too Similar" to Omeprazole.

At the time, Takeda evaluated lansoprazole and concluded it was "too similar to omeprazole" to be patentable (DTX703), an admission Plaintiffs seek to disavow. (D.I. 173 at 19.)

Plaintiffs question the circumstances of the creation and authorship of DTX703, but raised no such objection at trial. (Kubo Tr. 1150:10-12.) Because Takeda produced DTX703 in response to a discovery request, it is a party admission by Plaintiffs. See South Cent. Bank & Trust Co. v. Citicorp Credit Services, Inc., 863 F. Supp. 635, 644-46 (N.D. Ill. 1994) (finding, while evaluating a document with an unidentified author, that "the fact that [the company] produced the draft letter suffices to authenticate" it and it "may be construed as an admission" against the company) (emphasis added). Although the exact author of DTX703 is unknown, Takeda's production of the document is enough to "establish that it was drafted by a [Takeda] agent acting within the scope of his or her employment." See id. at 646. Thus, regardless of who authored it, any statements found within DTX703 are attributable to Plaintiffs. Plaintiffs, who are uniquely positioned to investigate these questions, brought no witness to trial to address them.

[14] Takeda's development work was recorded in PTX63-83, DTX406, DTX408, DTX416, DTX418-427, DTX508, DTX609-611, DTX614-619 and DTX621-622.

F. Plaintiffs' Alleged Secondary Indicia Do Not Rebut Teva's Prima Facie Case of Obviousness.

(1) Lansoprazole Exhibited No Unexpected Results Over Omeprazole.

Plaintiffs incorrectly argue that lansoprazole exhibited unexpected clinical advantages over omeprazole. Plaintiffs' expert Dr. Fennerty admitted at trial that omeprazole and lansoprazole are equally effective for healing and that he (a GERD sufferer) would take whatever PPI he has in his toiletry bag. (Fennerty Tr. 849:7-9 & 865:7-10.) Further, Plaintiffs' witness Mr. Cole admitted that when TAP launched Prevacid®, no studies approved by the FDA demonstrated any superiority relative to Prilosec®. (Cole Tr. 1064:6-23.) These admissions are supported by clinical literature and the testimony of Teva's expert Gastroenterologist Dr. Solny, which agree that all PPIs are equally effective. (Solny Tr. 583:4-19; DTX142 at TVL063405; see also Solny Tr. 574:5-575:15; DTX145 at TVL063411; DTX144 at TVL063991.)[15]

Plaintiffs failed to distinguish lansoprazole based on speed of symptom relief and bio-availability. The clinical literature, including papers written by Dr. Fennerty and others, dispel any notion that doctors would have prescribed lansoprazole over omeprazole. In 2003, Dr. Fennerty wrote that more data was needed to determine whether there were any clinical differences between the PPIs. (Fennerty Tr. 855:11-19.) In 2005, Dr. Fennerty wrote another paper stating there was no difference in efficacy between the PPIs for on-demand therapy. (Fennerty Tr. 855:20-25.) At trial, Dr. Fennerty admitted that after initial dosing, the bio-availability of omeprazole and lansoprazole are similar. (Fennerty Tr. 850:7-21.) Further, the OHSU meta-analysis containing more than 200 studies comparing the effectiveness of PPIs concluded that all PPIs are equally effective. (DTX 141 at TVL 063461.)

[15] Plaintiffs claim that Dr. Solny "admitted" that lansoprazole has a faster onset than omeprazole. Dr. Solny testified to exactly the opposite. Asked if he agreed with Dr. Fennerty's contention that lansoprazole had faster onset, Dr. Solny responded "No." (Solny Tr. 587:6-15.)

Plaintiffs cannot refute these studies. The 2001 Richter study, which was funded by TAP, concluded that "it remained to be seen" whether the study findings would be of clinical relevance. (DTX386 at TVL063694.) Indeed, a commentary on this study, which Dr. Fennerty admitted was "very widely read," dismissed the Richter findings as "clinically trivial." (Fennerty Tr. 854:9-19; DTX144; see also Solny Tr. 592:4-18.) Dr. Richter even concluded in 2007 that, "[d]espite the marketing hype, all PPIs are equally effective." (DTX137 at 626.)

Finally, Plaintiffs adduced no evidence that drug-to-drug interactions of PPIs effected the prescribing habits of physicians. Dr. Fennerty acknowledged that drug-to-drug interactions with omeprazole "were as rare as hen's teeth." (Fennerty Tr. 858:25-859:8.) Dr. Solny has never had a patient experience an interaction with omeprazole or lansoprazole. (Solny Tr. 593:20-594:7.)

(2) There Is No Evidence That Other Companies Failed to Develop a Me-Too PPI Compound Using the Substitution Approach.

Plaintiffs assert that 40 companies tried to produce a viable PPI and only four companies have PPI products on the market. This is irrelevant. Dr. Lenz articulated at least two reasons that other companies may not have gone to market. First, many companies likely adopted the "New Chemical Entity" approach to developing PPIs, not a "me-too" substitution approach. (Lenz Tr. 1432:13-1433:21.) For instance, Dr. Lenz's employer G.D. Searle & Co. insisted that its scientists adopt the NCE approach. (Id. at 1432:21-23.) Plaintiffs provided no evidence that companies such as Searle failed to produce an analog of omeprazole. Moreover, it is likely that any companies that did produce an analog concluded, as did Takeda, that the compound was "too similar to omeprazole" to be patentable. (DTX703.)

Second, the last 36 companies would have abandoned further PPI development. Drug companies have a strong financial incentive to stop development if they will not recover investment costs. (Lenz Tr. 1431:17-1432:7.) There is a significant "barrier to entry" for a new drug, and the sixth or seventh possible entrant would have a strong incentive to stop further work.

(Vandaele[16] Tr. 1021:4-14; Lenz Tr. 1431:17-1432:7.) Plaintiffs presented no evidence establishing that companies failed, rather than abandoning efforts because of the economics involved.

(3) Lansoprazole's Properties Did Not Result in Commercial Success.

No evidence links lansoprazole's (sold in the U.S. under the brand name Prevacid®) sales to its properties as a drug. Whatever success lansoprazole enjoyed is tied to other economic and commercial factors. At least four other factors fully account for Prevacid's sales: (1) TAP's highly aggressive marketing campaign, (2) lansoprazole's similarity to the pioneer, omeprazole (Prilosec), (3) lansoprazole's early entry into the PPI market, and (4) large pre-launch development investment expenses that created a barrier for other PPIs to enter the market. (Vandaele Tr. 1000:13-22.) Plaintiffs offered no rebuttal economic analysis at all.

Prevacid's aggressive marketing explain the volume of its sales. (Id. at 1002:13-24.) TAP, initially relying heavily on Abbott's well established sales force to market and distinguish its product, spent significant amounts on promotional expenses, doubling the amount spent to promote Prevacid each consecutive year after it was first launched. (Id. at 1013:1-1015:7; DTX163; see also Cole Tr. 1063:9-20.) Between 1995 and 2006, TAP spent more than $1 billion on promotional expenses alone to market Prevacid. (Vandaele Tr. 1015:7-10; DTX163.) Of the top ten pharmaceutical products on the market in 2003, TAP ranked second in spending for "direct to consumer advertising" for its promotion of Prevacid. (Vandaele Tr. 1011:14-1012:3; DTX156.) In 2004, TAP spent approximately $750 million marketing Prevacid, and approximately $2 billion in the three-year period from 2004 to 2006. (Vandaele Tr. 1008:23-1009:12; DTX162.) Such a marketing blitz significantly undercuts any relationship between Prevacid's sales and its

[16] Dr. Vandaele is a highly qualified economist. (Vandaele Tr. 993:23-999:18; DTX149.) He was also the only economist to testify at trial.

properties. McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1370 (Fed. Cir. 2003) (holding that launching a massive marketing and advertising campaign obscured any nexus that might have existed between the merits of the product and its commercial success).

Even with that level of spending, Prevacid's failed to cannibalize sales of Prilosec. Rather, Prilosec's sales volume continued to grow. (Cole Tr. 1067:10-13.) Indeed, Prevacid did not overtake Prilosec's sales until 2003, four years after the '431 omeprazole patent expired and eight years after Prevacid's launch. (Cole Tr. 1069:24-1070:9; Vandaele Tr. 1046:7-12.)

Plaintiffs assert that Dr. Vandaele tied Prevacid's properties with success. (D.I. 173 at 30.) That mischaracterizes his testimony; Dr. Vandaele testified that a product with a billion dollars worth of sales would be a good product from a "business perspective"; he did not suggest that such sales resulted from the properties of lansoprazole rather than economic and commercial factors. (Vandaele Tr. 1030:16-20.)

The similarities between lansoprazole and omeprazole also increased Prevacid's sales. Prevacid was launched six years after Prilosec entered the market. (DTX141 at TVL063422.) AstraZeneca established a large PPI market through its extensive marketing of Prilosec, which enhanced sales of Prevacid.[17] (Cole Tr. 1060:8-20; Vandaele Tr. 1017:6-14 & 1044:22-1045:8.) Prevacid, as the second entrant into the PPI market, also enjoyed the fruits of AstraZeneca's labor and maintained a significant advantage over subsequent PPIs, which did not begin entering the market for another four years after Prevacid was launched. (Id at 1022:6-1023:15; see also DTX141 at TVL063422.) Prevacid's sales were also enhanced because so few companies entered the already saturated PPI market. (Vandaele Tr. 1021:6-23; DTX186.1.)

[17] AstraZeneca (formerly known as Hässle), the maker of Prilosec, spent more than twice as much on marketing than it spent on research. (Vandaele Tr. 1005:7-16; see also DTX206.)

(4) Lansoprazole Filled No Unmet Needs.

Plaintiffs offer no support for the assertion that lansoprazole met any long-felt need for a safe and effective PPI that was not already met by omeprazole. Alza Corp. v. Mylan Labs., Inc., 388 F. Supp. 2d 717, 741 (N.D. W.Va. 2005) (finding no unmet need when the patentee identified no evidence indicating a long-felt or unsolved need for once-a-day dosing of a drug product and the need was substantially solved by prior art patents), aff'd 464 F.3d 1286, 1295 (Fed. Cir. 2006). Dr. Fennerty contradicted any such claim by testifying that omeprazole was a "miracle drug" and created a "paradigm shift in medicine." (Fennerty Tr. 829:22-830:11 & 849:12-850:6.)

CONCLUSION

For reasons set forth herein and in Teva's Opening Post-Trial Brief (D.I. 165), Teva respectfully submits that the Court should hold that the '098 patent is unenforceable due to inequitable conduct, claim 10 of the '098 patent is invalid as obvious, and claim 2 of the '321 patent is invalid as obvious.

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CERTIFICATE OF SERVICE

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