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Paper 36
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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 IPR2015-01773
Patent 8,858,996 B2

Before TONI R. SCHEINER, LORA M. GREEN, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

In this *inter partes* review, Lupin Ltd. and Lupin Pharmaceuticals Inc. (collectively, "Petitioner") challenge the patentability of claims 1 and 3–11 of U.S. Patent No. 8,858,996 B2 (Ex. 1001, "the '996 patent"), assigned to Pozen Inc. ("Patent Owner"). We have jurisdiction under 35 U.S.C. § 6. For the reasons discussed below, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1 and 3–11 ("the challenged claims") of the '996 patent are unpatentable. This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

A. Procedural History

Petitioner filed a Corrected Petition requesting an *inter partes* review of claims 1–19 of the '996 patent. Paper 4 ("Pet."). Patent Owner filed a Preliminary Response. Paper 14 ("Prelim. Resp."). On March 1, 2016, we instituted an *inter partes* review of claims 1 and 3–11 of the '996 patent on one asserted ground of unpatentability (i.e., Ground 4).[1] Paper 15 ("Dec."). After institution, Patent Owner filed a Patent Owner Response to the Petition (Paper 22, "PO Resp."), and Petitioner filed a Reply (Paper 24, "Reply").

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[1] Following our decision to institute on some, but not all, grounds presented in the Petition, Petitioner filed a Request for Rehearing. Paper 17. We denied the Request. Paper 32. We do not reconsider the arguments set forth in the Request for Rehearing because they are directed to the non-instituted grounds and/or non-instituted claims. Moreover, Petitioner was required to make its obviousness case in the Petition—not the Request for Rehearing. *See Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367 (Fed. Cir. 2015) (stating that the patent "challenger [is] obliged to make an adequate case in its Petition and the Reply [is] limited to a true rebuttal role." (citing 37 C.F.R. §§ 42.104(b)(5), 42.23(b))).

An oral hearing was held on November 29, 2016. A transcript of the hearing has been entered into the record. Paper 35 ("Tr.").

B. Related Matters

The parties identify the following district court proceedings in which the '996 patent has been asserted: *Horizon Pharma, Inc. v. Actavis Laboratories FL, Ltd.*, No. 3:15-cv-03322-MLC-DEA (D.N.J.); *Horizon Pharma, Inc. v. Dr. Reddy's Laboratories, Inc.*, No. 3:15-cv-03324-MLC-DEA (D.N.J.); *Horizon Pharma, Inc. v. Lupin Ltd.*, No. 3:15-cv-03326-MLC-DEA (D.N.J.); and *Horizon Pharma, Inc. v. Mylan Pharmaceuticals, Inc.*, No. 3:15-cv-03327-MLC-DEA (D.N.J.). Pet. 3–4; Paper 8, 8. The parties also identify a number of judicial and administrative matters involving patents related to the '996 patent or directed to similar subject matter. Pet. 3–4; Paper 8, 8–9; PO Resp. 2.

C. The '996 Patent

Non-steroidal anti-inflammatory drugs ("NSAIDs") are "widely accepted as effective agents for controlling pain." Ex. 1001 (col. 1, ll. 35–36). But their administration "can lead to the development of gastroduodenal lesions, e.g., ulcers and erosions, in susceptible individuals." *Id.* (col. 1, ll. 37–38). A "major factor contributing to the development of these lesions is the presence of acid in the stomach and upper small intestine of" those individuals. *Id.* (col. 1, ll. 39–41).

The '996 patent discloses pharmaceutical compositions "that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID)," such that there is "a reduced likelihood of causing unwanted side effects, especially gastrointestinal side effects, when administered as a treatment for pain." Ex. 1001 (col. 1, ll. 25–31).

Specifically, the ’996 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.* (col. 3, ll. 31–37), and an NSAID “in an amount effective to reduce or eliminate pain or inflammation,” *id.* (col. 4, ll. 3–5). “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.* (col. 4, ll. 46–49).

The ’996 patent teaches that the unit dosage form “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.” *Id.* (col. 4, ll. 49–53). Put differently, “the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen.” *Id.* (col. 4, ll. 53–55). The ’996 patent continues:

> 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, preferably at least 4 and more preferably, at least 5.

Id. (col. 4, ll. 56–63).

“The term ‘acid inhibitor’ refers to agents that inhibit gastric acid secretion and increase gastric pH.” *Id.* (col. 3, ll. 38–40). According to the ’996 patent, preferred acid inhibiters are H_2-blockers, such as famotidine, but “[o]ther preferred agents that may be effectively used as acid inhibitors are the proton pump inhibitors such as . . . esomeprazole,” for example, in a typical amount of 5–100 mg. *Id.* (col. 3, ll. 40–51, col. 8, ll. 17–18).

The ’996 patent also discloses that the NSAID may be a number of different options, such as aspirin, acetaminophen, etc., where the “most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount of between 200 mg and 600 mg.” *Id*. (col. 4, ll. 5–18).

D. Illustrative Claim

Claim 1, the only independent claim of the challenged claims, is illustrative of the claimed subject matter:

> 1. A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:
>
> naproxen in an amount of 200–600 mg per unit dosage form; and
>
> esomeprazole in an amount of from 5 to 100 mg per unit dosage form,
>
> wherein upon introduction of said unit dosage form into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium, and *release of at least a portion of said naproxen is inhibited unless the pH of said medium is 3.5 or higher*.

Id. (col. 21, ll. 24–35) (emphasis added).

E. Asserted Ground of Unpatentability

We instituted an *inter partes* review of claims 1 and 3–11 of the ’996 patent for unpatentability, under 35 U.S.C. § 103(a), for obviousness based

on a combination of the '225 patent,[2] Chandramouli,[3] and WO '185.[4] Dec. 39.

II. DISCUSSION

A. Principles of Law

To prevail in challenging claims 1 and 3–11 of the '996 patent, Petitioner must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be

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[2] U.S. Patent No. 5,698,225 (issued Dec. 16, 1997) ("the '225 patent") (Ex. 1013).

[3] Chandramouli et al., *Prevention and management of NSAID-Induced Gastropathy*, J. PHARM. PAIN AND SYMPTOM CONTROL, 8(4):27–40 (2000) ("Chandramouli") (Ex. 1009).

[4] PCT Int'l Patent Appl. WO 00/26185 (published May 11, 2000) ("WO '185") (Ex. 1015).

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements." *Magnum Oil*, 829 F.3d at 1380.

B. Analysis

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. § 103(a) for obviousness over the combination of the '225 patent, Chandramouli, and WO '185. Pet. 48–58. Relying in part on the testimony of its declarant, Umesh V. Banakar, Ph.D., Petitioner asserts that the combination of the '225 patent, Chandramouli, and WO '185 renders the challenged claims obvious. *Id.* at 29–53 (citing Ex. 1002). Patent Owner challenges Petitioner's contentions. PO Resp. 9–20. In reply, Petitioner maintains its position. Reply 4–21.

We have reviewed the Petition, Patent Owner's Response, and Petitioner's Reply, as well as the relevant evidence discussed in those papers. For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1 and 3–11 are unpatentable under 35 U.S.C. § 103(a) for obviousness over the '225 patent, Chandramouli, and WO '185.

1. Level of Ordinary Skill

The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Factors that may be considered in determining the level of ordinary skill in the art include, but are not limited to, the types of problems encountered in the art, the sophistication of the technology, and the educational level of active workers in the field. *Id.*

Dr. Banakar opines that a person of ordinary skill in the art "would include a pharmaceutical scientist having a Ph.D. degree in the field of pharmaceutical sciences or equivalent training or degree with at least two years of experience with pharmaceutical formulations." Ex. 1002 ¶ 26. Dr. Banakar explains that this definition is based on, *inter alia*, his evaluation of the '996 patent and his "over 35 years of experience working in the field of formulating pharmaceutical compositions." *Id.* at ¶ 26. Patent Owner does not directly challenge Dr. Banakar's testimony as to the level of ordinary skill in the art, but claims that Petitioner's definition should "extend to a person having a graduate degree in chemistry or chemical engineering." PO Resp. 5–6.

We determine that the level of ordinary skill proposed by Petitioner is consistent with the challenged patent and the asserted prior art, which are directed to pharmaceutical compositions and methods for treating patients with those formulations. Nevertheless, we also agree with Patent Owner that the ordinarily skilled artisan also may have a graduate degree in chemistry or chemical engineering, because as we discuss below, the interactions between chemical compounds inform our obviousness analysis. *See* PO Resp. 5–6.

We therefore adopt Dr. Banakar's definition of a person of ordinary skill in the art, as modified by Patent Owner's addition, for our obvious analysis herein. Our analysis would be the same, however, if we did not include a person having a graduate degree in chemistry or chemical engineering within that definition.

2. Prior Art and Knowledge of One of Ordinary Skill in the Art

a. Background knowledge

NSAIDs "cause gastrointestinal damage via topical injury of the mucosal barrier, systemic inhibition of prostaglandin synthesis or a combination of both." Ex. 1009, 27 (Abstract). Because they are weak acids, NSAIDs "freely diffuse across the lipid membrane of the epithelial cell" at gastric pH of 1–2, become "trapped in . . . ionized form," and promote the release of hydrogen ions. *Id.* at 32. "The bioconcentration of ionized NSAIDs and release of H^+ causes epithelial cell necrosis and sloughing exposing mucosal structures to gastric acid, pepsin, and NSAID." *Id.*

Studies showed that patients taking concomitant doses of an agent that suppresses gastric acid secretion experienced improved NSAID tolerability. *Id.* at 36. Proton pump inhibitors ("PPIs")—a particular class of acid inhibitors—were known in the art to "suppress acid secretion to a greater degree" than other known acid inhibitors. *Id.* The PPI omeprazole was known in the art as useful for the treatment of gastrointestinal disorders associated with NSAID therapy. Ex. 1008 (col. 1, ll. 37–40). Omeprazole exists as "a racemic mixture of its two single enantiomers, the (+)-enantiomer of omeprazole and the (-)-enantiomer of omeprazole," i.e.,

esomeprazole. *Id.* (col. 1, ll. 61–64); *see also* Ex. 1007 (col. 6, ll. 53–58). No clinical difference exists between the two enantiomers. Ex. 1008 (col. 2, ll. 4–10).

PPIs inhibit the secretion of gastric acid by "blocking the final step of acid production." Ex. 1007 (col. 2, ll. 57–60). Specifically, PPIs bind to the "proton pumps" (i.e., the H^+/K^+-ATPase enzyme) of parietal cells to "cause prolonged inhibition of gastric acid secretion." Ex. 2009, 2. "The normal human stomach contains approximately 1 billion parietal cells that secrete hydrogen ions into the gastric lumen in response to various physiological stimuli." Ex. 1022, S9. But PPIs do not affect resting parietal cells: "Acid catalysed activation of the drug is necessary, so only activated parietal cells will be inhibited, whereas resting parietal cells . . . will escape initial inhibition." Ex. 2009, 3. The prior art taught that PPIs were to be "given in association with food, so as to stimulate the parietal cell to make acid." Ex. 2011, 6; *see also* Ex. 1022, S14 (stating that because PPIs "are most effective when the parietal cell is stimulated to secrete acid in response to a meal, these drugs should *only* be taken before or with a meal").

As a consequence of the inability of PPIs to inhibit resting parietal cells, "[a]cid inhibition is not necessarily maximal after the first dose" of the PPI. Ex. 2009, 3; *see also* Ex. 1022, S14 ("Because all PPIs require accumulation and acid activation, their onset of inhibition is delayed . . . ."). Indeed, "[s]teady state [is] not achieved for several days" in clinical use. Ex. 1022, S14; *see also id.* at S15 (stating that once-daily dosing of PPI "results in 66% steady-state inhibition of maximal acid output after 5 days").

PPIs were well known in the art as "highly acid labile." *See, e.g.*, Ex. 1007 (col. 4, ll. 47–50); *see also id.* (col. 8, ll. 9–16) ("For example, the half-life of omeprazole in water solutions at pH-values less than three is shorter than ten minutes."). Thus, the art generally taught that PPIs had to be protected from gastric acid by a protective coating (e.g., an enteric coating). *See, e.g.*, Ex. 2017, 42 ("Proton pump inhibitors are inactivated by gastric acid and thus must be given as enteric-coated granules in gelatin capsules or enteric-coated tablets."); Ex. 2009, 3 ("The drugs are all acid-labile, so when administered orally they must be formulated in an enteric coating to protect them from rapid degradation in the stomach.").

Enteric coatings were well known in the art as useful for preparing "delayed-release" formulations. Specifically, enteric coatings "provide acid resistance" to a substrate by inhibiting release of the substrate in the stomach, but then allow for the release of the substrate "in near neutral or alkaline media" found further down the gastrointestinal tract. Ex. 1007 (col. 8, ll. 18–40; col. 12, ll. 33–40); *see also* Ex. 1013 (col. 6, ll. 33–36) (stating that the enteric coating aids in directing the dissolution of the core substrate "in the lower G.I. tract as opposed to the stomach"). Conversely, non-enteric coated substrates comprise "immediate-release" formulations: the unprotected substrates are released immediately in the stomach after ingestion. Ex. 1007 (col. 12, ll. 33–37). The prior art also taught that enteric coatings could be "formulated from any suitable enteric coating material, many of which are known to those skilled in the art and many of which are employed for coating commercially available NSAIDs." Ex. 1013 (col. 6, ll. 29–33).

b. The ’225 patent

The ’225 patent 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. 1013 (col. 1, ll. 20–24). “An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use.” *Id.* (col. 1, ll. 24–27). The ’225 patent continues: “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.* (col. 1, ll. 29–33). According to the ’225 patent, “[c]ertain prostaglandins have been shown to prevent NSAID induced ulcers.” *Id.* (col. 1, ll. 39–40). Misoprostol, for example, “is a pharmaceutically acceptable prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers.” *Id.* (col. 1, ll. 43–49).

The ’225 patent discloses a pharmaceutical composition comprising a tablet having an inner core and an outer mantle surrounding the inner core, designed to “counter[] (by inhibiting, reducing or preventing) the ulcerogenic side effects attendant to NSAID administration.” *Id.* (col. 1, ll. 61–63). The inner core consists of an NSAID (i.e., diclofenac or piroxicam or their salts) and the outer mantel consists of a prostaglandin (e.g., misoprostol). *Id.* (col. 1, ll. 11–17, 39–47).

Figure 2 of the ’225 patent, reproduced below, depicts tablet **16** in cross-section.

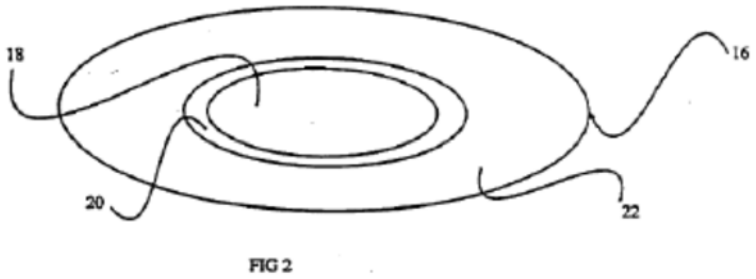


Figure 2 depicts tablet **16** in cross-section.

Tablet **16** contains diclofenac or piroxicam (or their salts) in the inner core **18**. *Id*. (col. 6, ll. 24–28). Enteric coating **20** surrounds core **18**, and mantle **22**—consisting of a prostaglandin, e.g., misoprostol—surrounds the coated inner core. *Id*. (col. 6, ll. 41–44). The ’225 patent teaches that the enteric coating “can be formulated from any suitable enteric coating material,” “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,” and also “aid[s] in the prevention of the degradation of the prostaglandin by the presence of the NSAID.” *Id.* (col. 6, ll. 29–38).

c. Chandramouli

Chandramouli is entitled “Prevention and Management of NSAID-Induced Gastropathy.” Ex. 1009, 27. Chandramouli states that “[g]astrointestinal complications from NSAID treatment are a major cause of morbidity and mortality,” and that “[p]roton pump inhibitors and misoprostol are the only agents proven beneficial in preventing GI adverse events from NSAIDs.” *Id.* at 27–28.

Chandramouli teaches that misoprostol works by replacing gastric prostaglandins depleted by NSAID use. *Id.* at 37. "It prevents both gastric and duodenal ulceration." *Id.* But, Chandramouli notes, "[s]ignificant dose-related diarrhea and abdominal pain limits its tolerability." *Id.* Moreover, misoprostol "is an abortifacient; therefore, its use in women of childbearing potential is contraindicated." *Id.*

Chandramouli continues that, because "NSAID-associated GI injury is dependent on the presence of acid, the prophylactic use of an H_2 blocker seems reasonable." *Id*. at 36. Chandramouli also states that PPIs "suppress acid secretion to a greater degree than H_2-receptor antagonists," and that "[n]evertheless, omeprazole is more effective against duodenal than gastric ulceration." *Id*. Chandramouli further states that a study called the "OMNIUM study (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management) concluded however that omeprazole may be as effective [as] or more effective than misoprostol for the prevention of NSAID-induced gastropathy." *Id.*

d. WO '185

WO '185 teaches that "[p]roton pump inhibitors such as omeprazole represent an advantageous alternative to the use of H_2 antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage." Ex. 1015, 8:12–15. But, WO '185 explains, "in their current form (capsules containing an enteric-coated granule formulation of proton pump inhibitor), proton pump inhibitors can be difficult or impossible to administer to patients who are unable . . . to swallow tablets or capsules." *Id.* at 8:15–22.

To solve this problem, WO ’185 describes solutions and suspensions of PPIs, such as omeprazole, that “can be enterally delivered to a patient thereby providing the benefits of the proton pump inhibitor without the drawbacks of the current capsule dose form.” *Id*. at 8:22–26. Specifically, WO ’185 teaches “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. WO ’185 states that the disclosed “omeprazole solution/suspension has significant pharmacokinetic advantages over standard time-release omeprazole capsules” including “a decreased drug absorbance time (~10 to 12 minutes) following administration for the omeprazole solutions versus (~2–3 hours) following administration for the enteric coated pellets.” *Id.* at 19:23–20:1.

WO ’185 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 19:16–23. Specifically, WO ’185 discloses that the enteric-coated pellets of omeprazole “completely breakdown” within 30 minutes. *Id.* at 35:8–10. WO ’185 explains that the sodium bicarbonate solution “protects the omeprazole from acid degradation prior to absorption” and “acts as an antacid while the omeprazole is being absorbed.” *Id.* at 20:1–4.

In addition to a solution or suspension, WO ’185 discloses dry formulations, such as a powder, tablet, capsule, or granules, in which 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. Those solid formulations “then create the present invention when acted upon by a suitable vehicle, for

example water." *Id*. at 27:2–4. As stated in WO '185, "[t]he 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.

3. Differences Between the Prior Art and the Claimed Invention

a. The prior art discloses or suggests each and every element of the challenged claims

Petitioner asserts that the prior art discloses or suggests each element of the challenged claims and presents a chart mapping the language of the claims to the disclosures of the '225 patent, Chandramouli, and WO '185. Pet. 51–56. We have reviewed Petitioner's claim chart and find that a preponderance of the evidence supports Petitioner's contention that the cited references collectively disclose or suggest each and every limitation of the challenged claims. We therefore adopt the claim chart as our own.

Patent Owner challenges Petitioner's argument only as to the claimed element "esomeprazole." Specifically, Patent Owner points out that esomeprazole is not specifically disclosed in the '225 patent, in Chandramouli, or in WO '185. PO Resp. 10.

Although Patent Owner is correct that none of the '225 patent, Chandramouli, and WO '185 explicitly recites esomeprazole, the case law is clear that "obviousness does not require the prior art to reach expressly each limitation exactly." *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 727 (Fed. Cir. 2002). Both Chandramouli and WO '185 disclose the PPI omeprazole and teach its use as an acid inhibitor. WO '185 teaches that

omeprazole is a PPI that inhibits gastric acid secretion, and that omeprazole "is a logical choice for stress ulcer prophylaxis." Ex. 1015, 4:8–15. And Chandramouli states that "omeprazole may be as effective [as] or more effective than misoprostol for the prevention of NSAID-induced gastropathy." Ex. 1009, 36. Dr. Banakar states that the skilled artisan would have understood at the time of the invention that omeprazole existed as a racemic mixture of two enantiomers, with the S-enantiomer (or (-)-enantiomer) known as esomeprazole. Ex. 1002 ¶ 34 (citing Ex. 1008, col. 1, ll. 50-55). Dr. Banakar further states that the skilled artisan would have understood that esomeprazole had a similar therapeutic effect as omeprazole, less inter-individual variability, and was considered safe and effective for human administration. Ex. 1002 ¶ 34 (citing Ex. 1008 (col. 2, ll. 4–12 & 29–33), Ex. 1026 (621), Ex. 1029 (23)).

We find that the evidence of record supports Dr. Banakar's statements, and we credit his testimony that a skilled artisan would have understood the disclosure of omeprazole in Chandramouli and WO '185 to encompass the (-)-enantiomer, i.e., esomeprazole. *Id.*; *see also* Ex. 1007 (col. 6, ll. 53–58) ("In certain preferred embodiments, the proton pump inhibitor is omeprazole, either in racemic mixture or only the (-)-enantiomer of omeprazole (i.e., esomeprazole) . . . ."). Thus, we find that the disclosure of omeprazole in Chandramouli and WO '185, combined with the skilled artisan's knowledge based on the prior art that esomeprazole is an active enantiomer form of the PPI, suffices to show that the prior art suggests the claim limitation "esomeprazole."

b. Motivation to combine the prior art references and reasonable expectation of success

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

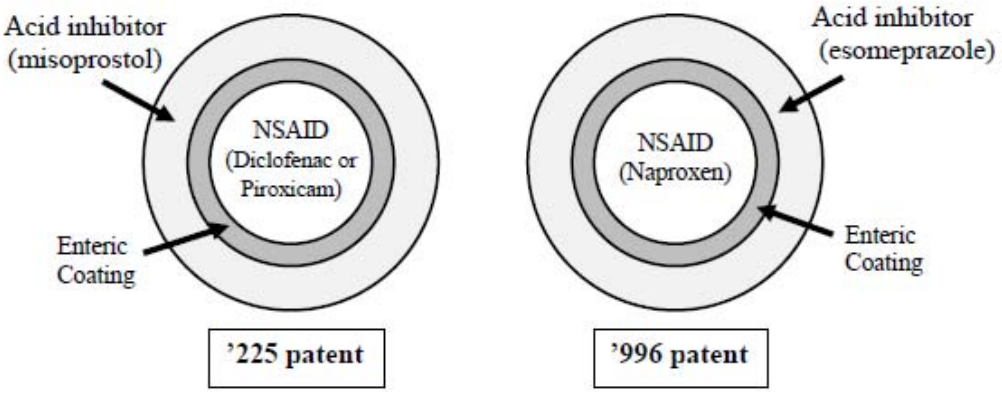
As noted above, claim 1 recites a pharmaceutical composition in the unit dosage form of a tablet containing naproxen (the NSAID) and esomeprazole (the PPI). Ex. 1001 (col. 21, ll. 25–30). As claimed, "at least a portion of [the] esomeprazole is released regardless of the pH of the medium," while "release of at least a portion of [the] naproxen is inhibited unless the pH of [the] medium is 3.5 or higher." *Id.* (col. 21, ll. 31–35).

According to Petitioner, claim 1 requires a combination tablet that allows for the immediate release of non-enteric coated esomeprazole in the stomach and the delayed release of at least some portion of naproxen in the gastrointestinal tract. Specifically, Petitioner states that "[t]he '996 patent claims a combination of an NSAID, naproxen, with an acid inhibitor, the PPI esomeprazole, in a single tablet," and "[t]he tablet releases the drugs in two stages: the esomeprazole is immediately-released when the tablet is taken and at least some portion of naproxen is delayed from being released until the pH of the surrounding medium is 3.5 or greater." Reply 4 (citing claim

1); *see also* Pet. 1 ("The challenged claims are directed to a naproxen/esomeprazole combination tablet wherein at least a portion of the *esomeprazole is not enteric coated* and at least a portion of the *naproxen is enteric coated* so that esomeprazole is *released immediately* and naproxen *is not released* until a particular pH of the surrounding medium is reached." (emphases added)).

Petitioner presents its obviousness case as whether the ordinarily skilled artisan would have found obvious a pharmaceutical composition containing an immediate-release esomeprazole and a delayed-release naproxen, based on a combination of the '225 patent, Chandramouli, and WO '185. *See* Reply 2 (stating that the prior art references "clearly point to the approach claimed in the '996 patent – a tablet combining a rapid release esomeprazole with a delayed-release naproxen"); *see also* Pet. 25 (stating that an ordinarily skilled artisan would have been motivated to create a combination tablet "with esomeprazole released first in the stomach followed by naproxen in the small intestine").

To aid its argument, Petitioner provides a schematic representation of the structure of the acid inhibitor-NSAID combination tablet disclosed in the '225 patent next to the acid inhibitor-NSAID combination tablet disclosed in the '996 patent. Reply 5. We find the schematic useful for understanding Petitioner's obviousness case and reproduce it here:



Id.

As shown on the left side of Petitioner's schematic, the dosage unit form disclosed in the '225 patent is a tablet containing an NSAID core (i.e., diclofenac or piroxicam) surrounded by an enteric coating. *Id.* The '225 patent teaches that the enteric coating protects the NSAID from the acidic environment of the stomach and delivers the NSAID into the lower G.I. tract for release. Ex. 1013 (col. 6, ll. 33–36). The outer layer, or mantle, is made up of a prostaglandin acid inhibitor (i.e., misoprostol). *Id.* (col. 2, ll. 1–2). The '225 patent describes the prostaglandin as preferably "orally available." *Id.* (col. 2, ll. 2–3). The right-hand schematic represents a tablet dosage form encompassed by claim 1 of the '996 patent. Petitioner asserts that an ordinarily skilled artisan would have been motivated to prepare the claimed pharmaceutical composition by substituting the PPI esomeprazole for the acid inhibitor misoprostol and the NSAID naproxen for the NSAIDs diclofenac or piroxicam, with a reasonable expectation of success. Pet. 48–50.

c. Reason to substitute esomeprazole for the misoprostol utilized in the '225 patent

We first consider whether a skilled artisan would have been motivated to substitute the PPI esomeprazole for the prostaglandin acid inhibitor (i.e., misoprostol) utilized in the '225 patent. *See* Reply 4 (asserting that "a POSA would have been motivated to replace misoprostol in the '225 patent with esomeprazole"). We find that, based on the evidence and arguments before us, Petitioner has shown by a preponderance of the evidence that an ordinarily skilled artisan would have been so motivated.

The teachings of Chandramouli directly support Petitioner's argument that an ordinarily skilled artisan, seeking to prepare a combination acid inhibitor-NSAID tablet for the prevention of NSAID-induced gastropathy, would have had a reason to utilize the PPI esomeprazole, rather than the acid inhibitor misoprostol, as the protective agent. *See* Pet. 48–49; Reply 8–9. First, Chandramouli expressly teaches that, although misoprostol "prevents both gastric and duodenal ulceration," it also possesses several negative attributes. Ex. 1009, 37. Specifically, Chandramouli teaches that "[s]ignificant dose-related diarrhea and abdominal pain limits [misoprostol's] tolerability." *Id.* Chandramouli also teaches that misoprostol "is an abortifacient; therefore, its use in women of childbearing potential is contraindicated." *Id.*

Second, Chandramouli teaches that "[s]ince NSAID-associated GI injury is dependent on the presence of acid, the prophylactic use of an H_2 blocker seems reasonable." *Id.* at 36. But then Chandramouli expressly points to PPIs for their ability to "suppress acid secretion to a greater degree than H_2-receptor antagonists." *Id.*; *see also id.* at 28 (stating that PPIs have

been "proven beneficial in preventing GI adverse effects"). And Chandramouli refers to the "OMNIUM" (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management) study as showing that "omeprazole may be as effective [as] or more effective than misoprostol for the prevention of NSAID-induced gastropathy." *Id.*

For these reasons, we find that an ordinarily skilled artisan, seeking to avoid the significant disadvantages associated with misoprostol, and to create a combination acid inhibitor-NSAID pharmaceutical composition that could be prescribed to women of childbearing potential, would have been motivated to seek a replacement acid inhibitor for misoprostol and would have turned to the PPIs omeprazole and its (-)-enantiomer, esomeprazole. Indeed, as Petitioner further points out, WO '185 expressly teaches that omeprazole possesses "a very good safety profile," Reply 8 (citing Ex. 1015, 4:8–15), and is a "'logical choice'" for stress ulcer prophylaxis, *id.* at 9 (quoting Ex. 1015, 4:8–15).

For completeness, we again reject Patent Owner's argument against substitution due to the fact that "none of the '225 patent, Chandramouli, or WO '185 even mention esomeprazole, an essential component of the challenged claims." PO Resp. 10. As we explain *supra*, the preponderance of the record evidence supports Petitioner's argument that a skilled artisan would have understood that omeprazole existed as a racemic mixture of two enantiomers, and that a skilled artisan would have understood the disclosures of omeprazole in Chandramouli and WO '185 to encompass both the (+)-enantiomer and the (-)-enantiomer (i.e., esomeprazole). Ex. 1008 (col. 1, ll. 50-55); Ex. 1002 ¶ 34; *see also* Ex. 1007 (col. 6, ll. 53–58). Thus, we find that the lack of explicit recitation of "esomeprazole" in Chandramouli

and WO ’185 does not detract from the ordinarily skilled artisan’s motivation to substitute esomeprazole for misoprostol.

d. Reason to use esomeprazole in immediate-release form

We next consider whether the skilled artisan would have been motivated to formulate esomeprazole in an immediate-release form (i.e., without an enteric coating). Reply 9–10. Patent Owner argues that, “even assuming a motivation to substitute the misoprostol in the ’225 patent with a proton pump inhibitor, based on the prior art, one of skill in the art would *not* use an immediate release PPI, but would instead use an enteric coated PPI.” PO Resp. 11. Patent Owner’s argument is based on the undisputed facts that PPIs are acid labile and that, in the prior art, PPIs were uniformly formulated with an enteric coating to protect them from acid degradation in the stomach. *Id.* at 10–11.

Patent Owner is correct that the prior art of record is replete with the teaching that PPIs had to be formulated with an enteric coating due to their extreme acid lability. *See, e.g.*, Ex. 1007 (col. 8, ll. 11–13) (stating that “the half-life of degradation of omeprazole in water solutions at pH values less than three is shorter than ten minutes”); Ex. 2009, 3 (“[PPIs] are all acid-labile, so when administered orally they must be formulated in an enteric coating to protect them from rapid degradation in the stomach.”); Ex. 2010, 2 (“As omeprazole is acid-labile, it is formulated as enteric-coated granules dispensed in a gelatin capsule.”); Ex. 2011, 5 (“As a class, [PPIs] are . . . acid-unstable, requiring protection against gastric acidity for oral

formulation . . . .").[5] But, given the teachings of WO '185, we are persuaded by Petitioner's argument that the ordinarily skilled artisan would have aspired to create an immediate-release esomeprazole formulation.

Petitioner relies on the testimony of Dr. Banakar to support its argument that "WO '185 would have provided additional motivation and teaching for a POSA to use non-enteric coated esomeprazole . . . ." Pet. 49. Dr. Banakar testifies that "WO '185 would have motivated a POSA to try a combination tablet with uncoated esomeprazole" because WO '185 teaches "that the immediate release formulation has 'significant pharmacokinetic advantages over standard time-release omeprazole capsules,'" Ex. 1002 ¶ 81 (citing Ex. 1015 at 19:24–25), and "that uncoated omeprazole is absorbed more quickly than enteric-coated omeprazole," *id.* (citing Ex. 1015 at 19:26–20:1). We credit Dr. Banakar's rationale because we find it supported by a preponderance of the evidence.

Specifically, one of the stated purposes of the WO '185 reference was to create immediate-release omeprazole formulations. *See* Reply 10; *see also* Ex. 1015, 9:17–18 (describing the disclosed omeprazole formulations as providing an "immediate anti-acid effect"). WO '185 teaches that, although enteric coatings protect the PPI from acid degradation in the stomach, they also delay the PPI's release and absorption into the circulation. *See id.* at

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[5] Additional record evidence—including testimony provided by an expert Petitioner retained in another proceeding—demonstrates that an ordinarily skilled artisan would have thought that PPIs had to be enterically coated to survive the acidic environment of the stomach. *See* Ex. 2018 ¶ 25 (Declaration of Michael Mayersohn, Ph.D.) ("Because PPIs are chemically unstable in the acidic environment of the stomach they must be protected from stomach acid. Drug manufacturers accomplish this by combining the PPI with . . . an outer layer (referred to as the 'enteric coat').").

19:23–28 (characterizing the enteric-coated omeprazole pellets of the prior art as disadvantageous in that they would take approximately 2 to 3 hours for absorption). WO '185 teaches that immediate-release formulations of omeprazole are desired because immediate dissolution in the stomach provides a patient with faster relief than an enteric-coated omeprazole. *See id.* (stating that the disclosed "omeprazole solution/suspension has . . . a decreased drug absorbance time" of approximately 10 to 12 minutes); *see also id.* at 9:16–17 (stating that the present invention provides "immediate anti-acid effect"). Given this disclosure, we find that an ordinarily skilled artisan would have been motivated to attempt an immediate-release esomeprazole formulation.

We further find that, although WO '185 focuses on suspensions/solutions of omeprazole, WO '185 would not have dissuaded a skilled artisan from pursuing solid formulations, such as a tablet. WO '185 specifically discloses 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. WO '185 teaches that those solid formulations may be delivered orally, and when acted upon by "water in the stomach secretions . . . produce the present invention." *Id*. at 27:2–9. Thus, although we agree with Patent Owner that WO '185 mainly teaches solution/suspensions formulations for patients experiencing difficulty swallowing tablets, *see* PO Resp. 9 (citing Ex. 1015 at 8:22–26), WO '185 also stresses the advantages of an immediate-release omeprazole formulation that is rapidly absorbed by the body.

e. Reasonable expectation of success in achieving the claimed invention

Although we find that Petitioner has shown by a preponderance of the evidence that a skilled artisan would have had reason to attempt an immediate-release esomeprazole formulation, Petitioner must also show by a preponderance of the evidence that the skilled artisan would have had a reasonable expectation of success in creating the pharmaceutical composition claimed in the '996 patent. In this, Petitioner fails.

"The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). Here, as Petitioner concedes, the limitations of claim 1 achieve coordinated release: the immediate release of esomeprazole (regardless of pH), and the delayed release of at least a portion of naproxen until pH is 3.5 or higher. *See* Reply 2 ("The references clearly point to the approach claimed in the '996 patent – a tablet claiming a rapid release esomeprazole with a delayed-release naproxen.").

Although we agree with Petitioner that a skilled artisan would have reasonably expected successful immediate release of the PPI esomeprazole based on the teachings of WO '185, we disagree that the skilled artisan would have *also* reasonably expected successful inhibition of at least some naproxen until pH reaches 3.5. *See* Reply 9–10 (stating that "the issue comes down to whether a POSA would have been motivated to use esomeprazole in an immediate release formulation . . . with a reasonable expectation of success); *id.* at 11 (stating that the use of bicarbonate buffer in WO '185 is entirely compatible with the teachings of the '225 patent).

WO ’185 achieves immediate release of omeprazole through the use of a bicarbonate buffer. Ex. 1015, 16:16–23. Specifically, WO ’185 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 19:16–23. WO ’185 explains that the sodium bicarbonate solution “protects the omeprazole from acid degradation prior to absorption” and “acts as an antacid while the omeprazole is being absorbed.” *Id.* at 20:1–4.

Patent Owner argues that a skilled artisan would not have had a reasonable expectation of success because “the artisan would reasonably expect that the sodium bicarbonate[6] would have an adverse effect on the enteric core, such as found in the ’225 patent” because “WO ’185 teaches that enteric coatings are not compatible with sodium bicarbonate solutions.” PO Resp. 12 (citing Ex. 1015 at 19:16–23). “Thus,” Patent Owner continues, “the sodium bicarbonate touted by the Petitioner as solving the problem of acid lability of the PPI . . . would defeat the purpose of the enteric coating and allow for early release of the NSAID.” *Id.* at 13.

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[6] We acknowledge that WO ’185 broadly discloses “bicarbonate salt of a Group IA metal,” Ex. 1015, 16:20–21, of which sodium bicarbonate is the preferred salt, *id.* at 19:12–14. But Petitioner has failed to establish that other bicarbonate salts of Group IA metals are relevant to our analysis. For example, Petitioner provides no argument or evidence suggesting that bicarbonate salts of other Group IA metals would have different properties than sodium bicarbonate. Thus, we consider the properties of sodium bicarbonate representative of the other bicarbonate salts disclosed in WO ’185.

We found in the Institution Decision that Patent Owner's lack-of-reasonable-expectation-of-success argument "has merit because Petitioner does not address the teaching on page 19 of WO '185 regarding the impact of a bicarbonate salt on an enteric coating, a coating that the '225 patent discloses as surrounding the NSAID, a coating that inhibits NSAID release until the pH is 3.5 or higher (i.e., in the lower G.I. tract), as recited in the challenge[d] claims." Dec. 36 (citations omitted). We further advised that "[n]either party, thus far, has addressed adequately whether an ordinary artisan would have had reason to believe that making a tablet as disclosed in the '225 patent, where misoprostol is substituted with the bicarbonate salt buffered PPI disclosed in WO '185 and the NSAID is naproxen, would have resulted in a tablet where release of at least some (even if not all) naproxen would have been 'inhibited unless the pH of said medium is 3.5 or higher,' even assuming bicarbonate in a PPI 'mantle' layer would have dissolved the enteric coating surrounding the NSAID eventually, for the reasons stated on page 19 of WO '185." *Id.* at 37 (citations omitted).

The question before us then, is whether at the time of the invention a skilled artisan would have reasonably expected that a non-enteric coated omeprazole formulation buffered from gastric acid by sodium bicarbonate (as taught in WO '185) would be compatible with an enteric coated, delayed-release NSAID (as taught in the '225 patent) in a medium. As with other factual questions, the burden of proving a reasonable expectation of success belongs to Petitioner, and that burden does not shift to Patent Owner. *Magnum Oil*, 829 F.3d at 1375 (burden-shifting "does not apply in the adjudicatory context of an IPR").

We find that Petitioner has not met its burden to show that a person of ordinary skill would have had a reasonable expectation of success. As explained above, WO '185 achieves immediate release of omeprazole through the use of a sodium bicarbonate buffer, which protects the omeprazole from acid degradation in the stomach. Ex. 1015, 20:1–4. That sodium bicarbonate, however, also dissolves enteric coatings in solution. *See id*. at 19:16–23 (stating that a sodium bicarbonate solution dissolves the enteric coating of omeprazole particles). Indeed, WO '185 teaches that mixing enteric-coated pellets of omeprazole with a sodium bicarbonate solution results in the "complete[] breakdown" of the enteric coating within 30 minutes. *Id.* at 35:8–10.

Petitioner has not adequately rebutted Patent Owner's argument that the skilled artisan would have expected, based on the teachings of WO '185, that the sodium bicarbonate would completely break down the enteric coating protecting the naproxen core of the '225 patent in a medium. In this scenario, Patent Owner reasonably explains, no portion of naproxen would remain to release only after pH reached 3.5. Again, challenged claim 1 recites a tablet where release of "*at least a portion of said naproxen is inhibited unless* the pH of said medium is 3.5 or higher." Ex. 1001 (col. 21, ll. 24–35 (emphasis added)). Thus, although claim 1 allows for release of at least some naproxen immediately (i.e., at any pH), claim 1 also *requires* that at least some naproxen releases only when pH is 3.5 or higher.[7]

[7] The parties have presented their respective cases based on this interpretation. *See, e.g.*, Pet. 1; PO Resp. 3; Reply 2, 4–5.

We find that an ordinarily skilled artisan would have understood that, because of the highly acidic environment found in the stomach, the naproxen had to be enterically coated to achieve delayed release. The prior art and Petitioner's statements support this finding. *See* Ex. 2017, 42; Ex. 2009, 3; Pet. 1 (stating that the challenged claims require "at least a portion of the naproxen is enteric coated so that . . . naproxen is not released until a particular pH of the surrounding medium is reached."). Put differently, without a coating, the skilled artisan would have understood that *all* the naproxen would immediately release in the stomach upon ingestion, regardless of pH. Ex. 1007 (col. 20, ll. 33–37). Thus, the delayed-release limitation of claim 1 would not be satisfied without an enteric-coated naproxen, which as Patent Owner persuasively explains and WO '185 supports, would have been expected to completely break down before the pH of the surrounding medium reached 3.5. PO Resp. 12–13.

Neither the Petition nor Dr. Banakar's Declaration addresses the incompatibility between sodium bicarbonate and enteric coatings in a medium. *See* Dec. 36 (stating the "Petitioner does not address the teaching on page 19 of WO '185 regarding the impact of a bicarbonate salt on an enteric coating . . . a coating that inhibits NSAID release until the pH is 3.5 or higher"). In the Reply, Petitioner sets forth several arguments as to why "[t]he use of bicarbonate buffer in WO '185 is entirely compatible with the teachings of the '225 patent." *See* Reply 11–15. For the reasons set forth

below, we find those arguments[8] impermissibly conclusory, unsupported by a preponderance of the record evidence, and/or untimely. We therefore reject them.

First, Petitioner asserts that a skilled artisan would have understood that "the non-enteric coated esomeprazole with solid bicarbonate salt from WO '185 could be incorporated into a tablet such as the '225 patent structure." Reply 12. Petitioner further asserts that Dr. Banakar's deposition testimony supports this argument. *Id.* (citing Ex. 2021 (111:20–112:1)). We disagree.

During his deposition, Dr. Banakar explained the mechanism by which sodium bicarbonate dissolves an enteric coating. *See* Ex. 2021 (111:20–112:1). Dr. Banakar testified that sodium bicarbonate and the enteric coating "interact to form a salt which is [] soluble in water." Ex. 2021 (111:20–24). Dr. Banakar emphasized that this chemical reaction occurs only in "a solvent or a medium"—not in a "dry state." *Id.* at 111:23–

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[8] We note that Petitioner's first argument under the subheading "The Use of Bicarbonate Buffer in WO '185 is Entirely Compatible with the Teachings of the '225," Reply 11–12, does not address the issue presented. Patent Owner's argument—to which Petitioner responds in this section—is directed to the issue of whether a skilled artisan would have reasonably expected sodium bicarbonate to overcome the known acid lability of PPIs. *See* PO Resp. 12 ("Thus, a skilled artisan would have no reasonable expectation that the use of a sodium bicarbonate buffer would be sufficient to overcome the problem associated with degradation of the omeprazole (or esomeprazole) in the presence of acid."). We agree with Petitioner that WO '185 expressly teaches that a sodium bicarbonate solution protects omeprazole from acid degradation in the stomach. Reply 12; Ex. 1015, 20:1–4. But that teaching does not answer the question of whether a skilled artisan would have reasonably expected compatibility between sodium bicarbonate and an *enteric coating* in a medium.

25. "In a dry state," Dr. Banakar explained, "they would not do that." *Id.* at 111:24–112:1.

We find that, although Dr. Banakar's testimony supports the notion that a tablet containing both sodium bicarbonate and an enteric coating would be shelf stable, it does not support Petitioner's implication that an ordinarily skilled artisan would have formulated such a tablet with a reasonable expectation of achieving delayed release of at least a portion of an enterically coated NSAID *in a medium*, as recited in claim 1. *See* Ex. 1001 (col. 21, ll. 31–35). Put differently, there is no "solvent or medium" in the dry state; thus, the interaction between sodium bicarbonate and an enteric coating in that dry state is irrelevant to the claim. And, contrary to Petitioner's argument, Dr. Banakar's testimony, in fact, suggests that sodium bicarbonate *would* dissolve the enteric coating in a medium. Ex. 2021 (111:20–25) (testimony of Dr. Banakar that sodium bicarbonate and the enteric coating "interact to form a salt which is [] soluble in water" and that this chemical reaction occurs in a "solvent or a medium").

Second, Petitioner asserts that Patent Owner's "suggest[ion] that the mere inclusion of a bicarbonate salt dissolves an enteric coating . . . ignores [the] fundamental characteristics of enteric coatings." Reply 12–13. "Enteric coatings," Petitioner continues, "by definition, dissolve above a particular pH." *Id.* at 13. With this statement, Petitioner appears to contend that only basic solutions (e.g., solutions having a pH greater than 3.5)—rather the bicarbonate salt itself—dissolve an enteric coating. And, if the enteric coating has dissolved, Petitioner's logic continues, it is because the pH of the medium has necessarily reached 3.5. *Id.*; *see also* Tr. 39:4–20 (attorney argument that increase in stomach pH is "logical based on the

environment in which this pill would be acting").

Petitioner, however, fails to direct us to any evidence supporting this argument. Petitioner refers to an "explanation" of enteric coatings by Dr. Banakar, but then cites to our Institution Decision, Patent Owner's Response, and the Petition, rather than to Dr. Banakar's declaration or deposition testimony. *See* Reply 13 (citing Dec. 15; PO Resp. 12–14; Pet. 21). Petitioner provides no reference in the cited pages to testimony from Dr. Banakar about the "fundamental characteristics of enteric coatings." And we decline to conduct our own search through the record for evidence supporting Petitioner's argument. Moreover, to the extent Petitioner relies exclusively on "logic" (or, by extension, "common sense") instead of evidence to reach this conclusion, we must reject it. *See Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989) (attorney argument is no substitute for evidence); *see also Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1362 (Fed. Cir. 2016) ("[R]eferences to 'common sense' . . . cannot be used as a wholesale substitute for reasoned analysis and evidentiary support . . . .").

But even if we considered Petitioner's argument, it appears to us that the weight of the evidence does not support it, and in fact may contradict it. For example, Dr. Banakar testified that, in a medium, sodium bicarbonate (because it is basic) and the enteric coating (because it is acidic) chemically react to form a soluble salt. Ex. 2021 (111:20–25). Dr. Banakar did not state that this chemical reaction only occurs because the pH of the medium has necessarily reached at least 3.5. *See id.*

Third, Petitioner asserts that the "prior art confirms that formulations containing bicarbonates are compatible with enteric coatings." Reply 13.

Petitioner reproduces a paragraph from U.S. Patent No. 6,365,184,[9] *id.* at 13–14 (quoting Ex. 1036 (col. 10, ll. 17–31)), and asserts that the skilled artisan would have understood that paragraph as teaching that "a POSA could successfully combine the use of bicarbonates taught in WO '185 with the enteric coating used in the structure of the '225 patent," *id.* at 14.

We find Petitioner's argument and citation to the '184 patent impermissibly conclusory and therefore unpersuasive. *Magnum Oil*, 829 F.3d at 1380. Instead of providing us with expert testimony explaining the import of the '184 patent disclosure, Petitioner merely block quotes a section of the reference and asserts that it "provides" a reasonable expectation of success. Reply 13–14.

In any event, it appears from our own review of the '184 patent that the enteric-coating layer described in that patent surrounds the PPI, rather than the NSAID as claimed in the '996 patent. Ex. 1036 (Abstract). The '184 patent teaches that "one or more separating layer(s)" may be placed in between the PPI and the enteric coating. *Id.* at col. 9, ll. 55–60. These separating layers "serve as a diffusion barrier and may act as a pH-buffering zone." *Id.* at col. 10, ll. 20–22. In other words, the '184 patent appears to teach that the separating layer further "buffers" the PPI from acid degradation *after* disintegration of the protective enteric coating. We find that this teaching adds nothing more to what WO '185 already teaches about PPIs and buffering solutions.

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[9] U.S. Patent No. 6,365,184 (issued Apr. 2, 2002) ("the '184 patent") (Ex. 1036). Petitioner first submitted the '184 patent with its Reply. *See* Reply 13–14.

Although expert testimony is not required in every case, we find that "the technology in [this] particular case . . . is sufficiently complex" "that expert testimony is essential" for Petitioner to prove its case. *Synopsys, Inc. v. Mentor Graphics Corp.*, 814 F.3d 1309, 1320 (Fed. Cir. 2016). And because Petitioner's reliance on the '184 patent raises more questions than it answers, we cannot say that it proves that the skilled artisan would have reasonably expected to achieve delayed release of at least a portion of the naproxen of claim 1. Moreover, to the extent Petitioner is *now* arguing that the skilled artisan would have added some type of "separating layer" between the enteric-coated naproxen and the PPI, that argument was not part of the Petition and is not within the proper scope of Reply. We, therefore, find it untimely. 37 C.F.R. §§ 42.104(b)(5), 42.23(b).

Fourth, Petitioner asserts that the '996 patent's examples of formulations containing both enteric coatings and sodium bicarbonate "further demonstrate that a POSA would have known that the disclosure of sodium bicarbonate buffer in the WO '185 is compatible with the use of enteric coatings." Reply 14. Petitioner's argument is unpersuasive. "Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art. That the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success." *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000) (citation omitted). Thus, the examples of the '996 patent prove nothing about what the ordinarily skilled artisan would have reasonably expected at the time of the invention.

Fifth, and finally, Petitioner points out that Patent Owner stated in its Response that, in a fasted state, the stomach will empty in 25 minutes. Reply 15 (citing PO Resp. 12). Petitioner asserts that Patent Owner's statement amounts to an admission that "at least a portion of the NSAID will be inhibited from release until after it has been emptied from the stomach into the small intestine, where the pH is greater than 3.5." *Id.* Again, we find Petitioner's assertion conclusory and unsupported by record evidence. As an initial matter, we note that WO '185 teaches complete dissolution of the enteric coating *within* thirty minutes, rather than necessarily *at* thirty minutes. Ex. 1015, 35:8–10. Nevertheless, Petitioner again points us to no evidence or expert testimony suggesting or explaining that "emptying" of the stomach necessarily results in the deposit of its contents into the portion of the small intestine where pH is, in fact, at least 3.5.

Put differently, Petitioner provides us with no evidence that succinctly explains the relationship between the time at which the enteric coating will dissolve and the status of the surrounding medium's pH. The relationship seems to us not a simple matter: PPIs, as Dr. Banakar testified and other record evidence supports, require repeated administration to achieve full therapeutic effect because they do not affect resting parietal cells. Ex. 1002 ¶ 33; Ex. 2009, 3; Ex. 1022, S14; *see also* Ex. 1022, S15 (stating that "[o]nce-daily PPI dosing results in 66% steady-state inhibition of maximal acid output *after five days* (emphasis added)). In fact, the prior art taught that PPIs were "given in association with food, so as to stimulate the parietal cell to make acid." Ex. 2011, 6; Ex. 1022, S14. And, we find Dr. Banakar's statement that "[a]n immediate increase in gastric pH occurs shortly after release of the PPI," Ex. 1002 ¶ 33, unhelpful in that it lacks not only a

citation to record evidence, but also in that it fails to tell us what that increase in gastric pH actually is.

Moreover, other record evidence suggests that stomach emptying may not necessarily place an enterically coated NSAID in a medium having a pH of at least 3.5. To begin, we note that Petitioner refers to the relevant "medium" for naproxen release as the "lower G.I. tract," rather than the duodenum as Petitioner now seems to imply. *Compare* Pet. 52, *with* Reply 15. Even so, we question whether the portion of the duodenum immediately following the stomach necessarily has a pH of 3.5 or higher. In this regard, Dr. Banakar testified that PPIs act on parietal cells that are located in the duodenal region, which "includes the stomach and the *early intestinal region*." Ex. 1002 ¶ 32 (emphasis added); *see also id.* at ¶ 35 (stating that "[p]arietal cells are located in the duodenum, which is located *immediately after the stomach* within the GI tract" (emphasis added)). We find that Dr. Banakar's testimony that parietal cells (which release acid) are located in the area immediately after the stomach suggests a low-pH environment in that area, rather than the higher-pH environment Petitioner now asserts. *See* Reply 15 (unsupported attorney argument that "at least a portion of the NSAID will be inhibited from release until after it has been emptied from the stomach into the small intestine, *where pH is greater than 3.5*" (emphasis added)).

In making our findings as to the "reasonable expectation of success" factor, we keep in mind that we cannot demand absolute certainty. *See Intelligent Bio-Sys.*, 821 F.3d at 1367 ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success."); *see also Pfizer*, 480 F.3d at 1364 ("[C]ase

law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."). But as the Supreme Court explained in *KSR*, a combination of elements "must do more than yield a predictable result." 550 U.S. at 416. Here, Petitioner has not met its burden to show that a skilled artisan would have reasonably expected or predicted that delayed release of at least some naproxen at pH 3.5 could have been achieved through modification of the '225 patent tablet with elements from Chandramouli and WO '185. The relevant evidence of record suggests the opposite: that the skilled artisan would have expected sodium bicarbonate to completely dissolve the enteric coating of the NSAID in the medium, resulting in complete release of the NSAID before pH of that medium necessarily reaches at least 3.5.

4. Summary

In sum, we find that Petitioner has shown by a preponderance of the evidence that the prior art discloses or suggests each and every element of the challenged claims. We also find that Petitioner has shown by a preponderance of the evidence that the skilled artisan would have been motivated, or had a reason, to replace misoprostol in the dosage unit formulation of the '225 patent with the PPI esomeprazole. And we find that Petitioner has shown by a preponderance of the evidence that a skilled artisan would have generally been motivated to utilize an immediate-release formulation of esomeprazole.

But, we find that Petitioner has failed to show by a preponderance of the evidence that the skilled artisan would have had a reasonable expectation of success in achieving the claimed invention. Because a reasonable

expectation of success is a necessary finding for a conclusion of obviousness, Petitioner's obviousness challenge fails. Accordingly, we do not address the remaining question of whether a skilled artisan would have been motivated to exchange the specific NSAIDs disclosed in the '225 patent with naproxen, as claimed in the '996 patent.

III. CONCLUSION

Based on the evidence and arguments, Petitioner has not demonstrated by a preponderance of the evidence that claims 1 and 3-11 are unpatentable under 35 U.S.C. § 103(a) for obviousness over the '225 patent, Chandramouli, and WO '185.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1 and 3–11 of U.S. Patent No. 8,858,996 have not been shown to be unpatentable;

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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