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Paper 15
Entered: March 1, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN LTD. AND LUPIN PHARMACEUTICALS INC.,
Petitioner,

v.

POZEN INC.,
Patent Owner.

Case IPR2015-01774
Patent 8,852,636 B2

Before TONI R. SCHEINER, LORA M. GREEN, and JACQUELINE WRIGHT BONILLA, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Lupin Ltd. and Lupin Pharmaceuticals Inc. (collectively "Petitioner") filed a Corrected Petition (Paper 4, "Pet.")[1] on August 31, 2015, requesting an *inter partes* review of claims 1–6 and 13–15 of U.S. Patent No. 8,852,636 B2 (Ex. 1001, "the '636 patent"). Pozen Inc. ("Patent Owner") filed a Preliminary Response (Paper 14, "Prelim. Resp.") on December 2, 2015. We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the information presented in the Petition and the Preliminary Response, we are not persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 1–6 and 13–15 of the '636 patent. Accordingly, we decline to institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner represents it is aware of a number of judicial matters involving the '636 patent (e.g., *Horizon Pharma, Inc. v. Actavis Labs. FL, Inc.*, 3:15-cv-03322 (D.N.J.); *Horizon Pharma, Inc. v. Dr. Reddy's Labs.*,

[1] We note that the Exhibit List in Petitioner's Corrected Petition (Paper 4) is incorrect. The Exhibit numbers on page iii of the Corrected Petition do not match the entries in PRPS, or the designations in the body of the Corrected Petition.

Inc., No. 3:15-cv-03324 (D.N.J.); *Horizon Pharma, Inc. v. Lupin Ltd.*, 3:15-cv-03326 (D.N.J.)), as well as a number of judicial and administrative matters involving the '636 patent (*Coalition for Affordable Drugs VII LLC v. Pozen, Inc.*, Case IPR2015-01680), and patents related to the '636 patent (e.g., *Dr. Reddy's Labs., Inc. v. Pozen Inc.*, Case IPR2015-00802 (PTAB)). Pet. 3–4. Patent Owner makes a similar representation. Paper 8, 8–9. Petitioner also filed other Petitions for *inter partes* review involving related patents directed to similar subject matter—IPR2015-01773, IPR2015-01775.

B. The Asserted Grounds of Unpatentability

Petitioner asserts the challenged claims are unpatentable on the following grounds. Pet. 10–58.[2]

References	**Basis**	**Claims Challenged**
Chen[3] and Chandramouli[4]	§ 103(a)	1–6 and 13–15

[2] Petitioner supports its challenges with the Declaration of Umesh V. Banakar, Ph.D., executed August 18, 2015 ("Banakar Declaration") (Ex. 1002).

[3] U.S. Patent No. 6,544,556 B1, issued April 8, 2003 to Chen et al. ("Chen") (Ex. 1004).

[4] Jane C. Chandramouli & Keith G. Tolman, *Prevention and Management of NSAID-Induced Gastropathy*, 8 J. PHARM. CARE PAIN & SYMPTOM CONTROL 27–40 (2000) ("Chandramouli") (Ex. 1011).

References	Basis	Claims Challenged
Chen and Gimet[5]	§ 103(a)	1–6 and 13–15
Goldman[6] and Gimet	§ 103(a)	1–6 and 13–15
Goldman, Gimet, and Lindberg[7]	§ 103(a)	1–6 and 13–15
Gimet, Chandramouli, and Phillips[8]	§ 103(a)	1–6 and 13–15

C. The '636 Patent (Ex. 1001)

The '636 patent, titled "PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS," discloses pharmaceutical compositions "that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID)" (Ex. 1001, 1:22–24), such that there is "a reduced likelihood of causing unwanted side effects, especially gastrointestinal side effects, when administered as a treatment for pain" (*id.* at 1:24–26).

[5] U.S. Patent No. 5,698,225, issued December 16, 1997 to Gimet et al. ("Gimet") (Ex. 1007).

[6] U.S. Patent No. 5,204,118, issued April 20, 1993 to Goldman et al. ("Goldman") (Ex. 1010).

[7] U.S. Patent No. 5,877,192, issued March 2, 1999 to Lindberg et al. ("Lindberg") (Ex. 1005).

[8] PCT Int'l Patent Appl. WO 00/26185, published May 11, 2000, by Phillips ("Phillips") (Ex. 1012).

Specifically, the ’636 patent discloses “a pharmaceutical composition in unit dosage form . . . contain[ing] an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5” (*id.* at 3:27–31), and an NSAID “in an amount effective to reduce or eliminate pain or inflammation” (*id.* at 3:67–4:1). “The term ‘unit dosage form’ . . . refers to a single entity for drug administration. For example, a single tablet or capsule combining both an acid inhibitor and an NSAID would be a unit dosage form.” *Id.* at 4:42–45.

> A unit dosage form of the present invention preferably provides for coordinated drug release, in a way that elevates gastric pH and reduces the deleterious effects of the NSAID on the gastroduodenal mucosa, i.e., the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen.
>
> In a preferred embodiment, the unit dosage form is a multilayer tablet, having an outer layer comprising the acid inhibitor and an inner core which comprises the NSAID. In the most preferred form, coordinated delivery is accomplished by having the inner core surrounded by a polymeric barrier coating that does not dissolve unless the surrounding medium is at a pH of at least 3.5[.]

Id. at 4:45–58.

The claims of the ’636 patent are directed to unit dosage forms where the acid inhibitor is esomeprazole (*id.* at 3:46), and the NSAID is naproxen (*id.* at 4:6).

D. Illustrative Claim

Petitioner challenges claims 1–6 and 13–15 of the '636 patent, of which claim 1 is the only independent claim. Claim 1, reproduced below, is illustrative.

> 1. A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:
>
> (a) esomeprazole present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;
>
> (b) naproxen present in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;
>
> and wherein:
>
> i) said unit dosage form is a tablet in which said naproxen is present in a core;
>
> ii) said tablet comprises a coating, wherein said coating surrounds said core and does not release said naproxen until the pH of the surrounding medium is 3.5 or higher; and
>
> iii) said esomeprazole is in one or more layers outside said core, wherein said one or more layers:
>
> A) do not include an naproxen;
> B) are not surrounded by an enteric coating; and
> C) upon ingestion of said tablet by a patient, release said esomeprazole into said patient's stomach.

Ex. 1001, 21:22–43.

II. ANALYSIS

A. Claim Construction

We determine that no claim term requires express construction for purposes of this Decision.

B. Claims 1–16 and 13–18—Asserted Obviousness over Chen and Chandramouli

1. Chen (Ex. 1004)

Chen discloses an oral dosage form comprising "an orally administrable dosage form comprising a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID, together with one or more pharmaceutically acceptable excipients." Ex. 1004, 3:65–4:3.

Chen discloses a number of suitable proton pump inhibitors (PPIs), and teaches "[i]n certain preferred embodiments, the proton pump inhibitor is omeprazole, either in racemic mixture or only the (-)enantiomer of omeprazole (i.e. esomeprazole)." *Id*. at 6:53–56. In addition, Chen lists naproxen among a large number of well-known examples of NSAIDs. *Id.* at 5:58–6:31.

According to Chen, "proton pump inhibitors are susceptible to degradation and/or transformation in acidic and neutral media," and the half-life of "omeprazole in water solutions at pH-values less than three is shorter than ten minutes." *Id.* at 8:9–17. Chen teaches "it is preferable that in an oral solid dosage form [proton pump inhibitors] be protected from contact

with the acidic gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where the pH is near neutral." *Id.* at 8:19–23.

Accordingly, Chen discloses an embodiment in which a "tablet contains the NSAID within a sustained release matrix and the proton pump inhibitor [is] coated into [sic] the tablet in an enteric coated layer." *Id.* at 12:4–7. Chen further discloses that:

> The dosage forms . . . may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the proton pump inhibitor in desired areas of the gastro-intestinal (GI) tract, e.g., the small intestine . . . . When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible and preferable to formulate compositions which release a portion of the dose, preferably the NSAID, in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose, preferably the proton pump inhibitor, in another area of the GI tract, e.g., the small intestine.
>
> Formulations . . . that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug, preferably the NSAID, is coated over the enteric coat and is released in the stomach, while the remainder, preferably containing the proton pump inhibitor, being protected by the enteric coating, is released further down the gastrointestinal tract.

Id. at 12:14–40.

2. Chandramouli (Ex. 1011)

Chandramouli teaches that, "[d]ue to the asymptomatic nature of NSAID-induced GI toxicity . . . prevention is crucial." Ex. 1011, 36. "Since NSAID-associated GI injury is dependent on the presence of acid," Chandramouli suggests that "the prophylactic use of an H_2 blocker seems reasonable." *Id*. Chandramouli teaches that "[c]oncomitant use of these agents prevents duodenal ulcers, but not gastric ulcers, which are 3 to 4 times more common . . . among NSAID users. Thus H_2 blockade alone does not constitute an adequate preventive treatment." *Id.* According to Chandramouli, proton pump inhibitors "suppress acid secretion to a greater degree than H_2-receptor antagonists. Nevertheless, omeprazole is more effective against duodenal than gastric ulceration." *Id*. Further according to Chandramouli, "[t]he OMNIUM study (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management) concluded however that omeprazole may be as effective or more effective than misoprostol for the prevention of NSAID-induced gastropathy." *Id*.

In addition, Chandramouli discloses that although misoprostol "is the only agent labeled for co-therapy with NSAIDs," and "prevents both gastric and duodenal ulceration," "[s]ignificant dose-related diarrhea and abdominal pain limits its tolerability," and "its use in women of childbearing potential is contraindicated." *Id*. at 37. The reference also teaches that "[i]n an attempt to be more cost-effective, [misoprostol] . . . was combined with diclofenac (Arthrotec®)," and the "combination is as effective for arthritis

pain and symptoms as diclofenac alone with a decreased incidence of ulcers." *Id*.

3. Analysis

Petitioner contends that the subject matter of claims 1–6 and 13–15 of the '636 patent would have been obvious over Chen alone, or Chen in view of Chandramouli. Pet. 10–26.

Asserted Obviousness over Chen

Specifically, Petitioner contends that Chen discloses an oral solid dosage form, e.g., a tablet, comprising a therapeutically effective amount of an NSAID and a proton pump inhibitor (PPI) in an amount effective to inhibit or prevent gastrointestinal side effects normally associated with the NSAID. Pet. 11 (citing Ex. 1004, Abstract, 4:30–33). Petitioner contends that Chen expressly discloses that the NSAID may be naproxen and the PPI may be omeprazole or omeprazole's *S*-enantiomer, esomeprazole, both of which were known in the art for reducing the risk of gastroduodenal injury associated with NSAID use. *Id.* at 11–12 (citing Ex. 1002 ¶¶ 31, 40; Ex. 1004, 5:53–58, 60–63, 6:43–49, 53–56; Ex. 1005, 1:50–55).

Petitioner acknowledges that Chen "discloses a preferred formulation that would release the NSAID in the stomach and omeprazole in the small intestine," but argues that Chen "is not limited to such formulations," and discloses generally "formulations with pH-dependent and pH-independent coatings to permit the coordinated release of one drug before the other." *Id.* at 12 (citing Ex. 1004, 12:17–18), 13 (citing Ex. 1002 ¶¶ 33, 38, 55; Ex.

1004, 12:27–32). Relying on Dr. Banakar's testimony for support, Petitioner contends that it would have been obvious for one of ordinary skill in the art "to develop a . . . tablet with esomeprazole released before naproxen" (*id.* at 13 (citing Ex. 1002 ¶ 55)), specifically, "a core with naproxen surrounded by a pH-dependent enteric coating and non-enteric coated esomeprazole" (*id.* at 12 (citing Ex. 1004, 12:17–18)—essentially the reverse of Chen's preferred formulation.

Again relying on Dr. Banakar's testimony, Petitioner contends that one of ordinary skill in the art "would have understood that PPIs are preferably released in the gastrointestinal tract prior to reaching the small intestine." *Id.* at 13 (citing Ex. 1002 ¶¶ 33, 38). Moreover, Petitioner contends that one of ordinary skill in the art would have understood Chen's description of "enteric-coated omeprazole as 'preferred'" to mean that "non-enteric coated esomeprazole would be effective" even though it would be released in the stomach and exposed to gastric fluid. *Id.* at 14 (citing Ex. 1002 ¶¶ 37, 38). That is, Petitioner, relying on Dr. Banakar's testimony, contends that one of ordinary skill in the art "would know partial degradation of the PPI would not prevent non-enteric coated esomeprazole from being therapeutically effective, but instead, a sufficient amount of PPI could exist and loss of the PPI could be overcome by adjusting the dosage." *Id.* at 14 (citing Ex. 1002 ¶ 48). Petitioner contends, therefore, that one of ordinary skill in the art "would have found it obvious to make a combination tablet with enteric-coated naproxen and immediate-release esomeprazole"

with a reasonable expectation that it would "be therapeutically effective." *Id.* at 14.

Additionally, in support of the assertion that one of ordinary skill in the art "would have known at least a portion of non-enteric coated, unbuffered esomeprazole would be bioavailable upon oral administration," Petitioner and Dr. Banakar cite a study by Pilbrant,[9] which according to Petitioner, "compar[es] the bioavailability of non-enteric coated omeprazole when administered with and without a buffer and teaches a substantial portion of the uncoated omeprazole is bioavailable." Pet. 15 (citing Ex. 1002 ¶¶ 38, 47, 48; Ex. 1008). Petitioner characterizes Pilbrant as contemplating "'two principle options for the formulation of an oral, solid dosage form of omeprazole': (1) a 'conventional' non-enteric coated form in which 'omeprazole is released an absorbed rapidly enough to avoid degradation in the stomach' and (2) and enteric coated form of esomeprazole." *Id.* (citing Ex. 1008, 114). Petitioner contends that Pilbrant "reports that 44% of uncoated, unbuffered omeprazole was not lost to degradation in the acidic stomach" (*id.* (citing Ex. 1008, 116–117), and one of ordinary skill in the art "would have been able to use well-known and routine techniques to compensate for the degraded amount" (*id.* (citing Ex. 1002 ¶¶ 48–51, 59). Additionally, Petitioner contends that the Court of

[9] Å. Pilbrant & C. Cederberg, *Development of an Oral Formulation of Omeprazole*, 20 SCAND. J. GASTROENTEROL. 113–120 (1985) ("Pilbrant") (Ex. 1008).

Appeals for the Federal Circuit "has acknowledged that Pilbrant teaches non-enteric solid dosage forms of PPIs as a 'viable alternative to enteric coating.'" *Id.* at 18 (citing *Santarus, Inc. v. PAR Pharm., Inc.*, 694 F.3d 1344, 1355–56 (Fed. Cir. 2012).

We are not persuaded that Petitioner has established that a unit dosage form comprising a naproxen core with a protective coating that does not release the naproxen unless the pH of the surrounding medium is 3.5 or higher, surrounded by a layer of esomeprazole which is released into the stomach upon ingestion, would have been obvious over Chen—which teaches essentially the opposite.

First, Petitioner relies on selective portions of Chen, without adequate consideration of the surrounding context. We do not agree that Chen's teachings regarding pH-dependent and pH-independent coatings are as broad and generic as Petitioner contends. As discussed above in Section II.B.1, Chen actually states:

> A pH-dependent coating serves to release the proton pump inhibitor in desired areas of the gastro-intestinal (GI) tract, e.g., the small intestine . . . When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. ***It is also possible and preferable to formulate compositions which release a portion of the dose, preferably the NSAID, in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose, preferably the proton pump inhibitor, in another area of the GI tract, e.g., the small intestine***.

> Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby ***unprotected drug, preferably the NSAID, is coated over the enteric coat and is released in the stomach, while the remainder, preferably containing the proton pump inhibitor, being protected by the enteric coating, is released further down the gastrointestinal tract***.

Ex. 1004, 12:19–40 (emphases added). Elsewhere, e.g., in columns 8 and 12, Chen repeatedly refers to using a pH dependent coating (e.g., an enteric coating) to facilitate release of the PPI in the small intestine, while not coating the NSAID so that it is released the stomach. *Id*. at 12:4–7, *see also id.* at 8:17–40 (disclosing protecting PPIs so they are released "where the pH is near neutral"). Petitioner has not pointed to where Chen discloses or suggests doing the reverse, i.e., enterically coating NSAID so that it is released further down the GI tract (where the pH is higher), and releasing "unprotected" PPI at any pH, such as in the stomach (where the pH is lower).

Second, to the extent Petitioner argues that Chen "does not suggest that formulas with non-enteric coated PPIs would result in no bioavailability of the PPI," we are not persuaded. Pet. 14. If we understand Petitioner's position, it is that Chen fails to teach away from non-enteric coated PPIs. Nevertheless, even if we were to agree that Chen does not explicitly teach away from the reverse of its preferred embodiments, it does not follow that it provides a suggestion to do so, or a reasonable expectation of success.

Nor are we persuaded by Dr. Banakar's testimony that one of ordinary skill in the art would have had a reason to do the opposite of what Chen teaches. Dr. Banakar cites Exhibits 1006, 1020, 1021, and 1022—none of which were cited in the Petition, with the exception of Ex. 1006—in support of the contention that "repeated administration of PPIs results in a self-propagating effect." Ex. 1002 ¶ 31. To the extent Exhibit 1006[10] is cited by Dr. Banakar and by Petitioner on page 16 of the Petition, its relevance to Petitioner's position is unclear as the reference discloses repeated administration of "capsules of enteric-coated omeprazole granules." Ex. 1006, 707. In addition, Dr. Banakar cites Exhibit 1021 and 1016 (neither of which were cited in the Petition) in support of the contentions that it was known that PPIs "function by inhibiting H2 receptors in the parietal cells" which "are located in the duodenum, which is located immediately after the stomach within the GI tract," and "NSAIDs, on the other hand, are absorbed later in the GI tract." Ex. 1002 ¶ 33. Dr. Banakar thereafter summarily concludes that one of ordinary skill in the art "would have understood that esomeprazole should be released early in the GI tract to reduce the acidity (inhibit proton pumps) while naproxen may be released simultaneously, or preferably later than the release of esomeprazole, in order to reduce the risk of NSAID-associated gastroduodenal injury," without citing additional

[10] C.W. Howden et al., *Effects of single and repeated doses of omeprazole on gastric acid and pepsin secretion in man*, 25 GUT 707–10 (1984) (Ex. 1006).

evidence in support thereof. *Id*. at ¶¶ 33, 38. Such conclusory statements by Petitioner and Dr. Banakar do not explain sufficiently, nor provide adequate support as to why one of ordinary skill in the art would have done the opposite of what Chen teaches in order to address the issue of PPI stability at lower pHs. *See* Ex. 1004, 8:17–40, 12:4–32. Petitioner's conclusory assertions that the subject matter of the challenged claims would have been "obvious to try" are likewise inadequate to address this point. Pet. 13, 19.

Nor are we persuaded that Pilbrant's teachings, relied on by Petitioner and Dr. Banakar, would have led one of ordinary skill in the art to do essentially the opposite of what Chen teaches. Pilbrant, like Chen, teaches that "[o]meprazole degrades very rapidly in water solutions at low pH-values." Ex. 1008, 113. In this context, Pilbrant describes the use of an "enteric-coated dosage form, which releases omeprazole for absorption in the small intestine," while stating that a conventional oral dosage "was ruled out" because "more than half of the omeprazole in a rapidly dissolving dosage form degrades in the stomach." *Id*. at 114. In addition, Pilbrant states that a "rapidly dissolving *suspension* of micronised omeprazole is the second best choice" to the enteric-coated dosage form. *Id*. at 116 (emphasis added). Pilbrant describes administering that suspension "together with sodium bicarbonate buffer," and states that "results clearly show that a conventional, non-buffered, oral dosage form of omeprazole will have a low systemic bioavailability owing to preabsorption degradation of omeprazole in the stomach." *Id*. at 117.

Petitioner's arguments regarding Pilbrant and *Santarus* do not acknowledge the distinction between a solid oral formulation (such as a tablet) and a solution/suspension comprising omeprazole. As stated by the court in *Santarus*, "Pilbrant discusses four options: 1) solutions; 2) suspensions of buffered non-enteric coated omeprazole; 3) conventional oral dosage forms—tablets, capsules or granules—with nonenteric coated PPIs; and 4) conventional oral dosage forms with enteric-coated PPIs." *Santarus*, 694 F.3d at 1355. As further stated by the court, "Pilbrant explicitly 'ruled out' the third option—non-enteric coated conventional oral dosage forms such as tablets, capsules, or granules—because they degrade too quickly in the stomach to be absorbed in sufficient amounts to be effective." *Id*. In contrast, regarding the second option, Pilbrant "teaches that, although suspensions of buffered non-enteric coated omeprazole may be the 'second best choice,' they are a viable alternative to enteric coating." *Id*. at 1355–56.

In other words, Pilbrant teaches preparing buffered suspensions of non-enteric coated omeprazole, but teaches away from preparing non-enteric coated tablets of the drug. Ex. 1008, 114, 116–117. Petitioner does not explain sufficiently why an ordinary artisan would have had a reasonable expectation of success in making a tablet comprising esomeprazole with no coating or a non-enteric coating, that releases the PPI regardless of the pH, i.e., in the stomach, as required by the claims of the '636 patent.

Asserted Obviousness over Chen and Chandramouli

Nor are we persuaded that the subject matter of claims 1–6 and 13–15 of the '636 patent would have been obvious over Chen in view of Chandramouli.

Petitioner contends Chandramouli teaches that "use of NSAIDs results in significant deleterious effects on the upper gastrointestinal tract," including the small intestine, and that "PPIs such as omeprazole can be used to reduce the risk of NSAID-associated gastrointestinal injury." Pet. 20 (citing Ex. 1011, 31–32, 36). Petitioner further contends "[g]iven the structure and function of the dosage form taught in [Chen], a [person of ordinary skill in the art] would have been strongly motivated by Chandramouli to make a combination tablet described in [Chen] with esomeprazole released in the stomach and naproxen in the small intestine." *Id*. at 20–21.

Petitioner's contentions here, once again, do not explain sufficiently, nor provide adequate support as to why an ordinary artisan would have done the opposite of what Chen teaches in order to address the issue of PPI stability at lower pHs, especially in view of Pilbrant's teachings regarding tablets comprising omeprazole, as discussed above. Ex. 1004, 8:17–40, 12:4–40; Ex. 1008, 114, 116–117.

4. Conclusion

Having considered the arguments and evidence presented in the Petition, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 1–6 and 13–15, on the basis of obviousness over Chen alone, or Chen in combination with Chandramouli.

C. Claims 1–6 and 13–15—Asserted Obviousness over Chen and Gimet

1. Gimet (Ex. 1007)

Gimet teaches that NSAIDs have "high therapeutic value especially for the treatment of inflammatory conditions such as . . . osteoarthritis (OA) and rheumatoid arthritis," but "also exhibit undesirable side effects." Ex. 1007, 1:20–24). "An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use." *Id.* at 1:24–27. "NSAID induced ulcers in the stomach . . . generally exhibit few or no symptoms and may cause dangerous bleeding when undetected . . . [and] [i]n some instances . . . can prove fatal." *Id.* at 1:29–33.

According to Gimet, "[c]ertain prostaglandins have been shown to prevent NSAID induced ulcers." *Id.* at 1:39–40. Misoprostol, for example, "is a pharmaceutically acceptable prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers." *Id.* at 1:45–47.

Gimet discloses a pharmaceutical composition comprising a tablet having an inner core and an outer mantle coating surrounding the inner core,

designed to "[counter] (by inhibiting, reducing or preventing) the ulcerogenic side effects attendant to NSAID administration." *Id.* at 1:11–14, 61–63. The inner core consists of an NSAID—disclofenac or piroxicam—and the outer mantel consists of a prostaglandin—e.g., misoprostol. *Id.* at 1:11–17, 39–47.

Figure 2 of Gimet, reproduced below, depicts tablet 16 in cross-section.

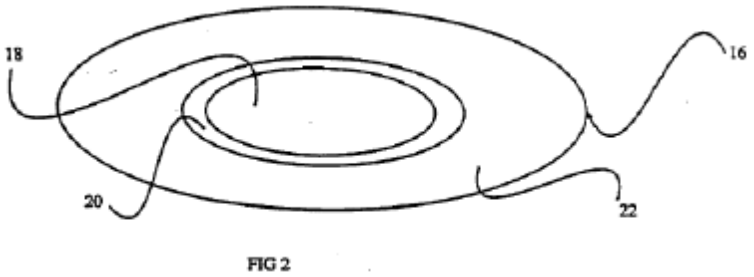

FIG 2

Figure 2 of Gimet depicts tablet 16. Tablet 16 includes an NSAID—diclofenac or piroxicam—in inner core 18. Enteric coating 20 surrounds core 18, and mantle 22—consisting of a prostaglandin, e.g., misoprostol—surrounds the coated inner core. Ex. 1007, 6:24–44.

The enteric coating "can be formulated from any suitable enteric coating material," and "aids in segregating the NSAID from the prostaglandin and in directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach." *Id.* at 6:29–30, 33–36.

2. Analysis

Petitioner contends that claims 1–6 and 13–15 of the '636 patent would have been obvious over Chen in view of Gimet. Pet. 26–36.

Petitioner relies on the arguments and evidence discussed above as to why "a person of ordinary skill . . . would have found it obvious to make a combination tablet with enteric-coated naproxen and immediate-release esomeprazole" and "would have reasonably expected non-enteric coated esomeprazole to be therapeutically effective." *Id.* at 28.

Petitioner acknowledges that the acid inhibitor disclosed in Gimet is a prostaglandin, but argues that person of ordinary skill in the art "would have known that like misoprostol, esomeprazole is an acid inhibitor that reduces the risk of NSAID-associated gastrointestinal injury by increasing the pH of the gastrointestinal environment to at least 3.5." *Id*. at 27–28 (citing Ex. 1002 ¶ 50). Accordingly, Petitioner contends that one of ordinary skill in the art "would have been motivated to select the naproxen and esomeprazole combination from [Chen] to create a tablet with the structure disclosed in [Gimet] from the disclosures of [Chen] and a [person of ordinary skill in the art's] understanding that the absorption and therapeutic active site for esomeprazole is located before the typical site of absorption of naproxen within the GI tract." Pet. 28.

Again, Petitioner does not explain sufficiently, nor provide adequate support as to why an ordinary artisan would have done the opposite of what Chen teaches in order to address the issue of PPI stability at lower pHs, especially in view of Pilbrant's teachings regarding tablets comprising omeprazole, as discussed above. Ex. 1007, 8:17–40, 12:4–40; Ex. 1008, 114, 116–117.

3. Conclusion

Having considered the evidence and arguments presented in the Petition, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 1–6 and 13–15 on the basis of obviousness over Chen and Gimet.

D. Claims 1–6 and 13–15—Asserted Obviousness over Goldman and Gimet

1. Goldman (Ex. 1010)

Goldman discloses "pharmaceutical compositions for treating the symptoms of overindulgence . . . [comprising] a combination of non-steroidal anti-inflammatory drug or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition." Ex. 1010, 1:10–16. Goldman teaches that acceptable histamine receptor (H_2) blockers include famotidine (*id.* at 3:27), acceptable proton pump inhibitors (PPIs) include omeprazole (*id.*), and acceptable NSAIDs include naproxen and piroxicam (*id.* at 3:17–22). Goldman discloses using "naproxen from 200 to 500 mg per dose" (*id*. at 5:18–19), and "omeprazole from 60 to 500 mg per dose" (*id*. at 9:25–27), while Examples 11 and 12 disclose tablets consisting of 500 mg of acetaminophen or 200 mg ibuprofen, 60 mg of omeprazole, "and other auxiliary agents and coloring agents" (*id*. at 7:24–42).

Finally, Goldman discloses "chewable and liquid dosage forms" (*id.* at 6:4–5), and further teaches that "[v]arious conventional techniques for

preparing medicament tablets or caplets can be employed as would be known to those skilled in the art." *Id.* at 6:26–30.

2. Analysis

Petitioner contends that claims 1–6 and 13–15 of the '636 patent would have been obvious over Goldman in view of Gimet. Pet. 36–43.

Petitioner contends that Goldman "describes combination tablets comprising therapeutic amounts of an NSAID and a PPI, where the PPI is not enteric coated," as well as 200–500 mg dosages of naproxen and 60–500 mg dosages of omeprazole. Pet. 36 (citing Ex. 1010, 5:18–19, 9:26–27). Petitioner further contends that although an ordinary artisan would have known that omeprazole and esomeprazole are acid labile, Goldman "makes no indication the PPI must be enteric coated in order to be effective," nor does it make "reference to enteric coating or use the term coating at all," referring to Examples 11 and 12, for example. *Id*. at 36–37 (citing Ex. 1010, 7:34–42, 6:1–9).

Citing paragraphs 33 and 38 of Dr. Banakar's Declaration (discussed above), Petitioner summarily asserts that a person of ordinary skill in the art "would have been motivated to create a combination tablet that releases esomeprazole prior to naproxen in the GI tract, given general knowledge in the art." Pet. 37 (citing Ex. 1002 ¶¶ 33, 38). Petitioner then argues that Gimet "discloses a structure that would allow for precisely this goal." *Id*. (citing Ex. 1007, 6:33–36).

We are not persuaded. Neither Petitioner, nor Dr. Banakar explains adequately why one would have prepared Gimet's dosage form (Ex. 1007, Fig. 2, 6:24–44) with an outer mantle of omeprazole or esomeprazole (instead of misoprostol) that is "not surrounded by an enteric coating," as required in claim 1, especially considering Pilbrant's teachings regarding tablets comprising omeprazole, discussed above. Ex. 1008, 113, 114, 116–17.

3. Conclusion

Having considered the evidence and arguments presented in the Petition, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 1–6 and 13–15 on the basis of obviousness over Goldman and Gimet.

E. Claims 1–6 and 13–15—Asserted Obviousness over Goldman, Gimet, and Lindberg

1. Lindberg (Ex. 1005)

Lindberg discloses omeprazole and its optically pure crystalline enantiomeric salts, including a magnesium salt of the (-)enantiomer of omeprazole (*S*-omeprazole), i.e., esomeprazole, in the form of a "dosage unit." Ex. 1005, 1:57–63, 5:25–27. Lindberg further discloses that "oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance." *Id.* at 6:24–25. Lindberg teaches that "[o]meprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents." *Id*. at 1:22–23. Lindberg states that its "novel salts of

single enantiomers of omeprazole" provide "improved pharmacokinetic and metabolic properties." *Id*. at 1:50–55.

In addition, Lindberg teaches that granules, tablets and capsules of "the optically pure compound" (i.e., esomeprazole) "may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach." *Id.* at 5:26–27, 36–39; *see* also 48–49, 56–57.

2. Analysis

Petitioner contends that claims 1–6 and 13–15 of the '636 patent would have been obvious over Goldman, Gimet, and Lindberg. Pet. 44–50.

Petitioner relies on the arguments and evidence discussed above in contending that Goldman "describes tablets with the combination of an NSAID and a PPI, and the PPI is not enteric coated" and Gimet "discloses a combination tablet comprising enteric coated NSAID in the core and further surrounded by an uncoated acid inhibitor." Pet. 44.

Petitioner contends that Lindberg discloses that "esomeprazole is the S-enantiomer of omeprazole and that omeprazole and esomeprazole have significantly similar characteristics for the purposes of pharmaceutical formulation development," thus, "esomeprazole can easily be substituted for omeprazole." *Id.* (citing Ex. 1005, 2:5–13, 4:40–42).

Nevertheless, as discussed above, neither Petitioner, nor Dr. Banakar explains adequately why one would have prepared Gimet's dosage form (Ex. 1007, Fig. 2, 6:24–44) with an outer mantle of omeprazole or esomeprazole

(instead of misoprostol) that is "not surrounded by an enteric coating," as required in claim 1, especially considering Pilbrant's teachings regarding tablets comprising omeprazole, discussed above. Ex. 1008, 113, 114, 116–17.

3. Conclusion

Having considered the evidence and arguments presented in the Petition, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 1–6 and 13–15 on the basis of obviousness over Goldman, Gimet, and Lindberg.

F. Claims 1–6 and 13–15—Asserted Obviousness over Gimet, Chandramouli, and Phillips

1. Phillips (Ex. 1012)

Phillips discloses pharmaceutical preparations containing a PPI, such as omeprazole. Ex. 1012, 1:5–28, 4:8–15. Phillips references Pilbrant (Ex. 1008, discussed above), noting that Pilbrant teaches a buffered omeprazole suspension that can be stored in the refrigerator or freezer. Ex. 1012, 15:3–6. Phillips describes solutions and suspensions of proton pump inhibitors, such as omeprazole, that may be stored at room temperature or in a refrigerator for longer periods of time. *Id*. at 15:19–24.

In particular, Phillips discloses "a pharmaceutical composition including a proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal." *Id*. at 16:16–23. In addition to a solution or suspension, Phillips discloses several dry

formulations, such as a powder, tablet, capsule, or granules, where the "dosage form is not enteric coated or time-released." *Id*. at 57:17–24 (claim 8), 16:24–17:7, 25:19–26:4, 26:26–27:9.

Phillips teaches that the dry formulations "then create the present invention when acted upon by a suitable vehicle, for example water." *Id*. at 27:2–4. For example, "water may be added either prior to ingestion or the dry formulation may be ingested first and then acted upon by the water utilized to swallow the solid formulation," or a "third mechanism enables water in the stomach secretions to produce the present invention." *Id*. at 27:4–9.

Finally, Phillips teaches that in a preferred embodiment, "enterically-coated omeprazole particles are obtained from delayed release capsules," and those "particles are mixed with a sodium bicarbonate ($NaHCO_3$) solution which dissolves the enteric coating and forms an omeprazole solution/suspension." *Id*. at 19:16–22.

2. Analysis

Petitioner contends that claims 1–6 and 13–15 of the '636 patent would have been obvious over Gimet, Chandramouli, and Phillips. Pet. 50–57.

Petitioner contends that Gimet "discloses a combination tablet comprising enteric coated NSAID in the core and further surrounded by an uncoated acid inhibitor, misoprostol." Pet. 50. Petitioner also argues that an ordinary artisan reading Gimet and Chandramouli would have known about

stability issues and contraindications associated with misoprostol, and that omeprazole could be used in its place. *Id*. at 50–51 (citing Ex. 1007, 1:51–53; Ex. 1011, 36–37).

Furthermore, according to Petitioner, upon reading Phillips, one of ordinary skill in the art would have had an additional reason to use, with a reasonable expectation of success, non-enteric coated omeprazole (and therefore esomeprazole as an equivalent) instead of misoprostol, as the acid inhibitor in Gimet's dosage form. *Id*. at 51 (citing Ex. 1012, 57:23–24; Ex. 1002 ¶¶ 68, 69). Specifically, Petitioner contends that Phillips discloses "pharmaceutical preparations of PPIs suitable for oral administration *without* enteric coating" (*id.* (citing Ex. 1012, 57:23–24)), and "solid oral compositions (tablets, capsules) comprising omeprazole and a bicarbonate salt as a pH adjusting solution" (*id.* (citing Ex. 1012, 17:25–27)). Petitioner contends that one of ordinary skill in the art "would understand addition of even a small amount of buffer would sufficiently increase bioavailability" of a PPI such as omeprazole or esomeprazole. *Id*. at 52 (citing Ex. 1002 ¶ 60).

Petitioner further contends that "the specification of the '636 patent contains examples where the proton pump inhibitor, omeprazole, is protected by a large quantity of buffers, alkali, and bicarbonates such as sodium bicarbonate" (Pet. 52 (citing Ex. 1001, 17:47–52, 18:19, 19:38)), and "the claims of the '636 patent are not limited to non-buffered esomeprazole" (*id.*).

If we understand Petitioner's rationale, it is that it would have been obvious for one of ordinary skill in the art to substitute esomeprazole or omeprazole for misoprostol in Gimet's dosage form, given Chandramouli's teachings, and further, to surround Gimet's enteric-coated NSAID core with a layer of esomeprazole, protected by a buffer or a bicarbonate, but *not* enteric-coated, given Phillips' teachings.

Nevertheless, claim 1 of the '636 patent requires, in pertinent part, a naproxen "core" with a "coating [that] surrounds said core and does not release said naproxen until the pH of the surrounding medium is 3.5 or higher." Ex. 1001, 21:23–37. As Petitioner states, Gimet "discloses a combination tablet comprising enteric coated NSAID in the core." Pet. 50. As discussed above, however, Phillips teaches that when "enterically-coated omeprazole particles . . . are mixed with a sodium bicarbonate ($NaHCO_3$) solution," the solution "dissolves the enteric coating and forms an omeprazole solution/suspension." Ex. 1012, 19:17–22.

Petitioner does not explain adequately why one would have surrounded Gimet's enteric-coated NSAID core with a bicarbonate salt buffered PPI, and still have had a reasonable expectation that no NSAID would be released until the pH of the surrounding medium reached 3.5 or higher—as required by claim 1—given Phillips' teaching that a sodium bicarbonate solution is capable of dissolving an enteric coating. *Id*. at 19:16–23.

3. Conclusion

Having considered the evidence and arguments presented in the Petition, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 1–6 and 13–15 on the basis of obviousness over Gimet, Chandramouli, and Phillips.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–6 and 13–15 of the '636 patent are unpatentable under 35 U.S.C. § 103(a).

IV. ORDER

Accordingly, it is

ORDERED that the Petition is denied and no *inter partes* review is instituted.

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