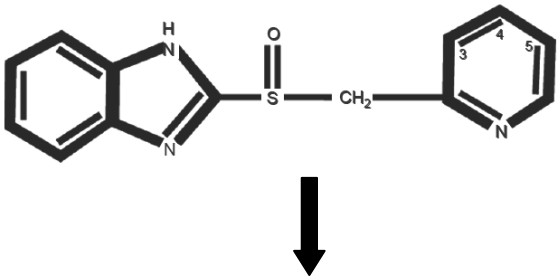
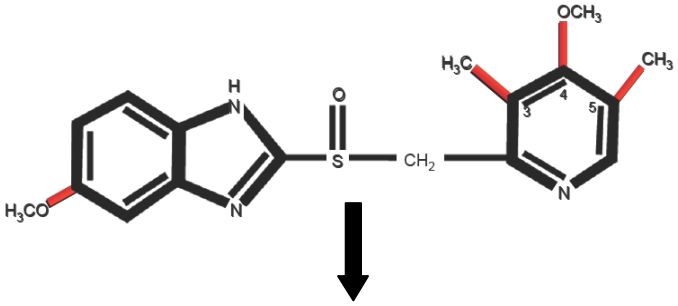
Timoprazole



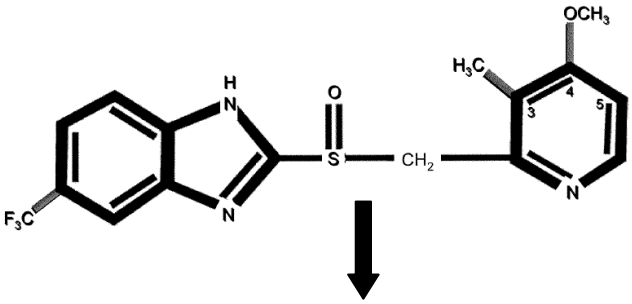
Backbone structure with screwdrivers and wrenches used on the benzimidazole ring

Omeprazole



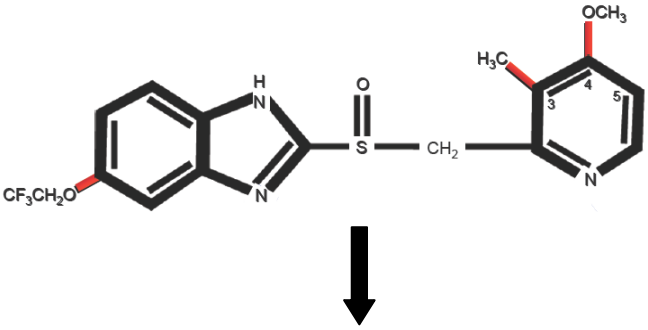
Hässle moves alkoxy (OCH_3) substituents to the pyridine ring

Byk Gulden



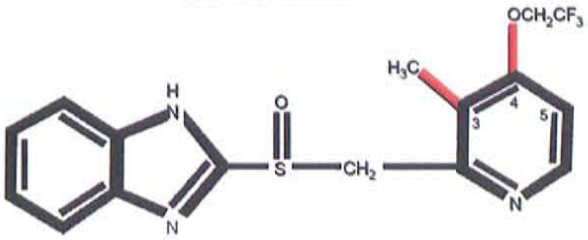
Byk Gulden keeps alkoxy at R_4 of the pyridine ring and adds fluorinated substituent (F_3C) to the benzimidazole ring

Byk Gulden



Byk Gulden keeps alkoxy at R_4 of the pyridine ring and adds trifluoroethoxy (CF_3CH_20) to the benzimidazole ring

Lansoprazole



Takeda moves trifluoroethoxy substituent (OCH_2CF_3) from benzimidazole ring to pyridine ring

Figure 9 - Development of PPI Compounds

Lansoprazole was the obvious next step in the development of PPIs. Hässle created the PPI class with the development of the structure that serves as the skeleton key for proton pump inhibition. After determining that the skeleton structure itself was toxic, Hässle adopted a substitution strategy first on the benzimidazole ring (*see* the '563 patent) and then on the pyridine ring (*see* the '431 patent). All of the compounds on the skeleton structure were active, but as explained by Sachs, the compounds substituted with an alkoxy at 4 position of the pyridine ring exhibited enhanced activity. (Lenz Tr. at 760, l. 14 – 762, l. 1.)

Byk Gulden likewise used the substitution strategy on the skeleton structure. (*See* '409 and '518 patents, DTX7 and DTX9.) Byk Gulden maintained the alkoxy substituent at 4 of the pyridine ring and inserted fluorinated substituents, including trifluoroethoxy, on the benzimidazole ring. Whereas Hässle started with benzimidazole substitutions and proceeded to use the same substituents on the pyridine ring, Byk Gulden substituted the benzimidazole ring and stopped there. Takeda then took the next logical step of synthesizing the same fluorinated alkoxy substituents on the pyridine ring. (Lenz Tr. at 767, l. 12 – 768, l. 24 and p. 771, l. 11 – p. 773, l. 20.) Indeed, Dr. Lenz testified that a big red arrow would have been pointed at trifluoroethoxy as a pyridine ring substituent. (*Id.* at 765, l. 20 – 766, l. 2.) This is particularly true given that Dr. Nohara testified in his deposition that trifluoroethanol, the chemical precursor to trifluoroethoxy, was selected during the development process in part because it was readily

available to purchase for use in the manufacturing process. (Nohara Tr. at 1518, l. 19 – 1519, l. 5.)

1. A Medicinal Chemist Would Try All Combinations of R_3 and R_5 Methylation

In addition to the trifluoroethoxy substituent at the 4 position pf the pyridine ring, lansoprazole has a methyl substituent (CH_3) at the position. In practice, a medicinal chemist testing a compound with a fluorinated alkoxy substituent at the 4 position would test the limited number of variations of the structure having methyl substitutions at both the 3 and 5 positions, a practice known in the art as "peppering" the compound with methyls. (Lipinksi Tr. at 1225, l. 24 – 1226, l. 8; *see also* Lenz Tr. at 767, l. 12 – 768, l. 7.) One variation would have a methyl substituent at only the 3 position; another variation would have a methyl at only the 5 position; and a third variation would have a methyl at both the 3 and 5 positions (i.e. "the 3,5 dimethyl substitution"). (*Id.*) Dr. Lipinski concedes that this peppering strategy was used in medicinal chemistry in August 1984 to determine whether the biological activity of a compound was sensitive to the presence of methyl substituents. (Lipinski Tr. at 1231, l. 18 – 1232, l. 15.)

The Hässle and Byk Gulden patents each disclose the use of a methyl substituent at only the 3 position, at only the 5 position, and at both the 3 and 5 positions. (Lenz Tr. at 761, l. 18 – 762, l. 1.) Where data is presented in those patents, all have acceptable levels of activity but different methyl substitution patterns show greater activity in different circumstances. For instance, the '518 patent has data indicating that the 3 methyl substitution is preferred over the 5 methyl substitution or the 3, 5 dimethyl substitution in compounds containing a 2,2,2-trifluoroethoxy substituent. (*Compare* entries 3, 4 & 8 in the table in column 25 at TVL059835 of DTX9.) The 3 methyl substitution, shown as table entry 3, inhibits the amount of gastric acid secretion (*i.e.*, HCl secretion) at a rate equal to the 5 methyl substitution, shown as table entry 4,

and a greater rate than the 3, 5 dimethyl substitution, shown as table entry 8, and has a lower ED_{25} and ED_{50} values than either.

The '409 patent shows the 3 methyl substitution to be more potent than the 3, 5 dimethyl substitution in reduction in the ulcer index or the inhibition of gastric acid secretion, and to have lower ED_{25} and ED_{50} values. (*Compare* entry 3 (3 methyl) *with* entry 4 (3, 5 dimethyl) in the table in columns 13-16 of DTX7.)

On the other hand, the '431 patent indicates that a PPI compound with 3, 5 dimethyl substitution is more effective in inhibiting gastric acid secretion than a compound with a 3 methyl substitution in some circumstances. (*Compare* entry 16 (3 methyl) *with* entry 17 (3, 5 dimethyl) in the table in DTX5 columns 9-12.)

Thus, a medicinal chemist would have known to synthesize and test each of the methyl variations when working on a new PPI compound to determine which one was appropriate. (Lenz Tr. at 767, l. 12 – 768, l. 7.) Dr. Lipinski does not contradict this point because this is not something new; it is simply part of the normal, methodical legwork in the design process. (Lipinski Tr. at 1231, 1. 18 – 1232, 1.15.).

2. No Need to Substitute the Benzimidazole Ring

Once the pyridine ring is set, a medicinal chemist would synthesize compounds both with and without substitutions on the benzimidazole ring with an expectation of similar potency. (Lenz Tr. at 767, l. 12 – 768, l. 7.) The potency would be similar because the benzimidazole ring has a much smaller effect on the pKa of the compound than the pyridine ring – and thus a smaller effect on the accumulation and activation of the PPI in the parietal cell. (*Id.* at 744, l. 10 – 745, l. 2 and 751, l. 23 – 752, l. 20.)

For instance, when Hässle began working with an alkoxy at the 4 position, it synthesized the omeprazole compound having a benzimidazole ring substituent (*see* the 5-OCH_3 for R_1 in

example 23 in Table 2 of DTX5) and an analog of omeprazole without a benzimidazole ring substituent (*see* the H for R_1 in example 25 in Table 2 of DTX5). Analysis of examples 23 and 25 in Table 2 demonstrates that there is no difference in potency between omeprazole and the related compound with the unsubstituted benzimidazole ring - with a difference of only 5% in gastric acid inhibition (65% vs. 60%). (DTX5 at col. 11-12.)

Where potency is equal, the selection of an unsubstituted benzimidazole ring would be based on other factors of drug development, such as the fact that it is easier to synthesize an unsubstituted benzimidazole ring from available commercial materials and manufacture commercial scale batches of the entire compound. (Lenz Tr. at 731, l. 15 – 732, l. 10.)

G. Takeda's Own Development Strategy Supports Obviousness

The actual steps taken by Takeda during the development of lansoprazole follow the logical progression described supra in section III.C.2. Takeda attempted both the NCE and me-too substitution strategies. Takeda first attempted an NCE strategy that involved splitting up the three components of the backbone structure and replacing one or more of those components. Takeda tried the NCE strategy for more than a year but failed to develop a new PPI. (Lenz Tr. at 810, ll. 13–16.)

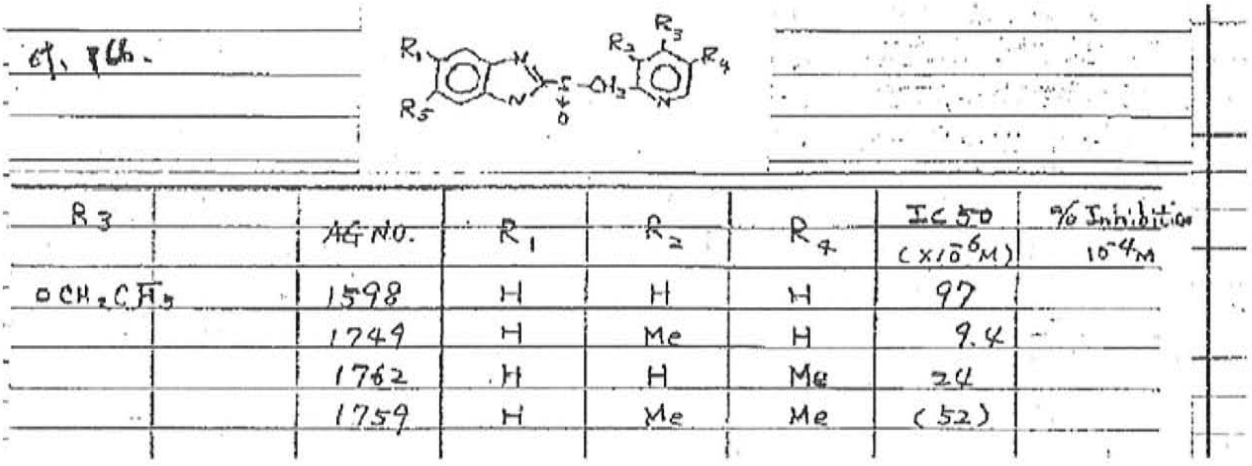
1. Takeda Focuses on Substitutions of Omeprazole

When Takeda's NCE strategy failed, Takeda turned its attention to development of a PPI compound using the me-too substitution strategy. Takeda's documents reveal that omeprazole was Takeda's choice as a lead compound. (*See, e.g.*, PTX0045 at TAKEDA-436696.) Takeda synthesized omeprazole for the first time in May 1983 and then began a pattern of synthesizing compounds having the backbone structure as well as an alkoxy at the 4 position of the pyridine ring. (*See, e.g.*, DTX604 at TAKEDA-040886; AG-1414 at TAKEDA-051141 in DTX428.)

In September 1983, shortly after the Byk Gulden '409 patent published, Takeda began using fluorinated substituents as part of its me-too substitution strategy. (*See, e.g.*, PTX0069 at LIPINSKI 001229; AG-1545 at TAKEDA-051157 in DTX428.) Shortly thereafter, Takeda synthesized the AG-1598 compound containing a trifluoroethoxy substituent at the 4 position of the pyridine ring. (*See* DTX428 at TAKEDA-051164.) This compound was the predecessor to lansoprazole. The only difference is that Takeda later added a methyl group to the 3 position of the pyridine ring, resulting in the final lansoprazole compound.

2. Takeda Tested Compounds With R_3 and R_5 Methylation

Takeda tested synthesized and tested each of the 3 methyl substitution, 5 methyl substitution and 3, 5 dimethyl substitution discussed *supra* in subsection III.F.1. (*See, e.g.*, the "Me" designations in compounds AG1749, AG1762 and AG1759 at Takeda 051183-84 in DTX428, reproduced in part in Figure 10 below.)[17] As predicted, each of those variants showed anti-ulcer activity. See Figure 10; *see also* screening data for AG1749, AG1762 and AG1759 at LIPINSKI 002188-90 in PTX0059.



R3	AG NO.	R1	R2	R4	IC 50 (x10⁻⁶M)	% Inhibition 10⁻⁴M
OCH2CF3	1598	H	H	H	97	
	1749	H	Me	H	9.4	
	1762	H	H	Me	24	
	1759	H	Me	Me	(52)	

Figure 10 - Selected portion of Takeda Notebook

[17] The parties designated as "R2 and "R4" in Figure 10 correspond to the 3 and 5 positions of the pyridine ring discussed throughout the brief.

3. Takeda Tested Compounds With and Without Benzimidazole Substitutions

Similar to the discussion *supra* in subsection III.F.2, Takeda also tested compounds having a trifluoroethoxy substituent on the 4 position both with and without substituents on the benzimidazole ring. (*See, e.g.*, screen data for AG1749, AG1734 and AG1731 at LIPINSKI 002191-92 IN PTX00569.)

4. Takeda Concluded That Lansoprazole Is Obvious

Takeda itself knows that the lansoprazole molecule is obvious in light of prior art PPI compounds. During the research that resulted in lansoprazole, Takeda undertook a review of lansoprazole's development to evaluate, in part, "the creativity of the research." (DTX703 at TAKEDA-044462, reproduced in part in Figure 11 below.) This included an assessment of the "patentability" of the lansoprazole *compound*. (*Id.*) Takeda concluded that the lansoprazole "[s]tructure is too similar to Omeprazole" to be patentable. (*Id.*) Now that litigation of the lansoprazole compound has arisen, Takeda should not be heard to deny its own internal conclusion on patentability.

The th Research Topic Evaluation Scorecard 8
Year month day
Rater:

Name of research topic or development code	Screening code	Stage
AG-1749		

I. Creativity of the research (Uniqueness/Usability)
- I-1: Uniqueness of biological activity
- I-2: Patentability
- I-3: Anticipated medical usability
- I-4: Influence on another areas

5	4	3	2	1	Notes
		o			Has simultaneous cytoprotective effect.
			o		Structure is too similar to Omeprazole.
	o				
				o	
Rating: 3					

Figure 11 - Takeda Research Topic Evaluation Scorecard

H. Lansoprazole Is Not Unexpectedly Superior to the Prior Art

As discussed *supra* in section II.A, Takeda's knowledge of the similarity between lansoprazole and the prior art forced Takeda to rely on a claim that lansoprazole was unexpectedly superior to the prior art. Thus, the '098 patent contains a single point of data purporting to show that lansoprazole is 20 times more potent than omeprazole. This single data point is not sufficient to rebut Teva's prima facie case of obviousness of claim 10 of the '098 patent. First, as explained *supra* in subsection II.B.2, Takeda was in possession of data showing that omeprazole was equipotent to lansoprazole in some animal tests and slightly more potent than lansoprazole in others. Thus, the evidence does not establish definitively that lansoprazole was superior to the prior art. Second, to the extent that some data does suggest that lansoprazole is superior in some animal models, that superiority would be expected because of the improved

bioavailability obtained by using a fluorinated substituent. (Lenz Tr. at 757. l. 4 – 758, l. 10; *see also In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("However, when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").)

Third, Teva's expert Gastroenterologist Dr. Meyer Solny[18] testified that there is no clinical difference between omeprazole and lansoprazole when used by humans. As Dr. Solny and the clinical literature relating to PPIs agree, "A PPI is a PPI." (Solny Tr. at 583, ll. 4-19; DTX142 at TVL063405.) Omeprazole and lansoprazole are equally effective at treating gastric acid related diseases. (*See* Solny Tr. at 574, l. 5 – p. 575, l. 15; *see also* DTX145 at TVL063411 and DTX144 at TVL063991.) Indeed, Plaintiffs' Gastroenterologist Dr. Fennerty admits that he would take whatever PPI is in his medicine kit if he needed treatment for a gastric acid related disease. (Fennerty Tr. at 865, ll. 7-10.) There can be no clearer evidence than that of Plaintiffs' own Gastroenterologist that there is no material difference in potency between lansoprazole and prior art PPI compounds – and thus no basis for rebutting a prima facie case of obviousness through a claim of unexpected superiority.[19]

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[18] Dr. Solny's expert qualifications include an M.D. from Columbia University, 28 years of private practice in internal medicine and gastroenterology, a position as Assistant Attending Physician in the Department of Medicine, Division of Gastroenterology & Hepatology at New York Presbyterian Hospital; board certification in gastroenterology; and memberships in multiple professional organizations. (Solny Tr. at 572-574; *see also* CV at DTX129.)

[19] It is anticipated that Plaintiffs will raise additional claims of secondary indicia evidence, such as commercial success, in opposition to Teva's prima facie case of obviousness. Teva will respond to any such claims in its reply brief.

IV. CLEAR AND CONVINCING EVIDENCE ESTABLISHES THAT CLAIM 2 OF THE '321 PATENT IS INVALID AS OBVIOUS UNDER 35 U.S.C. §103

The evidence presented at trial shows that available prior art renders claim 2 the '321 patent invalid as obvious under 35 U.S.C. § 103. The legal standards for obviousness are set forth *supra* in subsection III.B.

A. The '321 Patent

The '321 patent discloses a pharmaceutical composition containing a benzimidazole compound and a basic inorganic salt of magnesium and/or calcium, wherein the composition is made up into tablets or granules and then coated with a coating agent. (PTX3 at col. 17, ll. 63-65.) Enteric coats frequently are used with acid-labile compounds such as lansoprazole to prevent degradation when the formulation passes through the stomach on its way to the intestines. Enteric coats themselves, however, are acidic in nature and also can cause an acid-labile compound to degrade before reaching the intestines. (Chambliss Tr. at 497, ll. 10-20.) The technology claimed in the '321 patent addresses this problem.

Plaintiffs assert infringement of claim 2 of the '321 patent. (D.I. 146, at ¶ 21.) Claim 2, as a dependent claim, adopts the limitations set forth in claim 1. (D.I. 146, at ¶ 22.) Teva bases its invalidity analysis on the February 13, 1986 priority date.[20] (Chambliss Tr. at 501, l. 25 – p. 502, l. 5.)

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[20] The '321 patent issued from an application filed with the USPTO on February 13, 1987, and claims priority to two Japanese patent applications, filed on February 13, 1986 and February 26, 1986, respectively. (PTX0003.)

B. Each Limitation of Claim 2 Is Disclosed in the Prior Art

Teva's pharmaceutical formulation expert, Dr. Walter Chambliss,[21] testified at trial that the subject matter of the '321 patent would have been obvious based on the state of the pharmaceutical arts in February 1986. (Chambliss Tr. at 502, ll. 17-21.) In 1986, two basic methods of formulating an acid-labile drug that required an enteric coat to pass through the stomach were known. First, the acid-labile compound could be physically separated from the acidic enteric coat. (Chambliss Tr. at 497, l. 25 – p. 498, l. 5.) Second, an alkaline material could be added to the acid-labile compound to prevent degradation. (Chambliss Tr. at 498, ll. 6-8.) Claim 2 of the '321 patent claims a formulation using the second approach, wherein the alkaline material is magnesium carbonate and the acid-labile compound is lansoprazole. (PTX0003 at col. 17, l. 63 – col. 18, l. 34; see also Chambliss Tr. at 499, l. 16 – p. 500, l. 3.) Each of the elements of claim 2 is examined below to demonstrate the obviousness of this formulation.[22]

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[21] Dr. Chambliss's expert qualifications include a doctoral degree in pharmaceutics from the University of Mississippi; over 17 years of research and development experience at G.D. Searle, Bristol-Myers, and Schering Plough HealthCare Products, during which time he developed or supervised development of over 200 pharmaceutical products; membership on the executive committees of various Pharmaceutical Associations; service as Fellow of the American Pharmaceutical Association and of the American Association of Indian Pharmaceutical Scientists; and experience formulating pharmaceutical products containing acid-labile drugs during the relevant time. (Chambliss Tr. at 447-52.) Dr. Chambliss currently holds three positions at the University of Mississippi: Professor of Pharmaceutics, Director of Technology Management, and Research Professor in the National Center for Natural Products Research. (*Id.* at 452.)

[22] Teva respectfully submits that its invalidity analysis would be the same if the Court chooses not to construe any of the limitations for which the parties request construction or if the Court adopts one or more of Plaintiffs' proposed constructions. Because the claim construction issues are quite pertinent to non-infringement issues, Teva will address claim construction in response to Plaintiffs' infringement argument.

1. "A pharmaceutical composition..."

The prior art teaches the "pharmaceutical combination" of claim 2. U.S. Patent No. 4,686,230 ("the '230 patent"), which is discussed in more detail *infra* in subsection IV.B.4, discloses the combination of a benzimidazole compound with antacids and an inorganic basic salt of magnesium. (DTX16 at col. 40, ll. 22-28.)

2. "wherein the composition is made up into tablets or granules and then coated by a coating agent"

The prior art teaches the use of an enteric coated granule containing a substituted benzimidazole. The '230 patent discloses formulating benzimidazole compounds with pharmaceutical excipients in tablet form and that it was known in the art which excipients were suitable for making the desired formulation. (*Id.* at col. 39, ll. 48-67.) In "Omeprazole: A Study of Its Inhibition of Gastric pH and Oral Pharmacokinetics After Morning or Evening Dose," an article authored by Pritchard et al. regarding clinical studies testing omeprazole, the authors disclose that "omeprazole is a crystalline solid that is chemically labile and rapidly degraded in acidic media." (DTX33 at TVL065993.) The article teaches that a substituted benzimidazole, in the form of "encapsulated, enteric coated granulates" of omeprazole, were administered to participants of a clinical study. (*Id.*) The reference "Development of an oral formulation of omeprazole," a 1985 article authored by Pilbrant et al., also discloses the administration of an enteric coated granule formulation of omeprazole in a clinical study. (DTX42 at TVL059554.)

3. "which comprises an effective amount of the anti-ulcer compound 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl] methylsulfinyl] benzimidazole"

It is unquestioned that the compound lansoprazole, also known as 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl] methylsulfinyl], is disclosed in the '098 patent-in-suit, which is prior art to the '321 patent. (PTX1 at col. 6, ll. 5-28.) The '098 patent teaches that lansoprazole can

be formulated into an oral dosage form such as a tablet by "formulating with a pharmacologically acceptable carrier, excipient, diluent, etc." (*Id.*, at col. 6, ll. 53-60.)

4. "magnesium carbonate"

The prior art teaches the use of magnesium salts such as magnesium carbonate in combination with benzimidazole compounds. For instance, the '230 patent teaches the combination of a benzimidazole with antacids, which includes basic inorganic salts of magnesium. (DTX16 at col. 40, ll. 22-28.) While the '230 patent does not identify magnesium carbonate in its nonexclusive list of antacids available for combination with benzimidazoles, it is undisputed that magnesium carbonate is an antacid. (Chambliss Tr. at 504, ll. 2-11.)

Further, Japanese Unexamined Patent laid open No. S60-19715 ("the Ueno Japanese patent") discloses to one of ordinary skill in the art that basic inorganic salts of magnesium can stabilize acid-labile active pharmaceutical ingredients ("API"). Indeed, the Ueno Japanese patent provides a road map for the stabilization of an acid-labile API in a solid preparation through the use of basic inorganic salts of magnesium. (DTX18 at TAKEDA-681588-98.) The Ueno Japanese patent does not specifically disclose magnesium carbonate in its list of stabilizers. Instead, the Ueno Japanese patent teaches the use of a stabilizing compound selected from the group consisting of magnesium silicate, magnesium oxide and hydrotalcite (an inorganic basic salt of magnesium). (DTX18 at TAKEDA-681589.) Each of these basic salts of magnesium are claimed in claim 1 of the '321 patent, and magnesium carbonate would have been an obvious variation of the magnesium salts listed. (PTX3 at col. 17, l. 68 – col. 18, l. 27.) Finally, the Ueno Japanese patent also teaches that basic inorganic salts of magnesium are more effective stabilizers than basic inorganic salts of sodium. (DTX18 at TAKEDA-681593, Table 1; Chambliss Tr. at 509, l. 24 – p. 511, l. 7.) This disclosure would guide one of ordinary skill in the art to select a basic inorganic salt like magnesium carbonate to stabilize an acid-labile API.

5. "the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts per weight"

Teva, for the reasons that will be set forth in its response memorandum on non-infringement, submits that this phrase should be construed to mean that "the weight of the basic inorganic salt that is in even contact with the benzimidazole falls between about 0.3 to 20 parts by weight." (*See* D.I. 313 at 16; *see also* DTX734.) This ratio does not apply to the amount of a basic inorganic salt contained anywhere in a final dosage form, but only where the lansoprazole and the magnesium carbonate are homogenously mixed together. (*See, e.g.*, PTX3 at Ex. 1, col. 9, ll. 45-48.)

The prior art discloses the mixture of an acid-labile API and basic inorganic salts of magnesium in the claimed weight ratio. The Ueno Japanese patent teaches the use of basic inorganic magnesium salt stabilizers within the claimed weight ratio of about 0.3-20 parts per weight. (DTX18 at TAKEDA-681589.) This prior art reference discloses a uniform mixture of the acid-labile API with basic inorganic magnesium salts ranging between 0.5-20 parts by weight. (*Id.* at TAKEDA-681589-90.) While the lower limit of the allowable weight ranges differs, Dr. Chambliss testified that he would consider the difference between 0.3-20 parts by weight and 0.5-20 parts per weight trivial. (Chambliss Tr. at 509, ll. 15-23.)

The prior art also discloses the use of basic inorganic salts within this range to stabilize an acid-labile substituted benzimidazole. For example, the Pilbrant article discloses the mixture of 11 parts sodium bicarbonate to one part omeprazole in suspension form, a mixture which falls within the range claimed in the '321 patent. (Chambliss Tr. at 565, ll. 13-15; *see also* DTX42 at TVL059553.)

6. "the benzimidazole compound being in contact with the basic inorganic salt evenly" ("in contact … evenly")

The parties agree that the "in contact … evenly" limitation was not a term of art in February 1986 and requires construction by the Court. (Chambliss Tr. p. 479, l. 25 – p. 480, l. 5; *see also* DTX734.) For the reasons to be set forth in Teva's response memorandum concerning non-infringement, Teva submits that the '321 patent's specification and file history make clear that the "in contact … evenly" limitation should be construed to mean that the lansoprazole compound and the magnesium carbonate are homogenously mixed together. (*See* D.I. 131 at 8.)

The prior art teaches the homogenous mixture of an acid sensitive API with basic inorganic salts of magnesium. The Ueno Japanese patent discloses a roadmap for stabilizing an API through uniform mixture with basic inorganic magnesium salts. (DTX18 at TAKEDA-681589; Chambliss Tr. at 506, ll. 16-23.) In fact, the stabilized formulation taught in the Ueno Japanese patent very closely resembles the formulation claimed in the '321 patent: the preparation of pharmaceutical compositions, which contain a uniform mixture of the API with the magnesium salt stabilizer, in the form of granules; the patents claim several of the same inorganic salts of magnesium; the patents claim an almost identical weight ratio of basic inorganic salt and API; the patents both teach that the basic inorganic salt and API should be homogenously, or uniformly, mixed; and the patents address the same stabilization problem. (DTX18 at TAKEDA-681590-91; Chambliss Tr. at 475, ll. 19-23 and p. 506, ll. 8-23.) Moreover, given that the Ueno Japanese patent prevents the exact same type of degradation as experienced by lansoprazole, namely content decrease and significant color change in the presence of acid, a person of ordinary skill in the art seeking to stabilize lansoprazole would have

considered the teachings in the Ueno Japanese patent to be relevant. (DTX18 at TAKEDA-681589; Chambliss Tr. at 506, l. 24 – p. 508, l. 17.)[23]

C. Motivation Exists to Combine the Prior Art References

Finally, as set forth thoroughly in the testimony of Dr. Chambliss, motivation existed to combine the prior art references. As discussed above, the Ueno Japanese patent and the Pilbrant reference both teach the use of basic inorganic salts to stabilize acid-labile compounds. (DTX18 at TAKEDA-681589; Chambliss Tr. at 507, l. 10 – p. 508, l. 17; DTX42 at TVL059553.) In addition, both the '230 patent and the Pilbrant reference teach the combination of a benzimidazole compound with an antacid. (DTX16 at col. 40, ll. 22-28; DTX42 at TVL059556.) Therefore, ample motivation exists to combine the prior art references.

The prior art references discussed above teach each and every element of the '321 patent, regardless of whether the Court accepts Teva's proposed constructions or those of the Plaintiffs. The combination of lansoprazole and the basic inorganic salt magnesium carbonate thus would have been an obvious choice to a formulator charged with developing a stable lansoprazole formulation in February 1986.

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[23] Even if the Court accepts Plaintiffs' proposed construction of this phrase, the prior art still discloses this element. Plaintiffs' construction sets forth no physical touching or mixing of the lansoprazole and magnesium carbonate. Instead, the construction appears to require the mere presence of the two ingredients to be in proximity within the final dosage form. The '230 patent discloses the combination of a benzimidazole with an antacid. (DTX16 at col. 40, ll. 22-28). In addition, the Pilbrant article recognizes that omeprazole "degrades rapidly in an acid environment" and teaches the use of sodium bicarbonate to increase the formulation pH to 9.0 to stabilize omeprazole. (DTX42 at TVL059553.) Even Plaintiffs' expert Dr. Amidon admitted that the article teaches the "in contact evenly" limitation. (Amidon Tr. at 1086, ll. 11-16.)

V. CONCLUSION

For the foregoing reasons, Teva submits that the Court should hold that the '098 patent is unenforceable due to inequitable conduct, claim 10 of the '098 patent is invalid as obvious, and claim 2 of the '321 patent is invalid as obvious..

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December 10, 2007

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on December 10, 2007, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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