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Paper 40
Entered: February 21, 2017

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 IPR2015-01718
Patent 8,945,621 B2

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

SCHEINER, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 AND 37 C.F.R. § 42.73

I. INTRODUCTION

Coalition for Affordable Drugs VII, LLC ("Coalition" or "Petitioner") filed a Petition (Paper 1, "Pet.") on August 12, 2015, requesting an *inter partes* review of claims 1–16 of U.S. Patent No. 8,945,621 B2 (Ex. 1001, "the '621 patent"). Pozen Inc. ("Pozen" or "Patent Owner") filed a Preliminary Response (Paper 15, "Prelim. Resp.") on November 23, 2015. On February 22, 2016, we instituted trial as to all of the challenged claims (Paper 17, "Decision" or "Dec.") on the following grounds.[1]

References	**Basis**	**Claims Challenged**
Plachetka,[2] Graham,[3] and Goldstein[4]	§ 103(a)	1–16
Plachetka	§ 103(a)	1–16

[1] Petitioner supported its challenges with the Declaration of Leon Shargel, Ph.D., R.Ph., executed August 12, 2015 ("Shargel Declaration") (Ex. 1003).

[2] U.S. Patent No. 6,926,907 B2, issued August 9, 2005 (Ex. 1004, "Plachetka").

[3] David Y. Graham et al., *Ulcer Prevention in Long-term Users of Nonsteroidal Anti-inflammatory Drugs*, 162 ARCH. INTERN MED. 169–175 (2002) (Ex. 1005, "Graham").

[4] Jay L. Goldstein et al., *Ulcer Recurrence in High-Risk Patients Receiving Nonsteroidal Anti-Inflammatory Drugs Plus Low-Dose Aspirin: Results of a Post Hoc Subanalysis*, 26 CLINICAL THERAPEUTICS 1637–1643 (2004) (Ex. 1006, "Goldstein").

Pozen filed a Patent Owner Response (Paper 25, "PO Resp."),[5] and Coalition filed a Reply (Paper 31, "Reply"). Pozen did not move to amend any claim of the '621 patent.

We heard oral argument on November 16, 2016. A transcript of the argument has been entered into the record as Paper 39.

We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Coalition has not proved by a preponderance of the evidence that claims 1–16 are unpatentable.

A. Related Proceedings

Petitioner represents it is unaware of any judicial or administrative matters involving the '621 patent. However, Petitioner represents that the '621 patent is listed in the Food and Drug Administration's Orange Book for Vimovo®, and Petitioner has filed other Petitions for *inter partes* review

[5] Pozen supports its position with the Declarations of Robert W. Makuch, Ph.D., dated June 22, 2016 (Ex. 2021, "Makuch Declaration") and David A. Johnson, M.D., dated June 23, 2016 (Ex. 2022, "Johnson Declaration").

involving patents also listed in the Orange Book for Vimovo®, including Petitions filed in Case Nos. IPR2015-01241, IPR2015-01344, and IPR2015-01680. Pet. 2–3; *see also* Paper 7 (listing four district court matters involving Horizon Pharma USA, Inc., a real party-in-interest of Pozen) 2, 8–9.

B. The '621 Patent (Ex. 1001)

The '621 patent—titled "METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER"—issued on February 3, 2015, listing inventors Brian Ault, Clara Hwang, Everardus Orlemans, John R. Plachetka, and Mark Sostek.

According to the '621 patent, the cumulative incidence of gastroduodenal ulcers (GDUs) with conventional non-steroidal anti-inflammatory drug (NSAID) use has been reported to be as high as 25–30% at 3 months and 45% at 6 months versus 3–7% for placebo, and at any given time, the incidence of upper gastrointestinal (UGI) ulcers in NSAID users has been estimated to be as high as 30%. *Id.* at 1:25–30. Further according to the '621 patent, "[t]he risk factors associated with an NSAID user developing UGI ulcers include: age ≥ 50 years, history of UGI ulcer or bleeding, or concomitant aspirin use." Ex. 1001, 1:30–32.

The '621 patent discloses a pharmaceutical formulation comprising immediate release esomeprazole (an acid inhibitor, specifically a proton pump inhibitor (PPI)), and enteric-coated naproxen (an NSAID). *Id.* at 1:48–50. According to the '621 patent:

> [T]he pharmaceutical formulation comprising immediate release (IR) esomeprazole magnesium and enteric-coated (EC) naproxen has been found to reduce the incidence of ulcers in patients at risk for developing NSAID-associated ulcers when compared to EC-naproxen. Such a formulation has also been found to reduce the incidence of ulcers in patients taking low dose aspirin (LDA) who are at risk for developing NSAID-associated ulcers when compared to EC-naproxen. Furthermore, patients taking this new formulation of IR esomeprazole and EC-naproxen were able to continue treatment longer than patients taking EC-naproxen.

Id. at 1:48–58. "The term 'low dose aspirin' [LDA] refers to dosages of aspirin that are ≤ 325 mg." *Id.* at 5:9–10.

C. Illustrative Claim

Petitioner challenges claims 1–16 of the '621 patent, of which claims 1, 8, 15, and 16 are independent. Claim 1, reproduced below, is illustrative.

> 1. A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising:
>
> (a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in a form and route sufficient 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, and
>
> (b) 500 mg of naproxen, or pharmaceutically acceptable salt thereof;
>
> wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen,

> wherein at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium,
>
> wherein the unit dosage form releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37º C.+/-0.5º C.,
>
> wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated ulcers in said patient and *wherein administration of the unit dose form is more effective at reducing the incidence of the NSAID-associated ulcers in patients taking LDA than in patients not taking LDA who are administered the unit dose form*.

Ex. 1001, 26:61–27:20 (emphasis added).

II. ANALYSIS

A. Claim Construction

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

B. Claims 1–16—Asserted Obviousness over Plachetka, Graham, and Goldstein

Petitioner contends that the method of claims 1–16—administering a unit dosage form comprising the acid inhibitor, esomeprazole, and the NSAID, naproxen, to a subject also taking low dose aspirin ("LDA")—would have been obvious over the combined teachings of Plachetka, Graham, and Goldstein. Pet. 10–17. Moreover, Petitioner contends that one of ordinary skill in the art would have expected that the claimed method would be "more effective at reducing the incidence of NSAID-associated

ulcers in patients taking LDA than in patients not taking LDA," given the teachings of Graham and Goldstein. *Id.* at 17–19.

Patent Owner contends that the cited references do not suggest that LDA should be taken concurrently with an acid inhibitor and an NSAID, and moreover, nothing in the references would have led one of ordinary skill in the art to expect that administering a unit dose form of immediate-release esomeprazole and delayed release naproxen would be more effective at reducing NSAID-associated ulcers in patients taking LDA than in patients not taking LDA, an unexpected result "specifically recited in the final 'wherein' clause of the challenged claims." PO Resp. 3, 34–35, 43–44.

We begin our analysis with a discussion of the prior art cited by Petitioner.

1. Plachetka (Ex. 1004)

Plachetka teaches that NSAIDs are effective agents for controlling pain, but their administration can lead to the development of gastroduodenal lesions, e.g., ulcers and erosions, in susceptible individuals. Ex. 1004, 1:22–26. According to Plachetka:

> Attempts to develop NSAIDs that are inherently less toxic to the gastrointestinal tract have met with only limited success. For example . . . cyclooxygenase-2 (COX-2) inhibitors show a reduced tendency to produce gastrointestinal ulcers and erosions, but a significant risk is still present, especially if the patient is exposed to other ulcerogens . . . In this regard, it appears that even low doses of aspirin will negate most of the benefit relating to lower gastrointestinal lesions.

Id. at 2:31–40.

Plachetka discloses a "method for reducing the risk of gastrointestinal side effects in people taking NSAIDs for pain relief and for other conditions, particularly during chronic treatment." *Id.* at 3:3–6. Plachetka's method involves administering a pharmaceutical composition in unit-dose form "that combines: a) an agent that actively raises intragastric pH to levels associated with less risk of NSAID-induced ulcers; and b) an NSAID . . . specifically formulated to be released in a coordinated way that minimizes the adverse effects of the NSAID on the gastroduodenal mucosa." *Id.* at 3:8–13. According to Plachetka, "[t]his method has the added benefit of being able to protect patients from other gastrointestinal ulcerogens whose effect may otherwise be enhanced by the disruption of gastroprotective prostaglandins due to NSAID therapy." *Id.* at 3:12–17.

Specifically, Plachetka discloses administering "a pharmaceutical composition in unit dosage form suitable for oral administration . . . 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 3:18–22), and an enteric-coated NSAID "in an amount effective to reduce or eliminate pain or inflammation" (*id.* at 3:39–41).

Plachetka's preferred acid inhibiters are H_2-blockers, such as famotidine, cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, and loxtidine. *Id.* at 3:32–34. Plachetka also states that "[o]ther agents that may be effectively used include proton pump inhibitors such as omeprazole,

esomeprazole, pantoprazole, lansoprazole or rabeprazole." *Id.* at 3:36–38. In addition, according to Plachetka:

> Typical amounts for H2 blockers are: cimetidine, 100 to 800 mg/unit dose; ranitidine, 50–300 mg/unit dose; famotidine, 5–100 mg/unit dose; ebrotidine 400–800 mg/unit dose; pabutidine 40 mg/unit dose; lafutidine 5–20 mg/unit dose; and nizatidine, 50–600 mg/unit dose. Proton pump inhibitors will typically be present at about 5 mg to 600 mg per unit dose. For example . . . omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 20 mg per unit dosage form being preferred. Other typical amounts are: esomeprazole, 5–100 mg, with about 40 mg per unit dosage form being preferred; lansoprazole, 15–150 mg, with about 30 mg per unit dosage form being preferred; pantoprazole, 10–200 mg, with about 40 mg per unit dosage form being preferred; and rabeprazole, 5–100 mg, with about 20 mg per unit dosage form being preferred.

Id. at 7:2–18.

The NSAID in Plachetka's unit-dosage form "may be a COX-2 inhibitor such as celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib . . . [or] may be aspirin, acetaminophen, ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, nabumetone, or diclofenac." *Id.* at 3:41–47. "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.* at 3:48–50.

Plachetka discloses several specific unit dosage forms in which an acid inhibitor is released from the unit dosage form immediately upon

administration to a patient, while an enteric layer prevents release of the NSAID until the local pH is above about 4. For example, Plachetka discloses a unit dosage form with an enteric-coated naproxen core surrounded by an immediate-release layer of the H_2-blocker, famotidine, and another dosage form with an enteric-coated naproxen core surrounded by an immediate-release layer of the proton pump inhibitor, omeprazole. *Id.* at 8:14–67, 14:40–15:17.

2. Graham (Ex. 1005)

Graham discloses the results of a prospective, double-blind, active- and placebo-controlled study of the effectiveness of the acid inhibitors misoprostol (a synthetic prostaglandin) and lansoprazole (a proton pump inhibitor) in preventing gastric ulcers in long-term NSAID users. Ex. 1005, 169. The criteria for study participants included "treatment with stable, full-therapeutic doses of an NSAID (with the exception of nabumetone or aspirin [≥ 1300 mg/d; low-dose aspirin for cardiovascular protection was permitted]) for at least the previous month." *Id.* at 170. "Patients could have taken more than 1 NSAID." *Id.* at 171. "Forty percent of the patients used ibuprofen, 35% used naproxen, 32% used diclofenac, 22% used aspirin or aspirin combinations, 17% used piroxicam, and 34% used other NSAIDs" and "[t]he distribution across treatment groups was similar." *Id.*

According to Graham, "[p]roton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-

induced gastric ulcers but not superior to misoprostol, 800 µg/d." *Id.* at 169. However, Graham concluded that proton pump inhibitors and misoprostol are clinically equivalent, when the poor compliance and potential adverse side effects associated with full-dose misoprostol are considered. *Id.*

3. Goldstein (Ex. 1006)

According to Goldstein:

> Low-dose aspirin taken in combination with NSAIDs has been associated with an increased risk for complications of upper GI ulcer compared with NSAIDs alone; thus, concomitant aspirin use is a risk factor for NSAID-associated upper GI toxicity. The association of combined NSAIDs and low-dose aspirin with increased upper GI risk was supported by the results of a cohort study . . . in which patients taking low-dose aspirin (<150 mg/d) had a 2.6% incidence of GI bleeding, compared with a 5.6% incidence in those taking low-dose aspirin plus an NSAID.

Ex. 1006, 1638 (internal citations omitted).

Goldstein discloses a post hoc subanalysis of Graham's study (*see* Ex. 1005, discussed immediately above), "conducted to examine whether the efficacy of gastro-protective therapy [with misoprostol or lansoprazole] against ulcer recurrence extends to patients taking concomitant nonspecific NSAIDs and low dose aspirin." *Id.* at 1640 n.24. Goldstein's "subanalysis included data from [seventy] patients in [Graham's] intent-to-treat cohort who took aspirin at an amount ≤

325 mg/d." *Id.* at 1637. "The most frequently used nonaspirin NSAIDs were ibuprofen, naproxen, and diclofenac." *Id.* at 1639. "Antacids were provided for symptom relief as needed." *Id.* at 1638. Goldstein concluded that "[c]otherapy with misoprostol or lansoprazole lowered the risk of ulcer recurrence in these high risk individuals." *Id.* at 1641.

4. Analysis

Petitioner cites portions of Plachetka, Graham, and Goldman as disclosing various limitations of independent claims 1, 8, 15, and 16. Pet. 13–19, 22–25, and 28–33. For instance, with respect to the preambles of the independent claims, Petitioner cites Goldstein's disclosure of a study wherein patients taking both LDA and another NSAID were further administered misoprostol or lansoprazole. *Id.* at 13 (citing Ex. 1006, 1638, 1640). Petitioner cites Plachetka as disclosing a pharmaceutical composition in unit dosage form which provides for the coordinated release of 20 mg of esomeprazole and 500 mg of naproxen. *Id.* at 14–15 (citing Ex. 1004, 1:11–14, 3:19–36, 39–59, 3:63–4:2, 4:18–20, 6:6–11, 7:7–13, 20:20–32, 21:46–22:17).

Petitioner contends that Plachetka's "pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID)," result in "less risk of NSAID-induced ulcers." *Id.* at 15 (citing Ex. 1004, 1:11–14), 17 (citing Ex. 1004, 3:3–13). Petitioner further contends that an ordinary artisan, being aware of

the reduced incidence of gastric ulcers in patients taking both LDA and another NSAID who also were administered the acid inhibitor lansoprazole, as disclosed by Graham and Goldstein, would have had a reason to administer Plachetka's coordinated unit dosage form to patients in need of NSAID therapy and at risk of developing gastric ulcers, including those patients taking low dose aspirin in addition to another NSAID. Pet. 11 (citing Ex. 1004, 2:35–40). Petitioner contends "the results disclosed by Graham and Goldstein would indicate that the compositions disclosed in Plachetka could be used for treating patients on an LDA regimen to achieve the predictable result of lower gastric ulcer incidence." *Id.* at 12.

Patent Owner contends that the method of the challenged claims would not have been obvious over the cited art because "Plachetka includes only a single mention of LDA, in the context of co-administration [of] COX-2 inhibitors" (PO Resp. 34 (citing Ex. 1004, 2:31–40; Ex. 2021 ¶ 43)), and "never once mentions that LDA could or should be administered with the unit dosage forms taught therein" (*id.* (citing Ex. 2022 ¶ 60)). Similarly, Patent Owner contends that Graham "does not teach or suggest that LDA should be taken concurrently with an acid inhibitor and an NSAID." *Id.* at 35.

Nevertheless, the issue presented by Petitioner's rationale is not whether the cited art would have suggested administering LDA to a patient already taking Plachetka's unit dosage form. Rather, the salient issue is whether the art would have suggested that a patient already taking LDA in

addition to a non-aspirin NSAID—which Goldstein teaches was known to increase the incidence of gastric ulcers—would have benefited by taking the non-aspirin NSAID in the form of Plachetka's coordinated unit dose form containing an acid inhibitor in addition to the NSAID.

Having considered Petitioner's and Patent Owner's arguments and observations with respect to this aspect of the challenged claims, as well as evidence of record establishing that administering an acid inhibitor to a patient taking both LDA and a non-aspirin NSAID was known to reduce the incidence of NSAID-associated gastric ulcers, we determine that Petitioner has demonstrated that an ordinary artisan would have had a reason to administer Plachetka's coordinated unit dosage forms to patients in need of NSAID therapy and at risk of developing gastric ulcers—including those patients also taking low dose aspirin—in order to reduce the incidence of gastric ulcers.

Moreover, we are persuaded that Petitioner has established that the ordinary artisan would have had a reason to administer a coordinated release unit dosage form comprising an enteric-coated naproxen core surrounded by an immediate release layer of esomeprazole. The record developed by Petitioner indicates that naproxen is a preferred NSAID in Plachetka's combination NSAID/acid inhibitor unit dosage forms, and esomeprazole is one of a relatively small number of suitable acid inhibitors (which also includes lansoprazole) presented as essentially interchangeable for purposes of formulating the unit dosage forms. Moreover, Plachetka discloses ranges

for the acid inhibitors and NSAIDs that encompass the amounts required by the claims. Pet. 18; Ex. 1004, 3:36–38, 48–50, 7:2–18.

As for the limitation "wherein the unit dosage form releases less than 10% of the naproxen . . . after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37º C. +/-0.5º C" (the "Paddle Method clause"), the record indicates that this property would be a natural result when testing of a dosage form comprising 500 mg of enteric-coated naproxen and 20 mg of esomeprazole. *See* Pet. 16; Ex. 1001, 26:61–27:13.

As for Petitioner's contentions with respect to the limitations recited in dependent claims 2–7 and 9–14, we have reviewed the Petition and the cited art and are persuaded that Petitioner has demonstrated that these limitations are taught or suggested by the prior art relied on. For example, claim 2 depends from claim 1 and requires that "the risk is associated with chronic NSAID treatment," and Petitioner points out that "Plachetka discloses 'a risk of gastrointestinal side effects in people taking NSAIDs . . . particularly during chronic treatment.'" Pet. 20 (quoting Ex. 1004, 3:3–6). Similarly, claim 4 depends from claim 1 and specifies that the "patient is treated for a disease or disorder selected from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and a combination thereof," and Petitioner notes that Plachetka discloses "methods of treating a patient for . . . osteoarthritis or rheumatoid arthritis." *Id.* (citing Ex. 1004, 4:18–23).

Nevertheless, our determination that Petitioner has established that the ordinary artisan would have had a reason to administer Plachetka's

coordinated unit dosage forms to patients in need of NSAID therapy and at risk of developing gastric ulcers—including those patients also taking low dose aspirin—do not end our obviousness analysis.

The Final "Wherein" Clause; Unexpected Results

Secondary considerations, when present, must "be considered en route to a determination of obviousness." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citation omitted). Secondary considerations may include any or all of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). To be relevant, evidence of nonobviousness must be commensurate in scope with the claimed invention. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Each of independent claims 1, 8, 15, and 16 concludes with the clause: "wherein administration of the unit dose form is more effective at reducing the incidence of the NSAID-associated ulcers in patients taking LDA than in patients not taking LDA who are administered the unit dose form." Ex. 1001, 27:16–20, 59–63, 28:36–39, 61–64.

According to Patent Owner,

> at the time of the inventions claimed in the '621 patent, not only was it widely known and accepted that NSAIDs, including LDA, cause gastrointestinal toxicity including gastrointestinal ulcer and hemorrhage . . . , it was also widely known and accepted that

> taking LDA in addition to a non-aspirin NSAID *further increased* one's risk for such gastrointestinal complications.

PO Resp. 13 (citing Ex. 2022 ¶ 37; Ex. 2016, 827, 829).

Patent Owner, supported by the testimony of Dr. Johnson, contends that the inventors of the '621 patent unexpectedly found that a unit dose form comprising immediate-release esomeprazole and delayed-release naproxen is more effective at reducing NSAID-associated ulcers in patients taking LDA than in patients *not* taking LDA (PO Resp. 15–16 (citing Ex. 2022 ¶ 46)), "despite the expectation that these patients would be at an increased risk for developing such ulcers based on concomitant use of LDA" (*id.* at 17).

Dr. Johnson discusses Example 1 of the '621 patent and attests that it "supports the surprising and unexpected results" represented by the final wherein clause of the challenged claims. Ex. 2022 ¶ 46. Dr. Johnson testifies:

> This example describes the results of two large, randomized clinical trials which were conducted to evaluate the incidence of gastric ulcers following the administration of either a dosage form consisting of 20 mg of immediate-release esomeprazole and 500 mg of enteric-coated naproxen (PN400), or 500 mg of enteric-coated naproxen alone, in subjects at risk of developing NSAID-associated ulcers. ([Ex. 1001] at 12:37-46.) The study participants were stratified by LDA use and received either PN400 or naproxen twice daily. (*Id*. at 12:49-54, 12:63-67; 13:2-3.) The primary endpoint of the studies was the incidence of gastric ulceration. Secondary endpoints included incidence of endoscopic duodenal ulcer and other pre-specified NSAID-

> associated upper gastrointestinal adverse events. (*Id*. at 13:5-7, 13:9-12.) Consistent with other studies, approximately 20-25% of the subjects took LDA. However, a post-hoc analysis of gastric ulcer incidence in these patients was conducted and showed important findings. (*Id*. at 13:7-9.)
>
> In the both studies, the two treatment groups were well balanced with respect to baseline characteristics and did not have any relevant demographic differences. (*Id*. at 13:52-55; 14:7-11.) For example, in the first study (Study A), 24% of each set of patients also took LDA. (*Id*. at 13:57-59.) In the second study (Study B), of patients receiving PN400, 9% also took LDA, and of patients receiving naproxen-only, 11% also took LDA. (*Id*. at 14:13-15.)
>
> The results demonstrated that, overall, the incidence of gastric ulcers was lower in PN400 patients than in naproxen-only patients. (*Id*. at 15:67-16:3, 17:23-25.) Specifically, for the 201 subjects who were LDA users, the incidence of gastric ulcers was lower in PN400 patients than in naproxen-only patients, with 3% of PN400 patients having a gastric ulcer, while 28.4% of naproxen-only patients had gastric ulcer. (*Id*. at 17:26-34.) For the 653 patients who were not LDA users, the incidence of gastric ulcers was lower in PN400 patients than in naproxen-only patients, with only 6.4% of PN400 patients having a gastric ulcer, while 22.2% of naproxen-only patients having a gastric ulcer. (*Id*. at 17:34-37.)

Ex. 2022 ¶¶ 46–48.

Patent Owner summarizes: "[a]s expected, patients who took LDA in conjunction with naproxen had a higher incidence of gastric ulcers (28.4%) than those who took naproxen alone (22.2%)" (PO Resp. 17 (citing Ex. 1001, 17:26–37)), "[b]ut, surprisingly, patients taking PN400 in conjunction

with LDA had a decreased incidence of gastric ulcer (3%) as compared to patients taking PN400 without LDA (6.4%), despite the expectation that these patients would be at increased risk for developing such ulcers based on concomitant use of LDA" (*id.*). Patent Owner tabulates the percentage of patients exhibiting a gastric ulcer in Example 1 of the '621 patent as follows:

	LDA	Non-LDA	Outcome
PN400	3%	6.4%	Unexpected
Naproxen-only	28.4%	22.2%	Expected

PO Resp. 17 (citing Ex. 1001, 17:26–37).

We further note Patent Owner's assertion that the Examiner of the application that matured into the '621 patent concluded that these results would have been unexpected over Plachetka's disclosure (i.e., Plachetka alone) and that the unexpected results were commensurate in scope with the claims as ultimately allowed. PO Resp. 21 (citing Ex. 1002, 2 (Notice of Allowance) ("Applicants have demonstrated the unexpected result that patients taking low dose aspirin who were administered the instantly recited dosage form (PN400) showed a lower incidence of gastric ulcers than non-aspirin using patients administered PN400.")).

With respect to the present challenge over Plachetka in view of Graham and Goldstein, Patent Owner contends that "[n]one of these references . . . either alone or in combination, discloses that the combination of an acid inhibitor and an NSAID is more effective at reducing the

incidence of NSAID-associated ulcers in patients taking LDA than in patients not taking LDA." PO Resp. 33–34.

Petitioner, on the other hand, contends that the final wherein clause would not have been unexpected, because "Plachetka in view of Graham and Goldstein discloses this limitation." Pet 17 (citing Ex. 1033 ¶ 82). Nevertheless, neither Petitioner nor Petitioner's witness, Dr. Shargel, identifies sufficiently the basis for this assertion in the Petition. For example, according to Petitioner,

> Graham and Goldstein disclose that 6.25% of patients taking a combination of 15 mg of lansoprazole and an NSAID with LDA have gastric ulcers, while 23% of patients taking a combination of 15 mg of lansoprazole and an NSAID without LDA have gastric ulcers. . . . Similarly, Graham and Goldstein disclose that 0% of patients taking a combination of 30 mg of lansoprazole and an NSAID with LDA have gastric ulcers, while 17% of patients taking a combination of 30 mg of lansoprazole and an NSAID without LDA have gastric ulcers.

Pet. 17–18 (citing Ex. 1003 ¶ 83). Paragraph 83 of Dr. Shargel's Declaration is virtually identical to the Petition. Neither Petitioner nor Dr. Shargel identifies the basis for these purported results in the Petition, or in the cited portion of the Declaration, much less the basis for the conclusion that an ordinary artisan "would have understood that a combination of lansoprazole and naproxen was more effective at reducing the incidence of the NSAID-associated ulcers in patients taking LDA than in patients not taking LDA." Pet. 18 (citing Ex. 1003 ¶ 83). As we stated in the Decision

of Institution, "[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight"—accordingly, we are not persuaded by these conclusory and unsupported statements by Petitioner or Dr. Shargel. Dec. 15 (quoting 37 C.F.R. § 42.65(a)).

In its Reply, Petitioner concedes that it "did not quote Dr. Shargel's full analysis of the Graham and Goldstein results in the body of the Petition due to page-limit constraints" (Reply 13), but argues that "Dr. Shargel's full analysis—the basis for the conclusion that Graham and Goldstein render the final 'wherein' clause obvious—is located in Appendix B to the Shargel Declaration" (*id.*).

We determine that Petitioner has not established that the prior art at issue discloses or suggests that the combination of an acid inhibitor and an NSAID is more effective at reducing the incidence of NSAID-associated ulcers in patients taking LDA than in patients not taking LDA. Under our rules, a petition must contain a "full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence" (37 C.F.R. § 42.22(a)(2)), and arguments made in a supporting document may not be incorporated by reference into a petition (37 C.F.R. § 42.6(a)(3)). Here, the Petition not only failed to quote Dr. Shargel's analysis or any part of Appendix B, it did not even allude to it. Nor did paragraph 83 of the Declaration cite to any part of Appendix B. *See, e.g.*, *Fidelity Nat'l Info. Servs., Inc. v. Data Treasury Corp.*, Case IPR2014-

00489, slip op. at 9–11 (PTAB Aug. 13, 2014) (Paper 9) (declining to consider information presented in a supporting declaration, but not discussed in the petition).

Moreover, Patent Owner emphasizes that "Graham did not identify concurrent use of LDA with an NSAID as an issue to be studied or as a variable that could affect the outcome of the study." PO Resp. 38 (citing Ex. 2021 ¶ 47; Ex. 2022 ¶ 62). Supported by the testimony of Dr. Makuch and Dr. Johnson, Patent Owner contends that Graham and Goldstein, "despite performing extensive analyses of the cited data[,] never once conclude or even allude that patients taking an acid inhibitor and an NSAID with LDA might have a reduced incidence of gastric ulcers as compared to patients taking an acid inhibitor and an NSAID without LDA." *Id.* at 37. "Instead, Goldstein (which looked specifically at data from patients taking NSAIDs and LDA) repeatedly states that which was well known in the art, namely that co-administration of NSAIDs and LDA increases the risk of gastric injury."[6] *Id.*

[6] As discussed above, Goldstein discloses a post hoc subanalysis of Graham's study (*see* Ex. 1005), "conducted to examine whether the efficacy of gastro-protective therapy [with misoprostol or lansoprazole] against ulcer recurrence extends to patients taking concomitant nonspecific NSAIDs and low dose aspirin." Ex. 1006, 1640, 1643 n.24.

Patent Owner further contends that "Graham did not track patients' LDA use" and "does not explain if patients used LDA consistently and daily for the duration of the study, or if the patients stopped or started LDA use at any point during the study." PO Resp. 38 (citing Ex. 2021 ¶¶ 45–46; Ex. 2022 ¶ 62). Relying on the testimony of Drs. Makuch and Johnson, Patent Owner contends "[b]ecause patients' LDA usage was not tracked, it is impossible to know when or how the patients were provided with LDA, how often patients took LDA, and the dose of LDA taken by the patients, and thus, a POSA would not look to the Graham data to draw any conclusions regarding patients' LDA usage." *Id.* (citing Ex. 2021 ¶ 46; Ex. 2022 ¶ 65).

Patent Owner further contends that the "flaws of the Graham study with respect to patients' LDA use were admitted by Dr. Shargel during his deposition." PO Resp. 38 (citing Ex. 2020, 25:25–29:20 (Dr. Shargel explaining his understanding that the percentages of study participants taking various NSAIDs listed on page 171 of Graham represent "what they self-report that they're taking at the beginning. It does not give any clarification . . . that they are continuing to take it throughout the study.")).

In addition, Patent Owner contends that "Graham's participants were permitted to take more than one NSAID and antacids," but "Graham does not contain any information that identifies the participants who took multiple NSAIDs or which NSAIDs were taken with or without LDA" (PO Resp. 39 (citing Ex. 1005 at 170-71; Ex. 2022 at ¶ 64)) or "participants who took antacids (which complicate the analysis of any data generated within this population of patients), how often antacids were taken, and how many antacids were taken" (*id.* at 40 (citing Ex. 2022 ¶ 64)).

Patent Owner acknowledges that "Goldstein presents an analysis of [Graham's] subpopulation of patients taking NSAIDs and LDA" (PO Resp. 39), but contends, "[b]ecause Goldstein relies on the data obtained in the Graham study, . . . the Goldstein data suffers from all of the flaws inherent in the Graham data, as discussed above." *Id.* at 40.

Finally, we note that Petitioner observes "when Dr. Makuch was asked at his deposition whether a POSA would have relied on Graham to draw any conclusions about LDA use and NSAID associated GI injury, he admitted that, in his opinion, a POSA would have considered Graham." Reply 17. Thus, according to Petitioner, "both Petitioner's and Patent Owner's experts agree that a POSA would have considered the Graham study." *Id.* at 17–18. We do not disagree with Petitioner's assertion that one of ordinary skill in the art

would have considered Graham's study, but it does not follow, as Petitioner contends, that "the results of the Graham study, which are further reported in Goldstein, indicate that the administration of the combination of an acid inhibitor with an NSAID is more effective at reducing the incidence of NSAID-associated ulcers in patients taking LDA than in patients not taking LDA." *Id.* at 18.

Having considered the arguments and evidence cited in the Petition, Patent Owner's Response, and Petitioner's Reply, we agree with Patent Owner that Petitioner has not established that Plachetka, Graham, and Goldstein teach or suggest that "administration of the unit dose form is more effective at reducing the incidence of the NSAID-associated ulcers in patients taking LDA than in patients *not* taking LDA who are administered the unit dose form," as required by each of independent claims 1, 8, 15, and 16. PO Resp. 28 (emphasis added). We further agree with Patent Owner that Petitioner has not established, based on the arguments and evidence cited in the Petition, that the ordinary artisan would have expected the result represented by the final wherein clause.

Nevertheless, as discussed above, and in the Decision on Institution, although evidence of secondary considerations—in this case, unexpected results—must be taken into account, such considerations may or may not be sufficient to confer patentability upon a showing of obviousness. Dec. 20 (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("[W]e hold that even if Pfizer showed that amlodipine besylate exhibits

unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion.")).

In general, "'differences in degree' of a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind'—i.e., a new property dissimilar to the known property." *Bristol-Meyers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). For instance, in *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326 (Fed. Cir. 2014), evidence of efficacy somewhat greater than expected—i.e., a difference in degree—did not undercut a showing that there was a reasonable expectation of success in treating osteoporosis with a 150 mg monthly dose of ibandronate, where the prior art disclosed monthly dosing and there was a reason to set the dose at 150 mg. *Id.* at 1334. On the other hand, in *Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293 (Fed. Cir. 2015), a topical solution used for treating glaucoma—containing three-fold less of the active ingredient, bimatoprost, and four-fold more of a preservative, BAK, than a prior art solution—was nonobvious, in large part because the prior art taught that the higher amount of BAK would either have no impact on the permeability of bimatoprost or decrease it. That the "inventors surprisingly determined that the opposite was true, namely, that 200 ppm BAK enhanced the permeability of bimatoprost . . . is an unexpected difference in kind that supports nonobviousness." *Id.* at 1306.

Based on the evidence developed at trial, we find that Petitioner has shown that it would have been expected that the method of the challenged claims would be effective in reducing the risk of gastric ulcers in patients taking both LDA and a non-aspirin NSAID. But Petitioner has not established that that the claimed method would have been expected to be *more* effective in patients taking LDA than in patients *not* taking LDA, especially in light of evidence of record establishing that patients taking both LDA and a non-aspirin NSAID would be at *increased* risk for developing gastric ulcers relative to patients taking NSAID alone. We find that this surprising result—the opposite of what the ordinary artisan would have expected—represents a difference in kind, rather than degree.

Accordingly, we conclude that Petitioner has not demonstrated by a preponderance of the evidence that the subject matter of claims 1–16 would have been obvious over Plachetka, Graham, and Goldstein.

C. Claims 1–16—Asserted Obviousness over Plachetka

1. Analysis

Petitioner alternatively contends that

> Plachetka recognizes that NSAID "administration can lead to the development of gastroduodenal lesions, e.g., ulcers and erosions, in susceptible individuals." . . . Plachetka also recognizes that "[a]ttempts to develop NSAIDs that are inherently less toxic to the gastrointestinal tract have met with only limited success." . . . This limited success is due, in part, because even a patient's LDA regimen (e.g., chronic treatment with LDA for cardiovascular prophylaxis)

> may negate most of the lower gastrointestinal lesion benefits of less toxic NSAIDs. . . . Accordingly, Plachetka discloses that its invention is directed to "a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs for pain relief and for other conditions, particularly during chronic treatment." . . . Based on the foregoing, a POSA would have understood Plachetka to disclose claim 1's "method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers" because Plachetka identified the problem of adverse effects of chronic LDA usage on NSAID administration . . . and indicated its invention was directed at methods of addressing that problem. (Ex. 1003, ¶ 163. *See* Ex. 1004, col. 1, ll. 11-19 and col. 3, ll. 1-6.)

Pet. 33–34 (citing Ex. 1004, 1:11–19, 1:23–25, 2:31–33, 2:35–40, 3:1–6; Ex. 1003 ¶ 163) (emphases omitted).

Essentially, Petitioner contends that the particular unit dosage form required by the challenged claims would have been obvious over Plachetka's disclosure that esomeprazole in amounts between 5 and 100 mg is suitable for the immediate release layer of its dosage form, while enteric-coated naproxen in amounts between 200 and 600 mg is preferred for the core of the dosage form—and that it would have been obvious for the ordinary artisan to administer the dosage form to patients in need of NSAID therapy, and also taking LDA, given Plachetka's recognition of "the problem of adverse effects of chronic LDA usage on NSAID administration." *Id.* at 34–

36 (citing Ex. 1003 ¶¶ 163, 164, 166, 168, 170; Ex. 1004, 2:35–40, 3:19-36, 39–59, 4:18–20, 6:6–11, 7:7–13, 21:46–22:17).

Consequently, Petitioner contends that the final wherein clause of the challenged claims reflects the natural result of the obvious combination of elements explicitly disclosed by Plachetka. Pet. 40.

For the reasons discussed above in connection with the challenge over Plachetka, Graham, and Goldstein, we find that the unexpected result of administering Plachetka's unit dosage form to a patient also taking LDA, even if flowing naturally from the combination of elements disclosed by Plachetka, differs in kind from what would have been expected—thereby supporting a conclusion of nonobviousness. *See Allergan,* 796 F.3d at 1307 (rejecting the argument that unexpected results cannot support a conclusion of nonobviousness because they are merely the inherent properties of an otherwise obvious combination).

Accordingly, we conclude that Petitioner has not demonstrated by a preponderance of the evidence that the subject matter of claims 1–16 would have been obvious over Plachetka.

III. CONCLUSION

Coalition has not carried its burden of proving by a preponderance of the evidence that claims 1–16 would have been unpatentable over Plachetka, Graham, and Goldstein, or over Plachetka alone.

IV. ORDER

For the reasons given, it is:

ORDERED that claims 1–16 of U.S. Patent 8,945,621 B2 have not been shown to be unpatentable by a preponderance of the evidence; and

FURTHER ORDERED that, because this is a final 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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