**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

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

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

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Defendants and Counterclaim-Plaintiffs Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively "Teva") submit this post-trial memorandum in support of Teva's contentions that U.S. Patent No. 4,628,098 ("the '098 patent") (PTX0001) is unenforceable due to inequitable conduct, claim 10 of the '098 patent is invalid as obvious under 35 U.S.C. § 103, and claim 2 of U.S. Patent No. 5,045,321 ("the '321 patent") (PTX0003) is invalid as obvious under 35 U.S.C. § 103.

## I. EXECUTIVE SUMMARY

Plaintiffs asserted only two claims in this action: claim 10 of the '098 patent and claim 2 of the '321 patent. Claim 10 covers the structure of the anti-ulcer drug lansoprazole, one of a class of drugs known as proton pump inhibitors ("PPIs"). Claim 2 covers a formulation of lansoprazole and other inactive ingredients (excipients) made up into capsules and sold in the United States as Prevacid®.

Each of Teva's defenses to these claims stand on their own merit and are equally supported by the evidence. Teva's inequitable conduct and invalidity defenses for the '098 patent, however, are inextricably intertwined because they arise from the same basic fact – Plaintiff Takeda knew that lansoprazole's "structure is too similar" to the prior art PPI omeprazole to be patentable. Takeda admits as such in its own internal evaluation of the patentability of lansoprazole. So Takeda did the only thing it could do to get a patent. Takeda pulled out a single outlying piece of data from a single test model purporting to show that lansoprazole was 20 times more effective than omeprazole and put that data into its patent application. Takeda's intent was to get its patent by convincing the United States Patent and Trademark Office ("USPTO") that lansoprazole was surprisingly more effective than the prior art.

Takeda misled the USPTO, however, because Takeda failed to disclose that it was in possession of significant amounts of additional data from multiple animal models showing lansoprazole to be significantly less than 20 times more effective than omeprazole. Some Takeda tests, in fact, show lansoprazole and omeprazole to be equally effective, while others actually show omeprazole to be more effective. Nonetheless, Takeda went forward with the single data point because it knew that lansoprazole was an obvious progression from prior art PPI compounds developed by Hässle, such as omeprazole, and Byk Gulden. The prior art PPIs lansoprazole share the same core backbone structure and utilize one or more of a finite set of substituents on that structure. Any PPI having that structure reasonably could be expected to show anti-ulcer activity. Thus Takeda had no choice but to follow the path of submitting its single data point in hopes of getting a patent. Unfortunately for Plaintiffs, that path results in the inevitable conclusion that the '098 patent is both unenforceable and invalid.

The formulation set forth in claim 2 of the '321 patent also would have been obvious to one of ordinary skill in the art. The '321 patent claims a pharmaceutical composition wherein a substituted benzimidazole is mixed with a basic inorganic salt of magnesium and/or calcium. As shown below, the available prior art teaches this same combination.

## II. CLEAR AND CONVINCING EVIDENCE SHOWS THAT TAKEDA COMMITTED INEQUITABLE CONDUCT

### A. Summary: Takeda Withheld Highly Material Data During Prosecution

Takeda developed lansoprazole by focusing on omeprazole, then the industry standard, as a key comparator or "benchmark." When it came time to secure patent protection for lansoprazole, Takeda understood that it would have to convince the USPTO that lansoprazole was patently distinct over omeprazole and U.S. Patent No. 4,255,431 ("the omeprazole '431

patent"), which claimed omeprazole, despite the evident similarity between the compounds. (*See e.g.*, PTX0002, List of Prior Art Cited by Applicant, dated May 9, 1986.)

Understandably, Takeda had its doubts. Internal documents establish that Takeda was concerned that lansoprazole's "[s]tructure is too similar to Omeprazole" to be patentable. (DTX703 at TAKEDA-044462.)[1]

Takeda had this in mind when drafting the patent application covering lansoprazole. Rather than waiting for the USPTO to reject its application, Takeda argued in its initial application that lansoprazole was superior to omeprazole by a margin of "20 times or more." (PTX0001 at col. 6, ll. 30-34.) Takeda provided data purporting to show that the "$ID_{50}$"[2] for lansoprazole was less than 1.0 mg/kg, and that the $ID_{50}$ for omeprazole was 21.0 mg/kg. (PTX0002, Pyridine Derivatives and Their Production, dated July 19, 2005; PTX0001 at col. 6, ll. 15-23.) In short, Takeda represented to the USPTO in this application that it took 20 times more omeprazole than lansoprazole to achieve the same result.

Takeda's strategy succeeded. The patent application proceeded quickly through examination. Indeed, Examiner Fan issued a Notice of Allowance without any objections or rejections. (PTX0002, Notice of Allowability, dated May 12, 1986.)

Takeda's assertions about lansoprazole's "20-times" superiority over omeprazole were highly misleading to the USPTO. Only one set of data, taken in one particular animal testing model known as the "IMAU" model, supported this assertion. Unbeknownst to Examiner Fan, Takeda withheld data that directly contradicted this assertion. (*See, e.g.*, DTX705.) Takeda

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[1] As set forth below (*see infra*, section III) this similarity to omeprazole, and to other prior art compounds, renders the '098 patent obvious.

[2] $ID_{50}$, which is the dose at which there is 50% inhibition of ulcer activity, was the metric that Takeda used to measure potency.

withheld data – taken from the same animal model – that showed lansoprazole to be only slightly more potent than omeprazole. Takeda withheld other data taken from other animal models that showed lansoprazole and omeprazole to be equally potent. And Takeda withheld still more data that showed that omeprazole was the more potent compound, including data from testing in dogs. (*See, e.g.*, DTX705 at TAKEDA-0044310 and TAKEDA-044313-16.)

The evidence is more than clear and convincing that Takeda had this data; that the data contradicts Takeda's assertions in the patent application; that Takeda failed to disclose the data to the USPTO; and that this data is highly material to the prosecution of the lansoprazole application – a reasonable patent examiner would have considered the withheld data when determining whether lansoprazole was patently distinct over the prior art omeprazole '431 patent.

Clear and convincing evidence also establishes a strong inference of Takeda's intent to deceive the USPTO. Indeed, the Takeda scientist who drafted the application testified that he chose to include only data from the IMAU model in the patent application because of the results – in other words, because lansoprazole "showed strong activities in this model." (Satoh Tr. at 1569, ll. 9-19.) In contrast, Takeda disclosed the contradictory data to the United States Food and Drug Administration ("FDA") during drug development. (DTX120 at TAKEDA-571239-40.) When it came time to publish an article in a peer-reviewed journal, Takeda personnel relied on the withheld contradictory data – not the IMAU data – to demonstrate the activity of lansoprazole. (*See* DTX82.) And Takeda refused to bring a single live company witness to explain why Takeda chose to withhold data from the USPTO.

In summary, while Teva appreciates that the charge of inequitable conduct is a serious one, Teva respectfully submits that this is a case where the evidence compels a finding of inequitable conduct and such conclusion is appropriate.

## B. Clear and Convincing Evidence Establishes Inequitable Conduct

### 1. Takeda's Lansoprazole Development Effort Focused On Omeprazole As a Key Comparator

Takeda's lansoprazole development efforts plainly focused on omeprazole as a key comparator. Indeed, omeprazole was the "industry standard" or "benchmark," and is the proper "lead compound" for purposes of the section 103 invalidity analysis of the '098 patent. *See infra* section III.

### 2. Takeda, At the Time It Filed Its Patent Application, Undisputedly Had a Wide Range of Data In Its Hands Comparing the Attributes of Lansoprazole and Omeprazole

Takeda does not dispute that it possessed a wide array of data comparing lansoprazole and omeprazole when it filed the lansoprazole patent application; this data resulted from a number of different types of tests that Takeda relied upon in the lansoprazole development process. (*See, e.g.*, DTX705.)

Teva's pharmacology expert, Dr. Esam Dajani,[3] described the different types of tests that were utilized by scientists in the pharmaceutical field during the crucial period in 1984. (Dajani Tr. at 662-667.) Dr. Dajani testified that, in 1984, no one test methodology was superior: "All these models are useful models. I cannot really say that one model is particularly better than another model." (Dajani Tr. at 665, ll. 3-12.) Takeda's expert Dr. Whittle himself

[3] Dr. Dajani's expert qualifications include a doctoral degree in pharmacology and toxicology from Purdue University; 118 peer reviewed scientific papers; 128 presentations at national and international conferences; ten patents; private industry experience at G.D. Searle including experience with the animal tests at issue in this case; academic positions; editorial board positions; and prestigious award recipient. (Dajani Tr. at 654-661; *see also* CV at DTX103.)

acknowledged that there is no particular animal model for testing that is accepted as superior on an industry wide basis. (Whittle Tr. at 1295, ll. 3-8.) Dr. Whittle testified, "All models have some value, some intrinsic value. Otherwise, you would not conduct the model." (*Id.* at 1364, ll. 20-21.)

The lansoprazole/omeprazole comparative test data can be found in a number of different documents produced from Takeda's files. (Many of Takeda's documents refer to the internal compound numbers. There is no dispute that AG-1749 stands for lansoprazole or that AG-1414 stands for omeprazole.) These documents include a December 1984 report of Takeda's Central Research Division[4] entitled "Planning and Development Head Office Interim Research Meeting (125th) Document – AG-1749" ("1984 Head Office Report") (DTX705); a September 1986[5] report of Takeda's Central Research Division entitled "AG-1749 – $(H^+ + K^+)$-ATPase inhibitor," which Takeda undisputedly submitted to the FDA in connection with Takeda's investigatory new drug application ("1986 FDA IND Submission") (DTX120); and portions of Takeda's 1984-1985 laboratory notebooks ("Lab Notebooks") (DTX122).

Takeda's statements in the 1984 Head Office Report are particularly revealing. Takeda included in this report direct comparisons of the results of the same tests on lansoprazole and omeprazole. (DTX705 at TAKEDA-004307, reproduced below in Figure 1.) The Table of Contents summarizes the broad range of tests that Takeda was performing at that time:

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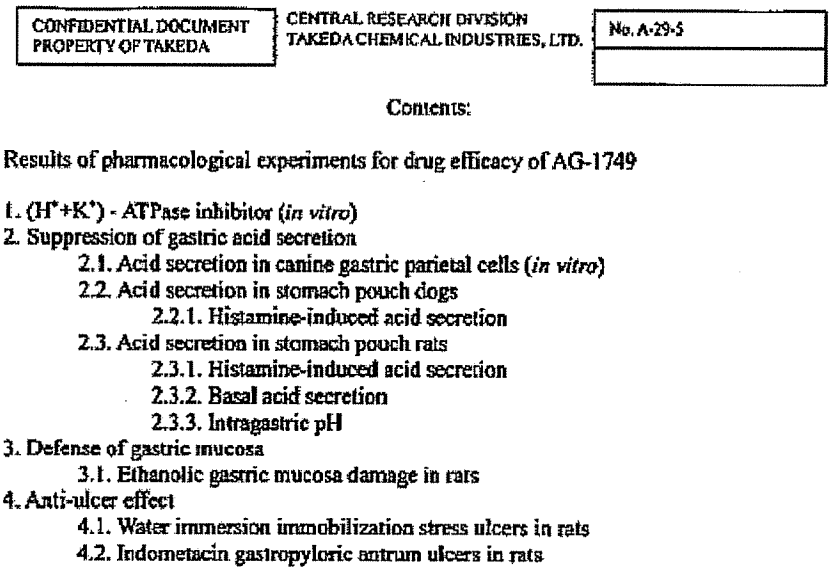
[4] In December 1984, Takeda's Central Research Division had several departments within it, including the Chemical Research Institute, which was responsible for synthesizing new compounds, and the Biological Research Institute, which was responsible for testing synthesized compounds. Dr. Akira Nohara, one of the named inventors of the '098 patent, worked in the Chemical Research Institute overseeing the synthesis of PPI compounds, and Dr. Yoshitaka Maki, the other named inventor, worked in the Biological Institute overseeing testing of PPI compounds. (*See* Kitao Tr. at 1459, ll.1-14.)

[5] This report is dated before the '098 patent issued on December 9, 1986 (see PTX0001) and the data reflected within was collected well before then. (Dajani Tr. at 669, ll. 3-5.)



CONFIDENTIAL DOCUMENT
PROPERTY OF TAKEDA

CENTRAL RESEARCH DIVISION
TAKEDA CHEMICAL INDUSTRIES, LTD.

No. A-29-5

Contents:

Results of pharmacological experiments for drug efficacy of AG-1749

1. ($H^+$+$K^+$) - ATPase inhibitor (*in vitro*)
2. Suppression of gastric acid secretion
    2.1. Acid secretion in canine gastric parietal cells (*in vitro*)
    2.2. Acid secretion in stomach pouch dogs
        2.2.1. Histamine-induced acid secretion
    2.3. Acid secretion in stomach pouch rats
        2.3.1. Histamine-induced acid secretion
        2.3.2. Basal acid secretion
        2.3.3. Intragastric pH
3. Defense of gastric mucosa
    3.1. Ethanolic gastric mucosa damage in rats
4. Anti-ulcer effect
    4.1. Water immersion immobilization stress ulcers in rats
    4.2. Indometacin gastropyloric antrum ulcers in rats

**Figure 1 - Table of Contents of 1984 Head Office Report**

(*Id.*) Dr. Dajani testified at length about this document and how it would be interpreted by one of ordinary skill in the art in 1984. (Dajani Tr. at 970-988). Focusing on the indomethacin test identified in the last section of the report (section 4.2), Dr. Dajani agreed that there was nothing to indicate that the authors thought that the indomethacin test was more important or more reliable than any of the other tests referred to in the table of contents. (Dajani Tr. at 973, ll. 2-8.)

Dr. Dajani also explained that none of the results within the 1984 Head Office Report, other than the single indomethacin test, support the assertion that lansoprazole performed 20 times better than omeprazole. In fact, other results that are reported show lansoprazole and omeprazole to be equal in potency, and sometimes even show omeprazole to be superior. For instance, the first set of tests on canines in the 1984 Head Office Report show lansoprazole (AG-1749) with an $IC_{50}$ of 5.9 and omeprazole with an $IC_{50}$ of 5.7. (*Id.*) Dr. Dajani testified that there is no material difference in these results. (Dajani Tr. at 974, ll. 11-13.) Similarly, tests at page 6 of the report show results in connection with intravenous administration where lansoprazole's

$ID_{50}$ was 0.14 and omeprazole's was 0.15. (DTX705 at TAKEDA-04413.) Again, no material difference. (Dajani Tr. at 979, ll. 4-8.)

Takeda's expert Dr. Whittle agreed with Dr. Dajani's assessment. With respect to dog models, he testified:

> Q. At the time that this [DTX705] was written by Takeda internally, they had observed already that omeprazole and lansoprazole were roughly equally potent in most of the dog models. Isn't that true?
>
> A. I am not sure of the exact timing. But, yes, in the model they had used, they seemed to be of approximately equivalent potency.
>
> Q. And where there was a difference, it was often omeprazole [that] was the more potent compound. Is that right?
>
> A. In dogs?
>
> Q. In dogs, yes.
>
> A. I haven't reviewed all of the data in detail. But that would be the case, except this comment about sustainability, which, as I say, as a pharmacologist, is an intriguing point.

(Whittle Tr. at 1360, l. 23 – p. 1361, l. 12 (emphasis added).)

The Takeda 1986 FDA IND Submission further underscores the range of comparative data in Takeda's possession regarding lansoprazole and omeprazole. (DTX120 at TAKEDA-571237–40.) This IND submission include tests similar to those described in the 1984 Head Office Report; the difference is that the 1986 FDA IND Submission does not include the IMAU test results that were included in the patent application. (*Compare* DTX120 *with* DTX705.) Dr. Dajani had experience with the submission of INDs while at Searle. He described the types of tests set forth in the "summary" portion of the 1986 FDA IND Submission as well as the data chart that follows the summary. (Dajani Tr. at 668-683.) For example, section 1 of the summary concludes that "[t]he inhibitory potency of AG-1749 was almost equal to that of Omeprazole."

(DTX120 at TAKEDA-571237.) Likewise, the discussion of the tests at summary point 3 concludes, "The inhibitory potency of AG-1749 was almost equal to that of omeprazole." (*Id.*) While some of the tests summarized did show better results for lansoprazole, none were anywhere close to a 20 times improvement. (*Id.* at TAKEDA-571237-238.) Based on his review of the summary and data chart that followed, Dr. Dajani observed:

> And what it really shows is that in all of these numbers, that in vivo and in vitro, both drugs have equal efficacies in inhibiting acid and promoting the formation of ulcers in rats.

(Dajani Tr. at 676, ll. 4-7 (emphasis added).)

The data reflected in Takeda's Lab Notebooks further confirms the wide range of tests and data in Takeda's possession at the time Takeda filed the lansoprazole patent application. (*See, e.g.*, DTX122 at TAKEDA-642702, TAKEDA-639115 and TAKEDA-639117.) Dr. Dajani reviewed the notebook pages as well as the characterization of this data in the report of Teva's statistician Dr. Robert Hirsch. (Dajani Tr. at 684, ll. 5-13; p. 697, l. 8 – p. 698, l. 21; DTX218.1[6].) Table 5 of Dr. Hirsch's report shows $ID_{50}$ values of omeprazole of 14.2, 4.3, 0.8, and 4.6 (DTX218.1 at 12), all well below the $ID_{50}$ of 21.0 set forth in the lansoprazole application and patent (see below). While there has been some debate regarding the data set forth in the Hirsch report, Takeda's expert Dr. Whittle made several important admissions regarding that data. For instance, Dr. Whittle conceded that the data from the Lab Notebooks establish that there were some IMAU tests following the same IMAU protocol as the disclosed test, but that the results of these other IMAU tests were not disclosed in the '098 Patent. (Whittle Tr. at 1338,

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[6] Takeda's objection to Dr. Dajani testifying based on the tables in Dr. Hirsch's report (DTX218.1) has no basis under Rule 703 of the Federal Rule of Evidence. The statistical analysis compiled by Dr. Hirsch is of the type reasonably relied on by pharmacologists in forming opinions or inferences. (Dajani Tr. at 698, l. 18 – p. 699, l. 13.) As such, the fact that Dr. Hirsch's report was not admitted into evidence has no bearing on the fact that Dr. Dajani properly should be allowed to rely on the statistical analysis therein when forming his opinions.

ll. 3-7.) Dr. Whittle also admitted that, when he made calculations based off of this undisclosed IMAU data, he derived an $ID_{50}$ of greater than 10 for omeprazole but he could conclude no more than that. (*Id.* at 1339, ll. 4-10.) Dr. Whittle never was able to point to any data from any test, other than the one IMAU test result disclosed in the patent, that came close to establishing that lansoprazole was 20 times superior to omeprazole.

**3. Takeda Undisputedly Disclosed Only the One Piece of the Comparison Data That Established Lansoprazole's 20 Times Superiority to the USPTO During the Prosecution of the Lansoprazole '098 Patent Application, and Withheld Everything Else.**

Takeda filed the U.S. application relating to the lansoprazole compound on July 29, 1985. (PTX0001.) This application (App. No. 760,568) claimed priority back to a Japanese application dated August 16, 1984. (*Id.*) The application contained only one piece of data regarding omeprazole, showing it to have an $ID_{50}$ of 21.0 based on an IMAU test. (PTX0002, Pyridine Derivatives and Their Production, dated July 19, 1985.) The $ID_{50}$ for lansoprazole was stated to be less than 1.0. The comparison of this data, when viewed alone in isolation, supports the notion that lansoprazole had 20 times superiority over omeprazole.

Takeda's U.S. patent counsel filed an invention disclosure statement on May 5, 1986. (*Id.*, Information Disclosure Statement Under 37 CFR 1.97(a), dated May 5, 1985.) This was the first significant activity after filing of the application. That disclosure statement includes disclosure of the omeprazole '431 patent as part of the List of Prior Art Cited. (*Id.*, List of Prior Art Cited by Applicant, May 9, 2006.) The omeprazole '431 patent is one of only three U.S. references cited by Takeda. Examiner Jane T. Fan noted that she reviewed this disclosure on May 7, 1986. (*Id.*) Examiner Fan issued a Notice of Allowability only five days later on May 12, 1986. (*Id.*, Notice of Allowability, May 12, 1984.) Examiner Fan did so without raising any

questions, objections or rejections regarding the application. It is rare that there are no preliminary objections or rejections by a USPTO examiner.[7]

It is undisputed that Takeda never disclosed to the Examiner that Takeda, at that time the lansoprazole application was prosecuted, possessed additional IMAU and other types of test data that compared lansoprazole to omeprazole. It also is undisputed that the undisclosed data in no way supports that lansoprazole is 20 times superior. Indeed, as noted, Plaintiffs' expert Dr. Whittle admits that the undisclosed data even shows omeprazole to be superior in dog models. (Whittle Tr. at 1360, l. 23 – p. 1361, l. 12.)

**4. Critical Takeda Pretrial Admissions**

Takeda failed to bring to trial any inventor, patent prosecutor, or other live lay witness to explain any alleged good faith basis for disclosing to the USPTO only one of the many pieces of comparative data regarding lansoprazole and omeprazole.[8] Takeda instead relied on hindsight, litigation-generated theories of its trial counsel and the admitted speculation of its expert Dr. Whittle.

There are, however, a number of pretrial admissions of Takeda employees that are probative on the inequitable conduct issue. Two come from Dr. Satoh – the person who developed the IMAU test and was involved in the decision to disclose the one IMAU data point in the lansoprazole application. (Satoh Tr. at 1561, ll. 2-19 and p. 1565, ll. 15-20.)

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[7] *See* Stephen Schreiner & Patrick Doody, *Patent Contaminations: How Proposed Rule Changes Will Undermine Our System and Create New Problems*, IPL Newsletter (The ABA Section of Intellectual Prop. Law, Chicago, Ill.), Spring 2006 at 46 n.26, *available at http://www.abanet.org/intelprop/newsletter/IPL_Spring_06.pdf.* (reporting initial rejections are made in 90% or more of the cases).

[8] While potential witnesses such as Dr. Satoh, Dr. Nohara, and Dr. Maki are no longer Takeda employees, Takeda arranged for each to provide deposition testimony in this action. As such, Takeda no doubt could have arranged for at least one of these witnesses to provide trial testimony as to the purported reason(s) why only certain data was selected to be disclose to the USPTO.

First, in 1988, Dr. Satoh and others from Takeda's Central Research Division (including '098 inventors Nohara and Maki) published a paper in The Journal of Pharmacology and Experimental Therapeutics entitled "Antisecretory and Antiulcer Activities of a Novel Proton Pump Inhibitor AG-1749 in Dogs and Rats." (DTX595.) Two admissions in the Abstract are key: (1) Dr. Satoh admits that the "inhibitory potency of AG-1749 in dogs was much the same as that of Omeprazole" and (2) with respect to rats, lansoprazole is "2 to 10 times" more potent. (*Id.* (emphasis added).) These statements in a peer-reviewed technical Journal, although made shortly after the patent issued, are consistent with the data that Takeda did not disclose to Examiner Fan, and directly contradict Takeda's assertions that lansoprazole is 20 times superior to omeprazole and the single disclosed data point that supported this assertion.

Second, at his deposition, Dr. Satoh testified regarding the decision to refer in the application to the single outlying IMAU data point as compared to the other tests that were available. Dr. Satoh did not identify IMAU as being a superior methodology as the reason the IMAU result was referenced. Instead, Dr. Satoh testified that Takeda selected the IMAU data point based on results – lansoprazole showed "strong activities in this model." (Satoh Tr. at 1569, ll. 9-19.)

Dr. Satoh's deposition testimony is consistent with Dr. Kubo's trial testimony regarding another technical paper published in 1990 by Dr. Satoh, Dr. Kubo, the named inventor Dr. Nohara, and others. (DTX82.) That paper described Takeda's strategy for developing lansoprazole. (Kubo Tr. at 1148, ll. 18-22.) Dr. Kubo admitted that the 1990 paper made no mention of the IMAU tests. (*Id.* at 1148, ll. 16-17.) It did, however, describe the biological activity and potency of lansoprazole, relying on entirely different tests. (*Id.* at 1148, ll. 4-15.)

Clearly, the pre-litigation evidence shows that Takeda did not view the IMAU model to be the critical, superior test it now claims (in hindsight) the IMAU model to be.

### C. Application of Legal Standards Governing Inequitable Conduct to Pertinent Facts of This Case Compels a Finding of Inequitable Conduct

This Court has found inequitable conduct in appropriate cases. *See, e.g., Praxair, Inc. v. ATMI, Inc.* 489 F. Supp. 2d 387, (D. Del. 2007) (Robinson, J.)[9]; *Bayer AG v. Housey Pharms., Inc.*, 386 F. Supp. 2d 578 (D. Del. 2005) (Robinson, J.). The Federal Circuit affirmed this Court's decision in *Bayer*, 189 Fed. Appx. at 969, as the Federal Circuit likewise has affirmed other district court findings of inequitable conduct. *See, e.g., McKesson Info. Solutions, Inc. v. Bridge Med., Inc.*, 487 F.3d 897 (Fed. Cir. 2007); *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359 (Fed. Cir. 2007).

The basic standards governing inequitable conduct remain the same as this Court summarized in *Praxair*. Teva must show by clear and convincing evidence that (1) Takeda's undisclosed comparative data was material to the patentability of the invention; (2) Takeda had knowledge of the materiality and existence of the undisclosed data; and (3) Takeda intended to deceive the USPTO. *See Praxair*, 489 F. Supp. 2d at 393. This Court then must balance the evidence to determine whether it should find inequitable conduct. *Id.*

#### 1. Takeda's Not-Disclosed Data Was Material to the Patentability of the Lansoprazole Compound

The materiality of information withheld during prosecution may be judged by the "reasonable examiner" standard. *See McKesson*, 487 F.3d at 913; *Cargill*, 476 F.3d at 1366. In *Cargill*, another case involving undisclosed test data, the Federal Circuit explained that the reasonable examiner standard is not focused on whether the undisclosed data would invalidate

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[9] Teva understands this case is on appeal.

the claims under sections 102 or 103, but whether the reasonable examiner would have wanted to have had the data before him/her when determining whether the claims should issue:

> "[M]ateriality is determined from the viewpoint of a reasonable patent examiner, and not the subjective beliefs of the patentee." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1238 (Fed. Cir. 2003) (internal citations omitted). A reasonable examiner would certainly want to consider test data that is directly related to an important issue of patentability, along with the applicant's interpretation of that data. Whether the examiner would have ultimately allowed the patent to issue is irrelevant because "[u]nder the 'reasonable examiner' standard, a misstatement or omission may be material even if disclosure of that misstatement or omission would not have rendered the invention unpatentable." *Digital Control*, 437 F.3d at 1318. Therefore, the district court's decision regarding the materiality of the undisclosed documents is not clearly erroneous.

476 F.3d at 1366 (emphasis added).

There can be no doubt that, in connection with the lansoprazole application, a reasonable patent examiner would have wanted to consider the undisclosed data set forth in one or more of the 1984 Head Office Report, the 1986 FDA IND Submission and the Lab Notebooks. *See supra* subsection II.B.2. The question of whether lansoprazole was patently distinct over omeprazole undisputedly was crucial to the prosecution of the lansoprazole application. Indeed, Takeda disclosed the '431 omeprazole patent as one of only three U.S. references in the IDS. *See supra* subsection II.B.3.

Takeda's primary responsive arguments, as enunciated through the testimony of Dr. Whittle, appear to be three-fold: (1) the disclosed IMAU data was accurate; (2) distinctions can be drawn to distinguish the IMAU data that was disclosed from the IMAU data and the data from non-IMAU tests that was not disclosed; and (3) the undisclosed data generally supports the superiority of lansoprazole over omeprazole. (*See, e.g.*, Whittle Tr. at 1293, ll. 10-25; p. 1303, ll.

11-16; p. 1337, l. 1 – p. 1339, l. 23.) None of these arguments, even if accepted as factually true, would negate a finding of inequitable conduct.

First, once Takeda decided to disclose objective data to support a 20 times comparison of lansoprazole over omeprazole, it was required to disclose sufficient data so that the examiner would have an accurate picture of what the full range of data showed. *See Hoffmann-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1367-68 (Fed. Cir. 2003); *Norton v. Curtiss*, 433 F.2d 779, 57 C.C.P.A. 1384, 1404 (C.C.P.A. 1970); *see also* RESTATEMENT OF TORTS (SECOND) § 529 ("A representation stating the truth so far as it goes but which the maker knows or believes to be materially misleading because of his failure to state additional or qualifying matter is a fraudulent misrepresentation."). Additionally, *comment a* to § 529 provides:

> A statement containing a half-truth may be as misleading as a statement wholly false. Thus, a statement that contains only favorable matters and omits all reference to unfavorable matters is as much a false representation as if all the facts stated were untrue.

(emphasis added.) The fact that Takeda disclosed to Examiner Fan that there was one IMAU test showing an $ID_{50}$ of 21 for omeprazole supporting a 20 times superiority argument simply does not paint an accurate comparative picture when the undisclosed data in Takeda's possession is considered.

Second, while certain distinctions admittedly can be made regarding certain of the undisclosed tests results and the disclosed IMAU test, such differences are not sufficient to avoid inequitable conduct. *See, e.g., Cargill*, 476 F.3d at 1365-67. The key point is that Takeda deprived Examiner Fan of the ability to review the undisclosed data and make her own determination regarding whether lansoprazole was patentable over the omeprazole '431 patent in light of all of the material data.

In *Cargill*, the applicant argued that the alleged inventive oil was strikingly superior to the prior art oil because it demonstrated "an oxidative stability of 35 to 40 AOM hours." *Id.* at 1365. The evidence, however, showed that the applicant had failed to disclose to the USPTO two documents showing prior art oil with oxidative stabilities of 32, 35, and 32 AOM hours. *Id.* The applicant argued that this other data was not material because, among other reasons, the testing conditions could not be compared. The trial court and Federal Circuit rejected this argument – the argument missed the key point that the reasonable examiner should have been able to review the data and assess its importance, but was deprived of the ability to do so by the applicant's non-disclosure. The Federal Circuit stated:

> Cargill argues that the data contained in the 1992 Report is not material because the tests underlying the Report were reported under unusual conditions and, thus, are not comparable to the data submitted to the examiner. For example, according to Cargill, the Report involved the testing of bench-refined IMC 129 oil, which has inherently higher oxidative stability than pilot-plant and commercially refined oil. Cargill also contends that, because the Oven Data does not set forth any testing conditions, it too cannot be compared with the data before the examiner.
>
> Even accepting as true the factual premises of those arguments, the documents withheld during prosecution remain material. "[M]ateriality is determined from the viewpoint of a reasonable patent examiner, and not the subjective beliefs of the patentee." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1238 (Fed. Cir. 2003) (internal citations omitted).

*Id.* at 1365-66 (emphasis added); *see also McKesson,* 487 F.3d at 915, 919 (rejecting a broad range of arguments for lack of materiality of the undisclosed items, the Federal Circuit noted "the existence of differences between Baker and the '716 claims does not, standing alone, render Baker immaterial" and "prior art need not be substantially similar in order to be material.").

Third and finally, the argument that some other population of data supports some conclusion that lansoprazole might be superior to omeprazole does not avoid a finding of

inequitable conduct. First, it ignores the fact that some of the data showed lansoprazole and omeprazole to be comparable under certain matrices, and omeprazole even to be superior in the dog tests. But, perhaps more important and fundamentally, the failure to disclose this information deprived Examiner Fan of the ability to gauge what level of superiority, if any, the data as a whole showed and whether it was sufficient to support the assertion that lansoprazole showed patentably distinct activity from omeprazole. Maybe these explanations would have satisfied Examiner Fan; more likely not. Maybe, if Examiner Fan had a clear picture of all the data, she would have issued a rejection requiring Takeda to submit a declaration with its explanations. The point is that Takeda deprived Examiner Fan of the opportunity to make these considerations. Under the reasonable examiner standard, the applicant must provide the examiner with all pertinent information at the time of the application and not, instead, rely on hindsight, litigation-created arguments regarding what the examiner would or would not have done with the undisclosed data.

**2. Takeda Had Knowledge of the Materiality and Existence of the Undisclosed Data**

There can be no dispute that Takeda was aware of the existence of the undisclosed data because the documents Teva relies upon all were produced from Takeda's files. *See supra* subsection II.B.2. Moreover, by their titles, these were not marginal handwritten notes found in some closet – this data was disclosed in major Takeda reports.

There likewise can be no real dispute as to Takeda's knowledge regarding the materiality of the undisclosed data. While in litigation hindsight Takeda attempts to diminish the importance of all tests, except the IMAU test it disclosed, it has failed to point to a single contemporaneous document to show that in 1984 Takeda thought the IMAU test methodology was superior to the others. Indeed, reports such as the 1984 Head Office Report simply show

IMAU as one of many tests being considered. Further, it strains credibility to suggest that the undisclosed non-IMAU data was unimportant, given that Takeda submitted only the non-IMAU data to the FDA with its 1986 FDA IND Submission to seek approval to market and sell lansoprazole. *See supra* subsection II.B.2.

**3. The Evidence Establishes a Strong Inference That Takeda Intended To Deceive the USPTO**

The Court need not find a "smoking gun" admission to conclude that there is sufficient evidence supporting a strong inference of intent to deceive. Indeed, "the law recognizes that deceptive intent is virtually never shown or disproved by direct evidence." *McKesson*, 487 F.3d at 902. The district court usually must make its determination based on all of the inferences that can be drawn from the evidence. *Id.*

Teva respectfully submits that the totality of the evidence in this case is clear and convincing and more than ample to support a finding of intent to deceive. This evidence includes:

a. The failure of Takeda to bring any live lay witness to attempt to explain a good faith basis for the non-disclosure of all data but the one favorable IMAU test result, *see supra* subsection II.B.4;

b. Dr. Satoh's admission at deposition that the IMAU data was not selected for disclosure because the methodology of the IMAU test was viewed as superior, but rather because the results allowed Takeda to assert that lansoprazole "showed strong activities" in this model, *see supra* subsection II.B.4;

c. Takeda's selective disclosure of data to the USPTO and FDA, *see supra* subsection II.B.2 and *Praxair*, 489 F. Supp. 2d at 395 n.9;

d. Takeda's subsequent disclosure in professional publications of data and test results contrary to that which was presented to the USPTO, *see supra* subsection II.B.4;

e. Takeda's failure even to mention the IMAU test in a professional publication that outlined the development strategy for lansoprazole, *see supra* subsection II.B.4;

f. Takeda's abject failure to articulate a reason -- even with litigation motivated hindsight -- to show why the undisclosed data was not material under the "reasonable examiner" test, *see supra* subsection II.C.1;

g. The high level of materiality of the undisclosed data, *see supra* subsection II.C.1 and *Praxair*, 489 F. Supp. 2d at 395 ("In view of the high materiality of the RFO art withheld from the PTO and the absence of any explanation for the disclosure, an intent to deceive may be properly inferred in this case"); and

h. The huge economic benefit that Takeda understood it could obtain if it could develop, market, sell, and obtain patent protection for the second PPI in the market following omeprazole (*see* Vandaele Tr. at 1022, l. 6 – 1024, l. 14.).

#### 4. The Balance of the Materiality and Scienter Evidence Weighs In Favor of a Finding of Inequitable Conduct

Finally, Teva respectfully submits that the balancing of the materiality and scienter evidence strongly weighs in favor of a finding of inequitable conduct. As discussed above, Teva submits that the evidence shows a high level of materiality. Teva also submits that the evidence to support a finding of intent to defraud is quite strong.

## III. CLEAR AND CONVINCING EVIDENCE ESTABLISHES THAT CLAIM 10 OF THE '098 PATENT IS INVALID AS OBVIOUS UNDER 35 U.S.C. §103

### A. Summary – The Prior Art Taught the Keys to a Successful PPI

During development, Takeda essentially acknowledged that lansoprazole is prima facie obvious in light of omeprazole. Takeda conducted its own internal evaluation of whether to focus on lansoprazole and concluded that lansoprazole may not be patentable because its "[s]tructure is too similar to Omeprazole." (DTX703 at TAKEDA-044462.) Although Takeda expresses a different view now, the evidence establishes that lansoprazole is obvious in light of the prior art. One of ordinary skill – whether he or she started with the prior art timoprazole, omeprazole, or the Byk Gulden compounds – would have analyzed the state of the art at the time

and would have proceeded, logically and inevitably, to synthesize and test lansoprazole and the related compounds claimed in the '098 patent.

At trial, Takeda described the Proton Pump to resemble (chemically) a padlock that can be stopped only with the correct key. That analogy perfectly describes the chemistry involved, but it does not go far enough. Timoprazole, the first compound discovered to stop the Proton Pump, has proved to be the "skeleton key." Virtually every compound that shares that skeleton fits the Proton Pump and stops it. Every time a chemist changes the timoprazole skeleton, the resulting compound does not work.

Scientists at Hässle discovered that timoprazole is the skeleton key in the 1970s. Timoprazole and a host of analog compounds based on the timoprazole skeleton were claimed in U.S. Patent No. 4,045,563 ("the '563 patent"). Those patents provide data and testing that show that nearly every compound based on the timoprazole skeleton fits the keyhole of the Proton Pump.

The next important compound discovered in the prior art was omeprazole, which was also based on the timoprazole skeleton. Omeprazole also was discovered by Hässle in the 1970s; omeprazole and a host of analogous compounds – all sharing the timoprazole skeleton – were claimed in the '431 omeprazole patent. That patent provided data on dozens of omeprazole analogs, all of which, except two, fit the Proton Pump and stopped it. The '431 omeprazole patent further taught that certain substitution patterns – specifically, methyl substitutions on the 3 and 5 positions of the pyridine ring and an oxygen-plus-carbon ("alkoxy") substitution at the 4 position – affected and enhanced potency. Omeprazole – which included methyl substitutions on the 3 and 5 positions and an oxygen-plus-carbon substitution at the 4 position – was the first PPI to reach the market, and later became the most successful drug ever sold. Ever.

The prior art included the scholarship of Dr. George Sachs. Although independent, Dr. Sachs worked with the Hässle inventors and published numerous papers. One paper described the importance of the substitution pattern of omeprazole. Dr. Sachs noted that a successful PPI would need to have a pKa[10] of approximately 4.0 – a "sweet spot" between the pH of the Proton Pump itself (around 1.0) and the blood (around 7.2). The key to engineering the timoprazole skeleton to have a pKa of 4.0 is the substitution patterns (at the 3, 4, and 5 positions) on the pyridine ring. (Lenz Tr. at 748, ll. 1-11 and p. 751, l. 23 – 752, l. 24.) This allows the compound to travel in the blood, to the Proton Pump where it is trapped and "activates" – the equivalent of sliding into the padlock and staying there.

Finally, the art included the work of Byk Gulden. The Byk Gulden also inventors adopted the timoprazole skeleton (as did every successful PPI program that followed). Byk Gulden adopted the oxygen-plus-carbon ("alkoxy") substitution at the 4 position of the pyridine ring that was taught by the '431 omeprazole patent (as did every successful PPI program that followed). Byk Gulden further discovered that adding fluorine to the skeleton could make the compound more active.

Regardless of whether a medicinal chemist started from the Hässle or Byk Gulden compounds, the development of lansoprazole was a logical, methodical exercise and lansoprazole was one of a finite set of compounds that inevitably would result. As of August 1984, one seeking to develop a PPI would have adopted the timoprazole skeleton. One seeking to develop a PPI would have used the teachings of Hässle and Sachs to include an alkoxy at the 4 position of the pyridine. One seeking to develop a PPI would have kept the pKa at approximately 4.0. One seeking to develop a PPI would have included fluorinated substitutions.

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[10] The term "pKa" is a measure of acidity; pKa is to a compound as pH is to a solution.

## B. The Law of Obviousness

### 1. The Claimed Invention Is Compared to the Prior Art

Something new is not necessarily an "invention." An invention is something more. That something more is sometimes described as a "Eureka moment" or a "lightbulb moment" or the product of an "inventive leap"; the law describes an invention as something that is "non-obvious." 35 U.S.C. § 103. If the discovery in question is the product of using known tools or known methods, if the result was reasonably predictable, then the discovery in question is not an invention – it is "obvious." *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1737 (2007).

The Supreme Court set forth the appropriate method for evaluating obviousness under 35 U.S.C. § 103 in *Graham v. John Deere Co.*:

1) The scope and content of the prior art must be determined;

2) Differences between the prior art and the claims at issue must be ascertained;

3) The level of ordinary skill in the art in the pertinent art is resolved; and

4) Secondary considerations such as commercial success, long felt but unsolved needs, failure of others, etc., can be considered.

*Graham*, 383 U.S. 1, 17-18 (1966). This process must be flexible and take into consideration the totality of knowledge possessed by one of skill. *See KSR*, 127 S. Ct. at 1737.

A discovery is obvious – and not a patentable invention – when it is the result of combining known elements, in the ordinary course of development. *See KSR*, 127 S. Ct. at 1741-42. When a design need has a "finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* at 1742.

### 2. Structurally Similar Compounds Are Obvious When There Is a Reasonable Expectation of Similar Properties

For chemical compounds, "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (citations omitted) (emphasis added). "The 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis*, 499 F.3d at 1301 (*citing In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (emphasis added).

A new compound is obvious when a chemist would have had a reason to make the claimed compound and "would have had a reasonable expectation of success in doing so." *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

The relevant time for the obviousness analysis with respect to the '098 patent is August 16, 1984, the date of filing of the Japanese patent application to which the '098 patent claims priority.

## C. The Art of Medicinal Chemistry

### 1. The Level of Ordinary Skill

In August 1984, one of ordinary skill in the art would have a Ph.D. in synthetic organic chemistry or in medicinal chemistry and at least two years of experience in the pharmaceutical

industry and in drug discovery, design and development. (Lenz[11] Tr. at 726, l. 23- 727, l. 21.) A person graduating with a Ph.D. would need two years of experience in order to learn the practical techniques of medicinal chemistry within the pharmaceutical industry and obtain training and experience in interpreting the biological activity and toxicity of compounds being considered for development. A person skilled in the art therefore would have been trained to understand how molecules function and how to design and make them. People in this field study compounds and the effect of these compounds on biologic activity. Every single witness who testified regarding the '098 patent, including Takeda's internal witness, Dr. Kubo, achieved this level of skill (Ph.D. in organic or medicinal chemistry, at least 2 years of experience in drug synthesis and design) before working unsupervised in the field. (Kubo Tr. at 1105, ll. 3-18; *see also* Lenz Tr. at 716, l. 17 – 719, l. 1 and p. 722, l. 9 – 724, l. 13.)

Plaintiffs argue for a (much) lower skill level. Plaintiffs' testifying medicinal chemist Dr. Lipinski conceded, however, that the level of skill Plaintiffs urge was not at all "ordinary" – it was "the lowest level" of skill that Dr. Lipinski would hire when he worked at Pfizer. (Lipinski Tr. at 1210, l. 20 – 1211, l. 2.) A person with such limited skills would not be skilled enough "to make extrapolations necessary to engage in drug design." (*Id.* at 1212, ll. 20-22.) Such a low level of skill may help Plaintiffs' case – lansoprazole might not be obvious to someone with too

[11] Dr. George Lenz is a semi-retired medicinal chemist who testified for Teva. He spent more than 25 years working for branded pharmaceutical companies. His expert qualifications include master's and doctoral degrees in medicinal chemistry from the University of Chicago; a master's degree in management from Northwestern University; twenty-five years of private industry experience performing and managing drug development and discovery at G.D. Searle, The B.O.C. Group Technical Center, Per Septive BioSystems and NeoGenesis Drug Discovery; a fellowship at the National Institutes of Health; memberships in prestigious chemical societies; a position at the Pharmaceutical Research and Manufacturers Association Foundation; work as a reviewer for multiple peer-reviewed journals; and numerous publications. (Lenz Tr. at 714-726; *see also* CV at DTX73.)

little education or experience to understand the prior art – but that does not describe the ordinary level of skill of practicing medicinal chemists.

**2. Methodology: A Medicinal Chemist First Analyzes the Art and Known Compounds and Works to Develop a Commercially Viable Drug**

Medicinal chemistry is a methodical, logical exercise. It is certainly not the random, serendipitous process that Plaintiffs suggest. In any drug development, there are potentially "trillions," indeed infinite numbers of possible analogs that could be synthesized. Resources, however, are finite, and chemists must take a more pragmatic approach. A medicinal chemist first surveys the art, reviewing the relevant literature, *e.g.*, prior art patents and publications, and looks for good prospects for development. (Lenz, Tr. at 728, ll. 3-24.) After this review, the medicinal chemist identifies compounds for further study. (*Id.*)

The medicinal chemist looks to identify elements in the structure of known compounds that may be related to the compounds' activity ("structure activity relationships" or "SAR"). (*Id.*) The medicinal chemist uses this SAR to design finite numbers of new compounds for further study. (*Id.*)

The medicinal chemist next selects a "lead compound" from among compounds known to have relevant biological activity. (*Id.*) The lead compound serves as a starting point for the effort to develop the new compound and, along with other prior art compounds, helps the chemist to identify desirable biological properties and associated ADME properties (absorption, distribution, metabolism and excretion) for a drug. (*Id.*) The medicinal chemist combines what he has learned from the SAR and ADME of the prior art with his existing knowledge of chemistry and drug design to identify compounds for synthesis. (*Id.*) The compounds synthesized will be evaluated in biological assays and the results are a factor in designing the next set of analogs (i.e., chemically similar compounds). (*Id.*)

Ultimately, compounds will be selected for further development and clinical testing. (*Id.*) This selection is driven by a number of factors, including market demand, the ability to avoid prior art patents, the ability to manufacture commercial scale batches of the compound, and the overall pharmacological and pharmacokinetic profile of the proposed drug. (*Id.*)

Dr. Lipinski concurred with Dr. Lenz's description of this methodical, step-wise approach to drug development. Dr. Lipinski testified that a medicinal chemist would study a lead compound to identify trends in activity and possible relationships between the molecular structure and that activity. (Lipinski Tr. at 1211, ll. 3-24.) He further testified that it is a common practice to make small changes in the structure of compounds under study to evaluate whether those changes altered biological activity. (*Id.* at 1225, ll. 17-23.) He testified to the strategy he called "peppering," in which a chemist would attach short alkyl components – methyl groups, or $CH_3$- components – or remove methyl components to see whether "methyls on the structure make a difference." (*Id.* at 1226, ll. 3-8.) While he testified that there were "millions" and "trillions" of possibilities, he acknowledged that a medicinal chemist would know a "short list" of what to try and what to avoid in terms of components (*Id.* at 1228-30), and would have made a short list of compounds to test. (*Id.* at 1211, ll. 16-24.)

**3. The "Substitution" Strategy Had Greatest Expectation of Success**

A medicinal chemist seeking to develop a new PPI in August 1984 would follow one of two strategies. The first possibility would be to develop an entirely new chemical entity ("NCE"), and the second would be to add substituents to the existing PPI backbone structure (a so-called "me-too," "substitution," or "analog" strategy). (Lenz Tr. at 728, l. 25 – 729, l. 7.)

Using the NCE strategy, a medicinal chemist would identify the lead compound and break it up into its component sections. (*Id.* at 729, ll. 10-15.) The chemist would then attempt to change each of the components in search of a new compound having similar biological

properties. (*Id.*) The NCE strategy is a high risk/high reward model. The risk is high because changing the components in a lead compound means that the medicinal chemist will not be able to rely upon information known about that lead compound. (*Id.* at 729, ll. 16-25.) Thus, the NCE approach often takes much longer to develop a compound and results in a higher failure rate.[12] (*Id.*)

Dr. Lenz and Dr. Lipinski agree that, with the "me-too substitution" strategy, on the other hand, there is lower risk and a much higher expectation of success. (*Id.* at 730, ll. 3-18; Lipinski Tr. at 1215, l. 23 – 1216, l. 24.) The substitution strategy also begins with identifying a lead compound. (*Id.*) Instead of changing that compound dramatically (*i.e.*, breaking it up), however, the medicinal chemist will tweak the lead compound by introducing substitutions on the same existing structure and then changing the pattern. (*Id.*)

In the case of PPIs, a medicinal chemist using the substitution strategy would synthesize different components (methyl,[13] ethyl, oxygen-ethyl, and halogen components) on the benzimidazole and pyridine rings. (*Id.*) These are the wrenches and screwdrivers on the tool belt of a medicinal chemist. The medicinal chemist would then identify the "short list" of substitutions to attach, synthesize them, and test the resulting compounds. (*Id.* at 767, l. 12 – 768, l. 7.) A chemist would not make a list of millions off potential substitutions. While a

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[12] Nonetheless, many companies have a mantra of developing only NCE compounds. For instance, Dr. Lenz testified that G.D. Searle exclusively followed an NCE strategy. (Lenz Tr. at 730, l. 19 – p. 731, l. 1.) The reason for this is that the NCE strategy has high rewards in terms of the ability to avoid the intellectual property of other companies and result in highly profitable pharmaceutical products. (*Id.* at 729, l. 16 – 730, l. 2.) He acknowledged, however, that the "substitution" strategy carried with it a higher expectation of success. (*Id.* at 730, ll. 3-18.)

[13] The nomenclature of carbon chains depends on the number of carbons. A methyl has one carbon (CH3-), an ethyl has two carbons (CH3-CH2-), propyl has three, butyl has four. After four carbons, they are named according to Greek numbers (five is "pentyl," six is "hexyl"). These are collectively known as "alkyl groups." If there is an oxygen at the end, they are called "alkoxy."

chemist could put methyl, ethyl, propyl, butyl, pentyl, and even longer chains on the structure, Dr. Lenz described the chemist's rule of thumb: "methyl, ethyl, propyl, futile" – there is no reason to make longer lists. (Lenz Tr. at 1438, ll. 17-23.)

As noted, the substitution strategy allows the medicinal chemist to draw upon information known about the lead compound. (*Id.* at 730, ll. 3-18.) Thus, it is often possible to develop products using this substitution strategy faster (and with a greater expectation of success) than through the NCE strategy. This allows companies to get to market faster if they are the second or third player in a profitable drug class such as PPIs. The downside to the substitution strategy is that it often leaves little differentiation between the "new" compound and the lead compound or other prior art compounds. (*Id.*) This, of course, may result in discovery of new compounds, but the compounds may not be patentable inventions.

**D. The Prior Art as of August 1984.**

**1. The Biology and Chemistry of the Proton Pump.**

$H^+/K^+$-ATPase, known as the "Proton Pump," is an enzyme found in parietal cells in the walls of the stomach. (Lenz Tr. at 732, l. 9 – p. 733, l. 2; *see* Figure 2 below.) The parietal cell is the most acidic part of the body; it has a pH of about 1.0. (*Id.* at 749, l. 25 – 750, l. 24.) The Proton Pump pushes hydrogen ion ("$H^+$") into the stomach, forming hydrochloric (HCl) gastric acid that helps us digest food. (*Id.* at 733, ll. 3-14.)

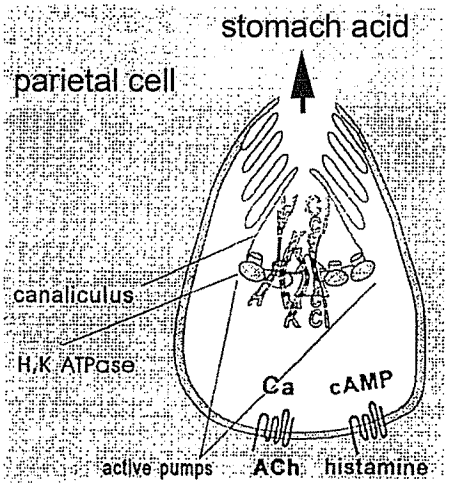


**Figure 2 - Parietal Cell**

A mucous layer protects the stomach wall from this acid. (Fennerty Tr. at 827, ll. 2-15.) Ulceration occurs when this mucous layer is damaged or eroded. (Dajani Tr. at 918, l. 24 – 919, l. 13.) This damage can be caused by non-steroidal anti-inflammatory drugs ("NSAIDS") such as aspirin, by stress, or by the presence of the bacterium *helicobacter Pylori*. (Fennerty Tr. at 827, ll. 2-15) When the mucous membrane is damaged, gastric acid erodes the more sensitive tissue underneath and causes ulcers. (*Id.*) Controlling acidity thus is the key to curing ulcers. (*Id.* at 829, l. 21–830, l. 11.)

Over the years, several approaches for controlling the amount of gastric acid in the stomach have been identified and commercialized. Among these were anti-acids (or "antacids"), anti-cholinergics, and histamine-2 blockers. (Lenz Tr. at 733, l. 15 – 735, l. 3.) None of these drugs truly stopped the Proton Pump, and none of these drugs prevented production of stomach acid for more than a few hours. PPIs were a significant advance in the control of gastric acid secretion and the treatment of ulcers over the previous drugs because PPIs act directly on the Proton Pump instead of indirectly affecting one of the various control pathways governing acid production. (*Id.* at 735, l. 25 – p. 736, l. 10.)

PPIs accumulate in the acidic environment found in the parietal cell. (Lipinski Tr. at 1174, ll. 12 – 1176, l. 19.) PPIs accumulate because, once they enter the parietal cell, they get trapped in the strongly acidic environment. (*Id.* at 1176, ll. 12-19.) The acid in the parietal cell "activates" the PPI by forming an intermediate that cannot leave the cell. (*Id.* at 1177, ll. 1-11.) PPIs are "pro drugs" in that they are not active until they are converted into that intermediate – they enter the parietal cells like a key sliding into a lock, they become activated as they turn the tumblers, and they remain in the locked-up Proton Pump. (*Id.* at 1177-79.)

**2. Hässle Learned That Timoprazole Was the "Skeleton Key"**

Hässle's timoprazole was the first PPI compound (Lenz Tr. at 736, ll. 7-14; *see* Figure 3 below). Timoprazole is the skeleton on which every successful PPI is based. That skeleton very much resembles a skeleton key: it has a benzimidazole double ring, a methyl-sulfinyl "linker" or bridge, and finally a pyridine ring. Timoprazole has no "substitutions" or components on any of the rings. (*Id.* at 737, l. 15 – p. 738, l. 1.)

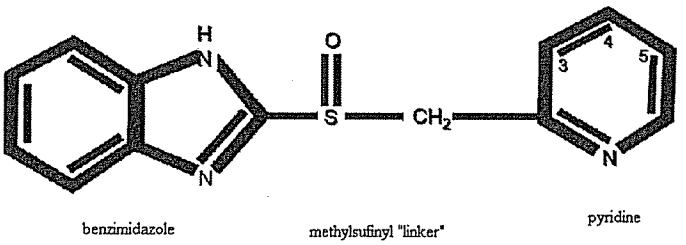


**Figure 3 - Timoprazole Backbone Structure**

Although timoprazole stopped the Proton Pump, it had a side effect: it blocked iodine uptake into the thyroid gland. (Lenz Tr. at 787, l. 25 – 788, l. 11.) Hässle therefore did not fully develop this drug, but recognized the value of this skeleton key and continued to experiment with substitution patterns.

In arriving at substitution patters on this skeleton, the Hässle scientists used the step-wise, logical method described by Dr. Lenz and Dr. Lipinski. Some of that work is reflected in

the '563 patent. (*See* Fig 4 below, reproduced from the '563 patent.) Hässle started with a benzimidazole linked to a methyl-sufinyl bridge, then added pyridine and variations of pyridine as the third component, then added precisely the substitutions that Dr. Lenz described – one, two and three carbons, oxygen-carbon combinations, and halogens.

Hässle started with substitutions on the benzimidazole ring. These substitutions on the benzimidazole ring are shown at 3 and R in the table; these are precisely the wrenches and screwdrivers that any medicinal chemist would use. (Lenz Tr. at 738, l. 16 – 739, l. 14.) They included methyls (-$CH_3$), ethyls (-$C_2H_5$), alkoxies (-$OCH_3$), carbonyls (-COOH, a kind of alkoxy), and halogens such as fluorine, chlorine, and bromine. (*Id.*) These substitutions would have adjusted the skeleton just slightly; whatever the substitution pattern, however, the timoprazole skeleton key still fits the Proton Pump's lock.

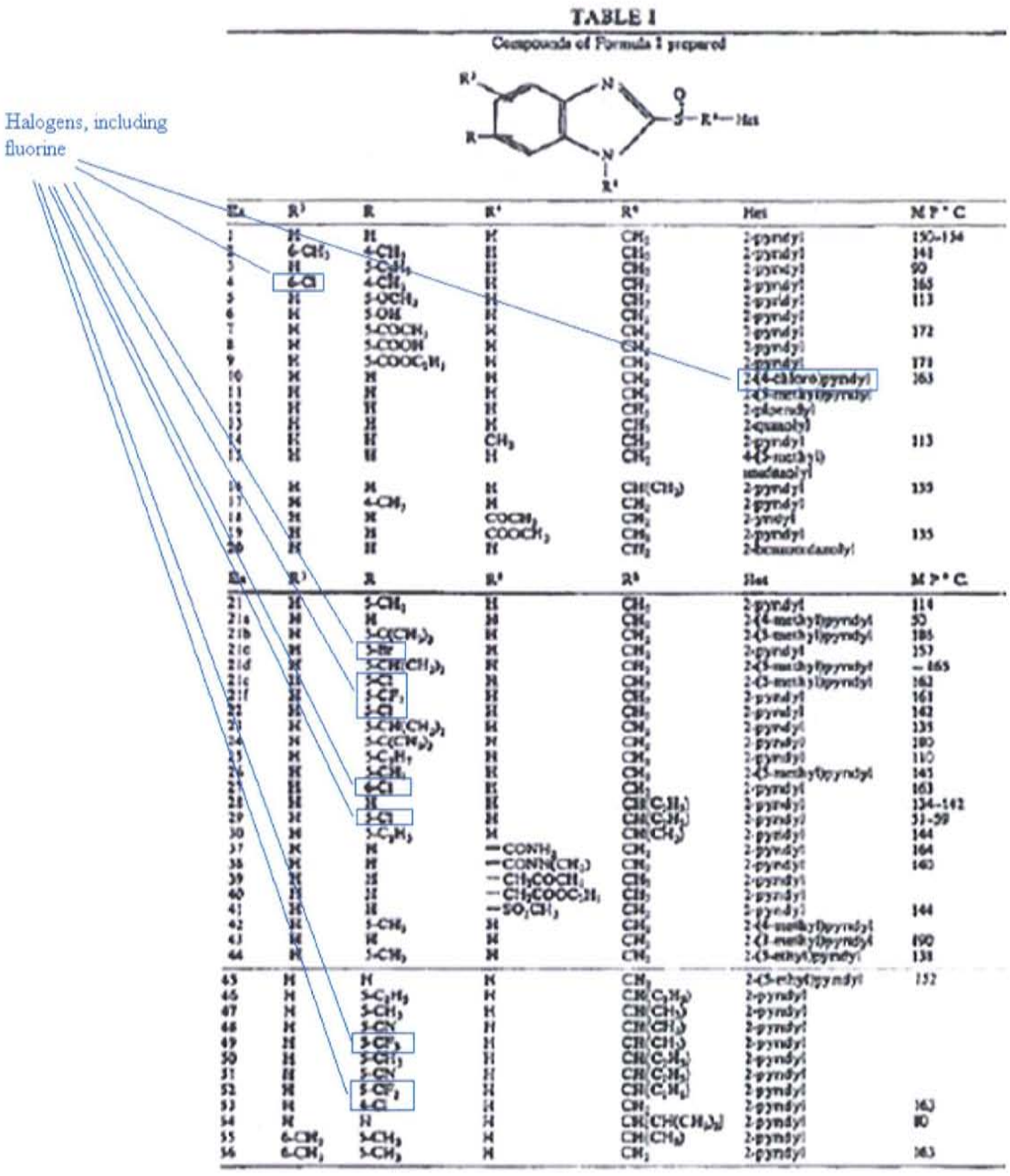


TABLE I

Compounds of Formula I prepared

| No. | $R^1$ | R | $R^2$ | $R^3$ | Het | M.P. °C. |
|---|---|---|---|---|---|---|
| 1 | H | H | H | $CH_3$ | 2-pyridyl | 150-154 |
| 2 | 6-$CH_3$ | 4-$CH_3$ | H | $CH_3$ | 2-pyridyl | 141 |
| 3 | H | 5-$CH_3$ | H | $CH_3$ | 2-pyridyl | 90 |
| 4 | 6-Cl | 4-$CH_3$ | H | $CH_3$ | 2-pyridyl | 165 |
| 5 | H | 5-$OCH_3$ | H | $CH_3$ | 2-pyridyl | 113 |
| 6 | H | 5-OH | H | $CH_3$ | 2-pyridyl | |
| 7 | H | 5-$COCH_3$ | H | $CH_3$ | 2-pyridyl | 172 |
| 8 | H | 5-COOH | H | $CH_3$ | 2-pyridyl | |
| 9 | H | 5-$COOC_2H_5$ | H | $CH_3$ | 2-pyridyl | 171 |
| 10 | H | H | H | $CH_3$ | 2-(4-chloro-pyridyl | 163 |
| 11 | H | H | H | $CH_3$ | 2-(3-methyl-pyridyl | |
| 12 | H | H | H | $CH_3$ | 2-quinolyl | |
| 13 | H | H | H | $CH_3$ | 2-quinolyl | |
| 14 | H | H | $CH_3$ | $CH_3$ | 2-pyridyl | 113 |
| 15 | H | H | H | $CH_3$ | 4-(5-methyl) imidazolyl | |
| 16 | H | H | H | $CH(CH_3)_2$ | 2-pyridyl | 133 |
| 17 | H | 4-$CH_3$ | H | $CH_3$ | 2-pyridyl | |
| 18 | H | H | $COCH_3$ | $CH_3$ | 2-pyridyl | |
| 19 | H | H | $COOCH_3$ | $CH_3$ | 2-pyridyl | 135 |
| 20 | H | H | H | $CH_3$ | 2-benzimidazolyl | |
| No. | $R^1$ | R | $R^2$ | $R^3$ | Het | M.P. °C. |
| 21 | H | 5-$CH_3$ | H | $CH_3$ | 2-pyridyl | 114 |
| 21a | H | H | H | $CH_3$ | 2-(4-methyl)pyridyl | 50 |
| 21b | H | 5-$OCH_2CF_3$ | H | $CH_3$ | 2-(3-methyl)pyridyl | 185 |
| 21c | H | 5-Br | H | $CH_3$ | 2-pyridyl | 157 |
| 21d | H | 5-$OCH(CH_3)_2$ | H | $CH_3$ | 2-(3-methyl)pyridyl | ~165 |
| 21e | H | 5-Cl | H | $CH_3$ | 2-(3-methyl)pyridyl | 162 |
| 21f | H | 5-$CF_3$ | H | $CH_3$ | 2-pyridyl | 161 |
| 22 | H | 5-Cl | H | $CH_3$ | 2-pyridyl | 142 |
| 23 | H | 5-$CH(CH_3)_2$ | H | $CH_3$ | 2-pyridyl | 135 |
| 24 | H | 5-$C(CH_3)_3$ | H | $CH_3$ | 2-pyridyl | 180 |
| 25 | H | 5-$C_3H_7$ | H | $CH_3$ | 2-pyridyl | 110 |
| 26 | H | 5-$CH_3$ | H | $CH_3$ | 2-(3-methyl)pyridyl | 145 |
| 27 | H | 6-Cl | H | $CH_3$ | 2-pyridyl | 163 |
| 28 | H | H | H | $CH(C_2H_5)$ | 2-pyridyl | 134-142 |
| 29 | H | 5-Cl | H | $CH(C_2H_5)$ | 2-pyridyl | 51-59 |
| 30 | H | 5-$C_2H_5$ | H | $CH(CH_3)$ | 2-pyridyl | 144 |
| 37 | H | H | $-CONH_2$ | $CH_3$ | 2-pyridyl | 164 |
| 38 | H | H | $-CONH(CH_3)$ | $CH_3$ | 2-pyridyl | 140 |
| 39 | H | H | $-CH_2COCH_3$ | $CH_3$ | 2-pyridyl | |
| 40 | H | H | $-CH_2COOC_2H_5$ | $CH_3$ | 2-pyridyl | |
| 41 | H | H | $-SO_2CH_3$ | $CH_3$ | 2-pyridyl | 144 |
| 42 | H | 5-$CH_3$ | H | $CH_3$ | 2-(4-methyl)pyridyl | |
| 43 | H | H | H | $CH_3$ | 2-(3-methyl)pyridyl | 190 |
| 44 | H | 5-$CH_3$ | H | $CH_3$ | 2-(3-ethyl)pyridyl | 138 |
| 45 | H | H | H | $CH_3$ | 2-(3-ethyl)pyridyl | 152 |
| 46 | H | 5-$C_2H_5$ | H | $CH(C_2H_5)$ | 2-pyridyl | |
| 47 | H | 5-$CH_3$ | H | $CH(CH_3)$ | 2-pyridyl | |
| 48 | H | 5-Cl | H | $CH(CH_3)$ | 2-pyridyl | |
| 49 | H | 5-$CF_3$ | H | $CH(CH_3)$ | 2-pyridyl | |
| 50 | H | 5-$CH_3$ | H | $CH(C_2H_5)$ | 2-pyridyl | |
| 51 | H | 5-Cl | H | $CH(C_2H_5)$ | 2-pyridyl | |
| 52 | H | 5-$CF_3$ | H | $CH(C_2H_5)$ | 2-pyridyl | |
| 53 | H | 6-Cl | H | $CH_3$ | 2-pyridyl | 163 |
| 54 | H | H | H | $CH(CH(CH_3)_2)$ | 2-pyridyl | 80 |
| 55 | 6-$CH_3$ | 5-$CH_3$ | H | $CH(CH_3)$ | 2-pyridyl | |
| 56 | 6-$CH_3$ | 5-$CH_3$ | H | $CH_3$ | 2-pyridyl | 163 |

**Figure 4 - Table I from the '563 Patent**

### 3. Hässle Discovers Omeprazole

#### a) Hässle Adds Substitutions to the Pyridine Ring

Hässle's development of PPI compounds having the timoprazole skeleton did not stop with substitutions on the benzimidazole ring. The next step in Hässle's methodical approach was

to move the substitution strategy to the pyridine ring. (Lenz Tr. at 738, l. 16 – 740, l. 14 and p. 741, ll. 9-17.) Hässle soon discovered that one tweak to the pyridine ring – an alkoxy group placed at the 4 position – resulted in greater potency. Hässle drafted a patent application that became the '431 patent which included, among other compounds, omeprazole. (DTX5; see also Lenz Tr. at 739, l. 25 – p. 740, l. 14.)

Omeprazole quickly became the gold standard in the PPI field. It would have been a logical starting point or "lead compound" for development of a PPI by a company such as Takeda. (PTX001) Indeed, Plaintiffs' Gastroenterologist, Dr. M. Brian Fennerty, proclaimed omeprazole to be "a miracle drug" that was considered "the most important development in gastroenterology in thirty years." (Fennerty Tr. at 829, l. 21 – 830, l. 11.) Further, several reports generated by Takeda scientists during 1984 refer to the PPI compounds being tested by Takeda as "omeprazole-related compounds." (*See, e.g.*, certified translations of Takeda reports at PTX0045 at LIPINSKI 001248, PTX0077 at TAKEDA-40930-931, and PTX0078 at TAKEDA-40938.)[14]

Omeprazole, shown in Figure 5 below, has an alkoxy substituent (specifically, a methoxy group represented as $-OCH_3$ or $H_3CO-$) at the 4 position of the pyridine ring, a methyl substituent (represented as $H_3C$ or $CH_3$) at the 3 and 5 positions of the pyridine ring, and a methoxy substituent on the benzimidazole ring.

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[14] Plaintiffs now take the position that one of skill in the art seeking to develop a new PPI in August 1984 would have used the toxic compound timoprazole, not omeprazole, as the lead compound. This defies common sense. Timoprazole contributed to the development of PPIs by providing the skeleton structure, but more than just the skeleton structure was known about PPIs in August 1984. Omeprazole also introduced the concept of substituting an alkoxy at the 4 position of the pyridine ring.

Whether or not one of skill started with omeprazole, however, a medicinal chemist would have used the teachings of the '431 omeprazole patent and made use of the alkoxy and methyl substitutions to arrive at lansoprazole.

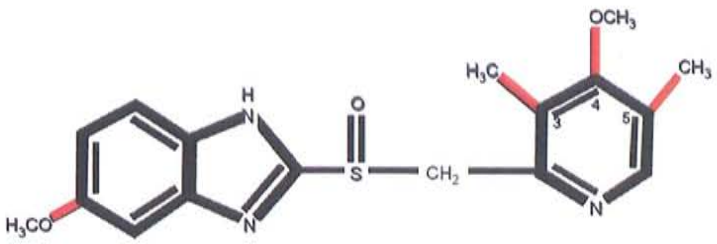


**Figure 5 – Omeprazole**

Omeprazole and closely-related omeprazole analogs disclosed in the '431 omeprazole patent are examples of Hässle's key discovery - the use of an alkoxy (methoxy, ethoxy, methoxyethoxy or ethoxyethoxy) substituent at the 4 position of the pyridine ring. Substituting the 4 position of the pyridine ring with an alkoxy adjusts the pKa of the overall compound to approximately 4.0 and results in increased potency of PPIs. (*See* DTX13 at TVL063219-20.)

**b) Data In '431 Patent Shows (Virtually) Everything Is Active**

The remarkable thing about the PPIs disclosed in the '431 patent is that virtually all of the compounds demonstrate activity in inhibiting gastric acid secretion, as can be seen from a review of Table 2 (*see* Figure 6 below). Table 2 contains a listing of both previously known compounds (denoted by a star in the left-hand column of the table) and compounds invented by Hässle. The right-hand column of Table 2 reflects the percentage of gastric acid secretion inhibited by each disclosed compound. (Lenz Tr. at 743, ll. 4-9.) Every compound for which data is disclosed in Table 2, save one,[15] shows activity in inhibiting gastric acid secretion:

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[15] The one compound in Table 2 showing zero activity as a PPI has a bromine (Br, a halogen similar to, but much larger than, a fluorine) substitution at the $R_3$ position of the pyridine ring. As Dr. Lenz explained in his testimony (and Dr. Lipinski did not contradict), bromine is very large and would be expected to interfere mechanically with orientation of the pyridine ring. (Lenz Tr. at 743, l. 10 – 744, l. 3.)

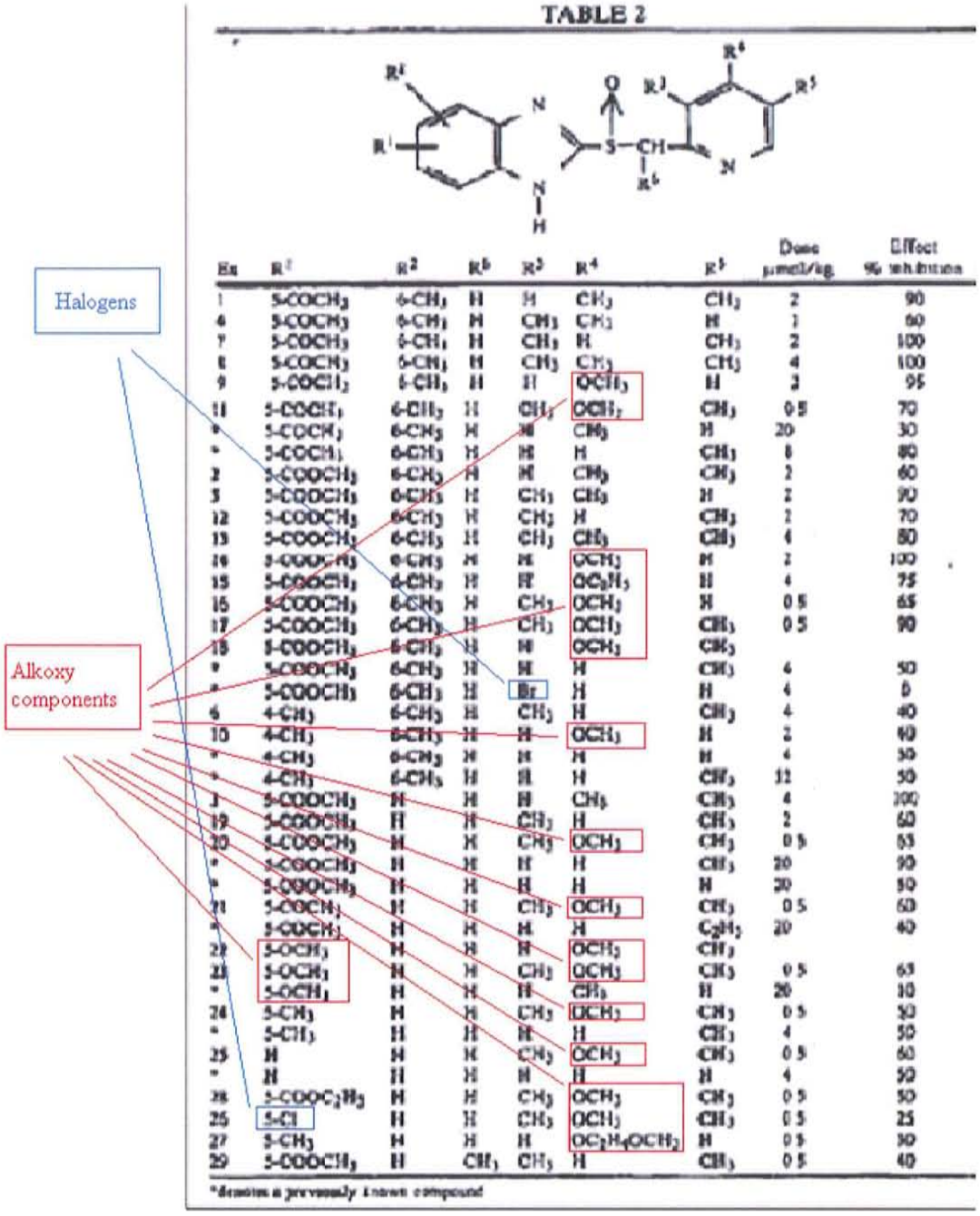


**Figure 6 - Table 2 of the '431 Omeprazole Patent**

(DTX5 at TVL011025–26.)

The PPI class of compounds is unique in that virtually all compounds show activity if they are built on the same backbone structure. (Lenz Tr. at 744, l. 10 – 745, l. 2.) This differentiates PPIs from other classes of compounds in which small changes in chemistry result

in big changes in biological activity. (*Id.*) Indeed, this action is notable for the very fact that it involves a class of compounds in which the presence or absence of activity does not depend on the type of substituents used on the molecule. (*Id.*)

**4. Sachs Teaches the Importance of the Pyridine Alkoxy**

The well-known pharmacologist Dr. George Sachs published a paper about omeprazole in the May 1984 edition of the New England Journal of Medicine. This paper described the importance of maintaining a pKa of approximately 4.0 in a PPI compound to achieve increased potency. (DTX13; *see also* Lenz Tr. at 746, l. 15 – p. 751, l. 22.) Sachs explained that, given the environment in the parietal cell, a PPI should have a pKa of approximately 4.0:

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

(DTX13 at TVL063220) (emphasis added). A pKa of approximately 4.0 allows the PPI compound to accumulate within the parietal cell and activate into the intermediate that inhibits the Proton Pump from secreting gastric acid. (*Id.*; *see also* Lenz Tr. at 747, l. 24 – 748, l. 22.) If the pKa is much above 4.0, the compound is likely to accumulate in other parts of the body (lysosomes, Golgi, etc.). (Lenz Tr. at 749, l. 25 – 751, l. 22.) And if the pKa is much below 4.0, it may not be trapped in the parietal cell. (*Id.*)

The pyridine ring is the portion of the skeleton that provides the pKa of approximately 4.0. (*Id.* at 750, ll. 10-15 and 752, l. 5 – 753, l. 1.) Adding a methoxy substituent at the 4

position of the pyridine ring in omeprazole allows a chemist to adjust the pKa to 4.0. (*Id.* at 753, l. 24 – 754, l. 9; *see also* DTX13 at TVL063220-21.)[16] With the pKa of the entire PPI compound adjusted to approximately 4.0, omeprazole accumulates and activates in the parietal cell, and the compound exhibits increased potency.

### E. Byk Gulden Used Flourinated Susbstituents In PPI Compounds

Byk Gulden also was involved in the development of prior art PPI compounds and has two prior art patents reflecting those compounds. The first Byk Gulden patent is U.S. Patent No. 4,472,409 ("the '409 patent") (DTX7), and the second Byk Gulden patent is U.S. Patent No. 4,555,518 ("the '518 patent") (DTX9).

#### 1. The Byk Gulden '409 Patent

Byk Gulden's '409 patent builds directly on the Hässle work by maintaining the skeleton structure. The '409 patent compounds also have an alkoxy (*i.e.*, methoxy) at the 4 position of the pyridine ring. This is a clear indication that those in the art appreciated the significance of substituting an alkoxy at the 4 position of the pyridine to maintain a pKa of approximately 4.0. (Lenz Tr. at 756, ll. 4–19.) On the benzimidazole ring, the '409 patent discloses the use of fluorinated substitutions, specifically trifluoromethyl groups (represented as $F_3C$ or $CF_3$), that are among the standard tools of a medicinal chemist. An example of the PPI compounds disclosed in the '409 patent is represented by Figure 7 below:

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[16] The effect of the methoxy substituent and other substituents on the pKa of the entire PPI compound can be calculated using the Hammett Equation. (*See* DTX81 at TVL063307-11.)

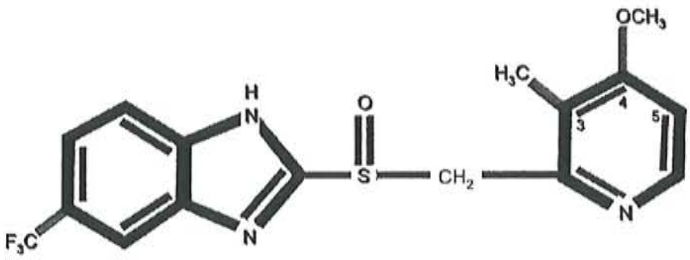


**Figure 7 - PPI Compound Disclosed in the '409 Patent**

Much like the data in the '431 patent discussed *supra* in subsection III.D.3.a, the '409 patent contains a table of data relating to the inhibition of gastric acid secretion. (DTX7 at col. 13, l. 43 - col. 16, l. 13.) Once again, the data demonstrates that virtually all PPI compounds built on the skeleton structure demonstrate activity in inhibiting the secretion of gastric acid. This can be seen in the column entitled "inhibition of % of HCI-secretion" and from the presence of "$ED_{25}$" and "$ED_{50}$" values which indicate effective gastric secretion dosages necessary to achieve a 25% and 50% reduction in the secretion of gastric acid, respectively. (*Id.*) The presence of data under each of these measurements that the compounds are active.

**2. The Byk Gulden '518 Patent**

The '518 patent likewise builds on the Hässle work by utilizing the skeleton structure and substituting a methoxy at the 4 position of the pyridine ring. On the benzimidazole ring, the '518 patent also discloses fluorinated substituents ($CF_3CH_2O$-). In particular, the '518 patent introduced the use of a 2,2,2-trifluoroethoxy substituent on the benzimidazole ring. (*See* Figure 8 below.) The 2,2,2-trifluorethoxy disclosed on the benzimidazole ring in the '518 patent is the same substituent that would later be used at the 4 position of the pyridine ring in lansoprazole.

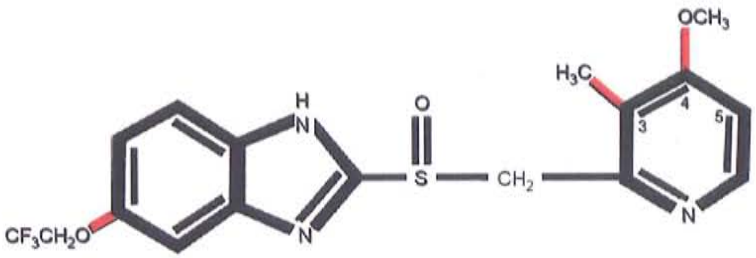


**Figure 8 - PPI Compound Disclosed in the '518 Patent**

The '518 patent likewise contains a table of data relating to the inhibition of gastric acid secretion. (DTX9 at col. 25, ll. 1-31.) Once again, the data demonstrates that virtually all PPI compounds built on the skeleton structure demonstrate activity in inhibiting the secretion of gastric acid. (*Id.*)

### 3. Use of Fluorinated Substituents Driven By Fluorine's Well-known Properties

The use of fluorinated substituents in the '409 and '518 patents is significant because those patents indicate that the Byk Gulden compounds possess enhanced activity for cytoprotection and gastric acid inhibition from omeprazole. (*See* table in columns 13-16 in DTX7 and table in column 25 in DTX9; *see also* Lenz Tr. at 759, ll. 16-20.) This points to the desirability of incorporating fluorine into appropriate substituents on PPI compounds as long as the substitution maintains the approximate pKa of 4.0 noted by Sachs to be important to the potency of PPIs. Moreover, as Dr. Lenz testified, the use of fluorinated substituents in PPI compounds would have been obvious to a medicinal chemist because of the well-known chemical properties of fluorine:

- Fluorine, the second smallest "atom" as measured by atomic radius and internuclear distance to carbon, would most closely resemble bioactive hydrogen analogs in size and with respect to steric requirements at enzyme receptor sites;

- Fluorine alters electronic effects, owing to its high electronegativity;

- Fluorine imparts increased oxidative and thermal stability because the binding energy of the carbon-fluorine bond exceeds that of the carbon-hydrogen bond; and.

- Fluorine leads to increased lipid solubility in membranes that would enhance the rates of absorption and transport, *in vivo*.

(Lenz Tr. at 757, l. 4 – 758, l. 10.) Dr. Nohara, one of the named inventors of the '098 patent, testified during his deposition that these known chemical properties played a role in his decision to use a fluorinated substituent during the development of lansoprazole. (Nohara Tr. at 1052, l. 23 – 1504, l. 16 and p. 1506, l. 16 – 1507, l. 17.) A 1990 publication authored by several Takeda employees, including Dr. Nohara and Takeda's lay trial witness Keiji Kubo, likewise cited these properties as one of the reasons for Takeda's decision to use a fluorinated substituent. (*See* DTX82 at Takeda 015682-87.)

**F. The Obvious Path to Lansoprazole**

Armed with the knowledge of the prior art PPI compounds discussed above and an understanding of the chemical properties of fluorine, the lansoprazole compound claimed in claim 10 of the '098 patent would have been obvious to one of skill in the art in August 1984. Lansoprazole contains the same PPI backbone structure as the prior art PPI compounds (see lansoprazole at bottom of Figure 9 below). Lansoprazole, however, is substituted with a 2,2,2-trifluoroethoxy at the 4 position of the pyridine ring and a methyl at the 3 position of the pyridine ring.