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. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES LTD., Defendants and Counterclaim-Plaintiffs.	)	C.A. No. 06-033 (SLR)

PLAINTIFFS' ANSWERING POST-TRIAL BRIEF

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I. PRELIMINARY STATEMENT

Teva's business strategy is clear. The proton pump inhibitor ("PPI") market is large and profitable. As a result, Teva has challenged the patentability of many branded PPIs currently on the market. By now, the nature of these challenges have become predictable: Teva routinely asserts that the discovery of the compound must have been obvious in light of the prior art, and the patent must have been procured by inequitable conduct.

As the evidence at trial demonstrates, Teva hit a dry well in the case of lansoprazole. At trial and in its opening post-trial brief, Teva fails to explain why the chemical structure of lansoprazole would have been an obvious choice from among more than 13 million possible modifications to the prior-art timoprazole compound. Teva also fails to explain why one would modify omeprazole (itself a modification of timoprazole) to construct lansoprazole, which employs different substituents in different positions. In fact, the omeprazole molecule cannot be directly converted into lansoprazole.

Teva's brief also ignores the testimony of Plaintiffs' expert, Dr. Lipinski, regarding the four unique hurdles to PPI design that hindered any "logical" development, the prior art which taught away from the chemical structure of lansoprazole, and the difficulties that dozens of pharmaceutical companies experienced in trying to develop a new PPI. Teva also does not rebut the secondary considerations supporting lansoprazole's novelty: Teva cannot explain away the failure of 40 or more pharmaceutical companies to develop a viable PPI, and the success of only a handful; the $34 billion commercial success of lansoprazole; or lansoprazole's unexpected advantages like faster onset of action and pain relief, fewer drug interactions, and greater solid-state stability. Teva's efforts to trivialize these objective indicia of nonobviousness defy common sense.

At core, Teva's obviousness challenge baldly contends, without record citation, that any substitution on the toxic prior-art timoprazole skeleton would work with the proton pump. Teva Br.[1] at 31 ("[W]hatever the substitution pattern … the timoprazole skeleton key still fits the Proton Pump's lock"). Dr. Lipinski's testimony showed why Teva was wrong: many variations of timoprazole unpredictably lead to compounds with potential ADME (Absorption, Distribution, Metabolism, Excretion) or toxicity problems. Lipinski 1180:7-1182:12; 1183:1-1184:16.[2] And many variations would not be stable in the blood, convert into an active species, or fit into the proton-pump protein. Lipinski 1173:15-1174:8. Indeed, Teva's contention is belied by the efforts of the more than 40 companies that failed to develop a viable PPI, including Searle, where Teva's experts, Drs. Lenz and Dajani, worked during the relevant invention period.

Teva contends that its obviousness and inequitable conduct challenges are "inextricably intertwined." Teva Br. at 1. Plaintiffs agree. Both challenges suffer from the same shortcomings. The evidence at trial demonstrates that: (1) the inventors and Takeda management relied on the same IMAU data reported in the '098 patent to pursue lansoprazole over other novel anti-ulcer compounds; (2) the raw data in the inventors' lab notebooks confirms the accuracy of the IMAU data in the '098 patent; and (3) the "additional data" that Teva contends is evidence of inequitable conduct is either irrelevant to, or supports, the inventors' belief in the '098 compounds' superior anti-ulcer effect. In light of this record, Teva presents no evidence that the inventors—Drs. Nohara and Maki—or anyone else who was substantively involved in the prosecution of the '098 patent, intended to mislead the PTO.

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[1] "Teva Br. at" refers to the corrected "Opening Post-Trial Brief of Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. Regarding the Invalidity and Unenforceability of the '098 Patent and Invalidity of the '321 Patent" submitted as D.I. 165 on December 11, 2007.

[2] Citations to the trial transcript are in the format "Witness page:line-page:line."

The '098 patent table Teva points to also demonstrates the inventors' good faith in asserting that the compounds of the invention have a superior anti-ulcer effect "about 1.5-20 times" that of known compounds. Teva glosses over the fact that the '098 patent's results include data from **two** prior compounds—the "Byk Gulden compound" and omeprazole. Teva focuses on the "20-fold" difference between lansoprazole's and omeprazole's IMAU ID_{50} values. But the '098 patent's inventors provided the PTO with data showing only a 5.5-fold superior anti-ulcer effect between lansoprazole and the Byk Gulden compound. Dajani Cross 943:14-23.

Teva's case boils down to the bare contention that the inventors should have provided the PTO each and every animal test conducted on lansoprazole. But Teva cites no law to support its contention. And Teva focuses on antisecretory testing that is distinguishable from and not comparable to anti-ulcer testing, despite the '098 patent's emphasis on its new compounds' superior anti-ulcer effects.

Finally, concerning Plaintiffs' '321 formulation patent, Teva's obviousness challenge largely rehashes art that the PTO already considered, with the exception of some allegedly invalidating references Teva proffered for the first time during trial. The new references hardly salvage Teva's challenge. Teva never explains why, from among thousands of possibilities, a person of ordinary skill in the art would select magnesium carbonate as a stabilizer, and then having done so, would contact it evenly with lansoprazole in order to stabilize lansoprazole. Certainly, none of the prior art Teva cites did so, leaving Teva with nothing more than obviousness by hindsight.

II. BACKGROUND TO ACID-RELATED GASTROINTESTINAL DISORDERS AND PROTON PUMP INHIBITORS

A. Peptic Ulcer Disease and Gastroesophageal Reflux Disease (GERD)

Drs. Maki and Nohara invented the Proton Pump Inhibitor ("PPI") lansoprazole to treat gastric ulcers and related diseases. The stomach's "parietal cells" secrete gastric acid when the "proton pump" within these cells is triggered by one of three receptors. Fennerty 824:17-825:8. Gastric acid is extremely acidic, having a pH of 1 to 2. *Id.* Normally, the stomach protects itself from gastric acid through a series of cytoprotective factors. *Id.* However, when the stomach's cytoprotective defense mechanisms are reduced, an imbalance results that can lead to ulceration. *Id.*

Gastric ulcers are formed in the stomach cavity itself, and duodenal ulcers are formed in the duodenum or upper small intestine. *Id.* Ulcers can also form in the esophagus due to gastroesophageal reflux disease or GERD. Fennerty 826:3-22. GERD results when the barrier between the esophagus and the stomach malfunctions and allows gastric acid to reflux into the esophagus, producing symptoms such as heartburn, nausea, trouble swallowing, and chest pain as well as esophageal ulcers and even esophageal cancer. *Id.*

B. Treatment for Peptic Ulcer Disease and Gastroesophageal Reflux Disease

Histamine 2 receptor antagonists or H_2 blockers were the first successful, non-surgical therapy to treat ulcers. Fennerty 829:16-830:2. There are currently four H_2 blockers on the market: Tagamet®, Zantac®, Pepcid®, and Axid®. *Id.* H_2 blockers targeted the histamine receptor, one of three known receptors that direct the proton pumps within parietal cells to produce gastric acid. *Id.* H_2 blockers could not fully stop the production of acid because they have no effect on the other two receptors that control the proton pumps. Lenz 734:18-735:3, 735:11-24.

In 1989, omeprazole (trade name Prilosec®), the first commercially-successful PPI, was launched. Fennerty 830:4-831:18. Omeprazole suffered from drawbacks such as delayed onset of action, a number of drug-drug interactions, and safety concerns over carcinoid tumors that led the FDA to require a "black box" warning. *Id.* Moreover, although omeprazole had strong antisecretory properties, it was believed to lack cytoprotective properties. Lipinski 1163:12-16. When lansoprazole (Prevacid®) was launched in 1995, it offered an attractive alternative due to its more rapid onset of action, reduced drug-drug interactions, and lack of a black-box warning. Fennerty 847:6-12. Lansoprazole has been one of the most successful PPIs, with total sales of over $34 billion since its launch in 1995 and sales over $1 billion annually since 1998. Cole 1056:24-1058:7; PTX 182. Only three other PPIs have subsequently been introduced: pantoprazole (Protonix), rabeprazole (Aciphex), and esomeprazole (Nexium).

C. Medicinal Chemists in 1984 Knew Little About How to Develop Lansoprazole or Other Successful PPIs

Drug design is very difficult with a very low success rate. Lipinski 1160:23-1161:25. In addition to the inherent biological activity of the compound, it cannot be toxic and must be safe. *Id.* The compound must also have adequate "ADME properties" (absorption, distribution, metabolism, and excretion). *Id.*; Lenz Cross 783:3-15.

Around 1984, a medicinal chemist typically would have to make an estimated 10,000 compounds before an approved compound was discovered. Lipinski 1162:3-9. Teva's expert, Dr. Lenz, conceded that more than 40 pharmaceutical companies had sophisticated medicinal chemistry groups in the 1980's and the financial desire to develop a PPI. Yet only four companies succeeded in discovering and developing a viable PPI. Lenz Cross 777:11-18; 778:21-779:1. In fact, Dr. Lenz's former employer, Searle, unsuccessfully tried to develop a PPI using state-of-the-art computer drug design technology, but found that "changes in substituents

led to such unpredictable effects in a PPI's properties" that the computer technology was largely useless. Lenz Cross 779:2-781:13.

III. LANSOPRAZOLE WAS A DIFFICULT AND SURPRISING DISCOVERY

Dr. Lipinski testified that even persons of extraordinary skill, like himself and Dr. Lenz, would have had extreme difficulty discovering lansoprazole. Lipinski Redirect 1277:23-1278:3. Dr. Lenz conceded that it was a rare medicinal chemist who succeeded in discovering any commercially-approved product, and that he had never done so. Lenz Cross 782:16-24.

The reason it was so difficult to develop a successful PPI was because, as Dr. Lenz admitted, even a single substituent change on a compound can mean the difference between the success and failure of the drug in clinical trials. Lenz Cross 785:3-15. Dr. Lenz admitted that a single change in a substituent can impact the efficacy, stability, side effects, toxicity, absorption, metabolism, distribution, and excretion of a drug, and that this was the nature of "medicinal chemistry." *Id.*

The effort to produce PPIs by successful companies was extraordinary. For example, Byk Gulden synthesized over 650 compounds before it succeeded with its PPI, pantoprazole, after seven years of development. Lipinski 1193:1-13; PTX 33 at Lipinski 0938. In another example, esomeprazole resulted from the efforts of over 30 Astra scientists and several hundred compounds synthesized. Lipinski 1193:15-25; PTX 53 at Lipinski 0857. Both pantoprazole and esomeprazole were developed and introduced after lansoprazole. Lipinski 1193:11-13.

A. Small Changes Affect Not Only Activity, but also Toxicity and ADME

A compound's toxicity and ADME characteristics are highly sensitive to seemingly small changes in chemistry. For example, replacing one hydrogen in vinegar with a fluorine results in toxic fluoroacetic acid. Lipinski 1171:5-1172:7. Adding a methyl group to methanol, which is toxic, results in ethanol, which you can buy at a liquor store. *Id.* Finally, Tagamet, the

successful H_2 blocker, was developed from a toxic compound that caused death during clinical trials. *Id.* One small substituent change transformed a toxic compound into a compound so safe that it is now sold over-the-counter. *Id.*

B. A Team of Takeda Scientists Devoted Over Two Years and Synthesized Over 400 Compounds Before Discovering Lansoprazole

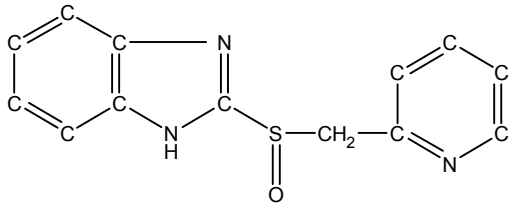
Takeda Pharmaceutical Company, Limited is the largest manufacturer of pharmaceutical products in Japan. Kubo 1105:25-1106:5. Takeda sought to develop an anti-ulcer drug superior to the drugs available at the time. Kubo 1108:2-4. Takeda recognized several problems with prior-art compounds. These prior-art compounds had good antisecretory properties, but did not have any protective effect on the gastric mucosa. The compounds also were unstable, that is, subject to rapid decomposition. Lipinski 1163:14-24; PTX 1 at Col. 1, ll. 13-19.

Takeda thus tried what more than 40 other pharmaceutical companies also tried—to develop an anti-ulcer drug that both inhibited gastric acid secretion and enhanced protection of the gastric mucosa. Lipinski 1163:22-24; PTX 1 at Col. 1, ll. 23-26; PTX 44 at Lipinski 0799. In 1982, Mr. Keiji Kubo began work on Takeda's anti-ulcer project as part of Dr. Akira Nohara's synthesis group. Kubo 1107:7-15. Dr. Nohara's group synthesized hundreds of different chemical compounds in its effort to develop a novel anti-ulcer agent. Another Takeda group, led by Dr. Yoshitaka Maki, evaluated the biological properties of compounds synthesized by Dr. Nohara's group. Kubo 1108:5-19. These groups pursued many synthesis strategies to develop an anti-ulcer drug and failed many times before ultimately succeeding with lansoprazole.

1. Takeda Scientists Synthesized a Lead Compound: Timoprazole

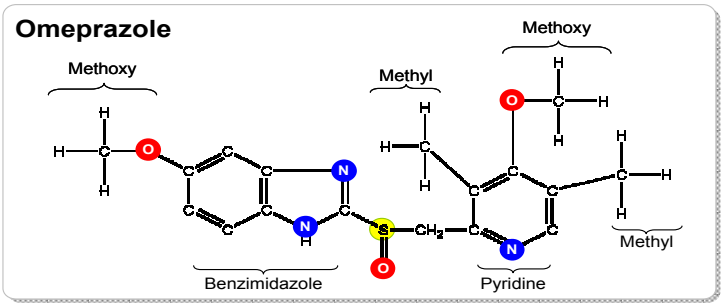
The inventors did not have an initial synthesis strategy to develop an anti-ulcer compound. Through trial and error, the inventors developed compounds and then tested them for

anti-ulcer activity. Kubo 1113:18-1114:5. As a result, the inventors had no lead compounds when the anti-ulcer project began. Instead, the inventors conducted random screening on compounds already synthesized for other projects to determine if those compounds had any anti-ulcer activity. Kubo 1109:7-13. Ultimately, the inventors settled on a compound identified internally as AA-1569 as their lead compound for its anti-ulcer project. AA-1569 was also known as timoprazole (PTX 60 at Lipinski 001476):



Takeda scientists originally synthesized timoprazole to determine its potential as an allergy medicine in January 1982. Kubo 1109:21-24, 1113:3-17; PTX 639 at 446543. Through testing, the inventors discovered that timoprazole showed promise as an anti-ulcer agent (identified as AG-879). What the inventors did not know at the time was that timoprazole was already known in the art, Kubo 1109:17-1110:5, and, as Dr. Lenz admitted, that timoprazole was toxic. Lenz Cross 787:22-799:2.

The inventors also learned of omeprazole at some point during their anti-ulcer compound development project. Omeprazole contained the same timoprazole skeleton that the inventors had been working with:

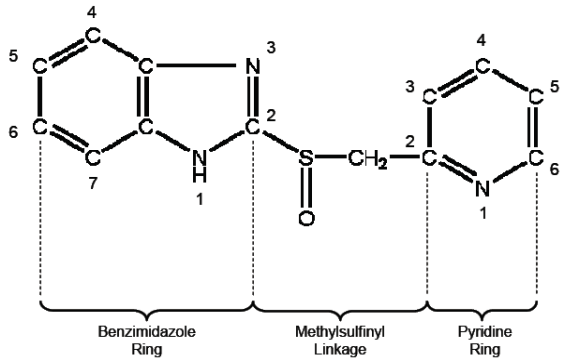


Takeda scientists recognized that they needed to find a compound superior to omeprazole that did not have the toxicity of the timoprazole skeleton. Omeprazole therefore became one of the benchmarks in their efforts, and work on the timoprazole skeleton proceeded. Kubo 1121:12-21; PTX 61 at Takeda 436712.

2. The Inventors' Efforts to Modify Timoprazole

The five PPIs commercially-available today (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) all share the timoprazole skeleton. Lipinski 1166:2-16. Due to timoprazole's toxicity, the need to modify it was critical. But how to do so? By using 20 common substituents selected from the '431 omeprazole compound patent, both Dr. Lipinski and Dr. Lenz agreed that there are over 13 million possible compounds that all shared the timoprazole skeleton, none of which is lansoprazole. Lipinski 1169:1-23; DTX 5; Lenz Cross 789:15-790:7. Indeed, one of the substituents that Takeda scientists ultimately discovered was useful, trifluoroethoxy, was not disclosed as a substituent in the '431 patent. Lenz Cross 792:20-793:8.

After selecting timoprazole as the lead compound, the inventors' strategy was to experiment by changing one or more of the three components of the timoprazole skeleton: the benzimidazole portion, the methylsulfinyl portion, and the pyridine portion. Kubo 1109:17-1110:5, 1115:21-25; PTX 45 at Takeda 436696.



This approach was unsuccessful. The inventors eventually determined that the unmodified timoprazole skeleton was useful for the compound to have anti-ulcer activity, and placed less emphasis on trying to modify the timoprazole skeleton itself. Kubo 1119:16-21; PTX 45 at Lipinski 001263.[3]

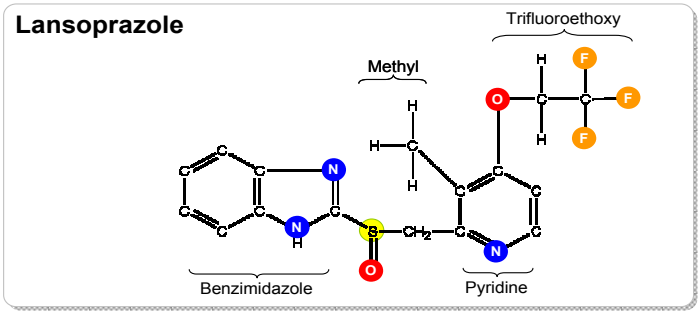
Takeda scientists began experimenting with the addition of various substituents to the timoprazole skeleton. PTX 61 at Takeda 436712. But they had no indication of which particular position on the timoprazole skeleton to start with, because there was no logical place to start. Kubo 1122:11-15. For example, they tried a number of substitutions on the benzimidazole ring, including several fluorinated substituents.[4] Kubo 1124:20-1125:3; PTX 60 at Lipinski 01582, 01559. But these scientists discovered that substituents on the benzimidazole ring did not increase anti-ulcer activity. Kubo 1124:17-21, 1125:6-18; PTX 61 at 436713. In fact, lansoprazole, unlike omeprazole, has no substituents on the benzimidazole ring.

[3] Yet, even after lansoprazole was synthesized, the anti-ulcer team at Takeda continued to create and test modifications of the timoprazole skeleton. Kubo 1118:8-13. Although many more examples exist, five examples of this strategy are: **AG-1758, AG-1779**, **AG-1780**, **AG-1781** & **AG-1782**. PTX 60 at LIPINSKI 001586, 001588-89.

[4] Although many more examples exist, five examples of this strategy are: **AG-1545**, **AG-1555**, **AG-1565, AG-1567** & **AG-1575**. PTX 60 at LIPINSKI 001559-60, 001562-63.

The inventors also tried numerous substituents at the 4-position of the pyridine ring.[5] Kubo 1124:4-10; PTX 60 at Lipinski 01564, 01580. In November 1983, 18 months after they first synthesized timoprazole, the inventors reported that a compound with a long alkoxy chain on the pyridine ring (AG-1511) showed superior anti-ulcer properties. Kubo 1123:14-21, 1124:15-16; PTX 70 at Takeda 040875.

The inventors thus began to focus on the 4-position in the pyridine ring. They experimented by adding trifluoroethoxy substituents to the timoprazole skeleton, and around October 1983, they synthesized AG-1598. Kubo 1126:8-1127:9; PTX 641 at Takeda 446784. Due to AG-1598's activity and stability, the inventors endeavored to enhance the activity of AG-1598 and introduced various other substituents onto it before coming up with lansoprazole. Kubo 1126:15-19; Lenz Rebuttal 1437:7-9; 1439:9-11. Finally, in May 1984, 28 months after it first synthesized timoprazole, Dr. Kubo (then Mr. Kubo), inventor Dr. Nohara's assistant, synthesized lansoprazole. Kubo 1127:15-23; PTX 648 at Takeda 039840:



It took the inventors 28 months to proceed from the timoprazole lead compound to lansoprazole. Kubo 1128:14-17. During this 28-month period, the inventors and their assistants

[5] Although many more examples exist, five examples of this strategy are: **AG-1511**, **AG-1586**, **AG-1587**, **AG-1598** & **AG-1599.** PTX 60 at LIPINSKI 001555, 001564, 001566.

synthesized more than 400 compounds in their search for a novel anti-ulcer agent. Kubo 1128:23-1129:2; PTX 60 *passim*.

In August 1984, well before the commercial release of omeprazole, the inventors filed Japanese Patent Application No. 59-171069 for lansoprazole and related compounds. On July 29, 1985, the inventors filed United States Patent Application 760,568, which matured into U.S. Patent No. 4,628,098 (the '098 patent). PTX 1. The Patent Office allowed the '098 patent during prosecution on the first office action. Lipinski 1165:17-23; DTX 2 *passim*. Claim 10 of the '098 patent claims 2-[3-methyl-4-(2,2,2,-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole, or lansoprazole. Lipinski 1154:21-155:2; PTX 1 at Col. 10.

C. Four Unique Hurdles Make PPI Development Unpredictable

PPI chemistry is unusually complex. Even today, the chemistry and mechanism of action of the proton pump inhibitor (PPI) class of drugs is considered one of the most novel and unusual in the history of the pharmaceutical industry, despite the existence of PPIs for over 30 years. Lipinski 1172:16-1173:8; PTX 18 at 365. Unlike other drugs, in PPI development, there are four additional and unique hurdles one must overcome for the drug to be successful. Lipinski 1173:15-1174:8.

1. Hurdle 1: The PPI must accumulate solely in the parietal cell

PPIs must accumulate solely in the parietal cell. If the drug accumulates in other tissues in the body, toxicity may result. Lipinski 1174:12-1175:15. It was understood in 1984 that accumulation in other tissues was a hurdle to PPI development. Teva makes much of the fact that DTX 13, a 1984 editorial, disclosed a preference to restrict pK_a to less than 4.5, and that a skilled scientist would prefer a range between 3 and 4.5. Lenz Cross 807:17-22, 808:1-5, 807:4-9, 807:13-16.

But knowing about accumulation alone would not provide a reasonable expectation of success, or show the way to choose the correct modifications, to develop a successful PPI. In fact, the omeprazole '431 patent did not even mention pK_a or describe its importance. Lenz Cross 806:20-24. The range of pK_as between 3 and 4.5 is enormous (it is a log scale), and only slightly reduces the millions of possibilities for how to modify the timoprazole skeleton. Lipinski 1175:7-11.

2. Hurdle 2: The PPI must be stable in the blood (*i.e.*, at neutral pH)

Teva ignores the second hurdle: after ingestion, the PPI must be absorbed from the gastrointestinal tract and travel through the blood to reach the parietal cell without breaking down. In other words, the PPI must have neutral pH stability. Lipinski 1175:12-1176:22. In 1984, people knew there was a problem concerning stability of PPIs at neutral pH, but they had no idea what the solution was, as demonstrated by PTX 30, a 1992 paper showing that scientists were still grappling with the issue. Lipinski 1176:8-11. There was no logical way in 1984 to identify particular substituents to address this hurdle.

3. Hurdle 3: The PPI must convert to an active species in the body

All PPIs are prodrugs. PPIs like lansoprazole convert to an active species (the "PPI active species") in the body. This PPI active species then inhibits the proton pump. Not all timoprazole-like compounds will successfully undergo this conversion. Lipinski 1179:12-15. In 1984, the chemistry for this conversion process was unknown, as demonstrated by PTX 31 and PTX 32, two papers from pharmaceutical companies, Upjohn and Hoechst, in 1985 that had the chemistry all wrong. Lipinski 1178:23-1179:10. In fact, the chemistry of this conversion process was worked out for the first time in PTX 17, a 2004 paper (20 years after lansoprazole was synthesized), and even this paper has not solved all of the mystery behind this chemistry. Lipinski 1179:16-1180:6.

4. Hurdle 4: The PPI active species must fit the proton pump

The proton pump is a very complex, three-dimensional protein. Lipinski 1180:10-1182:12. For inhibition of gastric acid to occur, the PPI active species must fit into the protein, much like a key fits into a lock. Id. The substituents on the timoprazole skeleton determine whether there will be a good fit. *Id.* For example, the three-dimensional structures of lansoprazole and omeprazole are very different, and thus the fit of their corresponding PPI active species into the proton pump will differ. Lipinski 1166:24-1167:24. The substituents on the timoprazole skeleton determine how well the PPI active species fits into the proton pump, and thus determine in part the activity. Lipinski 1181:18-22.

There was no way to know in advance what substituents would help or hurt this fit. Lipinski 1181:23-1182:12. Even today, medicinal chemists do not fully understand the structure of the proton pump. *Id.*

Teva's expert, Dr. Lenz, did not testify about any prior art that addressed three of these unique hurdles, Lipinski 1182:13-25, 1184:17-21, even on rebuttal.

D. Prior Art Would Have Led Medicinal Chemists Away from Developing Lansoprazole

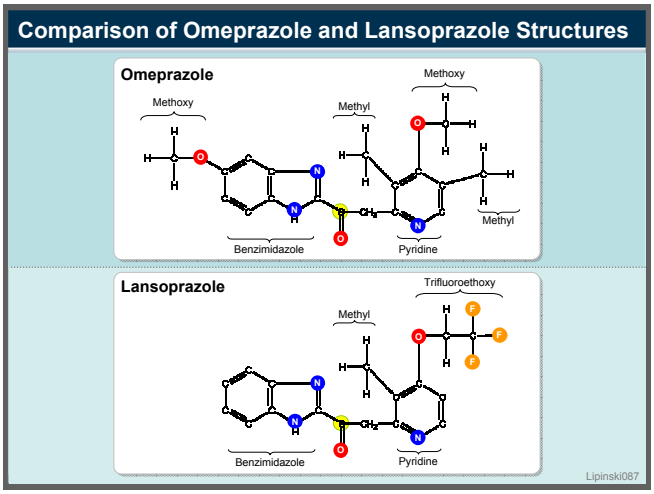
As Dr. Lipinski explained, and Teva's Dr. Lenz ignored, the principal prior art references Teva relies on actually teach away from the structure of lansoprazole.

1. The '431 Astra Patent

U.S. Patent No. 4,255,431 (DTX 5) claimed omeprazole and was considered by the PTO during the '098 patent prosecution. Lipinski 1164:10-15, 1195:11-15; DTX 5.

The '431 patent taught a preferred substitution on the pyridine ring of omeprazole: 3-methyl, 4-methoxy, and 5-methyl. Lipinski 1195:19-1196:12. Examples 11, 17, 20, 21, 23, 24, 25, and 28 in Table 2 of the '431 patent all share this substitution pattern. *Id.*; DTX 5 at TVL

011025-26; Teva Br. at 20. Lansoprazole shares only the 3-methyl substitution with the '431 patent's preferred substitution pattern. Lipinski 1196:14-1197:1.



In fact, there is no chemical means to convert omeprazole to lansoprazole. Lipinski 1187:3-9.

The '431 patent also taught that a shorter (1 carbon) substituent is preferred to a longer (2 carbon) substituent at the 4-pyridine position. Lipinski 1197:3-1198:15; DTX 5 at TVL 011026. Lansoprazole has a longer two carbon substituent at the 4-pyridine—trifluoroethoxy—precisely the kind of group the '431 patent taught away from. Lipinski 1198:8-15. Indeed, the '431 patent stressed 4-methoxy's importance, Lipinski 1196:20-22, while it did not even mention trifluoroethoxy. Lenz Cross 793:4-8.

The '431 patent also taught away from removing the 5-methyl on the pyridine ring, since its activity table showed that when 5-methyl was removed, the compounds were less active. Lipinski 1198:17-1199:15; DTX 5 at TVL 011026. Lansoprazole does not have a 5-methyl on the pyridine ring. *Id.* Dr. Lenz never explained why one would move from 5-methyl on the pyridine ring (as in omeprazole) to a compound with no substituent at the 5-position (as in lansoprazole). Lipinski 1186:12-19.

Finally, the '431 patent taught away from having an unsubstituted benzimidazole ring. Of the 29 examples in Table 2 in the '431 patent, 28 of them contain substituted benzimidazole rings. Lipinski 1199:17-1200:7; DTX 5 at TVL 011025-26. In particular, the 5-methoxy substitution in the benzimidazole ring was later found to make the omeprazole compounds much more stable to conversion at neutral pH (PPIs' unique hurdle 2). Lenz Cross 790:23-791:20; PTX 44 at Lipinski 0789. Lansoprazole has an unsubstituted benzimidazole ring, contrary to the teachings of the '431 patent. Lipinski 1168:2-20; 1196:14-19. Again, Dr. Lenz provided no explanation as to why one would go from using a substituted benzimidazole compound to an unsubstituted benzimidazole compound like lansoprazole. Lipinski 1186:2-11.

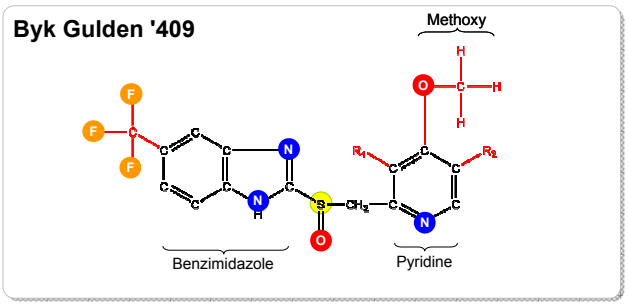
In its post-trial brief, Teva notes that one compound listed in Table 2 of the '431 patent had an unsubstituted benzimidazole ring (example 25). Teva Br. at 44-45. Dr. Lenz never addressed this point at trial. But that is hardly surprising. The unsubstituted example 25 is less potent than the 28 other substituted examples. Thus, the '431 patent taught one of ordinary skill in the art to substitute the benzimidazole ring.

Teva also contends that "virtually all" compounds disclosed in the '431 patent would have led to a successful PPI. Teva Br. at 35. But only the omeprazole compound described in the '431 patent was successful. One of skill in the art would have no idea whether the other compounds in the '431 patent would have been successful PPIs. Lipinski 1184:9-12. In fact, in 1984, it was uncertain that even omeprazole would be successful. Lenz Rebuttal Cross 1441:1-7. As Dr. Lenz admitted, adding or changing substituents in the omeprazole structure might produce unsafe or toxic compounds. Lenz Cross 793:9-15.

2. The '409 Byk Gulden Patent

U.S. Patent No. 4,472,409 (DTX 7) was considered by the PTO during prosecution of the '098 patent. Lipinski 1164:10-15. Like the omeprazole '431 patent, DTX 5, the '409 patent

taught solely compounds with a methoxy group at the pyridine ring's 4-position, so that a person of ordinary skill in the art would be taught away from replacing this methoxy group as the '098 inventors did. Lenz Cross 794:11-18; Lipinski 1200:18-1201:1 & 1201:24-1202:3. The '409 patent does not even mention trifluoroethoxy as a potential substituent. Lipinski 1202:22-1203:1; Lenz Rebuttal Cross 1445:1-3.



Furthermore, like the omeprazole '431 patent, the '409 patent's compounds are all substituted on the benzimidazole ring, so a person of ordinary skill in the art would be taught to maintain some substitution on the benzimidazole ring—and would be taught away from leaving it unsubstituted as in lansoprazole. Lipinski 1201:2-6.

3. The '518 Byk Gulden Patent

U.S. Patent No. 4,555,518's title—"Fluoroalkoxy Substituted Benzimidazoles Useful as Gastric Acid Secretion Inhibitors"—makes clear what this patent taught. DTX 9 (emphasis added). The '518 patent's compounds all have a fluoroalkoxy on the benzimidazole ring, not the pyridine ring. Lipinski 1203:13-23. A medicinal chemist would view the benzimidazole ring and pyridine ring in isolation, and would not switch substituents between these different ring systems. Lipinski 1203:2-12. Therefore, the '518 patent's fluoroalkoxy substituents on the benzimidazole ring would not suggest putting the same substituents on the pyridine ring. *Id.*

Like the '409 and '431 patents, the '518 patent taught a preferred methoxy substitution at the 4-pyridine position. Lipinski 1204:3-18; DTX 9 at Col. 24, ll. 15-59; 794:19-795:4. Thus, like the other patents Teva relied upon, the '518 patent taught away from replacing the 4-methoxy group.

In short, the '518 patent did not teach the use of trifluoroethoxy in the pyridine ring. Lipinski 1203:20-23, 798:2-8. Lansoprazole does not have a methoxy group at the 4-pyridine position, as the '431, '409, and '518 patents required. And even Dr. Lenz admitted that he would not have shifted a trifluoromethoxy, preferred in the '518 patent, from the benzimidazole ring to the 4-position of the pyridine ring, which shows how these rings differ. Lenz Cross 815:4-17.

Finally, Teva does not dispute that no commercially viable products resulted from the '409 or '518 patents, because the compounds disclosed in those patents suffered from neutral-pH instability or toxicity problems. Lenz Cross 795:6-15; 1165:1-10; 1201:7-23.

E. Medicinal Chemists Would Not Have Selected Trifluoroethoxy as a Substituent in 1984

Lansoprazole was synthesized with a trifluoroethoxy at the 4-position of the pyridine ring. This was a novel step. Teva argues that the use of "fluorinated substituents," like trifluoroethoxy, would have been obvious because of "fluorine's well-known properties." Teva Br. at 39-40. Teva grossly overreaches in several respects. *See*, *e.g.*, Lipinski 1171:12-14. "Fluoroethoxy" refers to an entire family of substituents having hundreds of members. Lipinski 1187:20-25; 1188:7-13. "Trifluoroethoxy" refers to a family of substituents having three members. Lipinski 1188:14-21. Lansoprazole has a particular trifluoroethoxy, called the "2,2,2-trifluoroethoxy." Lipinski 1188:22-1189:6. If 2,2,2-trifluoroethoxy were replaced by say 1,2,2-trifluoroethoxy, the result would be completely unpredictable, but most likely would not lead to a successful compound. *Id.*

Moreover, as Dr. Lipinski testified and his own investigation confirmed, far from being a logical or obvious choice, trifluoroethoxy was in fact an unusual "fluorinated substituent" to choose in 1984. As of August 16, 1984 (the date the patent application was filed in Japan), there were only two chemical compounds known with a trifluoroethoxy at the 4-position of a pyridine ring out of around 30 million compounds searched under Dr. Lipinski's direction. Lipinski 1189:12-1190:10, 801:5-802:13; PTX 37 at Lipinski 001325. One of the compounds was an herbicide and the other was an anti-malarial compound. In fact, only four compounds in clinical trials as of August 1984 contained a trifluoroethoxy at any position of the molecule. Lipinski 1190:11-1192:2, 801:5-802:11; PTX 38 at Lipinski 001335. None of those four identified compounds was a gastrointestinal drug. Dr. Lipinski also pointed out that a 1991 reference compiling information on 530 common substituents did not even include trifluoroethoxy in its compilation. Lipinski 1191:10-1192:3; 800:13-21; DTX 101 at TVL 63322-63329.

The use of trifluoroethoxy could hardly be considered an obvious substituent choice in 1984. In fact, lansoprazole is the only one of the five available PPIs that has a fluorine at any position on the pyridine ring. Lenz Rebuttal Cross 1446:11-13; Lipinski 1191:25-1192:3.

F. Teva's Reliance on DTX-703 is Baseless

Teva's brief relies heavily on DTX 703 for its obviousness positions. *See, e.g.,* Teva Br. at 2. DTX 703 contains the conclusory statement that the "structure [of lansoprazole] is too similar to Omeprazole." But there is no evidence concerning who authored DTX 703, nor the author's educational background or position, and no evidence concerning even its date or circumstances of creation. There is no evidence concerning the relationship between DTX 703's author and the inventors, or anyone else substantively involved in the '098 patent's prosecution. No one knows if the inventors or anyone else even read DTX 703. Dr. Kubo, the first person to synthesize lansoprazole, testified that he was unfamiliar with DTX 703. Kubo Cross 1149:23-

1150:9. Indeed, DTX 703 on its face appears to be a draft or uncompleted document, as a number of entries on it were not completed. *See* Teva Br. at 48 (title, date, rater, etc., blank).

Moreover, Dr. Kubo testified that he had never heard anyone at Takeda express the view that the inventors could not get a patent on lansoprazole because of omeprazole, contrary to Teva's interpretation of DTX 703. Kubo Redirect 1154:1-4. Teva has no evidence to the contrary.

IV. SUBSTANTIAL DIFFERENCES, SCOPE AND CONTENT OF THE PRIOR ART, LEVEL OF ORDINARY SKILL, AND OBJECTIVE INDICIA SHOW THAT LANSOPRAZOLE WAS NONOBVIOUS

Teva contends that a medicinal chemist in 1984 would have found lansoprazole an obvious and "logical" progression from the prior art.[6] Teva Br. at 20. But, as described in detail above, the testimony and documents in evidence refute this argument. First, Teva fails to demonstrate how one of skill in the art in 1984 would have a reasonable expectation of success by following the prior art teachings to construct lansoprazole. Second, Teva tries to construct lansoprazole from omeprazole without any explanation of why one of skill in the art would choose to make the necessary modifications to omeprazole to construct lansoprazole. Teva's conclusory construction is a paragon of hindsight, which the Federal Circuit and Supreme Court have expressly warned against in an obviousness analysis. Third, Teva completely ignores the prior art's teaching away from Teva's construction of lansoprazole. Finally, Teva ignores all objective indicia evidence that demonstrated lansoprazole's non-obviousness.

[6] Teva's confidence in its obviousness position is belied by the fact that their initially filed ANDA in August 2004 included a Paragraph III certification indicating they would not contest the validity of the '098 patent.

Under 35 U.S.C. § 282, each claim of the '098 patent is presumed valid. "Any facts supporting a holding of invalidity must be proved by clear and convincing evidence." *Budde v. Harley-Davidson, Inc.*, 250 F.3d 1369, 1376 (Fed. Cir. 2001).

Teva suggests, without any legal support, that an invention requires a "Eureka moment" or a "light-bulb moment" to be non-obvious. Teva Br. at 22. Teva is wrong. "It is immaterial whether the invention resulted from long toil and experimentation or from a flash of genius." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1340 (Fed. Cir. 2003) (citations omitted). Even "systematic variation" does not make compounds obvious. *Bayer AG v. Dr. Reddy's Labs., Ltd.*, No. 04-179-SLR, 2007 WL 3120794, at *8 & n.30 (D. Del. Oct. 25, 2007).

Although obviousness is a question of law, four factual underpinnings control an obviousness inquiry. These underpinnings are "[a] the scope and content of the prior art are ... determined; [b] differences between the prior art and the claims at issue are ... ascertained; [c] the level of ordinary skill in the pertinent art [is] resolved" and [d] evidence of objective indicia of nonobviousness is evaluated. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1729-30 (2007).

A. Teva Fails to Describe a Reasonable Expectation of Success

In evaluating these four factual underpinnings, a court may find obviousness only if it finds a reasonable expectation of success in arriving at the invention by combining prior art. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1360-62 (Fed. Cir. 2007); *Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006). A "reasonable expectation of success" requires more than "vary[ing] all parameters or try[ing] each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal citations omitted). Similarly, prior art fails to provide the requisite

"reasonable expectation" of success where it teaches merely to pursue a "general approach that seemed to be a promising field of experimentation." *Id.*

Teva contends that there was an "obvious path to lansoprazole" through a "logical, methodical exercise" from the prior-art compounds. Teva Br. at 21, 40. But if such a road map existed, Teva does not explain why more than 40 companies attempted but failed to produce a viable PPI product. Nor can Teva explain why Takeda scientists synthesized more than 400 compounds before arriving at lansoprazole. As Dr. Lipinski explained at trial, there was no "logical" progression from the prior art to lansoprazole given the unpredictability of substituents added onto the timoprazole skeleton and the complexity of PPI chemistry, which prevented accurately predicting how substituent changes would affect the reaction of a compound in each of the four unique PPI hurdles. Lipinski 1159:23-1160:7, 1208:15-24.

Teva's expert, Dr. Lenz, agreed with Dr. Lipinski that changing substituents would have unpredictable results in terms of a compound's ADME characteristics and toxicity. Lenz Cross 785:3-15. In fact, Dr. Lenz referred to this unpredictability as being at the heart of "medicinal chemistry," the relevant art in this case. *Id.* Teva does not, and cannot, dispute that changes to substituents in timoprazole resulted in unpredictable results in terms of the compound's ADME and toxicity characteristics. There was no reasonable expectation of success that the '098 inventors' choice of substituents in their particular positions on the timoprazole skeleton would have worked.

Teva never addresses why one of ordinary skill in the art would find a reasonable expectation of success by using a trifluoroethoxy substituent, as in lansoprazole, particularly at the 4-pyridine position. Teva does not refute that trifluoroethoxy was a highly unusual choice of substituent, and that trifluoroethoxy at the 4-pyridine position was extremely rare for all

chemicals. *See* Lipinski 1189:12-1190:10, 801:5-802:11; PTX 37 at Lipinski 001325. Nor did Teva respond at trial to Dr. Lipinski's opinion that at least three of the hurdles in PPI chemistry prevented one of skill in the art in 1984 from accurately predicting how a compound's substituents would work in the body.

Thus, a review of the scope and content of the prior art shows that lansoprazole's substituents were unusual, and that the expectation of success, especially in light of the four unique hurdles, was low.

B. Teva's Purported "Obvious Path to Lansoprazole" Uses Hindsight and Ignores the Prior Art's Teaching Away

"A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *Ecolochem, Inc. v. S. Cal Edison Co.,* 337 F.3d 1361, 1371 (Fed. Cir. 2000). The Federal Circuit has warned against using "the inventors' disclosure as a blueprint for piecing together the prior art to defeat patentability -- the essence of hindsight." *Id.* at 1371-72. As the Federal Circuit and Supreme Court have made clear, to establish a *prima facie* obviousness case, it remains necessary, even after *KSR*, to describe what would have led an ordinary chemist to modify a known compound in a particular manner. *Takeda v. Alphapharm*, 492 F.3d at 1357; *KSR*, 127 S. Ct. at 1741 (requiring courts "to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.").

To justify its theory that one of ordinary skill in the art would have a reason to modify omeprazole to construct lansoprazole, Teva uses hindsight to work backward from lansoprazole to omeprazole. Teva first argues that one of skill in 1984 would somehow know to remove the substituent from the benzimidazole ring in omeprazole. But 28 of the 29 compounds disclosed in

the omeprazole '431 patent had a substituted benzimidazole ring, and the 29th (the sole unsubstituted compound) had less activity than the comparable substituted counterpart. Lipinski 1186:6-11.

Teva's arguments regarding substituents in the pyridine ring fare no better. Teva argues that it would have been "logical" to replace the methoxy on the 4-pyridine position on omeprazole with a trifluoroethoxy, and to remove one methyl from the 5-pyridine position from omeprazole to construct lansoprazole. But none of Teva's references taught the use of a trifluoroethoxy substituent at any position on the pyridine ring of timoprazole, nor was there any evidence that this substitution was within the skill of one of ordinary skill in the art.

It is undisputed that changing the substituent at the pyridine 4-position has a profound effect on the pyridine ring as a whole. Lenz 753:24-754:1. Yet all of Teva's references taught that a methoxy at the pyridine 4 position was essential, and thus taught away from replacing this 4-methoxy with any other group. Lipinski 1200:18-1201:1, 1204:3-18. In fact, the '431 patent taught that a shorter 1-carbon substituent like methoxy is preferred to a longer 2-carbon substituent like trifluoroethoxy at the pyridine 4-position, thus showing how far this reference went in teaching away from lansoprazole. Lipinski 1197:3-1198:15.

Because each substituent is critical, Lenz Cross 781:11-13 & 785:3-15, Lipinski 1169:24-1170:3, 1170:23-25 & 1171:5-1172:7, and there are at least 3 substituents described above that differ, the differences between lansoprazole and the prior art are substantial. Yet in regard to each required modification, the '431, '409, and '518 patents teach away from Teva's proposed modifications. Teva offers no prior art that taught towards lansoprazole's chemical structure.

C. The Federal Circuit and this Court Have Rejected Similar Obviousness Theories Based on Similar Facts

Teva's brief erroneously suggests that "structural similarity" is sufficient to establish a *prima facie* case of obviousness. Teva Br. at 23. As described above, there were significant differences in the structure of lansoprazole and the prior art, and no teaching in that art to make the structural changes made by the '098 inventors to construct lansoprazole.

Moreover, the Federal Circuit has clarified that while "structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds … in order to find a *prima facie* case of unpatentability in such instances, a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention was also required." *Takeda v. Alphapharm*, 492 F.3d at 1355-56 (internal citations omitted) (emphasis added). "For a chemical compound, a *prima facie* case of obviousness requires 'structural similarity between claimed and prior art subject matter … where the prior art ***gives reason or motivation*** to make the claimed compositions.'" *Yamanouchi Pharm. Co. Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (emphasis added).

As demonstrated above, Teva does not demonstrate how a person of ordinary skill in the art would have been motivated to modify *specifically* the structure of omeprazole to construct the structure of lansoprazole.

The holding in *Takeda v. Alphapharm* is instructive. The difference between the prior art and the patented compound was a 6-pyridine methyl group (CH_3) versus a 5-pyridine ethyl group (CH_2CH_3). *Takeda v. Alphapharm*, 492 F.3d at 1354. Alphapharm suggested that one of skill in the art would routinely convert the methyl to an ethyl and "ring walk" the ethyl group from the 6-pyridine position to the 5-pyridine position to construct the patented compound. *Id.* at 1360-

61. The court disagreed and noted that even Alphapharm's expert conceded that the "biological activities of various substituents were unpredictable." *Id.* at 1361. *See also Yamanouchi*, 231 F.3d at 1341 (structurally similar prior-art compound does not make new compound obvious).

Alphapharm's expert's "ring-walking" theory is analogous to Dr. Lenz's unsupported move of a 2,2,2-trifluoroethoxy, only one of many possible substituents in the Byk Gulden '518 patent's choices on the benzimidazole ring, from the 5-position of the benzimidazole ring to the 4-pyridine ring position. Even worse, to construct lansoprazole, Dr. Lenz then further removed and replaced other substituents on the pyridine ring.

This Court's recent decision in *Bayer v. Dr. Reddy's Labs.* is similarly instructive. The Court found that Reddy did not demonstrate that the prior art taught modification of the lead compound with the necessary substituents to create the claimed compound, or that there was a reasonable expectation of success to create this compound. *Bayer*, 2007 WL 3120794, at *9. Yet in this case, Teva's prior art, unlike the prior art in *Yamanouchi*, *Bayer*, or *Takeda*, actually taught away from lansoprazole.

Teva's reliance on *Aventis Pharma Deutschland v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007), is misplaced. The *Aventis* patent covered one stereoisomer of the drug ramipril. The closest prior art included this ramipril stereoisomer in combination with its other isomers. *Id.* at 1294-95. Here, unlike in *Aventis*, no prior art specifically disclosed lansoprazole, and the differences between lansoprazole and the prior-art compounds were substantial.

D. The Person of Ordinary Skill in the Art

Teva's dispute with Plaintiffs' definition of the person of ordinary skill in the art has little relevance to the case. Even someone of Dr. Lenz's and Dr. Lipinski's high skill level would not find lansoprazole obvious. Lipinski 1277:23-1278:3.

Nonetheless, Plaintiffs have provided the more appropriate definition. Around August of

1984, the person of ordinary skill in the art would have been someone like witness Keiji Kubo when he synthesized lansoprazole—a person with a bachelor's degree in the fields of chemistry or medicinal chemistry with at least two years of experience in drug design, or with a master's degree in these fields without experience. Lipinski 1194:7-22. This was the level of a scientist that Dr. Lipinski would have hired at Pfizer to work on drug development. *Id.*

Unlike Dr. Lipinski, Dr. Lenz did not provide a reasoned explanation supporting his definition of a person of ordinary skill in the art in his direct testimony, other than to opine that a person of ordinary skill was a medicinal chemist. Lenz 726:23-727:8.

E. Teva Ignores the Objective Indicia of Nonobviousness

Teva has not demonstrated that lansoprazole is *prima facie* obvious. Hence, Plaintiffs have no burden to produce objective indicia (secondary considerations) evidence, and this step could be skipped here. *See Takeda v. Alphapharm*, 492 F.3d at 1363.[7] But once the Court considers this objective evidence, it overwhelmingly demonstrates that lansoprazole was not obvious.

"[S]econdary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000), *quoting Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538 (Fed. Cir. 1983).

[7] *See also Leviton Mfg. Co. v. Universal Sec. Instruments, Inc.*, 304 F. Supp. 2d 726, 751 (D. Md. 2004) ("Evidence of secondary considerations weighs in favor of non-obviousness although the lack of evidence does not weigh in favor of obviousness…. USI has failed to establish the prima facie case of obviousness; thus, there is no need for Leviton to rely on secondary considerations."); *Mobil Oil Corp. v. Amoco Chem. Corp.*, 779 F. Supp. 1429, 1498 (D. Del. 1991) (same), *aff'd*, 980 F.2d 742 (Fed. Cir. 1992).

1. Lansoprazole Exhibited Unexpected Results

Unexpected superior properties of an invention support the conclusion that the invention was not obvious to one of skill in the art. *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Unexpectedly, lansoprazole was found to be more chemically stable than the prior-art omeprazole compound. Lipinski 1206:3-12; PTX 90 at Lipinski 002681 (Conclusion).

Additionally, lansoprazole had several clinical advantages over omeprazole. Fennerty 831:2-21. Dammann (PTX 164) found that lansoprazole has a bioavailability of 85% versus 35% for omeprazole. Fennerty 831:25-832:15; PTX 164 at 363 (Col. 1, last paragraph). For this reason, several clinical studies demonstrated faster onset of action for patients taking lansoprazole versus omeprazole. Fennerty 836:12-839:20; PTX 166 at 224 (abstract); PTX 173 at 757 (summary results); PTX 163 at 1749 (abstract conclusions); PTX 169 at 413 (summary conclusion); and PTX 176 at 3089 (results section). Teva's expert, Dr. Solny,[8] admitted that this increased bioavailability translates into a faster onset of action which allows the effect of lansoprazole to be appreciated sooner than omeprazole in some patients. Solny 587:11-13.

And Pantoflickova (PTX 174) found that lansoprazole also attained a higher pH in the stomach for a longer period of time: 7.5 hours versus 3 hours for omeprazole. Fennerty 833:7-24; PTX 174 at 1511 (1st Col. 1st full paragraph).

Teva cites the OHSU study as evidence of no unexpected results. *See* DTX 744. But Dr. Fennerty explained that this study (which was done by his university) was not designed to look

[8] Dr. Solny, in contrast to Dr. Fennerty, has not published a paper in almost thirty years and is not a member of any review board for any peer-reviewed journal. Solny Cross 596:205; DTX 129. Dr. Solny is a professional expert witness serving in some 34 litigations. Solny Cross 594:24-596:1. He admitted he does not have the expertise to evaluate a meta-analysis of 200 different studies involving different protocols. Solny Cross 596:20-23.

for the optimal PPI for symptom relief, and did not include the Richter study (DTX 386) and other significant studies showing lansoprazole's superior symptom relief. Fennerty 841:5-20.

It is symptom relief that brings patients to doctors. Fennerty 819:19-20; Solny Cross 600:24-601:7; 602:4-9. Patients would rather get relief sooner than later. *Id.* Lansoprazole's faster onset of action, as demonstrated in the scientific literature, means it was better than omeprazole. Fennerty 842:5-10; 842:18-843:2; Fennerty Redirect 866:17-20.

Lansoprazole also has fewer drug-drug interactions than omeprazole. Fennerty 843:3-845:15. Dr. Fennerty explained that omeprazole is largely metabolized in the body through the 2C19 pathway versus lansoprazole which is metabolized more through the CYP384 pathway. Fennerty 843:3-844:4. Commonly-prescribed drugs Valium, Dilantin, and Coumadin are also largely metabolized through the same 2C19 pathway. *Id.* When any of these drugs is co-administered with omeprazole, there is more chance of drug-drug interactions due to this shared metabolic pathway in the body versus lansoprazole. *Id.* Dr. Solny acknowledged that the differences in chemical structure could account for the differences between the drugs. Solny Cross 598:1-3; 598:20-24; 598:4-8; Solny Redirect 610:1-11.

2. Many Other Companies Tried and Failed to Produce a PPI

Evidence of failed attempts by others supports a finding that the patented invention would not have been obvious. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000). As many as 40 different companies tried to produce a viable PPI. Out of these 40 companies, only 4 succeeded in developing a viable PPI. Lipinski 1208:4-13.

3. Prevacid®'s (lansoprazole) Commercial Success

Lansoprazole has been one of the most successful PPIs, with total sales of over $35 billion since its launch in 1995 and sales over $1 billion each year since 1998. Cole 1056:24-

1058:7[9]; PTX 182. Teva's expert, Dr. Vandaele, admitted that a drug having more than $1 billion in sales was a "commercial success." Vandaele Cross 1029:14-17; 1030:1-6. By 1999, lansoprazole had captured 40% of the PPI market from omeprazole despite the fact that Takeda and TAP were originally unknown entities in the gastroenterology field. Fennerty 845:16-846:21; Vandaele 1024:10-14; Cole 1054:21-1055:3; PTX 729 at TAP 437655. In 2003, Prevacid became the best selling PPI and the third best selling pharmaceutical product in the United States. Cole 1059:11-16.

Teva contends that there is no nexus between the patented lansoprazole compound and its commercial success, and attributes this success to "marketing" of the product. But a nexus is presumed when the commercially successful product is, as here, an embodiment of the invention disclosed and claimed in the patent. *Demaco Corp. v. F. Von Lansdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). "A patentee is not required to prove as part of its prima facie case [of secondary considerations] that the commercial success of the patented invention is not due to factors other than the patented invention." *Id.* at 1394. Rather, "[i]t is sufficient to show that the commercial success was of the patented invention itself." *Id.*

Prevacid's ability to take omeprazole's market share was due to its properties—properties that were highlighted by TAP when marketing Prevacid to physicians. Cole 1056:13-31. Even Teva's expert admitted that if even half of Prevacid®'s $36 billion in sales were due solely to marketing and promotion, Prevacid® would still be a commercial success. Vandaele Cross 1030:16-20.

[9] Doug Cole is the Vice President of Sales at TAP Pharmaceuticals and has been at TAP since 1992. Cole 1047:23-1049:1. TAP is a U.S.-based drug development and commercialization company that is the product of a joint venture between Abbott Laboratories and Takeda. Between 1999 and 2001, Mr. Cole was involved in Prevacid marketing and branding and served as Brand Director for Prevacid. *Id.*

Significantly, TAP and Abbott (which co-promoted Prevacid for a limited time just after launch) had no previous sales or marketing presence in the gastroenterology field, and their sales forces were not connected with gastroenterologists. Fennerty 846:22-847:1; Cole 1053:15-1054:17. In fact, Abbott sales personnel would usually put Prevacid® in the second or third position to sell to physicians. *Id.* In *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573-74 (Fed. Cir. 1996), the Federal Circuit found that Pro-Mold's "lack of previous experience in the relevant market combined with its high sales of the patented product provided an inference of a nexus between its commercial success and the patented invention."

In short, the overwhelming evidence supports a nexus between the commercial success of Prevacid® and the '098 patented compound. Fennerty Redirect 868:19-23.

4. There was an Unmet Need For Lansoprazole

Evidence of an unsolved need in the industry for the solution offered by the patented invention supports a finding that the invention would not have been obvious at the time the invention was made. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998). In 1984, there was an unmet need for a safe and effective PPI. Omeprazole was not commercially released until 1989. Even when omeprazole was released, it had a black-box warning. Lipinski 1207:5-11. Furthermore, the omeprazole label indicated that there were drug-drug interactions with what Teva's own expert agreed were commonly-prescribed drugs. Solny Cross 606:5-607:12.

* * *

In sum, the differences between lansoprazole and the prior art were significant. The scope and content of the prior art showed that one of ordinary skill in the art was unlikely to select lansoprazole out of over 13 million possibilities, especially in light of the difficult hurdles involved and the unusual 2,2,2-trifluoroethoxy substitution the inventors used. And if objective

indicia of obviousness are also considered, there is no basis upon which to find the '098 patent obvious.

V. THERE IS NO EVIDENCE THAT THE INVENTORS OR ANYONE ELSE WITHHELD MATERIAL INFORMATION WITH AN INTENT TO DECEIVE THE PTO

A. Different Animal Models Screen Compounds For Distinct Properties

Biological activity cannot be predicted from chemical structure alone. Kubo 1113:18-1114:5. Instead, scientists rely on animal models to screen compounds for biological activity. With animal models, scientists hope to reproduce the clinical situation in humans. Whittle 1297:6-12. But no animal model can reproduce the human situation. *Id.* Instead, only facets can be reproduced. *Id.*

No "standard" screening model existed in the mid-1980s and, as Plaintiffs' expert explained, "it's very much up to the company and scientists to decide their strategy of which models they will use and how much importance they'll put on those models." Whittle 1296:1-3. Pharmacologists' personal preferences determine which animal models take precedence. Whittle Cross 1364:23-1365:2. Such judgment calls differentiate pharmaceutical companies, and can determine whether a company's drug development will be successful or not. Whittle 1296:22-1297:5.

In the mid-1980s, when lansoprazole was invented, scientists did not fully understand the cause of gastric ulcers. Whittle 1297:16-20. Instead, scientists merely understood that ulceration meant that the stomach's ability to defend itself against its own stomach acid was somehow diminished; and the stomach's indigenous protection, known as gastroprotection or cytoprotection, needed to be increased, or stomach acid needed to be decreased, to reduce ulceration. Whittle 1297:21-1298:19; PTX 1 at 1:20-26.

Accordingly, the screening models for prospective gastric ulcer agents fall into three

broad groups—antisecretory models, gastroprotective models and anti-ulcer models. Whittle 1299:3-14. Antisecretory models measure only the effect of a chemical compound on mechanisms of acid secretion. Whittle 1299:23-1300:1. Gastroprotective models measure only the effect of a compound on mechanisms of protection. Whittle 1300:2-13.

In contrast to antisecretory and gastroprotective models, anti-ulcer models try to assess the true anti-ulcer activity of a compound. Whittle 1300:14-19. These models measure the end result or ultimate effect of preventing ulceration, and do not provide information on the mechanism by which a decrease in ulceration is achieved. Whittle 1300:14-1301:1. The indomethacin-induced antral ulcer, known as the "IMAU model," is an anti-ulcer disease model; and the IMAU model generated the data submitted in the '098 patent. *Id.*; Dajani 663:3-15.

B. The IMAU Model Provides Advantages Over Other Models; It Mimics the Location, Shape, and Histology of Human Ulcers

Dr. Satoh, a Takeda scientist and an assistant to inventor Dr. Maki, developed the IMAU model. Dr. Satoh first disclosed the IMAU model in 1981 in the highly-regarded journal *Gastroenterology,* PTX 122. In the '098 patent, the inventors cited to Dr. Satoh's 1981 *Gastroenterology* article as disclosing a model "which is considered to be of value as an experimental model." PTX 1 at 5:33-40; Dajani Cross 904:12-20.

Dr. Satoh believed that this IMAU model provided advantages over other models. Satoh 1569:9-16; Dajani Cross 908:25-909:3. As reported in his 1981 *Gastroenterology* article (PTX 122), the gastric antral ulcers produced in the IMAU model "mimic human gastric ulcer with regards to location, shape and histology." PTX 122 at 725; Whittle 1302:11-17, 1302:21-23, 1302:24-25, 1303:6-10.

The location of the ulcers produced by the IMAU model is a key advantage. The stomach of humans and rats can be roughly divided into two regions—the corpus and the

antrum—and measurements in these regions provide different and distinct information. Dajani Cross 948:20-23, 948:24-949:2; Whittle 1302:24-1303:15. In the IMAU model, fasted rats must be re-fed for one hour to create actual ulcers in the antrum. Dajani Cross 914:20-22, 915:1-8; Whittle 1331:25-1332:3, 1332:14-21. By contrast, if the fasted rats are not re-fed, as in another model called the "indomethacin corpus model," superficial erosions form in the corpus region. *Id.*; Dajani 948:1-16; PTX 122, Abstract. Because most human ulcers occur in the antrum, the IMAU model therefore more closely mimics the development of ulcers in man and provides an advantage over other models available in the 1980s. Whittle 1303:16-24.

The shape and characteristics of ulcers formed in the IMAU model is a second key advantage. The IMAU model is "one of the first models which showed a development of a chronic lesion"—a deep penetrating and lasting lesion, unlike the lesions that form from prior models, like the indomethacin corpus model, which produces only superficial lesions that heal within 12 to 24 hours. Whittle 1303:25-1304:21, 1308:1-6; PTX 122, Abstract & at 724.

Although Takeda scientists believed the IMAU model had certain advantages, this model was not as widely used in the 1980s as some of the other, older models. Dajani Cross 909:18-20. But the IMAU model has been adopted in at least 99 publications, as Teva's expert Dr. Dajani admitted. Dajani Cross 909:21-25; Whittle 1305:4-9. Indeed, some of the top pharmacologists in academia and industry have adopted Takeda's IMAU model, as shown by important publications. Whittle 1305:19-1307:25; PTX 107; PTX 113; PTX 118.

C. The Inventors Did Not Intend to Deceive the Examiner by Providing IMAU Data

1. The Inventors and Takeda Management Relied on the IMAU Values Disclosed in the '098 Patent to Select Lansoprazole

The IMAU model played a critical role in the '098 inventors' and Takeda management's decision to select lansoprazole over other novel Takeda anti-ulcer compounds for further

development. Whittle Cross 1357:7-15, 1358:7-16; Maki 1483:15-16. As shown by Takeda's September 1984 internal research report to management, PTX 134, the inventors believed that lansoprazole was superior to prior compounds, including omeprazole, in a number of different areas, but particularly in the IMAU results. Dajani Cross 921:25-922:17. Indeed, an internal Takeda report informed management that lansoprazole "at least shows 21 times or more higher potency … as compared to the relative standard [omeprazole]" based on the same IMAU results reported in the '098 patent. Dajani Redirect 988:2-11.

According to PTX 134, in late August 1984, in view of the IMAU results submitted to the PTO, Takeda management decided to perform further testing of lansoprazole against omeprazole and the H_2 blocker ranitidine in order to provide standard test information for an IND (Investigational New Drug application) to the FDA. Whittle 1316:6-17.

Other exhibits at trial support the IMAU test's primacy for the inventors and Takeda management. In Takeda internal report PTX 132, Takeda management selected lansoprazole and compound AG-1760 for further study, because these two compounds showed superior activity in the IMAU test compared to omeprazole or the prior-art Byk Gulden compound. PTX 132; Whittle 1313:7-21. In PTX 133, data for new Takeda compound AG-1710 showed more favorable results than lansoprazole in non-anti-ulcer models: an *in vitro* antisecretory assay, and an *in vivo* gastroprotective assay (the ethanol model). Whittle 1321:22-1322:10. But the inventors chose lansoprazole, and not AG-1710, as the compound to pursue, because lansoprazole performed better in the anti-ulcer IMAU model. Whittle Cross 1374:7-25; Whittle 1322:21-23.

Professor Whittle testified that he saw no indication that the inventors lacked faith in the IMAU ID_{50} values that they reported to both Takeda management and the Patent Office. Whittle

1353:16-22.

2. The Inventors and Their Assistants Testified to Their Good Faith in Submitting Data From the IMAU Model in the '098 Patent

Teva mischaracterizes the testimony of Dr. Satoh, inventor Dr. Maki's assistant. According to Teva's brief, Dr. Satoh "admitted" that "Takeda" selected the IMAU model because lansoprazole showed "strong activity in this model," and not because it was a valuable model. Teva contends that Dr. Satoh "did not identify IMAU as being a superior methodology as the reason the IMAU result was referenced." Teva Br. at 12. But Dr. Satoh testified that he believed data from the IMAU model was more significant than data from other animal models:

> So, lansoprazole and a series of compounds showed strong activities in this model. So, I thought the results from this model were more important as compared to other test results such as those of rat acute gastric ulcer model, and that was the reason that we put the data or the result of indomethacin-induced antral ulcer model in the patent with priority. Satoh 1569:9-16.
>
> * * *
>
> Therefore, because of these characteristics of the models, the valuable data or the results from the indomethacin gastric antral ulcer model was more valued and other performances were—there were no need to cite the results of other models. Satoh 1570:21-1571:1.

Likewise, the inventor, Dr. Maki, confirmed that he selected the IMAU model because he considered it to be the best model:

> We think that this is the best model to see the action of the human gastric ulcer. Maki 1482:12-14.
>
> * * *
>
> As I have been telling you, this rat gastric antral ulcer model can indicate very close data as is found in human gastric ulcer. That's why we submitted this data. Maki 1485:10-14.

Thus, the testimony of the inventors and their assistants is consistent with the '098 patent and internal reports to Takeda management.

3. The Raw Data Submitted in the '098 Patent's Disclosure Is Consistent With Raw Data Reported in Takeda's Own Internal Reports

Teva contends that the inventors selectively reported a 20-fold difference in efficacy between lansoprazole and the prior art. On direct, Teva's expert, Dr. Dajani, testified that he did not see any internal Takeda data that supports a 20-times greater effect of lansoprazole versus omeprazole. Dajani 674:15-20. Yet Dr. Dajani admitted that in Takeda's internal report DTX 705, the IMAU data showed that omeprazole's ID_{50} was 21 mg/kg, and lansoprazole's was less than 1 mg/kg. Dajani Cross 989:16-24. In other words, the IMAU data in Takeda's internal reports supports a 20-times or more greater effect of lansoprazole than omeprazole. Whittle 1340:12-16.

In fact, it is undisputed that the ID_{50} values reported in Takeda's internal report DTX 705 are identical to the ID_{50} values in the '098 patent. Indeed, Takeda's internal reports only report the IMAU ID_{50} values reported in the '098 patent. Dajani Cross 900:22-901:8, 901:14-18, 901:20-23; Dajani Redirect 989:16-24; Whittle 1344:22-1345:2; DTX 705 at TAKEDA 044329-30; Whittle 1318:16-22 (describing PTX 133); PTX 133, at TAKEDA 436726.

Moreover, data reported in the inventors' publications likewise show a 20-fold difference between lansoprazole and omeprazole. As Dr. Dajani acknowledged, PTX 862, a peer-reviewed journal article by the inventors, showed that lansoprazole was 20 times more effective than omeprazole at inhibiting reflux esophagitis in rats. Dajani Cross 941:17-19; PTX 862 at 440 & Fig. 2 (reporting ID_{50}s for lansoprazole (0.7 mg/kg) and omeprazole (13.7 mg/kg)).

Teva's contention that the '098 patent's inventors selectively reported a 20-fold difference between lansoprazole and the prior art is without merit. The '098 patent provides a broad comparison range to prior-art compounds of "*about* 1.5-20." PTX 1 at 6:30-32. The inventors submitted IMAU data showing a mere 1.5-fold difference between the '098 patent's

claimed compounds and the prior-art Byk-Gulden compound—at the lower end of the range. PTX 1 at 6:5-29; Dajani Redirect 988:23-989:12.

4. The Inventors' Non-Attendance at Trial is Not Evidence of Intent to Deceive the PTO

Another indication of the weakness of Teva's challenge is that Teva lists as primary evidence of deceptive intent "[t]he failure of Takeda to bring any live witness …." Teva Br. at 18.

As Teva knows from the depositions it took in Japan of the inventors and their assistants, inventors Drs. Nohara and Maki, and assistant Dr. Satoh, no longer work for Takeda, they live in Japan, and are full-time employees of other companies. Kubo 1107:13-15, 1108:20-1109:1. Because Takeda has no control over these witnesses, their absence at trial cannot give rise to an adverse inference. *Governali v. Am. Tempering, Inc.*, No. 85-7305, 1988 WL 3843, at *3 (E.D. Pa. Jan. 20, 1988) ("[A] defendant's failure to produce a former employee does not automatically give rise to any unfavorable inference"), *aff'd*, 856 F.2d 83 (3d Cir. 1988); *Louis Marx & Co. v. Buddy L. Corp.*, 453 F. Supp. 392, 400 (S.D.N.Y. 1978). Moreover, since Teva cites their deposition testimony in its brief, and never sought their appearance at trial, there is no basis for any adverse inference of deceptive intent.[10]

5. Takeda's Regulatory Affairs Department's Selection of Tests to Submit to the FDA in its IND is Not Evidence of Intent to Deceive the PTO

Teva contends that the absence of IMAU data in Takeda's IND application is evidence of

[10] "[B]y offering their deposition testimony instead of pursuing their live testimony or raising this issue earlier, [a party] … should not now be permitted to benefit from a negative inference …." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 106 F. Supp. 2d 667, 694 (D.N.J. 2000); *see also Bogosian v. Woloohojian Realty Corp.*, 323 F.3d 55, 67 (1st Cir. 2003).

intent to deceive the PTO.[11] Teva Br. at 18. Yet again, Teva relies on an adverse inference of deceptive intent.

But Takeda's Regulatory Affairs Department selected tests for submission to the FDA in Takeda's IND for purposes that are irrelevant to the inventor's earlier, independent decision to submit IMAU testing to the PTO. In the IND, the Regulatory Affairs Department submitted the types of tests that were used in successful IND submissions for prior anti-ulcer agents, such as ranitidine (an H_2 blocker) and omeprazole. Dajani Cross 927:15-928:3. When dealing with regulatory agencies like the FDA, and in submitting an IND, a company is most likely to take a conservative approach and to copy the selection of models used by prior successful applicants for anti-ulcer agents. Whittle Cross 1363:17-1364:13. The IMAU test did not exist or was too new when other companies filed IND applications for omeprazole, ranitidine, or other prior anti-ulcer agents. Dajani Cross 927:8-11; Whittle 1350:11-16.

Moreover, at the time of Takeda's IND submission, the regulatory agencies would expect comparative data with the prior anti-ulcer agent, ranitidine. But the IMAU model cannot be used to compare lansoprazole and ranitidine, because ranitidine is inactive in the IMAU model. Whittle 1350:17-1351:8. Since the IMAU model had not been submitted in previous INDs for gastric-ulcer drugs and did not work with ranitidine, the submission of different models previously adopted in the INDs for ranitidine and omeprazole made perfect sense. Whittle Cross 1363:17-1364:3. As explained by Dr. Maki, one of the '098 inventors:

> Q: If [the IMAU] model was the best model, why is it not reflected in [DTX 595]?

[11] Teva's theory that the absence of the IMAU in the IND is evidence of intent seems to have been a last gambit. Dr. Dajani never discussed the issue in his expert report. Whittle 1348:24-1349:5.

> [Dr. Maki]: These [other] models were used by many pharmaceutical companies, so in order to show the actions of [lansoprazole] for anti-ulcer and the acid antisecretion, the models were used because other companies were using them.

Maki 1494:1-8.

D. The Allegedly Withheld Data Is Not Material

1. The Patent Asserts that Its New Compounds Have "about 1.5-20 times or more" Superior Anti-Ulcer Effect, and Does Not Assert the 20-Fold Difference in Any Model that Teva Alleges

Teva crop-quotes the '098 patent to make it read that "lansoprazole was superior to omeprazole by a margin of '20 times or more.'" Teva Br. at 3. This mischaracterization permits Teva to contend that any data that does not show a 20-fold difference between lansoprazole and the prior art, taken from any model, is inconsistent with the data submitted by the inventors in the '098 patent.

But the '098 patent provides a fairly broad comparison range of *about* 1.5-20 between compounds claimed by the invention and prior-art compounds, and this comparison is limited to **anti-ulcer** models only: "As shown by the above data, the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5-20 times or more." PTX 1 at 6:30-32; Dajani Cross 918:6-19; Whittle 1328:16-22. Indeed, Dr. Dajani admitted that the use of the term "about" indicates that the 1.5-20 range was only an approximation, and that a reader would understand the "about 1.5-20" to refer solely to results from the IMAU anti-ulcer model. Dajani Cross 918:6-23.

Consistent with this comparison, the '098 patent also reports that the new compounds show activity in other antisecretory, gastroprotective, and anti-ulcer models: "Besides the above, the compound of this invention shows excellent actions of inhibiting gastric acid secretion, protecting gastric mucous membranes and preventing ulceration." PTX 1 at 6:33-36. Takeda's

internal reports, like PTX 133, confirm lansoprazole's and the '098 compounds' substantial antisecretory activity, Whittle 1329:3-20, and other internal reports, like DTX 705, confirm lansoprazole's substantial gastroprotective activity, Whittle 1344:1-10.

2. Teva's Contentions Concerning Dog and *In Vitro* Antisecretory Testing Ignore the Patent's Emphasis on Anti-ulcer Effect

Teva's inequitable conduct challenge appears to boil down to the fact that Takeda did not disclose certain dog and *in vitro* antisecretory tests conducted by Takeda. Teva Br. at 7-8.

But Teva's focus on antisecretory test results misses the point of the '098 patent: to disclose compounds showing superior anti-ulcer properties. Whittle 1325:13-1326:9. The patent so states:

> However, while 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….
>
> It is considered that gastrointestinal ulcer is induced by unbalance between aggressive factors … and defensive factors …. Therefore, a medicine having both an action of inhibiting gastric acid secretion and an action of enhancing protection of gastric mucosa has been desired.
>
> 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 present invention. PTX 1 at 1:13-26.

Thus, the inventors did not view the presence of an antisecretory effect as sufficient in and of itself. Instead, the '098 patent focuses on the ability of the new compounds to show an anti-ulcer effect, in contrast to prior compounds like omeprazole that had only a specific antisecretory effect. PTX 1 at 6:33-34.

a. Dog antisecretory data is irrelevant to the '098 patent.

Dogs cannot be used in anti-ulcer models, because dogs would need to be sacrificed in

these models. Whittle 1341:12-1342:8. Thus, there is no dog data that is material to the issue presented by the inventors in the '098 patent—whether the new claimed compounds performed better than prior compounds in **anti-ulcer** models.

Moreover, Teva inaccurately describes the inventors' conclusions from their antisecretory dog studies. The inventors found that lansoprazole was superior to omeprazole in antisecretory dog studies with respect to lansoprazole's longer duration of its action. Whittle 1341:1-8. And this is significant because healing requires that the acid be kept low for long periods of time. Fennerty 833:10-24; PTX 174.

Teva's contention that antisecretory dog data must be disclosed in a patent for anti-ulcer drugs is also contrary to common sense and industry practice. It is the inventors' role as scientists to select what data is relevant. Whittle Cross 1364:23-1365:2. Indeed, Teva's expert Dr. Dajani did not report dog data for anti-ulcer drugs in his own patents. He reported only rat data as the '098 inventors did, consistent with typical industry practice. Dajani Cross 895:11-896:3.

b. *In vitro* antisecretory data is irrelevant to the '098 patent.

Similarly, the *in vitro* studies Teva relies upon address solely antisecretory effects. It is undisputed that *in vitro* studies are less probative of activity compared to *in vivo* models like the IMAU model. Dajani 666:10-15; Whittle Redirect 1384:3-7. And Teva selectively cites to "the first set of tests," Teva Br. at 7, because in certain *in vitro* tests, lansoprazole has a more potent antisecretory effect than omeprazole. Whittle Cross 1378:14-20.

3. Other Models Confirm Lansoprazole's Superiority, and are Consistent With the Patent's Statements

As Dr. Whittle explained, data from non-IMAU anti-ulcer models cannot be compared (as consistent or inconsistent) against the IMAU data submitted to the PTO. Whittle 1331:11-17,

1347:9-14. But when the animal data is looked at across the board, lansoprazole produced superior results compared to omeprazole. It is undisputed that in rat studies, including mechanistic studies for antisecretion and gastroprotection and non-IMAU anti-ulcer disease models, lansoprazole was 2 to 10 times more potent than omeprazole. DTX 595; Dajani 874:25-875:3; 674:18-675:6; Whittle 1342:15-19. Moreover, lansoprazole was shown by the inventors to heal gastric ulcers 77% faster and duodenal ulcers 28% faster in rats than omeprazole. Whittle 1348:15-21.

Indeed, the non-IMAU anti-ulcer models included in Takeda's IND report (DTX 120) consistently found that lansoprazole was superior, with ID_{50} ratios (measuring relative potency) well within the '098 patent's broad range of about 1.5-20:

	Lansoprazole	**Omeprazole**	**Lansoprazole's Potency Relative to Omeprazole**
Acute gastric ulcers in rats	**ID_{50} (mg/kg, p.o. or i.d.)**	**ID_{50} (mg/kg, p.o. or i.d.)**	
Water-immersion stress-induced	2.5	7.0	**2.8x stronger**
Aspirin-induced	0.7	3.1	**4.4x stronger**
Ethanol-induced	8.5	15.3	**1.8x stronger**
Acute duodenal lesions in rats	**ID_{50} (mg/kg, p.o.)**	**ID_{50} (mg/kg, p.o.)**	
Cysteamine-induced	1.1	5.7	**5.2x stronger**
Mepirizole-induced	0.3	3.0	**10x stronger**
Chronic gastric ulcers in rats	**(healing rate %)**	**(healing rate %)**	
Acetic Acid at 10 mg/kg, p.o.	60%	-17%	**77% faster**
at 30 mg/kg, p.o.	64%	55%	**11% faster**
Chronic duodenal ulcers in rats	**(healing rate %)**	**(healing rate %)**	
Acetic Acid at 10 mg/kg, p.o.	41%	13%	**28% faster**
at 30 mg/kg, p.o.	67%	49%	**18% faster**

The same is true of the data presented in Takeda's 1984 internal report—lansoprazole showed a superior effect to omeprazole in each and every anti-ulcer model. DTX 705; Whittle 1345:8-17.

4. There is No Other IMAU Data that is Materially Different from the Data Reported in the '098 Patent

Teva also asserts that the inventors improperly withheld "other" IMAU data from the

Patent Office. In PTX 136, Professor Whittle recalculated the ID_{50} values from the inventors' IMAU data on lansoprazole and omeprazole that used the '098 patent's IMAU protocol, as well as other compounds listed in the '098 patent. Whittle 1338:10-15. Specifically, Professor Whittle's recalculation shows an ID_{50} value of less than 1 mg/kg for lansoprazole ("AG-1749"), *id.* at WHITTLE 550, and an ID_{50} value of 21 mg/kg for omeprazole ("AG-1414"), *id.* at WHITTLE 551. Whittle 1338:21-1339:3. Thus, Professor Whittle confirmed that the raw data supported the inventors' reported values, and that no tests contradicted these reported values.

Teva contends in its brief, without a single citation to the record, that "Takeda withheld data—taken from the same animal model—that showed lansoprazole to be only slightly more potent than omeprazole." Teva Br. at 3-4. However, Teva never identifies the other "IMAU data" it believes to be withheld.

Similarly, Dr. Dajani testified that the inventors had "contradictory data." But Dr. Dajani was relying on a failed study. He admitted on cross-examination that his conclusions and testimony were erroneous because he relied on a failed study with useless data. Dajani Cross 890:18-24. His only explanation for failing to recognize this fact—"We're not perfect." Dajani Cross 890:24.

Teva also attempts to rely on the work of Robert Hirsch, an expert Teva had hired to analyze the inventors' 1984 data. But Dr. Hirsch did not show up at trial. And it is no surprise why. Professor Kaunitz elaborated on the invalidity of Dr. Hirsch's work at great length, and showed how Dr. Hirsch provided incorrect ID_{50} values. Kaunitz 1402:12-1403:2; Kaunitz 1396:25-1400:1, 1400:15-1402:8.

Despite failing to call Dr. Hirsch, Teva nonetheless seeks to rely on a portion of his expert report, DTX 218.1, which is a table that purports to show ID_{50} values Dr. Hirsch

calculated for the inventors' IMAU tests. Teva used DTX 218.1 to support its theory that "other IMAU data" contradicts the IMAU data reported in the '098 patent. Teva Br. at 9. But this table groups IMAU tests with the indomethacin corpus lesion test, a non-IMAU test. As Plaintiffs' experts explained, the indomethacin corpus lesion test measures only superficial (as opposed to deep and penetrating) lesions in the corpus (as opposed to antral) region of the stomach. Dajani Cross 947:16-949:2, 949:5-8 & Whittle 1335:20-1336:3. More importantly, one cannot compare ID_{50} values from the IMAU test to the ID_{50} values from the corpus test—they're "like chalk and cheese." Whittle 1336:4-8. In fact, the inventors and Takeda management never relied on the results of corpus model tests to determine which compounds to pursue, and the inventors never submitted corpus model data to management in any internal reports. Whittle 1333:12-20, 1336:22-1337:4, 1345:18-21.

Moreover, Dr. Hirsch's table, DTX 218.1, also includes tests that Dr. Dajani admitted at trial were failed tests, Dajani Cross 947:9-15, as well as tests using different protocols that cannot be compared with the IMAU tests of the patent, Whittle 1337:21-1338:2. Once DTX 218.1 was analyzed by Professor Whittle, he found it included only six relevant IMAU tests—two for each of omeprazole, lansoprazole, and the Byk Gulden patent:

IMAU Experiments

Compound	Date of Experiment	ID50 Value
Lansoprazole	9/6/84	1.6
Lansoprazole	7/12/84	< 1.0
Omeprazole	7/4/84	> 10.0
Omeprazole	7/13/84	21.0
Byk-Gulden	8/7/84	7.5
Byk-Gulden	7/20/84	5.5

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Whittle 1338:21-1339:10. As can be seen from Professor Whittle's table, Teva fails to identify any IMAU tests that the inventors conducted that were inconsistent with the IMAU data reported in the '098 patent. Finally, the values in DTX 218.1 are all incorrect, for the reasons provided by Dr. Kaunitz. Kaunitz 1402:12-1403:2; Kaunitz 1396:25-1400:1, 1400:15-1402:8.

Under cross-examination, Dr. Dajani admitted that he had no idea what methods Dr. Hirsch used to create DTX 218.1. Dajani Cross 882:18-23 , 883:2-886:11. This response was not surprising given that Dr. Dajani signed his expert report only one day after he received Dr. Hirsch's expert report. *Id.* "A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty." *Dura Auto. Sys. of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002). Because Dr. Dajani could not testify on the validity of Dr. Hirsch's methods, DTX 218.1 and the testimony surrounding it should be excluded.

5. A Reasonable Examiner Would Not Rely On The IMAU Results in Evaluating the *Prima Facie* Obviousness Case

The prosecution history of the '098 patent did not discuss, or even suggest, that the IMAU data was a factor in the examiner's decision to allow the '098 patent, much less a material factor. As Teva's brief admits, the prosecution history reflects only the following facts: the inventors disclosed the omeprazole patent and the Byk Gulden '409 patent to the PTO in an information disclosure statement, the examiner reviewed those patents (as well as other prior art), and after considering the prior art, allowed the '098 patent "without raising any questions, objections or rejections regarding the application." Teva Br. at 10-11.

The legal concept of *prima facie* obviousness is a procedural tool that has long been

employed in patent examination. *See* MPEP § 2142.[12] The examiner who seeks to reject an application on obviousness grounds bears the initial burden of showing that the prior art renders the claimed invention *prima facie* obvious. *Id.* If the examiner provides the requisite *prima facie* showing, the burden shifts to the applicant to present evidence showing non-obviousness. *Id.* If the examiner does not present a *prima facie* case of obviousness, the applicant is under no burden to present additional evidence of non-obviousness.

The examiner made no *prima facie* obviousness rejection of the '098 application. Despite this, Teva's theory assumes without evidence that the examiner: (1) determined that the '098 patent was *prima facie* obvious over the prior art; (2) envisioned that the inventors would rely on the IMAU data as evidence of '098 compounds' superior properties; and (3) then considered and accepted the IMAU data as sufficient to overcome a *prima facie* obviousness rejection. Teva's imaginary fact scenario is neither credible nor based on evidence.

In its imaginary recreation of the '098 patent's prosecution history, Teva focuses only on omeprazole and ignores the prior-art Byk Gulden compound. Teva again ignores the undisputed fact that the inventors presented a difference between the '098 compounds and the Byk-Gulden compound in the IMAU model, which was as low as 1.5. PTX 1 at 6:5-29; Dajani Redirect 988:23-989:12. Teva does not address the fact that the examiner allowed broad claim 1 and all of the other claims for individual compounds having only 1.5 times more potency in the IMAU test. Given the inventors' good-faith presentation that the claimed compounds may be only 1.5 times more effective than prior compounds in the IMAU test, a comparison between the claimed compounds and omeprazole was not important to the examiner's decision—*especially since*

[12] Manual of Patent Examining Procedure ("MPEP"), *available at* http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2142.htm#sect2142. The description of *prima facie* obviousness in the current MPEP was based on the standards articulated in decisions from the 1960's and 1970's and was well established at the time the '098 patent was examined.

omeprazole was never described as the most important prior compound anywhere in the specification or prosecution history.

E. Teva Provides No Evidence that the Inventors Knew of the Alleged Materiality of Antisecretory Models to the '098 Patent

Teva's brief cursorily addresses its burden to prove that the inventors had knowledge that antisecretory tests would be material to the '098 patent. Teva Br. at 17-18. Instead of evidence, Teva offers attorney argument. *Id.* at 17. Substantial evidence at trial showed, however, that the IMAU testing—and not the antisecretory dog tests on which Teva now relies—helped select lansoprazole for development. Whittle Cross 1357:7-15, 1358:7-16.

F. The Record Also Contradicts Teva's Other Inequitable Conduct Allegations At Trial, Which It Now Ignores in Its Brief

At trial, Teva contended that the inventors misled the Patent Office by not including a "statistical analysis" of the submitted IMAU ID_{50} values. Dajani 653:2-9, 880:6-12.

It is undisputed that ID_{50} values were commonly used to estimate relative potency in the 1980s. Dajani 678:3-6. Moreover, it is undisputed that it would have been unusual in the 1980s to perform statistical analysis of "screening data," which was used principally to identify compounds for further investigation. Dajani 873:15-23; Dajani Cross 902:14-903:11, 924:7-10; Whittle 1328:3-15, 1336:17-21, 1352:1-4. Instead, the inventors estimated the ID_{50} values reported in the '098 patent by using a conventional log paper method, Dajani Cross 899:20-23, a method that Professor Whittle, Plaintiffs' expert, also used in the 1980s, Whittle Cross 1379:21-1380:2.

Likewise, Dr. Dajani compared the potency of compounds in his own patents and publications based on ID_{50} values, without performing a statistical analysis. Dajani Cross 898:3-6, 898:18-20. At trial, Dr. Dajani compared compound potencies with his "eyeball" method that also did not use statistical analysis. Dajani Cross 882:7-16. And the prior art, like DTX 7 and 9

(the Byk Gulden patents), reports ID_{50} values without statistical analysis. Whittle 1354:13-19. Thus, the record consistently shows that it was unnecessary and unusual for scientists to perform statistical analysis in the 1980s.

Further, Teva's post-trial brief does not discuss Teva's alleged reproduction of the inventors' IMAU testing, performed on Teva's behalf by scientists from PSL. Nor should it. Since the PSL scientists who created this data did not testify at trial, this data should be excluded. And Dr. Dajani could not vouch for this data at trial. He did not supervise the PSL scientists, meet with them, or discuss with them what they did. Dajani Cross 953:9-18. *See Dura*, 285 F.3d at 613-14.

G. Teva's Conclusory Allegations Cannot Comprise Clear and Convincing Evidence of Intent, Materiality, or the Inventors' Knowledge of Materiality, and Leave Little to No Evidence to Balance

As explained in *Eisai Co. v. Teva Pharmaceuticals USA, Inc.*, 472 F. Supp. 2d 493, 525 (S.D.N.Y. 2006). Teva must overcome a high hurdle to establish that a patentee committed inequitable conduct by selecting data to present to the Patent Office:

> [I]t must be noted that defendants face an unusually high hurdle in proving inequitable conduct on this particular set of allegations. In patent cases, courts have found less suspect applicants' choices in presenting scientific data than they have, for instance, applicants' concealment of key prior art references. *See, e.g., Purdue Pharma L.P.*, 438 F.3d 1123 …. Further, affirmative misrepresentations may be considered more material, and thus more suggestive of deceptive intent, than are misleading omissions. *Hoffman-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1367 (Fed. Cir. 2003)…. [T]he inherently selective nature of presentations that cannot possibly disclose all data from experimental work suggests caution in permitting competitors, after the fact, to defeat patent enforcement by highlighting stray bits of unfavorable experimental data that did not find their way into an otherwise accurate presentation.

This heavy burden of proof is imposed on a challenger to prevent the misuse of the inequitable conduct defense as a "magic incantation to be asserted against every patentee." *FMC Corp v. Manitowoc Co.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987). Teva's clear and convincing

evidence burden is to show that (1) non-disclosed data was material to patentability, (2) the inventors or someone else substantively involved in prosecuting the '098 patent had knowledge of the materiality of this data, and (3) these individuals intended to deceive the Patent Office by withholding the data. *Bayer AG v. Dr. Reddy's Labs., Ltd.*, No. 04-179-SLR, 2007 WL 3120794, at *10 (D. Del. Oct. 25, 2007); *compare* Teva Br. at 13.

As described above, Teva offers only farfetched conjecture as to why any additional test is material to patentability. And if material, Teva offers no evidence that the inventors or Dr. Satoh knew that that other types of testing—tests that cannot be compared with the IMAU tests discussed in the '098 patent— were material. Finally, Teva offers no evidence that the inventors intended to deceive the Patent Office.

Of course, much of Teva's case rests solely on the fact that other data was not submitted. But intent cannot be inferred solely from the fact that data was not disclosed to the PTO. Teva Br. at 19. Instead, "there must be a factual basis for a finding of deceptive intent." *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1289 (Fed. Cir. 2002). "[I]nference without any probative evidence is insufficient to show culpable intent." *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1482 (Fed. Cir. 1998). Nor is it sufficient to infer intent from materiality as the "[m]ateriality of an undisclosed reference does not presume an intent to deceive." *Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1442 (Fed. Cir. 1991) (citation omitted).

In this respect, the *Takeda v. Mylan* case is particularly instructive. Since "Takeda … relied upon the data in [its internal] report in making critical business decisions, and it was entirely appropriate for Takeda to rely on that same data in preparing Table 1 for the PTO," the court did not find intent to deceive. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 417 F. Supp.

2d 341, 390 (S.D.N.Y. 2006) (Cote, J.), *aff'd sub nom. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). Instead, "Takeda had every incentive to reflect in [its internal] reports its best judgment about what the test results showed so that the companies' money and the scientists' energies would be spent as productively as possible." *Id.* at 389. No meaningful differences exist between the facts here and the facts in *Takeda v. Mylan*, and similarly, no intent to deceive should be found.

In support of its argument that all tests must be submitted, Teva relies on *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359 (Fed. Cir. 2007). Teva Br. at 16. But this reliance is misplaced. In *Cargill*, the test data constituted the "crucial issue during prosecution" and, after repeated rejections, the examiner allowed the claims based on the patentee's arguments with respect to that test data. *Id*. at 1365. In contrast, the '098 examiner issued no rejections and allowed the patent without any discussion of the IMAU data.

Further, the undisclosed test data in *Cargill* was also obtained from the same test as the data reported in the specification. *Id*. at 1365-66. But here, Teva builds its case on results from animal models that substantially differ from the submitted IMAU model, and whose results cannot be compared to the IMAU model. For this reason, these other animal models are not material. "The mere existence of these tests does not establish why a reasonable administrator would be interested in reviewing them. Without a threshold showing of relevance to the Examiner's ultimate determination …, the fact that [other] tests were among the massive volume of materials submitted to the FDA is of no moment." *Ortho-McNeil Pharms., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 742 (N.D.W. Va. 2004), *aff'd*, 161 F. App'x 944 (Fed. Cir. 2005); *see also Hoffman-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1361 (Fed. Cir. 2003) (reversing district court and finding no inequitable conduct where the evidence "shows that [the

inventors] believed that the … [other] experiment [was] not comparable and the results of the [other] experiment not pertinent to patentability").

Finally, "notwithstanding [the challenger's] suggestion to the contrary, the Court cannot infer intent from the mere failure to submit material to the PTO that was later submitted to the FDA, because there are different standards for disclosure." *Ortho-McNeil Pharm.*, 348 F. Supp. 2d at 742 n.15. "The Federal Circuit has specifically counseled against imputing deceptive intent merely from differences between the data submitted by an applicant to the PTO and to the FDA." *Eisai v. Teva,* 472 F. Supp. 2d at 525, *citing Purdue Pharma L.P. v. Endo Pharms., Inc.*, 438 F.3d 1123, 1134 (Fed. Cir. 2006).

Teva's conclusory allegations of inequitable conduct follow a pattern set by its other cases. For example, in *Eisai v. Teva*, 472 F. Supp. 2d at 523-26, Teva alleged that the inventors of rabeprazole, a later-invented PPI, committed inequitable conduct, because data concerning this PPI was disclosed to the FDA but not the Patent Office.[13] But the court rejected all of Teva's inequitable conduct challenges. *Eisai Co. v. Teva Pharms. USA, Inc.*, 2007 WL 1437834, at *1 (S.D.N.Y. May 14, 2007).

Moreover, in the present case, Plaintiffs explained why the IMAU data would not be given to the FDA. See discussion concerning other models in Takeda's IND at § V.C.5, *supra*.

* * *

In sum, Teva fails to meet its burden of proof that Plaintiffs engaged in inequitable conduct.

[13] Teva later dropped this allegation before trial. *Eisai Co. v. Teva Pharms. USA, Inc.*, 2007 WL 1437834, at *3 (S.D.N.Y. May 14, 2007).

VI. '321 PATENT CLAIM 2 WAS A NONOBVIOUS INNOVATION THAT PROVIDED A VIABLE COMMERCIAL LANSOPRAZOLE PRODUCT

A. The Problem in the Prior Art and the Solution

Lansoprazole is unstable in the presence of acid. Chambliss 497:8-20. Thus, it must be enteric-coated to protect it from stomach acid. *Id.* But because the enteric coat itself is acidic, it too can degrade lansoprazole. *Id.*

The inventors of the '321 patent overcame this problem by stabilizing lansoprazole in an enteric-coated formulation by using magnesium carbonate in even contact with lansoprazole. Amidon 1077:23-1078:3; Chambliss Cross 555:2-4. This novel approach was not obvious, as a review of the prior art makes clear.

B. The Difficulty in Formulating Drugs In Solid Oral Dosage Forms

Pharmaceutical formulation is an unpredictable discipline. Amidon 1076:11-1077:6. The mechanism whereby drugs in the solid state degrade is still a matter of debate, and is made more complicated once the drug is formulated with excipients, as explained in Plaintiffs' expert Professor Amidon's treatise, PTX 442.[14] Chambliss Cross 546:14-547:10, 548:2-15; Amidon 1081:5-1082:5; PTX 442 at 115. Further compounding the difficulty, there are an almost unlimited number of formulations that could be tried to stabilize a new drug, but there is no way to know in advance which one, if any, would work. Chambliss Cross 542:15-23; Amidon 1077:7-12; Amidon Cross 1092:16-24.

To make a commercially-viable solid oral drug formulation, it is desirable to have a 15 to 18 month shelf-life. Chambliss Cross 540:19-24, 541:12-15. But not all drugs can be successfully formulated into a 15 to 18 month shelf-life product. Chambliss Cross 541:18-22.

[14] Dr. Amidon's The Chemical Stability of Pharmaceuticals was and is a principal reference on this topic. Amidon 1075:2-15.

Indeed, Teva's expert Dr. Chambliss recounted an experience where he made 20 different formulations of the same drug but could not find a formulation that worked. Chambliss Cross 542:7-11. One option for a drug that is difficult to formulate is simply to abandon it and try a different drug. Chambliss Cross 542:3-6.

Pharmaceutical formulation experiments are also extremely time consuming. Even "accelerated studies" could take 6 months. Chambliss Cross 543:21-544:3. And the FDA requires room-temperature studies lasting as long as the amount of time the drug company requests as a shelf-life. Chambliss Cross 544:7-14. That means for a 15-18 month shelf-life, room temperature studies must last 15-18 months. Efforts to conduct accelerated and room-temperature studies may well fail, requiring a formulation scientist to start again with a different formulation. Chambliss Cross 543:3-13.

Despite these complications, Teva's expert Dr. Chambliss opined that the solution to lansoprazole's stability problem was just to add an excipient that increased pH, such as sodium bicarbonate. Chambliss 508:18-509:1. However, it turns out that Dr. Chambliss's "simple solution" was no solution at all. Experiments conducted by the '321 patent's inventors to stabilize lansoprazole showed that sodium bicarbonate (also known as "sodium hydrogen carbonate") did not work well. PTX 3 16:26-52 (Table 1). Moreover, as Dr. Chambliss admitted, even the compound claimed in claim 2, magnesium carbonate, is not a magic excipient capable of stabilizing any drug. Chambliss Cross 548:21-549:10, 549:19-23.

C. Teva Does Not Provide Any Motivation To Combine Its References, or Explain How They Were to be Combined

Dr. Chambliss's obviousness case relies principally on the prior art listed on the face of the '321 patent. Chambliss 502:22-503:2. His expert report listed four references, and each was considered by the examiner in detail during prosecution. Chambliss Cross 553:4-554:22. These

references were the lansoprazole '098 patent (PTX 1), the Rainer '230 patent (DTX 16), the omeprazole '431 patent (DTX 5), and the Ueno JP 60-019715 application (DTX 18). *Id.*

At trial, Teva and Dr. Chambliss took a different approach. Dr. Chambliss dropped the lansoprazole '098 patent, hardly mentioned the omeprazole '431 patent, and sought to add new references from outside his expert report's analysis—Pilbrant (DTX 42) and Prichard (DTX 33).

Regardless, none of the references from his report or the new ones he raised at trial make claim 2 obvious. For purposes of his obviousness analysis, the elements of claim 2 were summarized by Dr. Chambliss as: (1) pharmaceutical composition that is enteric-coated; (2) effective amount of lansoprazole; (3) magnesium carbonate; (4) parts by weight; and (5) in contact evenly. Chambliss 516:3-11.

The parties agreed that no reference teaches all of claim 2's elements. Chambliss Cross 540:6-7. In fact, most of the references are missing several elements.

The Rainer '230 patent (DTX 16) concerns proposed PPIs that, like lansoprazole, were benzimidazole compounds. However, Rainer did not mention stability problems. Chambliss Cross 555:10-15. To the contrary, Rainer teaches away from claim 2, because it discloses compounds having high stability. Chambliss Cross 556:8-19; Amidon 1087:11-1088:5; DTX 16 at 39:40-43. Not surprisingly, there is no mention in the Rainer patent of how these compounds were formulated or the need to formulate them in any special way. Chambliss Cross 567:7-14.[15]

Moreover, the Rainer '230 patent demonstrates that stability was strongly determined by the exact structure of the compounds, even where the compounds were PPIs having

[15] The patent makes no reference to magnesium carbonate, Chambliss Cross 558:20-23, Amidon 1089:24-25; nor how to combine magnesium carbonate with any benzimidazole compound to increase stability, Chambliss Cross 557:3-21. It says nothing about mixing or contacting evenly, Chambliss Cross 567:23-568:1, Chambliss 504:22-505:12, Amidon 1089:13-19, does not mention lansoprazole, Chambliss Cross 567:3-5, Amidon 1089:21-23, and does not mention a weight ratio of lansoprazole to magnesium carbonate, Amidon 1090:1-3.

benzimidazole structures. Amidon 1088:3-5.

The only reason Teva relies on Rainer '230 is that it includes antacids in a long list of ingredients. In principle, magnesium carbonate, although not mentioned in Rainer, could be used as an antacid. DTX 16 at 40:22-34. But Rainer refers to antacids solely because Rainer was suggesting combination therapy of a PPI and an antacid for immediate relief. Amidon 1088:19-1089:12. This list of ingredients has nothing to do with stability. *Id.* Indeed, Dr. Chambliss had no idea if combining any of the list of ingredients in this section of Rainer would increase lansoprazole's stability. Chambliss Cross 557:24-558:8, 558:14-19.

The '431 omeprazole patent (DTX 5) also did not mention stabilization, Chambliss Cross 558:25-559:19, nor any of claim 2's elements, *id.*, and Dr. Chambliss did not explain why it related to the claim 2 invention.

Ueno's Japanese patent application (DTX 18), and its equivalent U.S. Patent No. 4,666,919, were both considered by the examiner during the '321 patent's prosecution. Chambliss Cross 554:2-19. Ueno does not mention lansoprazole, magnesium carbonate, parts by weight of magnesium carbonate to lansoprazole, or contact evenly or the content uniformity test that relates to it. Amidon 1091:18-25; Chambliss Cross 566:12-17, 566:19-567:2.

Moreover, the active pharmaceutical ingredient ("API") discussed in Ueno is very different from lansoprazole and PPIs. Amidon 1090:25-1091:9. As Dr. Amidon explained, the API is all important with respect to stabilizing a formulation. Amidon 1091:13-17. Thus, a person of ordinary skill in the art would not look to Ueno for a solution to lansoprazole's stability problem. Amidon 1090:25-1091:9.

As a new reference, Dr. Chambliss relied at trial on his own "Background and Experience" reference which he "authored." Chambliss Cross 568:5-14. But in a

contemporaneous 1983 article, he made no mention of chemical instability due to the interaction between coatings and drugs, nor did he mention magnesium carbonate, nor magnesium or calcium alkaline salts. Chambliss Cross 569:1-7, 569:14-24.

The new Pilbrant reference (DTX 42) describes an enteric-coated formulation for omeprazole, used by Astra to test omeprazole in a short Phase I study with a small group of healthy volunteers. DTX 42.[16] Pilbrant contains no information at all regarding the enteric-coated omeprazole formulation that was used, nor whether this formulation was stable for a reasonable shelf-life. Chambliss Cross 561:1-562:5; Amidon 1084:17-19.

There is no mention of magnesium carbonate in Pilbrant or using magnesium carbonate in an enteric-coated pharmaceutical composition. Amidon 1084:4-6, 1084:14-16, 1086:3-5. There is not even a mention of combining a basic inorganic salt with omeprazole into an enteric-coated formulation, and no reference to the kind of contact needed between a benzimidazole and a basic inorganic salt to stabilize the benzimidazole. Chambliss Cross 564:11-16, 566:4-7.[17] Pilbrant's only reference to alkaline salts is to sodium bicarbonate, which is not claimed in the '321 patent due to its inadequacy in stabilizing lansoprazole. Chambliss Cross 562:11-15, 563:8-11.[18]

This is not the first time Dr. Chambliss has relied on the Pilbrant reference. Dr.

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[16] Plaintiffs objected to the use of Pilbrant DTX 42. Chambliss 511:21-512:1. It was not used in Dr. Chambliss's expert report as an invalidating reference, but only to provide background on some scientific concepts. Chambliss Cross 550:6-9, 551:21-552:22. And not only did Dr. Chambliss not describe Pilbrant as a reference he was relying on for his obviousness analysis in his expert report, but he also failed to identify it at his deposition. *Id.* Plaintiffs ask that this reference and testimony surrounding it be excluded.

[17] Pilbrant also does not mention lansoprazole, or the parts-by-weight ratio needed to stabilize benzimidazole compounds. Chambliss Cross 564:7-10; Amidon 1086:6-10.

[18] In fact, subsequent to the invention of the '321 patent, DTX 42's author Dr. Pilbrant invented the first stabilized omeprazole formulation, and patented it as U.S. Patent Nos. 4,786,505 (PTX 671) and 4,853,230 (PTX 672). Amidon 1084:23-1085:19.

Chambliss was involved in a challenge to the validity of Astra's '505 patent (PTX 671), where he unsuccessfully contended that the '505 patent was obvious based on Pilbrant. Chambliss Cross 559:24-560:11& 560:12-15. *In re Omeprazole Litig.*, 490 F. Supp. 2d 381, 523-24 (S.D.N.Y. 2007).

Finally, Dr. Chambliss provided almost no testimony regarding the new Prichard reference (DTX 33).[19] Chambliss 514:17-515:21.[20] Moreover, Teva provided no explanation regarding a motivation to combine Prichard with the other references. Teva Br. at 56.

In sum, Teva's references do not suggest '321 patent claim 2, let alone provide clear and convincing evidence of invalidity. Teva also provides virtually no evidence on the motivation to combine its references other than the unsupported statement that "ample motivation exists." Teva Br. at 56. Yet a motivation to combine is still required to prove obviousness, even after *KSR*. *Cordis Corp. v. Medtronic AVE, Inc.*, -- F.3d --, 2008 WL 60499 (Fed. Cir. Jan. 7, 2008) ("The Supreme Court … stated that '[t]here is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis."), *citing KSR*, 127 S. Ct. at 1741 (requiring courts "to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.").

VII. CONCLUSION

Based on the trial evidence and the arguments presented above, the Court should find that the '098 patent's claim 10 and the '321 patent's claim 2 were not obvious in view of the prior art Teva relies upon, and that there was no one substantively involved in the '098 patent's prosecution who engaged in inequitable conduct.

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[19] Teva's brief erroneously refers to this reference as "Pritchard." Teva Br. at 52.

[20] Plaintiffs objected to the use of DTX 33, Chambliss. 514:20-21, for the same reasons they objected to DTX 42, and also respectfully request that it be excluded.

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CERTIFICATE OF SERVICE

I hereby certify that on January 10, 2008, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send electronic notification of such filing to the following:

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Additionally, I hereby certify that true and correct copies of the foregoing were caused to be served on January 10, 2008, upon the following individuals in the manner indicated:

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