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Paper 18
Entered: February 11, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VII LLC,
Petitioner,

v.

POZEN INC.,
Patent Owner.

Case IPR2015-01680
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

The Coalition for Affordable Drugs VII LLC ("Petitioner") filed a Petition (Paper 2, "Pet.") on August 7, 2015, requesting an *inter partes* review of claims 1–18 of U.S. Patent No. 8,852,636 B2 (Ex. 1001, "the '636 patent"). Pozen Inc. ("Patent Owner") filed a Preliminary Response (Paper 15, "Prelim. Resp.") on November 17, 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 1–18 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. Inc.*, 3:15-cv-03322 (D.N.J.)), as well as a number of judicial and administrative matters involving patents related to the '636 patent (e.g., *Dr. Reddy's Labs., Inc. v. Pozen Inc.*, Case IPR2015-00802 (PTAB)). Pet. 2–3. Patent Owner makes a similar representation. Paper 7, 8–9. Petitioner also filed other Petitions for *inter partes* review involving patents related to the '636 patent

or directed to similar subject matter, including Case Nos. IPR2105-01241 and IPR2015-01344.

B. The Asserted Grounds of Unpatentability

Petitioner asserts the challenged claims are unpatentable on the following grounds. Pet. 4–5, 12–60.[1]

References	**Basis**	**Claims Challenged**
Goldman,[2] Remington,[3] and Lindberg[4]	§ 103(a)	1–18
Gimet,[5] Goldman, and Lindberg	§ 103(a)	1–6 and 13–15
Ouali[6] and Lindberg	§ 103(a)	7–12 and 16–18

[1] Petitioner supports its challenges with the Declaration of Leon Shargel, Ph.D., R.Ph., executed August 7, 2015 ("Shargel Declaration") (Ex. 1003).

[2] U.S. Patent No. 5,204,118, issued April 20, 1993 to Goldman et al. ("Goldman") (Ex. 1004).

[3] Robert E. King & Joseph D. Schwartz, *Oral Solid Dosage Forms*, *in* REMINGTON'S PHARMACEUTICAL SCIENCES 1603–43 (Alfonso R. Gennaro et al., eds.) (17th ed. 1985) ("Remington") (Ex. 1005).

[4] U.S. Patent No. 5,714,504, issued February 3, 1998 to Lindberg et al. ("Lindberg") (Ex. 1007).

[5] U.S. Patent No. 5,698,225, issued December 16, 1997 to Gimet et al. ("Gimet") (Ex. 1006)

[6] U.S. Patent No. 6,183,779 B1, issued February 6, 2001 to Ouali et al. ("Ouali") (Ex. 1008).

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)" (*id.* at 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).

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 1–18 of the '636 patent, of which claims 1 and 7 are independent. 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.

Independent claim 7 is similar to claim 1, except that the unit dosage form is a capsule, instead of a tablet. *Id.* at 22:1–20.

II. ANALYSIS

A. Claim Construction

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

B. Claims 1–18—Asserted Obviousness over Goldman, Remington, and Lindberg

1. Goldman (Ex. 1004)

Goldman teaches that "[t]he symptoms of overindulgence due to excessive or inappropriate intake of food and/or alcoholic beverage are well known and include headache as well as indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis." Ex. 1004, 1:28–32. "The treatment of the symptoms of overindulgence often requires the co-administration of an analgesic to relieve the headache along with an agent to reduce gastric acidity which is generally believed to cause the indigestion and heartburn." *Id.* at 2:52–56.

In order to "more effectively treat all the symptoms concurrently" (*id.* at 2:67–68), 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" (*id.* at 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).

According to Goldman, "statistical methods are used to show that on the average, acetaminophen or non-steroidal inflammatory agents with H_1 histamine and/or H_2 histamine receptor blocking drugs are more efficacious" in treating the symptoms of overindulgence. *Id.* at 5:61–65.

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 as is disclosed for example by Remington's Pharmaceutical Sciences."[7] Ex. 1004, 6:26–30.

2. Remington (Ex. 1005)

Remington discusses generally the production of oral solid dosage forms, such as tablets and capsules, and the many considerations that influence the choice of a particular dosage form. Ex. 1005, 1603–43. Among the many dosage forms mentioned, Remington discusses various

[7] This is the same publication submitted as Exhibit 1005.

coated tablets, including enteric-coated tablets—"compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine." *Id*. at 1604.

Remington teaches that "[e]nteric coatings can be used for tablets containing drug substances which are inactivated or destroyed in the stomach, for those which irritate the mucosa, or as a means of delayed release of the medication." *Id*. Remington also teaches that tablets may be coated in order to "[r]educ[e] the risk of interaction between incompatible components . . . by using coated forms of one or more of the offending ingredients (particularly active compounds)." *Id.* at 1633. The reference further states that enteric coatings "can be used to give a simple repeat-action effect where unprotected drug coated *over* the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract." *Id*. at 1637.

3. Lindberg (Ex. 1007)

Lindberg discloses omeprazole and its optically pure crystalline enantiomeric salts, including a magnesium salt of *S*-omeprazole, esomeprazole,[8] in the form of a "dosage unit." Ex. 1007, 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." Ex. 1007, 6:24–25. Lindberg teaches that "[o]meprazole and its alkaline salts are effective

[8] *See, e.g.*, Exhibit 1003 ¶ 32 (citing Ex. 1023, 33) ("esomeprazole . . . is the enantiopure (S)-isomer of omeprazole).

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.

4. Analysis

Petitioner contends that Goldman discloses the combined use of acid inhibitors with NSAIDs, such as naproxen, to prevent the incidence of gastric ulcers and bleeding resulting from the use of the NSAIDs. Pet. 11 (citing Ex. 1003 ¶ 64). Petitioner also argues that an ordinary artisan would have known that "acid inhibitors are a well-known class of drugs that provide gastric acid inhibiting efficacy." *Id*. Thus, according to Petitioner, an ordinary artisan would have had a reason, with a reasonable expectation of success, for "substituting different acid inhibitor compounds into a given combination therapy formulation," including substituting with "more effective compounds, such as PPIs, over previously known, less therapeutically effective compounds, such as prostaglandins and H2 blockers." *Id*. at 11–12 (citing Ex. 1003 ¶ 65). In addition, according to Petitioner, it would have been obvious to substitute Lindberg's PPI,

esomeprazole, for Goldman's PPI, omeprazole, because it was known that the "enantiomeric magnesium salt of omeprazole" would have provided "improved pharmacokinetic and metabolic properties." *Id*. at 12 (citing Ex. 1007, 1:50–63; Ex. 1003 ¶ 65).

Petitioner also contends that Goldman would have provided an ordinary artisan with a reason "to look to conventional techniques for preparing medicament tablets as set forth in Remington," which Goldman incorporates by reference. *Id*. at 11, 15, 23. Petitioner points to Remington's teaching that an enteric coating can be used to give an effect "where unprotected drug . . . coated over the enteric coat is released in the stomach, while the remainder . . . , being protected by the coating, is released further down the gastrointestinal tract." *Id*. at 16 (citing Ex. 1005, 1637; Ex. 1003 ¶ 86), 25. Petitioner also contends that Remington teaches using enteric coatings to delay the release of drugs, such as those that "may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin . . .)," and that many enteric coatings "remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5." *Id*. at 15 (citing Ex. 1005, 1637; Ex. 1003 ¶ 84), 22–23.

Patent Owner responds that Goldman "does not disclose formulations with an immediate release acid inhibitor and a delayed release NSAID that would provide coordinated release," or that "coordinated release of an acid inhibitor with an NSAID is in any way desirable." Prelim. Resp. 15. Patent

Owner further argues that Remington and Lindberg, individually or collectively, "do[] not cure this deficiency" (*id.)*.

Patent Owner contends that neither Lindberg nor Remington teaches or suggests non-enteric-coated esomeprazole, as required by the claims. *Id.* at 16. In particular, Patent Owner contends that "Lindberg teaches enteric coated esomeprazole to protect it from the acidic environment of the stomach" (*id.*), in that it states that granules and tablets [and capsules] of 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*. (citing Ex. 1007, 5:36–39, 48–50, 56–57)). Similarly, Patent Owner contends that an ordinary artisan would have coated a PPI like esomeprazole with an enteric coating, rather than use non-enteric coated esomeprazole, because "PPIs were well known in the art to be acid labile" (*id.* at 17, 21 (citing Ex. 2008, 3; Ex. 2009, 2; 2010, 5)), and Remington teaches "that enteric coated tablet formulations are used with acid labile drug substances" (*id.* at 16 (citing Ex. 1005, 1604)).

We agree that Petitioner has not established that the teachings of Goldman, Remington, and Lindberg would have given an ordinary artisan a reason to formulate a tablet or capsule with the structural and functional features required by the challenged claims. Although Goldman discloses a combination dosage form comprising a PPI and an NSAID (discussed above), Petitioner does not point to anything in Goldman that describes or suggests adequately why one would have prepared, for any reason, a

composition as claimed, where at least some PPI (i.e., esomeprazole) is released regardless of pH and the release of at least some NSAID (i.e., naproxen) is inhibited unless the pH is 3.5 or higher (e.g., via a coating).

Moreover, although Goldman incorporates Remington's discussion of oral solid dosage forms by reference (Ex. 1004, 6:26–33), Petitioner does not identify anything in Goldman that points to any particular dosage form among the many disclosed by Remington. Goldman's citation to Remington generally in relation to "[v]arious conventional techniques for preparing medicament tablets or caplets" does not persuade us that an ordinary artisan would have made the connection that Petitioner contends. *Id*.; Pet 11, 14–16, 21–27. Nor does Petitioner explain adequately how Lindberg remedies the deficiencies discussed above in relation to Goldman and Remington.

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 independent claims 1 and 7, or their dependent claims, on the basis of obviousness over Goldman, Remington, and Lindberg.

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

1. Gimet (Ex. 1006)

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.

1006, 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.

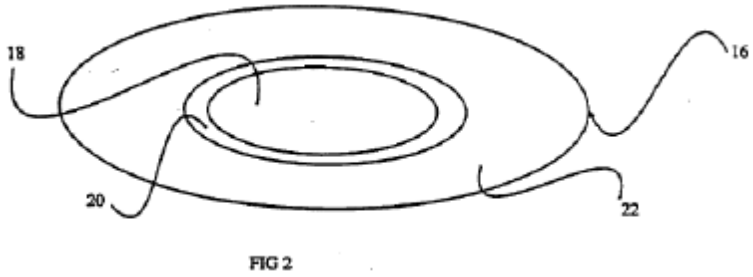

Figure 2 of Gimet depicts tablet 16. Tablet 16 includes an NSAID—diclofenac or piroxicam—in inner core 18. Enteric coating 20 surrounds core 18, and mantle 22—consisting of a prostaglandin, e.g., misoprostol—surrounds the coated inner core. Ex. 1006, 6:24–44.

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 an ordinary artisan would have known that both Gimet and Goldman disclose a combination therapy oral unit dosage form comprising an acid inhibitor (e.g., misoprostol, a prostaglandin, in Gimet) in combination with an NSAID (e.g., naproxen in Goldman). Pet. 34 (citing Ex. 1003 ¶¶ 196, 197). In relation to naproxen, Petitioner also argues that an ordinary artisan would have had a reason, as well as a reasonable

expectation of success, to substitute different NSAID compounds—i.e., to replace diclofenac or piroxicam in Gimet's composition, as shown in Figure 2, with naproxen disclosed in Goldman—"because doing so would be a simple substitution of one known element for another to obtain predictable results." *Id*. at 35 (citing Ex. 1003 ¶ 198).

The only evidence that Petitioner cites for its assertion regarding "predictable results" in relation to NSAIDs is Dr. Shargel's Declaration at paragraph 198, which repeats the statements presented in the Petition on this point, without citing any evidence itself. *Id*. Conclusory assertions by Petitioner, merely repeated in conclusory and unsupported statements by an expert witness in support, are not persuasive here. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.").

In relation to esomeprazole, Petitioner also argues an ordinary artisan would have had a reason, with a reasonable expectation of success, to substitute different acid inhibitors—i.e., to replace misoprostol in Gimet's composition with the esomeprazole disclosed in Lindberg—"where the acid inhibitor compound contributes its individual therapeutic attributes (e.g., acid inhibition and gastric pH raising) to the combination." Pet. 35–36 (citing Ex. 1003 ¶ 199). Petitioner further contends that an ordinary artisan would have had a reason, with a reasonable expectation of success, "in employing more recently obtained and therapeutically more effective compounds, such as PPIs, over previously known, less therapeutically

effective compounds, such as prostaglandins and H2 blockers." *Id*. at 36 (citing Ex. 1003 ¶ 200).[9]

Petitioner also argues that it would have been obvious to select "Lindberg's disclosed PPI esomeprazole and substitute it for Gimet's disclosed acid inhibitor (prostaglandin) because Goldman specifically teaches that '[p]roton pump inhibitors have been recently introduced as effective gastric acid inhibitors.'" *Id*. at 36 (citing Ex. 1004, 1:25–27; Ex. 1003 ¶ 200). Petitioner also points to teachings in Lindberg indicating that its "novel salts of single enantiomers of omeprazole" provide "improved pharmacokinetic and metabolic properties" and "high stability against racemization." *Id*. at 36–37 (quoting Ex. 1007, 1:50–63, 3:48–55) (citing Ex. 1003 ¶ 200), 38 (citing Ex. 1007, 1:50–63; Ex. 1003 ¶ 207).

In response, Patent Owner points to a number of references indicating that an ordinary artisan would have understood that PPIs were acid labile and should be protected from degradation in acidic environments, such as the stomach. Prelim. Resp. 20–24 (citing Ex. 2003, 15, 17; Ex. 2008, 3; Ex. 2009, 2; Ex. 2010, 5; Ex. 1041, 114, 115, 117). For example, a review article by Stedman et al., published in 2000, comparing the "pharmacokinetics, acid suppression and efficacy of proton pump inhibitors," indicates that PPIs "are all acid-labile, so when administered

[9] In support of these contentions, Petitioner once again cites paragraphs in Dr. Shargel's Declaration that simply repeat statements presented in the Petition on these points, without citing supporting evidence themselves. Pet. 35–36 (citing Ex. 1003 ¶¶ 199, 200).

orally they must be formulated in an enteric coating to protect them from rapid degradation in the stomach. They are rapidly absorbed in the duodenum." Ex. 2008, 1 (Title), 3. Similarly, in an article published in 1992, Bell et al. state in relation to the related parent compound of esomeprazole: "As omeprazole is acid-labile, it is formulated as enteric-coated granules dispensed in a gelatine capsule." Ex. 2009, 2.

In addition, in an article published in 1985, Pilbrant et al. teach that "[o]meprazole degrades very rapidly in water solutions at low pH-values." Ex. 1041, 113. In this context, Pilbrant et al. teach 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.

As an initial matter, we are not persuaded that Petitioner establishes adequately that esomeprazole administered in a non-enteric-coated form (thereby allowing it to be released regardless of pH) would have obtained "improved pharmacokinetic, metabolic, and therapeutic properties" as compared to misoprostol in any formulation. Pet. 37–38 (citing Ex. 1007, 1:50–63; Ex. 1003 ¶ 207). For example, we are not persuaded that Lindberg indicates such an improvement. Rather, Lindberg suggests that esomeprazole may have improved properties over omeprazole (a related PPI). Ex. 1007, 1:17–63.

Moreover, even if we assume that one would have understood that prostaglandins and H2 blockers were "less therapeutically effective compounds" than PPIs (Pet. 36), Petitioner has not explained adequately why one would have had reason to make the composition taught in Gimet, e.g., in Figure 2, with a PPI rather than a prostaglandin in "mantle 22" located on the outside of "enteric coating 20" surrounding "inner core 18" of an NSAID. Ex. 1006, 6:15–44, Fig. 2. Petitioner does not address teachings in the art indicating that PPIs were acid liable, nor explain adequately why one would have used any PPI (much less esomeprazole) in place of a prostaglandin in an uncoated form (as taught in Gimet), when other relevant references taught the use of PPIs with an enteric coating to avoid degradation of the drug. *See*, *e.g.*, Ex. 2008, 3; Ex. 2009, 2; Ex. 1041, 114 (discussed above); *see also* Prelim. Resp. 21–24 (discussing other references along similar lines).

Petitioner's contention that Lindberg discloses "uncoated dosage units of esomeprazole in the form of tablets" does not persuade us otherwise. Pet. 42 (citing Ex. 1007, 5:25–36; Ex. 1003 ¶¶ 232, 235). For example, immediately after the first quoted passage in Lindberg (Ex. 1007, 5:25–36), Lindberg teaches that "[g]ranules and tablets 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." Ex. 1007, 5:36–39. Likewise, in Example 13, Lindberg teaches preparing an enteric-coated tablet and a capsule comprising pellets with a second coating (*id*. at

12:13–13:15). Thus, even Lindberg suggests using an enteric or some type of protective coating when administering esomeprazole. Petitioner does not persuade us that Lindberg adequately suggests a composition where at least a portion of esomeprazole "is released regardless of the pH" (e.g., in the stomach where pH is low), much less such a composition that also includes other elements recited in the challenged claims.

Accordingly, we agree with Patent Owner that Petitioner has not established that the teachings of Gimet, Goldman, and Lindberg would have given an ordinary artisan a reason to formulate a composition with the structural and functional features required by the challenged claims. Prelim. Resp. 17–25.

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 claim 1, or its dependent claims 2–6 and 13–15, on the basis of obviousness over Gimet, Goldman, and Lindberg.

D. Claims 7–12 and 16–18—Asserted Obviousness over Ouali and Lindberg

1. Ouali (Ex. 1008)

Ouali discloses "a composition for administering an NSAID wherein the undesirable gastrointestinal side effects of the drug are minimized but wherein the drug's therapeutic effectiveness is maintained." Ex. 1008, 2:14–18. Specifically, Ouali discloses "a stabilized pharmaceutical composition

for [oral] administration of an NSAID and a prostaglandin, wherein the NSAID is enterically coated." *Id.* at 4:22–24. Suitable NSAIDs include naproxen, and the preferred prostaglandin is misoprostol. *Id.* at 4:36–50, 6:35. "[T]he enteric coating . . . prevents NSAID release in the low pH environment of the stomach but . . . ionizes at a slightly higher pH, typically a pH of 4 or 5, and thus dissolves sufficiently in the small intestines to gradually release the active agent therein." *Id.* at 5:2–7. Ouali also teaches that "prostaglandins are unstable compounds and degrade readily in the presence of NSAIDs, thus requiring a stabilizing agent such as hydroxypropyl methylcellulose . . . which can, in turn, lessen the activity of an NSAID." *Id.* at 1:65–2:3.

Figures 1 and 2, reproduced below, are schematic representations of certain embodiments of Ouali's dosage forms.

FIG. 1

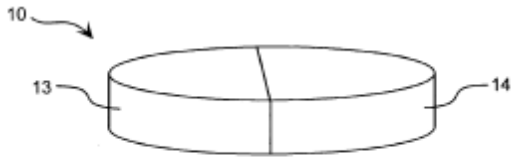

FIG. 2

Figure 1 of Ouali depicts bilayer tablet 10 with layers 11, 12, "wherein the enterically coated NSAID is present in a first region and the prostaglandin is present in a second region, along with a prostaglandin stabilizing agent." Ex. 1008, 4:26–29. Figure 2 of Ouali depicts a tablet wherein the enterically coated NSAID is present in first region 13, and the stabilized prostaglandin is present in adjacent second region 14. *Id.* at 4:34–35. "In an alternative embodiment [not depicted], the enterically coated NSAID and the stabilized prostaglandin are mixed into a single granulation, and the admixture is compressed into a tablet or filled into a capsule." *Id.* at 7:65–8:1.

2. Analysis

Petitioner contends that an ordinary artisan "would have understood that Ouali discloses a combination therapy oral unit dosage form (e.g., a capsule) comprising an acid inhibitor (e.g., prostaglandin) in combination with an NSAID (e.g., naproxen)." Pet. 47 (citing Ex. 1003 ¶ 269). With respect to the acid inhibitor, Petitioner contends that the ordinary artisan would have had a reason, with a reasonable expectation of success, to substitute different acid inhibitor compounds—i.e., to replace the prostaglandin in Ouali's composition with Lindberg's esomepraxole—"where the acid inhibitor compound contributes its individual therapeutic attributes (e.g., acid inhibition and gastric pH raising) to the combination." *Id.* at 47–48 (citing Ex. 1003 ¶ 270). Petitioner further contends that "doing so would be a simple substitution of one known element for another to obtain improved pharmacokinetic, metabolic, and therapeutic properties as

taught by Lindberg with predictable results." *Id.* at 50 (citing Ex. 1007, 1:50–63; Ex. 1003 ¶ 278).

The only evidence Petitioner cites for its assertion regarding "predictable results" in relation to acid inhibitors is Dr. Shargel's Declaration at paragraph 278, which repeats the statements presented in the Petition on this point, without citing any evidence itself. *Id.* Again, conclusory assertions by Petitioner, merely repeated in conclusory and unsupported statements by an expert witness in support, are not persuasive here. *See* 37 C.F.R. § 42.65(a).

Patent Owner reiterates its arguments regarding prior art teachings that PPIs, such as Lindberg's esomeprazole, must be enteric-coated, and contends that "[t]here is nothing in the combination of Ouali and Lindberg that negates that teaching." Prelim. Resp. 26.

Again, as an initial matter, we are not persuaded that Petitioner establishes adequately that esomeprazole administered in a non-enteric-coated form (thereby allowing it to be released regardless of pH) would have obtained "improved pharmacokinetic, metabolic, and therapeutic properties" as compared to prostaglandins in any formulation. Pet. 50 (citing Ex. 1007, 1:50–63; Ex. 1003 ¶ 278). We are not persuaded that Lindberg suggests such an improvement. Rather, Lindberg suggests that esomeprazole may have improved properties over omeprazole (a related PPI). Ex. 1007, 1:17–63.

Moreover, even if we assume that one would have understood that prostaglandins and H2 blockers were "less therapeutically effective compounds" than PPIs (Pet. 48), Petitioner has not explained adequately why one would have had reason to make a capsule, with a PPI rather than a prostaglandin, located on the outside of an enterically-coated NSAID core, as required by independent claim 7. Petitioner does not address the teachings in the art indicating that PPIs were acid liable, nor explain adequately why one would have used any PPI (much less esomeprazole) in place of a prostaglandin in an non-enterically-coated form, when other relevant references taught the use of PPIs with an enteric coating to avoid degradation of the drug. *See*, *e.g.*, Ex. 2008, 3; Ex. 2009, 2; Ex. 1041, 114 (discussed above).

Petitioner's contention that Lindberg discloses "uncoated soft gelatin capsules containing a mixture of esomeprazole or hard gelatin capsules containing uncoated granules of esomeprazole" does not persuade us otherwise. Pet. 53 (citing Ex. 1007, 5:46–52; Ex. 1003 ¶ 290). For example, as discussed above, just above the quoted passage in Lindberg (Ex. 1007, 5:46–52), Lindberg teaches that "[g]ranules and tablets 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 5:36–39. Likewise, in Example 13, Lindberg teaches preparing an enteric-coated tablet and a capsule comprising pellets with a second coating (*id*. at 12:13–13:15). Thus, even Lindberg suggests using an enteric or some

type of protective coating when administering esomeprazole. Petitioner does not persuade us that Lindberg adequately suggests a composition where at least a portion of esomeprazole "is released regardless of the pH" (e.g., in the stomach where pH is low), much less such a composition that also includes other elements recited in the challenged claims.

Accordingly, we agree with Patent Owner that Petitioner has not established that the teachings of Ouali and Lindberg would have given an ordinary artisan a reason to formulate a composition with the structural and functional features required by the challenged claims. Prelim. Resp. 25–26.

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 claim independent 7, or its dependent claims 8–12 and 16–18, on the basis of obviousness over Ouali and Lindberg.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–18 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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