APPENDIX

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APPENDIX A

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NUVO PHARMACEUTICALS (IRELAND) DESIGNATED ACTIVITY COMPANY, HORIZON MEDICINES LLC,
Plaintiffs-Cross-Appellants

v.

DR. REDDY'S LABORATORIES INC., DR. REDDY'S LABORATORIES, LTD., MYLAN, INC., MYLAN PHARMACEUTICALS INC., MYLAN LABORATORIES LIMITED,
Defendant-Appellants,

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,
Defendants-Appellees.

2017-2473, 2017-2481, 2017-2484, 2017-2486, 2017-2489, 2017-2491, 2017-2492, 2017-2493

Appeals from the United States District Court for the District of New Jersey in Nos. 3:11-cv-02317-MLC-DEA, 3:13-cv-00091-MLC-DEA, 3:13-cv-04022-MLC-DEA, Judge Mary L. Cooper.

DECIDED: May 15, 2019

JAMES B. MONROE, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for plaintiffs-cross-appellants. Plaintiff-cross-appellant Horizon Medicines LLC also represented by CHARLES COLLINS-CHASE.

STEPHEN M. HASH, Baker Botts, LLP, Austin, TX, for plaintiff-cross-appellant Nuvo Pharmaceuticals (Ireland) Designated Activity Company. Also represented by JEFFREY SEAN GRITTON.

ALAN HENRY POLLACK, Windels Marx Lane & Mittendorf LLP, Madison, NJ, argued for all defendants-appellants. Defendants-appellants Dr. Reddy's Laboratories Inc., Dr. Reddy's Laboratories, Ltd. also represented by STUART D. SENDER.

ANDREW DUFRESNE, Perkins Coie LLP, Madison, WI, argued for all defendants-appellants. Defendants-appellants Mylan, Inc., Mylan Pharmaceuticals Inc., Mylan Laboratories Limited also represented by AUTUMN N. NERO; DAN L. BAGATELL, Hanover, NH; SHANNON BLOODWORTH, Washington, DC.

SAILESH K. PATEL, Schiff Hardin LLP, Chicago, IL, for defendants-appellees Lupin Ltd., Lupin Pharmaceuticals, Inc.

Before PROST, *Chief Judge*, CLEVENGER and WALLACH, *Circuit Judges*.

CLEVENGER, Circuit Judge.

Dr. Reddy's Laboratories, Inc., Mylan Pharmaceuticals, and Lupin Pharmaceuticals (collectively, "the Generics") appeal from the final judgment of the United States District Court for the District of New Jersey following a bench trial upholding the asserted claims of U.S. Patent Nos. 6,926,907 ("the '907 patent") and 8,557,285 ("the '285 patent") as nonobvious under 35 U.S.C. § 103, enabled under 35 U.S.C. § 112, and adequately described under § 112. Nuvo Pharmaceuticals, Inc. and Horizon Pharma (collectively, "Nuvo") cross-appeal from the district court's grant of summary judgment of noninfringement to Dr. Reddy's, concluding that one of its drug products will not infringe the claims of the '907 patent. For the reasons set forth below, we reverse the appeal and dismiss the cross- appeal.

BACKGROUND

I

Non-steroidal anti-inflammatory drugs, also known as NSAIDs, control pain. Common NSAIDs include, among others, aspirin and naproxen. While NSAIDs control pain, they also have the undesirable side effect of causing gastrointestinal problems such as ulcers, erosions, and other lesions in the stomach and upper small intestine. Some theorize that the

undesirable side effect is tied to the combination of NSAID with the presence of acid in the stomach and upper small intestine. So, to treat the side effect, some practitioners began prescribing acid inhibitors to be taken by a patient along with the NSAID. The NSAID treats the pain while the acid inhibitor reduces the acidity in the gastrointestinal tract, which is achieved by increasing the pH level in the tract. Common acid inhibitors include, among others, proton pump inhibitors ("PPIs") like omeprazole and esomeprazole.

The combination therapy had complications. First, stomach acid degraded the PPI before it could reach the small intestine. To fix that issue, an enteric coating that wears off after a certain amount of time has elapsed was placed around the PPI. Second, if the NSAID was released before the acid inhibitor had enough time to raise the pH level in the tract, patients would continue to suffer gastrointestinal damage. To address those complications, Dr. John Plachetka invented a new drug form that coordinated the release of an acid inhibitor and an NSAID in a single tablet. The tablet contained a core of an NSAID like naproxen in an amount effective to treat pain, an enteric coating around the NSAID that prevents its release before the pH increases to a certain desired level, and an acid inhibitor like PPI around the outside of the enteric coating that actively works to increase the pH to the desired level. Dr. Plachetka's invention contemplates using some amount of uncoated PPI to allow for its immediate release into a patient's stomach and upper small intestine. Dr. Plachetka recognized problems associated with uncoated PPI, namely that without a coating, the PPI

is at risk of destruction by stomach acid—thereby undermining the therapeutic effectiveness of the PPI.

Dr. Plachetka received the '907 patent on his invention, which he assigned to Pozen Inc. He also received the '285 patent, which is a division of an abandoned application that was a division of another application that itself was a continuation-in-part of the application that resulted in the '907 patent. The '285 patent is also assigned to Pozen. The two patents bear the same title, "Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs," and have nearly identical specifications.

Claim 1 of the '907 patent and claim 1 of the '285 patent are representative. They read as follows:

> 1. A pharmaceutical composition in unit dosage form suitable for oral administration to a patient, comprising:
>
> > (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of aid unit dosage forms;
> >
> > (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

and wherein said unit dosage form provides for co-ordinated release such that:

> i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher;
>
> ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

'907 patent col. 20 ll. 9–32.

> 1. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:
>
> (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and
>
> (b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher;

> wherein said unit dosage form provides for release of said esomeprazole such that 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.

'285 patent col. 22 ll. 9–19.

The shared specification discloses that the invention "is directed to a pharmaceutical composition in unit dosage form suitable for oral administration to a patient" that "contains an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5, preferably to at least 4, and more preferably to at least 5, when one or more unit dosage forms are administered." '907 patent col. 3 ll. 19–25.[1] It discloses exemplary acid inhibitors like PPIs, which the patents teach includes omeprazole and esomeprazole. It recites amounts of omeprazole between 5 and 50 mg and amounts of esomeprazole between 5 and 100 mg, "with about 40 mg per unit dosage form being preferred." *Id*. at col. 7 ll. 9–13. The specification discloses that "[t]he pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation." *Id*. at col. 3 ll. 39–41. It provides that "[t]he most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in

[1] Because the '907 and '285 patents have nearly identical specifications, we cite to the '907 patent only un- less stated otherwise.

an amount of between 200 mg and 600 mg." *Id.* at col. 3 ll. 48–50.

The specification teaches methods for preparing and making the claimed drug formulations, including in tablet dosage forms. It provides examples of the structure and ingredients of the drug formulations that comport with the invention. It is undisputed that there is no experimental data demonstrating the therapeutic effectiveness of any amount of uncoated PPI and coated NSAID in a single dosage form. Appellant's Opening Br. 23, 33; Appellee's Resp. Br. 35, 43; Oral Arg. at 34:08–40, http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2017-2473.mp3. Furthermore, although the specification expressly provides that PPIs are "enteric coated to avoid destruction by stomach acid," there is no alternative disclosure explaining that uncoated PPI could still be effective to raise pH. '907 patent col. 2 l.6; Oral Arg. at 34:08–39:28.

Pozen ultimately sold its rights to the '907 and '285 patents to Nuvo Pharmaceuticals, and Horizon Pharma maintained its previously obtained license under those patents. Nuvo makes and sells a drug called Vimovo®, which is a commercial embodiment of the '907 and '285 patents. The Generics want to market a generic version of Vimovo®. They submitted Abbreviated New Drug Applications ("ANDAs") to the U.S. Food and Drug Administration ("FDA") seeking approval to market products covered by the claims of the '907 and '285 patents. Dr. Reddy's also submitted a second ANDA covering a product slightly different than Vimovo® because it contains a small amount of

uncoated NSAID in the outer layer of the tablet, which is separate from the enteric-coated NSAID that releases only when the pH rises to about 5.5.

II

Nuvo sued the Generics in the United States District Court for the District of New Jersey to prevent their ANDA products from going to market, if approved, before the expiration of the '907 and '285 patents. Nuvo alleged that all the Generics' ANDA products will infringe claims 5, 15, 52, and 53 of the '907 patent and claims 1–4 of the '285 patent.[2] The Generics stipulated to infringement, except with respect to Dr. Reddy's second ANDA product, which it alleged will not infringe the claims of either patent. The Generics defended against the infringement assertions by alleging that the asserted patents are invalid as obvious over the prior art under 35 U.S.C. § 103 and for lack of enablement and an adequate written description under 35 U.S.C. § 112.

Dr. Reddy's moved for summary judgment of noninfringement, arguing that its second ANDA product does not infringe the asserted claims of the '907 patent. It argued that, because the claims of the '907 patent prevent "essentially any NSAID" from being released from the unit dosage form until the pH reaches at least 3.5, its second ANDA product containing some amount of NSAID in the outer layer that is released immediately, regardless of the pH, cannot infringe those claims. Nuvo countered that the

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[2] All the asserted claims of the '907 and '285 patents are dependent on claim 1 of those respective patents.

phrase "essentially any NSAID" in the claim language prevents only NSAID in the core of the tablet from being released before the pH rises to 3.5 or higher and that the claimed invention allows for a small amount of additional NSAID to be released immediately. The district court agreed with Dr. Reddy's and granted its summary judgment motion.

The court then held a six-day bench trial on the validity of the '907 and '285 patents, as well as Dr. Reddy's contention that its second ANDA product does not infringe the asserted claims of the '285 patent. It concluded that none of the asserted claims are obvious over the prior art because it was nonobvious to use a PPI to prevent NSAID-related gastric injury, and persons of ordinary skill in the art were discouraged by the prior art from using uncoated PPI and would not have reasonably expected it to work. It also determined that the asserted claims of both patents are enabled because the specification teaches how to make and use the invention and expert testimony demonstrated that an ordinarily skilled artisan would have accepted the usefulness of an NSAID–PPI combination therapy for treating pain.

The district court went on to reject all three of the Generics' written description arguments. First, the court rejected the "comprising" written description argument. The Generics argued that, because of the "comprising" language in the '285 patent's claims, they allow for the drug formulation to include some uncoated naproxen that is released immediately regardless of the pH, which is not supported by the specification and goes against the concept of

coordinated release that is at the heart of the patent's invention. The court disagreed because it viewed uncoated naproxen as a less preferred embodiment of the claimed invention and thus found that the invention was supported by the general disclosure in the specification.

Second, the district court rejected the "inhibit" written description argument. The Generics contended that, although the patent discloses only delayed release formulations, the claims of the '285 patent recite a broader undescribed invention, namely sustained release as op- posed to coordinated release of naproxen. That is because the claims cover any formulation having a coating that merely "inhibits" the release of naproxen before the pH reaches 3.5 or higher, which would include sustained release drugs that immediately discharge naproxen albeit at a slower rate than is typical. The court disagreed that the word "inhibits" meant that the claims contemplated sustained release drug formulations and thus concluded that the claims do not lack written description support on that basis.

Third, the district court rejected the "efficacy" written description argument. The Generics argued that, if they lose on their obviousness contention, then the claims lack written description support for the claimed effectiveness of uncoated PPI because ordinarily skilled artisans would not have expected it to work and the specification provides no experimental data or analytical reasoning showing the inventor possessed an effective uncoated PPI. Nuvo responded that experimental data and an

explanation of why an invention works are not required, the specification adequately describes using uncoated PPI, and its effectiveness is necessarily inherent in the described formulation. The court rejected the notion that effectiveness does not need to be described because it is necessarily inherent in the claimed drug formulation. It also held that the specification of the '907 and '285 patents did not disclose information regarding the efficacy of uncoated PPI. But the court nonetheless concluded that the claims were adequately described because the specification described the immediate release of uncoated PPI and the potential disadvantages of coated PPI, namely that enteric-coated PPI sometimes works too slowly to raise the intragastric pH. The district court did not explain why the mere disclosure of immediate release uncoated PPI, coupled with the known disadvantages of coated PPI, is relevant to the therapeutic effectiveness of uncoated PPI, which the patent itself recognized as problematic for efficacy due to its potential for destruction by stomach acid.

Finally, the district court held that Dr. Reddy's second ANDA product infringes the claims of the '285 patent because it satisfies all the limitations recited in those claims.

The Generics now appeal the first "comprising" and third "efficacy" written description rulings. They do not appeal the obviousness holding, the enablement decision, or the second "inhibit" written description issue. Nuvo cross-appeals the district court's grant of summary judgment of

noninfringement. We have jurisdiction to decide the appeals under 28 U.S.C. § 1295(a)(1).

DISCUSSION

The Generics' appeal and Nuvo's cross-appeal present three main issues. First, the Generics argue that the district court clearly erred when it concluded that the specification of the '907 and '285 patents adequately describes the claimed effectiveness of uncoated PPI. The Generics emphasize the circumstances in which the written description issue arises in this case. The asserted claims recite the therapeutic effectiveness of uncoated PPI, but the prior art taught away from such effectiveness. In those circumstances, the Generics argue that satisfaction of the written description requirement requires either supporting experimental data, or some reason, theory, or alternative explanation as to why the claimed invention is possessed by the inventor, and that mere recitation of claim language in the specification cannot suffice. Second, the Generics argue that the district court clearly erred when it concluded that the specification of the '907 and '285 patents adequately describes uncoated naproxen. Finally, Nuvo argues that the district court should not have granted summary judgment of noninfringement in favor of Dr. Reddy's because it incorrectly construed the term "essentially any NSAID" in the claims of the '907 patent to prevent even small amounts of uncoated NSAID in the unit dosage form.

Whether a claim satisfies the written description requirement is a question of fact. *Allergan, Inc. v. Sandoz Inc.,* 796 F.3d 1293, 1308 (Fed. Cir. 2015). Therefore, on appeal from a bench trial, we review a written description determination for clear error. *Id.* "Under the clear error standard, the court's findings will not be overturned in the absence of a 'definite and firm conviction' that a mistake has been made." *Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.,* 528 F.3d 1365, 1374 (Fed. Cir. 2008) (quoting *Pfizer, Inc. v. Teva Pharm. USA, Inc.,* 518 F.3d 1353, 1366 (Fed. Cir. 2008)).

Our analysis begins and ends with the "efficacy" written description issue.

I

The written description requirement of 35 U.S.C. § 112, ¶ 1 provides, in pertinent part, that "[t]he specification shall contain a written description of the invention."[3] That requirement is satisfied only if the inventor "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate[s] that by disclosure in the specification of the patent." *Centocor Ortho Biotech, Inc. v. Abbott Labs.,* 636 F.3d 1341, 1348 (Fed. Cir. 2011) (quoting *Carnegie Mellon Univ. v. Hoffmann–La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008)). "The essence of

[3] Because the applications resulting in the '907 and '285 patents were filed before the enactment of the Leahy–Smith America Invents Act ("AIA"), Pub. L. No. 112–29, § 4(c), 125 Stat. 284, 296–97 (2011), we apply the pre-AIA version of 35 U.S.C. § 112.

the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.,* 759 F.3d 1285, 1298 (Fed. Cir. 2014).

The Generics argue that the district court clearly erred when it concluded that the claimed effectiveness of uncoated PPI in the '907 and '285 patents is supported by adequate written description. Their argument is straightforward. The '907 and '285 patents claim uncoated PPI effective to raise the gastric pH to at least 3.5, the district court found upon Nuvo's insistence as part of its obviousness analysis that ordinarily skilled artisans would not have expected uncoated PPIs to be effective, and nothing in the specification would teach a person of ordinary skill in the art otherwise.

Nuvo counters that the district court correctly concluded that the claimed uncoated PPI is supported by adequate written description. It argues that the claims do not require any particular degree of efficacy of the uncoated PPI itself, it is enough that the specification discloses making and using drug formulations containing effective amounts of PPI and NSAID, and experimental data and additional explanations demonstrating the invention works are unnecessary.

The district court held that the Generics failed to prove by clear and convincing evidence that the

asserted claims of the '907 and '285 patents are invalid for lack of written description. But its analysis does not support its conclusion. The district court, after finding that the specification lacks "information regarding the efficacy of uncoated PPIs," said it was enough that the specification described the immediate release of uncoated PPI and the potential disadvantages of enteric-coated PPI formulations. J.A. 82–83. But that disclosure it pointed to in no way provides support for the claimed efficacy of uncoated PPI. Even if the district court thought that it was enough that the patents taught how to make and use drug formulations containing uncoated PPI, it flatly rejected Nuvo's argument "that the efficacy of uncoated PPIs need not be described because it is 'necessarily inherent' in a formulation." J.A. 83. Nevertheless, because we review the district court's decision for clear error, we will scour the record created below for evidence supporting the district court's written description finding.

A

At trial, the parties and the district court understood that the plain words of the patents claim effectiveness of uncoated PPI. Beyond the plain language of the claims, the district court was not asked to define further the effectiveness limitation. The parties and the district court also understood that written description of effective uncoated PPI is required. Nuvo nonetheless for the first time on appeal, and as its lead argument, contends that we can affirm the district court's written description finding because the claims do not recite an efficacy

requirement for uncoated PPI. The Generics of course disagree. We read Nuvo's appellate brief as presenting at least five arguments aimed at either recharacterizing the written description dispute or rewriting the claim language. We reject them all as meritless.

Claim 1 of the '907 patent recites "[a] pharmaceutical composition in unit dosage form suitable for oral administration to a patient, comprising:… an acid inhibitor present in an amount *effective to raise the gastric pH of said patient to at least 3.5* upon the administration of one or more of said unit dosage forms" and wherein "at least a portion of said acid inhibitor is not surrounded by an enteric coating:…" '907 patent col. 20 ll. 9–29 (emphasis added). Claim 1 of the '285 patent recites "[a] pharmaceutical composition in unit dosage form comprising *therapeutically effective amounts of*: (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating" and "wherein said unit dosage form provides for release of said esomeprazole such that 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." '285 patent col. 22 ll. 9–19 (emphasis added). The claim also recites "naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher," which means the esomeprazole must be acting to raise the pH to effect the release of the naproxen from the dosage form. *Id*. at col. 22 ll. 13–15. Both patents-in-suit therefore recite claims requiring amounts of

uncoated PPI effective to raise the gastric pH to at least 3.5. No argument was made below that the claims of the '907 patent should be treated any differently than those of the '285 patent with respect to the efficacy limitation. And the district court treated the claims the same with respect to that limitation. So we do not treat them differently on appeal either.

First, Nuvo argues that there is no requirement that the dosage form as a whole be effective to raise the gastric pH. While we agree, we do not understand the Generics to be arguing that the claims require the entire drug to be effective to raise the gastric pH to a certain level. Instead, the uncoated PPI must effectively do so.

Second, Nuvo contends that the claims do not require an effective amount of the combined uncoated PPI and coated naproxen in a single dosage form, but only amounts of each component effective on their own. The Generics respond that Nuvo's argument is divorced from the claim as a whole, which requires coordinated release achieved by an effective amount of uncoated PPI that raises the gastric pH to at least 3.5 and an effective amount of naproxen that is released to treat pain when the pH reaches the desired level. Nuvo's argument was not raised below and thus is forfeited. See *TVIIM, LLC v. McAfee, Inc.*, 851 F.3d 1356, 1363 (Fed. Cir. 2017) ("[A] party may not introduce new claim construction arguments on appeal or alter the scope of the claim construction positions it took below. Moreover, litigants waive

their right to present new claim construction disputes if they are raised for the first time after trial.").

Third, Nuvo argues that the claims do not require that the uncoated PPI be effective to raise the gastric pH to a certain level, but only that the dosage forms contain an effective amount of uncoated PPI. The Generics disagree. Nuvo forfeited the argument by not raising it below. Additionally, it is nonsensical to read the claims to require effective amounts of uncoated PPI without specifying the result effectively achieved. Claim 1 of the '907 patent expressly states that the PPI, which is uncoated, must be effective to raise the gastric pH to at least 3.5. Claim 1 of the '285 patent at least impliedly requires the same since the naproxen is only released when the pH reaches at least 3.5 and the uncoated esomeprazole is the only other agent available in the dosage form to achieve that goal.

Fourth, Nuvo contends that the '907 patent allows multiple dosage forms rather than a single dosage form to satisfy any perceived efficacy requirement, so the specification does not need to show an effective amount of uncoated PPI in one dosage form. We disagree. As stated above, Nuvo forfeited any argument that the '907 and '285 patents should be treated differently with respect to the efficacy requirement by not raising it to the district court. And the '285 patent does not allow for more than one dosage form. Even if it were true that the '907 patent allows more than one dosage form to effectively raise the gastric pH to at least 3.5 using uncoated PPI, the

specification would still need to provide support for the notion that uncoated PPI is effective.

Last, Nuvo argues that the Examiner interpreted the '907 patent claims as merely requiring certain amounts of PPI and NSAID effective on their own rather than requiring an overall efficacy for the combined drug. The Generics counter that the Examiner never considered the effectiveness of uncoated PPI because it was not a claim limitation at the time of the initial rejection. We already rejected Nuvo's argument that the difference between a dosage form as a whole containing an effective amount of uncoated PPI and an effective amount of uncoated PPI as a component meaningfully impacts the written description analysis. And we also already rejected its argument that the Generics were contending that Nuvo had to demonstrate the overall effectiveness of the entire drug combination. Furthermore, the argument is forfeited because it was not presented below. Finally, the Examiner appears to have interpreted the claims to require an amount of PPI, whether coated or uncoated, effective to raise the gastric pH to the desired level. We agree with that understanding and written description support must be provided for that limitation.

In sum, the parties appear to have assumed before the district court that the claims require a therapeutically effective amount of uncoated PPI that can raise the gastric pH to at least 3.5. We see no reason to change course on appeal. Because the parties' assumption at the trial court is a fair reading of the claim language, we will proceed as everyone did

before the district court and search the specification for written description support for the efficacy of uncoated PPI.

B

Nuvo argues that credible expert testimony from its witness, Dr. Williams, identified written description support in the specification for the claimed dosage forms comprising an effective amount of uncoated PPI. Specifically, Nuvo points to Dr. Williams's testimony that every limitation of the asserted claims in the '907 and '285 patents has adequate written description support in the shared specification.

Dr. Williams identified four parts of the specification that he thought provide written description support for amounts of uncoated PPI, and specifically esomeprazole, effective to raise the gastric pH of a patient to at least 3.5. He pointed to the specification's statement that "[t]he composition contains an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5." *See* J.A. 10787 (quoting '907 patent col. 3 ll. 21–23), 10797 (similar). He also pointed to the claims themselves for written description support. *See* J.A. 10787 (citing '907 patent col. 20 ll. 9–32, 42–45), 10798 (similar). He then said the sixth example in the specification provides support for uncoated PPI because it includes "omeprazole immediate release" in the title and provides that a layer of the composition embodied in the example "contains an acid inhibitor in an effective amount which is released from the

dosage form as soon as the film coat dissolves," where the acid inhibitor is the PPI omeprazole. J.A. 10788–89 (quoting '907 patent col. 14 ll. 40–41, col. 15 ll. 1–3). His last piece of support from the specification was its statement that "[p]roton pump inhibitors will typically be present at about 5 milligrams to 600 milligrams per dose" and "[e]someprazole is 5 to 100 milligrams." J.A. 10798 (quoting '907 patent col. 7 ll. 7–13).

The Generics argue that the parts of the specification Dr. Williams identified are not enough to satisfy the written description requirement. They argue that the specification provides only typical dosage amounts of uncoated PPI and the use of uncoated PPI in a drug formulation, but it never discusses or explains its efficacy. We agree with the Generics that Dr. Williams's testimony does not identify parts of the specification sufficient to satisfy the written description requirement. The statements he points to recite the claim limitation by simply calling generally for effective amounts of uncoated PPI, but our precedent clearly establishes that is not enough.

We have expressly rejected the "argument that the written description requirement … is necessarily met as a matter of law because the claim language appears in *ipsis verbis* in the specification." *Enzo Biochem, Inc. v. GenProbe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002). We explained that "[t]he appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy" § 112, ¶ 1 because it may not both put others on notice

of the scope of the claimed invention and demonstrate possession of that invention. *Id.* at 968–69.

It is true that our case law does not require experimental data demonstrating effectiveness. *Allergan*, 796 F.3d at 1309; *see also In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("Typically, patent applications claiming new methods of treatment are supported by test results. But it is clear that testing need not be conducted by the inventor."). It also does not require theory or explanation of how or why a claimed composition will be effective. *Allergan*, 796 F.3d at 1308–09. Moreover, we have repeatedly stated that the invention does not actually have to be reduced to practice. *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004).

Nevertheless, as the Generics point out and Nuvo cannot reasonably dispute, the record evidence demonstrates that a person of ordinary skill in the art would not have known or understood that uncoated PPI is effective. And there is nothing in the specification of the patents-in-suit showing "that the inventor *actually invented* the invention claimed." *Centocor*, 636 F.3d at 1348 (emphasis added); *accord Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). There must be some description, such as a constructive reduction to practice, establishing that the inventor "was in possession of the…claimed invention, including all of the elements and limitations." *Univ. of Rochester*, 358 F.3d at 926 (quoting *Hyatt v. Boone*, 146 F.3d 1348, 1353 (Fed. Cir. 1998)). Patents are not rewarded for

mere searches, but are intended to compensate their successful completion. *Ariad*, 598 F.3d at 1353. That is why the written description requirement incentivizes "actual invention," *id*., and thus "[a] 'mere wish or plan' for obtaining the claimed invention is not adequate written description," *Centocor*, 636 F.3d at 1348 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997)).

In light of the fact that the specification provides nothing more than the mere claim that uncoated PPI might work, even though persons of ordinary skill in the art would not have thought it would work, the specification is fatally flawed. It does not demonstrate that the inventor possessed more than a mere wish or hope that uncoated PPI would work, and thus it does not demonstrate that he actually invented what he claimed: an amount of *uncoated* PPI that is *effective* to raise the gastric pH to at least 3.5. That conclusion is confirmed by the inventor's, Dr. Plachetka's, own testimony at trial during which he admitted that he only had a "general concept of coordinated delivery with acid inhibition" using uncoated PPI at the time he filed his first patent application. J.A. 9942, 10000–01. Although Dr. Plachetka said he thought he "put a rationale in [the specification] as to why [uncoated PPI] would work," he did not identify any particular part of the specification supporting that understanding. J.A. 9997. And his only support in the specification for "a rationale explaining why [he] thought the uncoated PPI would be effective for treating gastric related injury" was that, in its "entire context," he explained "why the coordinated delivery

system would be of benefit for patients." *Id.* Although inventor testimony cannot establish written description support where none exists in the four corners of the specification, it illuminates the absence of critical description in this case.[4]

C

Nuvo's final arguments are that it is enough to satisfy the written description requirement that the specification of the '907 and '285 patents teaches how to make and use the claimed invention, and that we should accept the therapeutic effectiveness of uncoated PPI as a matter of inherency. The Generics respond that Nuvo is wrong because that only satisfies the enablement requirement, which is

[4] At oral argument, Nuvo also encouraged us to find written description support for the therapeutic effectiveness of uncoated PPI based on testimony of Dr. Kibbe, the Generics' expert. Oral Arg. at 50:51–52:26. But in that part of the trial transcript Nuvo directed us to, Dr. Kibbe only discussed what the patent claims require and he never testified about the written description support in the specification for the efficacy of uncoated PPI. Furthermore, although Dr. Kibbe later confirmed during his trial testimony that he thought "an enteric-coated NSAID surrounded by an uncoated PPI would be effective for treating chronic pain," his confirmation was ambiguous because he qualified it with "I think I have got that right. I'm not sure." J.A. 10513. Even if we accepted his statement that uncoated PPI would be effective for treating chronic pain, the district court rejected the notion that ordinarily skilled artisans would have used uncoated PPI in its obviousness analysis, and his testimony only speaks to treating pain and not to raising the gastric pH to at least 3.5. Dispositively, Dr. Kibbe's testimony is irrelevant to the written de- scription inquiry, because it does not point to any disclosure in the specification to which the testimony could relate.

separate and distinct from the written description requirement. As for inherency, the Generics note that the district court rejected that ground for written description support, and assert that Nuvo has not made out a case for inherent disclosure.

1.

Teaching how to make and use an invention does not necessarily satisfy the written description requirement. We have recognized that the enablement requirement, which requires the specification to teach those skilled in the art how to make and use the claimed invention without undue experimentation, is separate and distinct from the written description requirement. *Ariad*, 598 F.3d at 1343–51. And the fact that an invention may be enabled does not mean it is adequately described, and vice versa. *Univ. of Rochester*, 358 F.3d at 921–22. That is because "[t]he purpose of the written description requirement is broader than to merely explain how to 'make and use' [the invention]." *Id.* at 920. The focus of the written description requirement is instead on whether the specification notifies the public about the boundaries and scope of the claimed invention and shows that the inventor possessed all the aspects of the claimed invention. *Id.* at 926.

Nuvo cites our decision in *Alcon Research Ltd. v. Barr Laboratories, Inc.*, 745 F.3d 1180 (Fed. Cir. 2014), to support its position that it is enough that the patents teach making and using the claimed combination drug formulation. The Generics argue

that case is distinguishable. We agree that *Alcon* does not save the claims of the '907 and '285 patents.

In *Alcon*, patent claims were directed to a method for enhancing the chemical stability of an aqueous solution containing a therapeutically effective amount of a known drug. 745 F.3d at 1184. We held that the claims were adequately described because the disclosure in the specification demonstrated that the inventor possessed and actually invented the claimed stability enhancing features of the method. *Id*. at 1191. We noted that the patent referenced the unexpected nature of the discovery, gave exemplary formulations, and disclosed data showing stability testing using the claimed invention. *Id*.

The factual circumstances in *Alcon* are markedly different than the facts presented here. Unlike the specification of the patent at issue in *Alcon*, the specification of the '907 and '285 patents does not provide any data showing that uncoated PPI is effective in raising the gastric pH of a patient to at least 3.5. Even though we said in *Alcon* that "written description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described" and "is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work," we found that the written description requirement was satisfied at least in part by accelerated stability testing data showing the claimed effect. *Id.* Under those circumstances, it was not necessary for the patentee to demonstrate or otherwise "prove" beyond the data disclosed in the

specification that the invention works. Here, there is no similar hook or disclosure in the specification that an ordinarily skilled artisan can rely on to understand that the inventor possessed effective uncoated PPI.

2.

Our case law has recognized that, under a narrow set of circumstances, the written description requirement may be satisfied without an explicit disclosure if the claimed features are necessarily inherent in what is expressly described. *See, e.g.*, *Allergan*, 796 F.3d at 1309 ("A claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described."); *Yeda Research & Dev. Co. v. Abbott GmbH & Co. KG*, 837 F.3d 1341, 1345 (Fed. Cir. 2016) ("Under the doctrine of inherent disclosure, when a specification describes an invention that has certain undisclosed yet inherent properties, that specification serves as adequate written description to support a subsequent patent application that explicitly recites the invention's inherent properties."); *cf.* Manual of Patent Examining Procedure § 2163 (9th ed. Rev. 3, Jan. 2018) (recognizing that inherency may satisfy the written description requirement).

Nuvo cites our decision in *Allergan* to support its position that the claimed efficacy of uncoated PPI is necessarily inherent in the specification's explicit disclosure of methods for making and using drug formulations containing uncoated PPI. The Generics

contend that, like *Alcon*, *Allergan* is also factually distinguishable. We agree.

In *Allergan*, the patentee claimed a drug combination effective for reducing intraocular pressure that included 0.01% bimatoprost and 200 ppm benzalkonium chloride ("BAK"). 796 F.3d at 1300. But the prior art taught away from the claimed combination of ingredients and the specification did not explicitly describe its clinical efficacy. *Id.* at 1298, 1305–07, 1309. While we upheld the nonobviousness of the claimed invention given the unexpected results of and teaching away from increasing the amount of BAK to decrease the amount of intraocular pressure, we also held that the claims were supported by adequate written description. *Id.* at 1305, 1309. We reasoned that the parties did not dispute that "the inherent properties of a formulation comprising 0.01% bimatoprost and 200 ppm BAK produce the claimed clinical profile." *Id.* at 1309. It was enough that the specification described the formulation, its components, and how to make and use it. *Id.* at 1308–09. Moreover, there were experimental results for similar drug formulations demonstrating a trend in their clinical effectiveness, even if the data were not specifically related to the exact formulation claimed. *Id.* at 1299–300.

Here, unlike in *Allergan*, whether uncoated PPI is inherently effective in raising the gastric pH to at least 3.5 is disputed. And there is no written disclosure that in any way relates to the efficacy of immediately released PPI. Neither party has identified any evidence in the record that uncoated

PPI necessarily is effective in a certain amount, consistent with the specification, to raise the gastric pH to 3.5 or higher. Nor can we find any evidence in the record demonstrating the inherency of the claimed feature. That failure of proof thus dooms Nuvo's inherency argument.

D

Written description analyses are highly fact specific. See *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1377 (Fed. Cir. 2017) ("[E]ach case involving the issue of written description must be decided on its own facts." (alterations and internal quotation marks omitted) (quoting *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004))); *VasCath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991) ("The CCPA's 'written description' cases often stressed the fact-specificity of the issue."). Based on the specific facts of certain cases, it is unnecessary to prove that a claimed pharmaceutical compound actually achieves a certain result. But when the inventor expressly claims that result, our case law provides that that result must be supported by adequate disclosure in the specification. In this case, the inventor chose to claim the therapeutic effectiveness of uncoated PPI, but he did not adequately describe the efficacy of uncoated PPI so as to demonstrate to ordinarily skilled artisans that he possessed and actually invented what he claimed. And the evidence demonstrates that a person of ordinary skill in the art reading the specification would not have otherwise recognized, based on the disclosure of a formulation containing uncoated PPI, that it would be efficacious because he or she would

not have expected uncoated PPI to raise gastric pH. Under those facts, the patent claims are invalid for lack of adequate written description pursuant to §112, ¶ 1.

II

Because we hold that the '907 and '285 patents are invalid for lack of an adequate written description given that the shared specification does not adequately describe the claimed effectiveness of uncoated PPI, we do not need to address the Generics' alternative argument that the patents are also invalid under § 112, ¶ 1 for failing to adequately describe uncoated, immediate release naproxen. Similarly, because we conclude that the asserted claims are invalid, Nuvo's cross-appeal challenging the district court's grant of summary judgment of noninfringement with respect to Dr. Reddy's second ANDA product and the '907 patent is moot.

CONCLUSION

For the reasons stated above, we reverse the district court's determination that the asserted claims of the '907 and '285 patents are not invalid for lack of an adequate written description. Those claims are invalid. We dismiss as moot Nuvo's cross-appeal challenging the district court's grant of summary judgment of noninfringement to Dr. Reddy's with respect to its second ANDA product and the now-invalidated '907 patent claims.

REVERSED AS TO 17-2473, 17-2481, 17-2484, 17-2486; DISMISSED AS TO 17-2489, 17-2491, 17-2492, 17-2493.

COSTS

No costs.

APPENDIX B

In the United States District Court
For the District of New Jersey

Case No. 11-02317 (MLC) (DEA)

HORIZON PHARMA, INC. and
POZEN INC.,
Plaintiffs,

v.

DR. REDDY'S LABORATORIES INC. and
DR. REDDY'S LABORATORIES LTD.,
Defendants.

ISSUED: July 10, 2017

REDACTED AMENDED MEMORANDUM OPINION

I. COOPER, District Judge

I. Background

This is a patent dispute between Plaintiffs Horizon Pharma, Inc. and Pozen Inc. (together, "Horizon") and two groups of generic drug manufacturers: (1) Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. ("DRL"); and (2) Mylan, Inc.; Mylan Pharmaceuticals Inc.; and Mylan Laboratories Ltd. ("Mylan," and together with DRL, "Defendants"). Horizon holds New Drug Application ("NDA") No. 022511 for Vimovo, a branded drug product whose active pharmaceutical ingredients are naproxen and esomeprazole magnesium. (Dkt. 421 at 6.)[1]

This case arises out of Defendants' submission of Abbreviated New Drug Applications ("ANDAs") to the FDA pursuant to the Hatch-Waxman Act, 21 U.S.C. § 355(j), for the purpose of obtaining FDA approval for the commercial manufacture, use, import, offer for sale, and sale of a generic version of Vimovo. Specifically, DRL filed ANDA No. 202461 ("DRL ANDA I") and ANDA No. 204206 (DRL ANDA II"). Mylan filed ANDA No. 204920 ("Mylan ANDA"). Based on submissions by the parties in the pre- trial order, all three ANDAs relate to tablets containing 375 mg or 500 mg of naproxen and 20 mg

[1] The Court will cite documents filed on the Electronic Case Filing System ("ECF") by referring to the docket entry numbers as "dkt." Pincites reference ECF pagination.

esomeprazole magnesium. (Dkt. 421 at 7–8.)[2] All three ANDAs included so-called "Paragraph IV" certifications that the products would not infringe Horizon's patents and/or that those patents are invalid or unenforceable. (Id.) The Paragraph IV certifications covered U.S. Patent No. 6,926,907 ("the '907 patent") and No. 8,557,285 ("the '285 patent") (together, the "Asserted Patents"). In response to those Paragraph IV certifications, Horizon asserted infringement of claims 5, 15, 52, and 53 of the '907 patent.[3] Horizon has also asserted claims 1 through 4 of the '285 patent.[4]

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[2] Lupin Pharmaceuticals, Inc. and Lupin Ltd. ("Lupin") submitted an ANDA filing (No. 202654). Horizon's case against Lupin (Case No. 11-4275) has been stayed pending the outcome of this case. (Dkt. 455.)

[3] The asserted claims of the '907 patent (together with claim 1 for context) are:

> **1.** A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:
> (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient
> to at least 3.5 upon the administration of one or more of said unit dosage forms;
> (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms; and wherein said unit dosage form provides for coordinated release such that:
> i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher;

ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon
ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

5. The pharmaceutical composition of claim 1, wherein said acid inhibitor is a proton pump
inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole,
pantoprazole and rabeprazole.

15. The pharmaceutical composition of…claim[] 1…wherein said acid inhibitor is a proton pump inhibitor.

51. A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 15.

52. The method of claim 51, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

53. The pharmaceutical composition of any one of claims 5-11 wherein said unit dosage form is a multilayer tablet comprising a single core and one or more layers outside of said single core,
wherein:

i) said NSAID is present in said core;

ii) said coating that does not release said NSAID unless
the pH of the surrounding medium is 3.5 or higher surrounds said core; and

iii) said acid inhibitor is in said one [or] more layers outside said core. ('907 patent at col. 20, line 9 to col. 24, line 6.)

[4] The asserted claims of the '285 patent are as follows:

1. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:

(a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and

(b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher; wherein said

Mylan has stipulated that its ANDA product would infringe the Asserted Patents. (Dkt. 421 at 8.) DRL has admitted that its DRL ANDA I Product would infringe the Asserted Patents. (Id.) We previously granted summary judgment in DRL's favor that its ANDA II Product does not infringe the '907 patent. (Dkt. 380). Accordingly, the only infringement dispute at trial was whether DRL's ANDA II Product infringes the '285 patent. Most of the trial was focused on Defendants' contentions that claims in the Asserted Patents are invalid under 35 U.S.C. § 103 and/or § 112.

We held a six day bench trial on those issues from January 12–20, 2017 and heard closing arguments on May 17, 2017.[5] We heard live testimony from seven witnesses. Dr. John Plachetka,

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unit dosage form provides for release of said esomeprazole such that 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.

2. The pharmaceutical composition of claim 1, wherein naproxen is present in said unit dosage form in an amount of 200-600 mg.

3. The pharmaceutical composition of claim 1, wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.

[5] The trial transcript is separated into seven volumes, but the pages are numbered consecutively. (See dkt. 458 (Vol. 1), dkt. 461 (Vol. 2), dkt. 463 (Vol. 3), dkt. 466 (Vol. 4), dkt. 468 (Vol. 5), dkt. 471 (Vol. 6), and dkt. 491 (Vol. 7).) We will cite to the trial transcript using the designation "Tr." without indicating the specific volume.

called by Horizon, was the named inventor on the Asserted Patents. (Tr. 15– 192.) Dr. David Metz, called by Defendants, was qualified as an expert in gastroenterology, including the treatment of acid peptic disorder. (Tr. 260–396.) Dr. Arthur Kibbe, called by Defendants, was qualified as an expert in pharmaceutical formulation and development. (Tr. 408–565.) Dr. Michael Mayersohn, called by Defendants, was qualified as an expert on pharmacokinetics and pharmacodynamics. (Tr. 569–603; Tr. 610–707.) Dr. Robert Williams, III, called by Horizon, was qualified as an expert in pharmaceutical formulation. (Tr. 716–842; Tr. 849–1017.) Dr. David Taft, called by Horizon, was qualified as an expert in pharmacokinetics. (Tr. 1018–1102.) Dr. David Johnson, called by Horizon, was qualified as an expert in gastroenterology. (Tr. 1108–1266.) The parties also submitted designated deposition testimony from Brian Ault (DTX-1393); Mark Sostek (DTX-1396); Jeff Sherman (DTX-1397); Dennis McNamara (DTX-1398); Abhijit Desmukh (PTX-581); John Horn (PTX-582); T. Sudhakar Koudinya (PTX-583); Snehalatha Movva (PTX-584); and Badri Viswanathan (PTX-585).[6]

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[6] Defendants object to Dr. Horn's deposition testimony as inadmissible hearsay. (Dkt. 472.) We conclude that Dr. Horn's testimony is admissible because it satisfies the requirements of the hearsay exception in Federal Rule of Civil Procedure 32(a) for deposition testimony of an unavailable witness. See Novozymes A/S v. Genencor Int'l, Inc., No. 05-160, 2006 WL 318936, at *1 (D. Del. Feb. 10, 2006). We note, however, that the exclusion of Dr. Horn's testimony would not have changed any of our conclusions in this opinion.

This opinion follows the parties' division of the relevant legal issues raised at trial and addresses the interrelated infringement and § 112 issues in Section III, infra, and the interrelated obviousness and § 112 issues in Section IV, infra. In support of their arguments, Horizon and Defendants submitted separate post-trial briefs on the issues addressed in Section III (dkt. 489-2; dkt. 489-3) and Section IV (dkt. 489; dkt. 489-1).

For the reasons below, we conclude that DRL's ANDA II Product infringes the '285 patent and that the asserted claims are not invalid under 35 U.S.C. § 103 and/or § 112. Accordingly, we will grant judgment in Horizon's favor and issue an appropriate order.

II. Legal Standards

A. Infringement

The standard for patent infringement is set forth in 35 U.S.C. § 271, which states that "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). The burden to prove infringement rests with the patentee who must prove infringement by a preponderance of the evidence. Medtronic, Inc. v. Mirowski Family Ventures, LLC, 134 S. Ct. 843, 846 (2014). To prove infringement, the patentee must show that an accused product is within the claim limitations of the patent-in-suit either literally or under the doctrine of

equivalents. See Warner Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 21 (1997); Amgen Inc. v. F. Hoffman La Roche Ltd., 580 F. 3d 1340, 1374 (Fed. Cir. 2009). In a Hatch-Waxman case, the actual act of infringement is the filing of an ANDA to obtain approval to engage in the commercial manufacture, use, or sale of a patented drug or method of use. 35 U.S.C. § 271(e)(2). Specifically, § 271(e)(2)(A) provides that it shall be an act of infringement to submit an ANDA "if the purpose of such submission is to obtain approval…to engage in the commercial manufacture, use, or sale of a drug…claimed in a patent or the use of which is claimed in a patent before the expiration of such patent."

The infringement analysis is a two-step process in which we must: (1) determine the scope and meaning of the disputed patent claim terms; and (2) compare the properly construed claims to the allegedly infringing product or device. Advanced Steel Recovery, LLC v. X-Body Equip., Inc., 808 F.3d 1313, 1316 (Fed. Cir. 2015).

B. Written Description

A patent specification must contain "a written description of the invention." 35 U.S.C. § 112(a). To satisfy that requirement, "the specification must describe an invention understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010). "The purpose of the written description requirement is to prevent an applicant from later asserting that

he invented that which he did not." Amgen Inc. v. Hoechst Marion Roussel, 314 F.3d 1313, 1330 (Fed. Cir. 2003). The requirement thus mandates that the applicant "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed. Cir. 1991).

The "hallmark of written description is disclosure," and the test for its sufficiency is "whether the disclosure . . . reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad, 598 F.3d at 1351. "It is the specification itself that must demonstrate possession" and analysis of the adequacy of the written description "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." Id. at 1351–52. The disclosure must "allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 968 (Fed. Cir. 2002).

"There is no rigid requirement that the disclosure contain 'either examples or an actual reduction to practice.'" Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting Ariad, 598 F.3d at 1352). Rather, "the proper inquiry is whether the patentee has provided an adequate description that 'in a definite way identifies the claimed invention' in sufficient detail such that a

person of ordinary skill would understand that the inventor had made the invention at the time of filing." Id. at 1308. Moreover, "an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention." See Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003). The challenging party must show lack of adequate written description by clear and convincing evidence to rebut the patent's presumption of validity. Alcon Research Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1188–91 (Fed. Cir. 2014).

C. Enablement / Utility

35 U.S.C. § 112 requires applicants to describe the manner of making and using the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art … to make and use the same…" The Federal Circuit has explained that "the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1323 (Fed. Cir. 2005) (citing In re Cortright, 165 F.3d 1353, 1356 (Fed. Cir. 1999)). As a result, "an applicant's failure to disclose how to use an invention may support a rejection under . . . section 112…when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." Id. (internal quotations omitted). Conversely, "a specification disclosure which contains a teaching of the manner and process of making and using the

invention…must be taken as in compliance with the enabling requirement of the first paragraph of [section] 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." Id. The challenging party bears the burden of showing by clear and convincing evidence that the specification lacks adequate enablement. ALZA Corp. v. Andrx Pharms., 603 F.3d 935, 940 (Fed. Cir. 2010).

D. Obviousness

Under 35 U.S.C. § 103, a "patent may not be obtained…if the differences between the subject matter sought to be 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 to a person having ordinary skill in the art to which said subject matter pertains." "Obviousness is a question of law, which depends on several underlying factual inquiries." See Senju Pharm. Co. v. Apotex Inc., 717 F. Supp.2d 404, 418 (D. Del. 2010), aff'd, 485 Fed. App'x 433 (Fed. Cir. 2012). Those inquiries include the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)). We also consider as part of the obviousness analysis "secondary considerations," including commercial success, long felt but unsolved needs, and failure of others. Id. "A nonmovant may rebut a prima facie showing of obviousness with objective indicia of nonobviousness." Ormco Corp. v.

Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006). "Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." In re Huai–Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 418; see also Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1360 (Fed. Cir. 2011). Instead, proof of obviousness requires proof that a person of ordinary skill in the art ("POSA") "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and…would have had a reasonable expectation of success in doing so." Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009). A POSA would interpret prior art references "using common sense and appropriate perspective." Unigene Labs., 655 F.3d at 1361. The party challenging the validity of the patent must prove obviousness by clear and convincing evidence. See Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., 719 F.3d 1346, 1352 (Fed. Cir. 2013)

III. Infringement and Related § 112 Challenges to the '285 Patent

The only infringement question at trial was whether DRL's ANDA II Product infringes claims 1, 2, 3, and 4 of the '285 patent. See Section I, supra. Horizon submitted evidence that DRL's ANDA II Product satisfies each limitation of the asserted claims. In response, Defendants offer a pair of

arguments in the alternative. One argument (and, per Defendants, the "better decision" for us to reach) is that the asserted '285 patent claims are invalid for lack of written description on two distinct grounds. The other is that DRL's ANDA II Product cannot infringe the '285 patent if we construe the claims such that they survive the written description challenges. In this section, we reject both written description challenges and conclude that DRL's ANDA II Product infringes the '285 patent.

A. Written Description (Uncoated Naproxen)

Defendants' first written description challenge involves two primary contentions. First, Defendants contend that claim 1 of the '285 patent encompasses formulations that include naproxen that is released immediately. Second, they contend that the '285 patent specification discloses a coordinated release product that does not permit the immediate release of naproxen. This purported disconnect between the scope of the claims and the specification forms the basis of the written description challenge. This section consequently proceeds in two parts. First, we review the parties' evidence and arguments related to the scope of the '285 patent claims and the written description of the invention in the '285 patent specification. Second, we assess whether the '285 patent claims are adequately described by the patent specification under the applicable legal standards.

1. Parties' Evidence and Arguments

(i) Scope of the '285 patent claims

Claim 1 of the '285 patent reads:

> A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:
>
> (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and
>
> (b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher;
>
> wherein said unit dosage form provides for release of said esomeprazole such that 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.

('285 patent at col. 22, lines 8–14.)

Any product alleged to infringe claim 1 must, of course, satisfy the enteric coated naproxen claim limitation set forth in subsection (b). The question before us is the scope of claim 1 as it pertains to ***uncoated*** naproxen that may be released into the

body immediately regardless of pH level.[7] The plain language of claim 1 does not explicitly restrict the amount of uncoated naproxen that may be present in the claimed formulation and indeed the parties agree that the claim encompasses formulations that have ***at least some*** uncoated naproxen. The real dispute between the parties is whether claim 1 limits how much uncoated naproxen may be present in the claimed formulation. Broadly, Defendants urge us to adopt the "plain meaning" of the claim, which "imposes no limitation on the amount of naproxen that may be outside the enteric coating." (Dkt. 489-2 at 12.) Horizon argues that the claim covers formulations that contain uncoated naproxen so long as it is less than a "therapeutically effective amount."[8] (Dkt. 489-3 at 16–17.)

Defendants' proposed reading of claim 1 is straightforward: the plain language of the claim imposes no limitation on the amount of uncoated naproxen that may be present in claimed formulations, and it would be improper to read in

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[7] We follow the parties in using the phrase "enteric coating" as shorthand to describe the pH-sensitive coating used to satisfy the limitation in claim 1, subsection (b). We use the term "uncoated naproxen" to mean naproxen without an enteric coating that may be released immediately regardless of pH. Because the enteric coating in Vimovo is applied around a naproxen "core" of the tablet, the term "uncoated naproxen" can also refer to the naproxen outside the (enteric coated) core.

[8] The parties appear to use the term "therapeutic amount" and "therapeutically effective amount" interchangeably.

such a limitation. (Dkt. 489-2 at 12–14.) Defendants argue that a POSA "would recognize that any amount of naproxen outside the enteric coating (and that could fit in a "unit dosage form") would be covered by the '285 patent claims." (Id. at 12.) They note that Horizon expert Dr. Williams testified that a POSA would understand the term "comprising" to permit the inclusion of additional elements. (Id.; Tr. 821:6-25.) Dr. Williams also explained, in his infringement analysis, that he could "ignore" uncoated naproxen given the "comprising" language. (Tr. 855:12-24.)

Defendants submit that their interpretation is consistent with the history of the '285 patent because Horizon deliberately removed the claim limitation related to uncoated naproxen. (Dkt. 489-2 at 8–9.) As Defendants explain, the '285 patent differs somewhat from the earlier-issued '907 patent. Claim 1 of the '907 patent restricts the amount of uncoated naproxen that may be present by requiring NSAID surrounded by a coating that prevents the release of "essentially any NSAID…unless the pH of the surrounding medium is 3.5 or higher." ('907 patent at col. 20, lines 8–32.) Allegedly to avoid infringement of the '907 patent, DRL formulated its ANDA II Product with some naproxen ***outside*** of the enteric coated core of the tablet. (Dkt. 489-2 at 7.) As part of this litigation, we previously construed the term "essentially any NSAID" to mean "the minimum amount of NSAID released by an enteric coated dosage form, or tablet." (Dkt. 380 at 18–22.) Because DRL's ANDA II product **[redacted]**, we concluded that DRL's ANDA II Product does not

infringe the '907 patent. (Id. at 22–23.) Horizon was later granted the '285 patent, which does not contain the "essentially any NSAID" language that formed the basis of our non-infringement finding for the '907 patent.

Horizon disagrees with Defendants' proposed reading of claim 1 of the '285 patent, and urges us to interpret the claim to limit the amount of permissible uncoated naproxen to less than a "therapeutic amount."[9] Dr. Williams testified that a POSA would understand the claim to allow only "less than a therapeutic amount" of uncoated naproxen. (Tr. 821:15–822:7.) Horizon also points to a decision from the Patent Trial and Appeal Board ("PTAB") denying Inter Partes review of the '285 patent and purportedly supporting Horizon's "therapeutic amount" limitation.[10] The PTAB concluded that

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[9] The '285 patent states that the "most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount between 200 mg and 600 mg." ('285 patent at col. 4, lines 11–14.) The parties accordingly appear to agree that the smallest "therapeutic amount" of Naproxen would be 50 mg. The distinction is irrelevant for infringement purposes in this case because DRL's ANDA II Product **[redacted]**.

[10] See Dr. Reddy's Laboratories, Inc. v. Pozen Inc., IPR2015-00802, Paper No. 28 (P.T.A.B. Oct. 9, 2015). For ease of reference, we will cite this PTAB decision by its trial exhibit number, PTX-351. We acknowledge Defendant Mylan's concern that it was not a party to the PTAB proceeding. (Tr. 547:23–459:19.) None of our conclusions depend on the PTAB's decision but, as discussed below, we are mindful of instances where the PTAB rejected arguments comparable to those made at trial.

claim 1 of the '285 patent "does not exclude the presence of additional naproxen outside of the coating" and "does not exclude a unit dosage form that has an amount of naproxen outside the coating that is not therapeutically effective." (PTX-351 at 13.) Consequently, the PTAB rejected the argument that claim 1 "encompass[ed] a composition where the vast majority of the naproxen, i.e., a therapeutically effective amount, would be *outside* the coating." (PTX-351 at 12.)

Defendants argue that Horizon's proposed therapeutic amount limitation is inconsistent with an FDA Citizen's Petition filed by Horizon. (Dkt. 489-2 at 26–27; DTX-1248.) In that petition, Horizon argued to the FDA that "locating ***any naproxen*** outside the enteric coated core will result in the immediate release of at least some portion of the naproxen at the same time as esomeprazole is released. ***Any portion*** of the generic product's naproxen that is released prematurely in the stomach will act both topically and systemically without the benefit of the raised gastric pH produced by the esomeprazole component." (DTX-1248 at 7 (emphasis added).) In the same petition, Horizon argued that esomeprazole/naproxen combination tablets with uncoated naproxen "could subject patients to significantly increased risk of potentially fatal side effects." (DTX-1248 at 7; Tr. 436:19–437:5.) Because Horizon has separately argued to the FDA that any amount of uncoated naproxen might pose a safety risk, Defendants claim that Horizon's

therapeutic amount limitation is not credible. Defendants further argue that a therapeutic amount limitation does not make sense because the FDA rejected the notion that the sequential release of esomeprazole and naproxen in Vimovo is clinically significant. (DTX-1250 at 7; Tr. 358:11-23; Tr. 462:10-23.)

Defendants also ask us to reject Horizon's proposed therapeutic amount limitation because it was not raised during discovery. (Dkt. 489-2 at 18.) Dr. Williams did not explicitly propose a therapeutic amount limitation in his deposition. Instead, Dr. Williams testified at his deposition that some amount of naproxen outside of an enteric coating might pose a safety issue but did not quantify how much. (Tr. 855:19–858:11.) Moreover, Defendants claim that Horizon "admitted" that the "plain meaning of the '285 patent claims applied and they had no limitation on the amount of naproxen that could be outside of an enteric coating." (Id. at 15.) They point to statements in Horizon's invalidity contentions that "the disclosed dosage forms [in the '285 patent] may include additional naproxen outside the coating." (DTX-1333 at 48–49.)

Horizon in turn rejects the relevance of its Citizen's Petition to understanding the scope of the '285 patent claims. They argue that the relevant time period for our analysis is the priority date, and that any statements made in the Citizen's Petition (which was submitted years later) should not bear on our analysis. (Dkt. 489-3 at 25.) Horizon also notes that its Citizen's Petition merely "requested that the

FDA require testing to ensure that products containing non-enteric coated naproxen were as safe as those that contained only enteric coated naproxen." (Id.; DTX-1248 at 2.)

(ii) Invention as described

Defendants submit that the '285 patent specification discloses a "coordinated release" product that does not immediately release any NSAID (*e.g.*, naproxen). The first part of Defendants' argument—that the '285 patent specification discloses a coordinated release product—is not particularly controversial. The title of the '285 patent is "Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS" and the patent itself notes that the invention is directed to "pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and an [NSAID]…." ('285 patent at col. 1 lines 20–23.) As explained by defense expert Dr. Kibbe, "coordinated release" is the mechanism by which a formulation achieves "coordinated delivery." (Tr. 420:11–422:12.)

Evidence from both sides also indicates that coordinated release refers here to sequential delivery. The '285 patent itself discloses "the coordinated release of therapeutic agents, *i.e.*, for the sequential release of acid inhibitor followed by analgesic." ('285 patent at col. 6, lines 23–35.) Dr. Kibbe and Horizon expert Dr. Williams both described coordinated release as sequential release. (Tr. 420:20–421:7; Tr. 861:9-12.) The description of the invention offered by the named inventor, Dr. Plachetka, also supports this view. Dr. Plachetka

explained that the coordinated delivery is the immediate release of the proton pump inhibitor followed by the release of the NSAID when the pH rises to a certain level. (Tr. 43:22–44:10.) According to Dr. Plachetka, "[t]he whole point of the idea here is to get acid inhibition before the administration of the NSAID…" (Tr. 134:4-5.)

The parties disagree on Defendants' second contention—namely, that the '285 patent specification does not describe formulations where some naproxen is released immediately. Dr. Kibbe testified that there were no teachings in the '285 patent specification related to formulations where naproxen is released before esomeprazole. (Tr. 431:19–432:5.) He also said that "[t]here is no support for any release of naproxen until the enteric coat comes off." (Tr. 437:11-17.) In Dr. Kibbe's view, a product that releases even some naproxen early cannot have a coordinated release within the meaning of the patent specification. (Tr. 422:14–423:16.)

Defendants point to our previous statements regarding the '907 patent specification as evidence of the nature of the invention disclosed in the '285 patent specification. Both Dr. Kibbe and Dr. Williams noted that the specifications of the two patents are essentially the same. (Tr. 419:9-22; Tr. 856:14-17.) We did observe earlier in this litigation discussing the '907 patent:

> The '907 patent's distinction from prior art is the "coordinated drug release…[and

> reduction of] intragastric acid levels to a non-toxic level prior to the release of NSAID." The specification does not contemplate an embodiment that releases a small amount of NSAID before the GI tract reaches a pH of 3.5 or above, nor does the specification state that releasing a small amount of NSAID would be "acceptable or part of the invention."

(Dkt. 380 at 19) (internal citations omitted).[11]

Defendants also point to Horizon's FDA Citizen's Petition as evidence that the invention disclosed in the '285 patent does not extend to formulations that immediately release some naproxen. In that petition, Horizon told the FDA that a formulation with some uncoated naproxen (*i.e.*, DRL's ANDA II Product) "obviates VIMOVO's careful design and allows release of a measureable amount of naproxen before the gastroprotective benefits of esomeprazole can take effect" and "that VIMOVO's design is intended to produce a sequential delivery of gastroprotective esomeprazole before systemic (or local) exposure to naproxen." (DTX-1248 at 2, 5.) In Defendants' view, these statements are evidence that Horizon viewed any early release of naproxen as antithetical to the

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[11] Horizon disagrees that our previous statements on the '907 patent are useful in characterizing the invention and notes that the statements were made in the context of construing "essentially any NSAID," a claim term that does not appear in the '285 patent. (Dkt. 489-3 at 23–24.)

key aspect of the invention—that is, delaying the release of naproxen until after the esomeprazole can take effect. (Dkt. 489-2 at 25–26.) In sum, Defendants argue that coordinated release is the "central feature" of the invention disclosed in the specification and that formulations with uncoated naproxen are "not the invention and even . . . contrary to it." (Dkt. 489-2 at 19.)

To illustrate how the '285 patent claims encompass formulations that do not have a coordinated release, Defendants offered an example of a hypothetical product containing a 50 mg naproxen core surrounded by an enteric coating, an esomeprazole layer immediately above, and an outer layer with 49 mg of naproxen. Defendants submit that this product cannot be considered to have a "coordinated release" because nearly half of the naproxen is released immediately. (Dkt. 489-2 at 23.) They argue that such a formulation is fundamentally at odds with what Dr. Plachetka says he invented. (Tr. 134:4-5.)

Dr. Williams disagreed with Defendants and testified that a formulation with some uncoated naproxen would still have a coordinated release. (Tr. 884:4-12.) Horizon likewise rejects Defendants' use of a hypothetical formulation, which, in their view, "in no way represent[s] any of Defendants' ANDA products" and for which there is no evidence "that a person of skill in the art exercising any sort of reason would actually contemplate making or using them." (Dkt. 489-3 at 15.) Horizon argues that "even if Defendants' unrealistic, hypothetical embodiments

fell within the literal scope of the claims, one of skill in the art would understand them to be unreasonable and inoperable embodiments and would not pursue them." (Id.)

2. Analysis

We turn now to the question of whether the '285 patent claims are adequately described by the '285 patent specification. As summarized above, the parties dispute both the scope of the claimed invention and the adequacy of the written description. As to the scope of the claims, we agree with Defendants that claim 1 of the '285 patent—whose only naproxen-related limitation relates to enteric coated naproxen—does not limit the amount of uncoated naproxen that may be present in claimed formulations.[12] It is well understood in patent law that the term "comprising" does not exclude additional elements in addition to the elements named in the claim. See Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1344–45 (Fed. Cir. 2003) ("Comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."). The language of the claim itself does not preclude uncoated naproxen. We are not persuaded by Horizon's argument that we should read in a

[12] Any such uncoated naproxen would necessarily be in addition to the therapeutic amount of enteric coated naproxen required by subsection (b) of claim 1.

"therapeutic amount" limitation on uncoated naproxen, particularly as that interpretation finds little support in the claim language, specification, or anywhere else. See Omega Eng'g, Inc, v. Raytek Corp., 334 F.3d 1314, 1323 (Fed. Cir. 2003) (noting "heavy presumption that claim terms carry their full ordinary and customary meaning" (internal quotations omitted)).

We disagree with Defendants, however, that the '285 patent specification precludes the inclusion of uncoated naproxen in the formulations it describes. The specification itself is silent on whether the formulation can include uncoated naproxen ***in addition to*** the enteric coated naproxen present in the claimed formulation. Defendants point out, fairly, that the '285 patent specification describes a product whose embodiments "preferably" provide for coordinated drug release such that "the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract is risen." ('285 patent at col. 4, lines 45–51.) It is likewise true that the specification explains that the invention is at least in part directed toward resolving injuries associated with NSAIDs being released "before the pH of the gastrointestinal tract can be raised…." (Id. at col. 1, lines 60–64.) We agree that these and other statements in the specification might counsel a POSA against incorporating uncoated naproxen when formulating the described invention. Indeed, Horizon expert Dr. Williams expressed skepticism about a hypothetical formulation that contained uncoated naproxen because he did not "know why someone would want to do this" when the patent was

"about preventing the release of…of the therapeutic amount of NSAID from that enteric coating until the pH is above 3.5." (Tr. 883:12-24.)

That the specification can be read to convey a preference for formulations without uncoated naproxen, however, does not warrant invalidating the claims under § 112(a). To hold otherwise would be to invalidate the claims simply because they encompass less preferable embodiments—a reading of § 112(a) that we find incompatible with patent law principles. See, e.g., Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003) ("an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention"); Gillette Co. v. Energizer Holdings, Inc., 405 F.3d 1367, 1371 (Fed. Cir. 2005) ("a patentee typically claims broadly enough to cover less preferred embodiments as well as more preferred embodiments, precisely to block competitors from marketing less than optimal versions of the claimed invention"); Golight, Inc. v. Wal-Mart Stores, Inc., 355 F.3d 1327, 1331–32 (Fed. Cir. 2004) ("An applicant is not necessarily required by 35 U.S.C. § 112 …to describe more embodiments than its preferred one, and…[it has] outright rejected the notion that disclosure of a single embodiment necessarily limits the claims.")

We note that Defendants have offered an unusual written description challenge here that appears to have little support in the law. Rather than allege that a specific element of the claim lacks support in the specification, Defendants argue that

the claim is invalid for merely ***allowing the possibility*** of the addition of uncoated naproxen in view of the specification. The question of whether a POSA would view the '285 patent specification (and Defendants' other extrinsic evidence) as limiting the plain language of the claim to preclude the presence of uncoated naproxen would seem a more natural fit for claim construction proceedings. The law of written description requires us to evaluate whether the four corners of the specification "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad, 598 F.3d at 1351–52. Our inquiry is therefore whether the '285 patent specification would reasonably convey to a POSA that Dr. Plachetka had possession of the "invention"—here a combination drug product featuring enteric coated naproxen and an uncoated proton pump inhibitor ("PPI"). As Dr. Williams explained at trial, those elements are indeed present and described in the specification. (Tr. 812:17–824:10.) Whether there is extrinsic evidence, such as Horizon's FDA Citizen's petition, suggesting that the presence of uncoated naproxen was against the spirit of the invention does not bear on our written description analysis. Because Defendants have not demonstrated by clear and convincing evidence that any element of the claimed invention lacks written description support, we decline to invalidate the '285 patent on those grounds.

B. Written Description (Sustained Release Formulations)

Defendants' second written description challenge arises out of the use of the term "inhibits" in claim 1 of the '285 patent. In their view, the use of the word "inhibits" extends the scope of the claim to include "sustained release" formulations while the specification discloses only "delayed release" formulations. As above, we first review the parties' evidence and arguments related to the scope of the claims and the description in the patent specification. We then analyze whether the claims satisfy the written description requirement of § 112(a) on this issue.

1. Parties' Evidence and Arguments

(i) Scope of the '285 patent claims

Claim 1 of the '285 patent requires, *inter alia*, "naproxen surrounded by a coating that ***inhibits its release*** from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher." ('285 patent claim at col. 22, lines 12–14 (emphasis added).) Defendants submit that the term "inhibits" should be given its plain meaning, "to slow down." (Dkt. 489-2 at 12; Tr. 887:1-7.) They highlight a previous filing in this case where Horizon agreed that the plain meaning of "inhibit" was "slow down or stop" and that "inhibit" in the '285 patent claims takes on this plain meaning. (DTX 1333 at 51.)

Defendants also contend that the term "inhibits" should be understood to be broader than

the term "prevents" because the term was consciously selected by the inventor to expand the scope of the '285 patent claims beyond what was claimed in the '907 patent. (Dkt. 489-2 at 30.) Claim 1 of the earlier-issued '907 patent requires an "NSAID…surrounded by a coating that…***prevents the release*** of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher." ('907 patent at col. 20, lines 22–27 (emphasis added).) Horizon expert Dr. Williams agreed that a POSA might presume that "inhibits" in the '285 patent means something different than "prevents" in the '907 patent because the language is different in the two claims. (Tr. 892:20-24; see also Tr. 885:8-17.) Per defense expert Dr. Kibbe, the term "inhibits" (understood as "slows down") extends the scope of the claim to "sustained release" formulations. (Tr. 416:4-23; 438:12–441:14.) A sustained release product, as described by Dr. Kibbe, is one that "begins releasing right away, but it does so at a slower rate than you would see if you were comparing it to an immediate-release product." (Tr. 441:10-13.) Dr. Kibbe contrasted sustained release products, which allow for immediate (albeit slowed) release of the active ingredient, with formulations that "stop" drug release, meaning that "for a fixed period of time, no drug will come out until the dosage form migrates into an area where the pH is above the pH of the enteric coat." (Tr. 441:6-9.)

Horizon argues that a POSA "would recognize that the term 'inhibit' in the '285 patent describes the same goal as the term 'prevent' in the context of

the '907 patent." (Dkt. 489-3 at 27.) As Dr. Williams testified, "inhibit" would be understood by a POSA "to accomplish the goal of no release in the stomach, in acid, or until the pH is 3.5 or higher." (Tr. 814:21–815:2.) That understanding, according to Horizon, would arise out of a POSA's reading of the specification (discussed below). Horizon also urges us to reject Dr. Kibbe's trial testimony as incredible in light of previous statements in his expert report that "[a] person of ordinary skill in the art would understand the word 'inhibit' to mean 'prevent' based upon the specification of the '285 patent." (Tr. 556:7-12.)

(ii) Invention as described

Defendants submit that the '285 patent specification does not contain any disclosure related to "sustained release" products—*i.e.*, formulations that slowly but immediately release the active ingredient. Instead, Dr. Kibbe pointed to various instances in the '285 patent specification that refer specifically to "prevent[ing]" the release of naproxen. (Tr. 439:14–440:17; see, e.g., '285 patent at col. 4, lines 64–67; id. at col. 5, lines 34–39; id. at col. 9, lines 30–33.) As he explained, the term "inhibits" is not used in the specification to refer to the release of naproxen; to the extent it is used at all, it describes proton pump inhibition. (Tr. 438:15–439:2.) Horizon expert Dr. Williams agreed that the specification does not "talk[] about" sustained release formulations. (Tr. 890:19-24.)

Horizon submits that the specification does disclose what it means to "inhibit" in the context of a

coating. (Dkt. 489-3 at 27; Tr. 814:18-20.) The '285 patent describes two types of coatings that may be used to surround the NSAID. (Dkt. 489-3 at 28.) One is the pH-sensitive enteric coating that does not dissolve until the pH of the surrounding medium is 3.5 or higher. (See, e.g., '285 patent at col. 4, lines 54–59.) The other coating described "controls the release of NSAID by time, as opposed to pH, with the rate adjusted so that NSAID is not released until after the pH of the gastrointestinal tract has risen to at least 3.5." (Id. at col. 4, lines 59–67.) In Horizon's view, these alternatives describe coatings that either ***prevent*** the release of naproxen at low pH or ***delay*** its release until sufficient time has passed to allow the pH to rise. (Dkt. 489-3 at 28.)

2. Analysis

Defendants argue that claim 1 of the '285 patent fails the written description requirement of 35 U.S.C. § 112(a) because the claim encompasses sustained release formulations and the patent specification does not describe sustained release formulations. (Dkt. 489-2 at 29–30.) Their argument primarily rests on the assertion by defense expert Dr. Kibbe that the use of the term "inhibits" in claim 1 broadens the claim to encompass "sustained release" formulations. (Tr. 438:15–439:2.)[13]

[13] As with Defendants' written description challenge in Section III.A, supra, the question of whether use of the claim term "inhibits" broadens the scope of the claim appears more properly considered a claim construction issue than a written description challenge.

We note that the PTAB recently rejected a similar argument from DRL. In that proceeding, as here, the parties argued over whether "inhibits" should be afforded its ordinary meaning or interpreted to mean something akin to "prevents." (PTX-351 at 13.) DRL argued then that claim 1 of the '285 patent "encompass[es] formulations that release all of its naproxen slowly at any pH, instead of preventing release until the formulations are in a medium with a pH of 3.5 or higher." (Id. at 14.) The PTAB declined to provide an explicit definition of "inhibits" because it did not "discern a significant difference between the definitions offered by the parties." (Id.) The PTAB, however, "disagree[d] with [DRL]'s interpretation of the difference in breadth between 'inhibit,' 'prevent,' and 'delay,' [which] would lead to the conclusion that the claims of the '285 patent encompass a formulation that releases all of its naproxen slowly at any pH." (Id. at 14–15.) Accordingly, the PTAB concluded that the claims of the '285 patent, including the term "inhibits," were adequately supported by the relevant specification. (Id. at 19.)

We conclude that Defendants have failed to meet their burden to show by clear and convincing evidence that claim 1 of the '285 patent lacks written description support. We are not convinced that use of the term "inhibits" in claim 1 expands the scope of the claim to include sustained release formulations. A POSA reading the specification would understand that the term "inhibits" in the context of the patent refers back to the enteric coatings described in the

patent specification that encompass both preventing and delaying the release of naproxen. (See, e.g., '285 patent at col. 4, lines 54–67.) Put another way, given the description in the specification of coatings that "inhibit" the release of an NSAID in specific ways, (Tr. 815:6–9), we are unconvinced that a POSA would understand that claim 1 of the '285 patent encompasses sustained release formulations. Because we conclude that the claim does not encompass sustained release formulations, we need not reach the question of whether the specification adequately describes such formulations.

C. Infringement

Horizon alleges that DRL's ANDA II Product infringes claims 1– 4 of the '285 patent. Having evaluated the scope and meaning of the pertinent claim terms above, we now compare those claims against the allegedly infringing product. Advanced Steel Recovery, LLC v. X-Body Equip., Inc., 808 F.3d 1313, 1316 (Fed. Cir. 2015). DRL's ANDA II Product **[redacted].** (PTX-234 at 25.) DRL's "500 mg/20" dose ANDA II Product **[redacted].** (Id.) DRL's "375 mg/20 mg" dose ANDA II Product **[redacted]. [redacted].** (Id.) **[redacted]. [redacted].** (Id.) In addition, **[redacted]. [redacted].** (PTX-014 at 15.) We now turn to whether the product satisfies the various claim limitations of the asserted claims.[14]

[14] Mylan takes no position on whether DRL's ANDA II Product infringes the '285 patent. (Dkt. 489- 2 at 6.)

1. Claim 1 of the '285 patent

(i) "a pharmaceutical composition in unit dosage form"

Horizon provided unrebutted testimony that the DRL ANDA II Product is "a pharmaceutical composition in unit dosage form." (Tr. 833:18-834:1.)

(ii) "therapeutically effective amounts of: (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating"

Horizon provided unrebutted testimony that the DRL ANDA II Product includes a "therapeutically effective amount[] of esomeprazole." (Tr. 834:5–835:5.) Further, the esomeprazole in the DRL ANDA II Products is not surrounded by an enteric coating. (Tr. 835:6-20; PTX-234 at 25.)

(iii) "therapeutically effective amounts of: (b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher"

Horizon provided unrebutted testimony that the DRL ANDA II Product **[redacted]. [redacted].**, both of which are therapeutically effective amounts. (Tr. 835:22–836:12.) **[redacted].** DRL II ANDA Products **[redacted]. [redacted].** (Tr. 838:8-21.)

[redacted]. DRL II ANDA Products **[redacted]. [redacted].** (Tr. 838:8-21)

> *(iv) "wherein said unit dosage form provides for release of said esomeprazole such that 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"*

Horizon provided unrebutted testimony that DRL's ANDA II Product **[redacted].**

(Tr. 838:22–839:15.)

Because DRL's ANDA II Product satisfies each limitation of claim 1 of the '285 patent, we find that Horizon has proven by a preponderance of the evidence that DRL's ANDA II Product infringes that claim.

2. Claim 2 of the '285 patent

Claim 2 of the '285 patent reads: "The pharmaceutical composition of claim 1, wherein naproxen is present in said unit dosage form in an amount of 200-600 mg." ('285 patent at col. 22, lines 19–21.) Horizon provided unrebutted testimony that DRL's ANDA II Product **[redacted].** (Tr. 840:1-8.)

Because DRL's ANDA II Product satisfies each limitation of claim 2 of the '285 patent, we find that Horizon has proven by a preponderance of the

evidence that DRL's ANDA II Product infringes that claim.

3. Claim 3 of the '285 patent

Claim 3 of the '285 patent reads: "The pharmaceutical composition of claim 1, wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg." ('285 patent at col. 22, lines 22–24.) Horizon provided unrebutted testimony that DRL's ANDA II Product **[redacted].** (Tr. 840:9-15.)

Because DRL's ANDA II Product satisfies each limitation of claim 3 of the '285 patent, we find that Horizon has proven by a preponderance of the evidence that DRL's ANDA II Product infringes that claim.

4. Claim 4 of the '285 patent

Claim 4 of the '285 patent reads: "The pharmaceutical composition of claim 1, wherein naproxen is present in said unit dosage form in an amount of between 200-600 mg and esomeprazole in an amount of from 5 to100 mg per unit dosage form." ('285 patent at col. 22, lines 25–29.) Horizon provided unrebutted testimony that the naproxen in DRL's ANDA Product **[redacted]**. (Tr. 840:1-8.) **[redacted]**. DRL's ANDA II Products **[redacted]**. (Tr. 840:9-15.)

Because DRL's ANDA II Product satisfies each limitation of claim 4 of the '285 patent, we find that Horizon has proven by a preponderance of the

evidence that DRL's ANDA II Product infringes that claim.

IV. Obviousness and Related § 112 Challenges

Defendants at trial offered a second line of interrelated invalidity challenges under 35 U.S.C. § 103 and § 112. These issued were briefed separately from the infringement and § 112 issues argued in Section III, supra, and are consequently considered together in this section. Section IV.A addresses the Defendants' obviousness challenge under § 103. Sections IV.B and IV.C address the Defendants' related enablement and written description challenges under § 112.

A. Obviousness

We undertake several factual inquiries to determine whether the Asserted Patents are invalid under § 103, including determining the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007). In this section, we recount the parties' evidence at trial pertaining to the prior art as well as so-called secondary considerations of nonobviousness. We then assess that evidence and ultimately conclude that the Defendants have failed to meet their burden to show that the Asserted Patents are invalid under § 103.

1. Parties' Evidence and Arguments on Prior Art

Defendants maintain that a POSA would have been "motivated to combine the teachings of the prior art references to achieve the claimed invention, and…would have had a reasonable expectation of success in doing so." Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009). They submit two theories as to why the invention disclosed in the Asserted Patents (the "Invention") was obvious under the prior art.[15] (Dkt. 489 at 15–27.) Those theories primarily involve prior art pertaining to existing combination drug products and other art describing NSAID/PPI co-therapies, and are discussed in Section IV.A.1.i, infra. Horizon's primary defense is that the invention cannot be considered obvious because the invention uses an "uncoated" PPI. The parties' extensive dispute over the prior art as it relates to uncoated PPIs is discussed in Section IV.A.1.ii, infra.

(i) Defendants' obviousness theories

Defendants offer two theories of why the Invention was obvious under the prior art. The first theory is that it would have been obvious to a POSA

[15] We undertake our obviousness analysis from the perspective of a POSA as of June 1, 2001, the date on which Provisional application No. 60/294,588 was submitted. Horizon expert Dr. Williams stated at trial that he used a priority date of May 31, 2002 but later agreed to use the earlier 2001 priority date. (Tr. 729:8–731:8; dkt. 489 at 18.)

to improve upon the combination product described in U.S. Patent No. 5,601,843 (the '843 patent) (DTX-1063) and commercialized as Arthrotec. (Dkt. 489 at 25.)[16] Arthrotec is a branded drug product that combines an NSAID (diclofenac) with misoprostol (a synthetic prostaglandin). (DTX-1095 at 2.) Arthrotec is used to treat conditions such as osteoarthritis and rheumatoid arthritis in patients with a high risk of developing NSAID- related injuries such as gastric and duodenal ulcers. (Tr. 322:15-20.) The misoprostol in Arthrotec was designed to reduce the risk of NSAID-related injury by: (1) replacing prostaglandin in the stomach to protect the stomach from acid exposure; (2) inhibiting acid production in the stomach. (Tr. 456:10–15; Tr. 495:4–9; Tr. 501:18–21.) Of these mechanisms, the prostaglandin replacement mechanism was the "primary" mechanism by which misoprostol would help reduce the risk of NSAID-related injury. (Tr. 502:16–503:10.) In Defendants' telling, the only significant difference between Arthrotec and the Invention is the choice of "acid inhibitor" (a PPI instead of misoprostol) and NSAID (naproxen instead of diclofenac). (Tr. 456:23–457:17; Tr. 461:12-24.)

Defendants submit that the Invention was obvious because a POSA would have been motivated

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[16] Horizon argues that some of Defendants' arguments at trial constituted new (and therefore impermissible) combinations of prior art. (Dkt. 489-1 at 23–24.) Because we conclude that the Invention was nonobvious under Defendants' proffered combinations, we do not reach the question of whether Defendants waived particular combinations during discovery.

to replace the misoprostol in Arthrotec with a PPI, and particularly esomeprazole. They argue that a POSA would have replaced misoprostol with esomeprazole because: (1) misoprostol was understood to have harmful side effects; and (2) misoprostol was understood to be less effective than esomeprazole for treating NSAID-related injuries. As to the first point, experts from both sides testified that misoprostol carried significant side effects, including diarrhea, flatulence, and even spontaneous abortion. (Tr. 311:7-10, Tr. 330:12-23; Tr. 463:17-23; Tr. 1180:11– 1182:14; DTX-1095 at 2.) These side effects were well documented in the prior art. ('907 patent at col. 2, lines 52–56.) As to the second point, Defendants submit that it was understood in the prior art that PPIs, and especially esomeprazole, were superior to other acid inhibitors, including misoprostol, for treating NSAID-related injuries. (Tr. 309:11– 317:9; Tr. 464:4-10.)

Defendants highlight academic literature indicating that PPIs were understood to be a better treatment option for NSAID-related injuries than other available acid inhibitors such as H2-receptor antagonists and prostaglandins. Much of the literature relies on two studies comparing PPIs with alternative treatments. The Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (or "OMNIUM") study compared the PPI omeprazole to misoprostol. (DTX-1077; Tr. 312:19-25.) The Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer treatment (or "ASTRONAUT") study compared omeprazole with the H2-receptor antagonist ranitidine. (DTX-1069.)

Subsequent articles reviewing the safety and efficacy of treatments for NSAID-related injuries cite the OMNIUM and ASTRONAUT studies. As recounted in Brown (DTX-1080), the OMNIUM study reported that use of omeprazole resulted in a reduction in the reoccurrence of NSAID-related ulcers and increased compliance compared with misoprostol. (DTX-1080 at 7; Tr. 316:5-25; Tr. 1207:3–1209:12.) Per Brown, "[PPIs] have demonstrated efficacy in the prevention of the adverse gastrointestinal effects of NSAIDs" and have "clear benefits" over alternatives. (DTX-1080 at 8.) Another article, Wolfe (DTX-1089), explained that the "more potent inhibition of gastric acid secretion provided by PPIs enhances their healing properties." (DTX 1089 at 10; Tr. 310:20– 311:10.) Citing the ASTRONAUT study comparing omeprazole with H2-agonist ranitidine, Wolfe and Brown both recommended the use of PPIs over H-2 antagonists. (Tr. 316:6-11.) Relying in part on these articles, defense expert Dr. Metz testified that PPIs were understood to be the best acid inhibitor as of the priority date for both effectiveness and tolerability. (Tr. 309:22-24.) Moreover, Dr. Metz testified that a POSA would have been motivated to replace the misoprostol in Arthrotec with esomeprazole in particular because it was understood to be the most potent PPI. (Tr. 331:19–332:13; Tr. 337:13-17.) Dr. Kibbe testified that it would have been a routine modification to use a PPI instead of misoprostol in formulating the product. (Tr. 461:21– 462:4.)

Defendants argue that a POSA would have had additional motivation to replace the misoprostol in Arthrotec with a PPI because NSAID/PPI combination therapies were already known in the prior art. (Tr. 332:8-13.) For example, International Patent Pub. No. WO 97/25064 ("Depui") (DTX-1064) disclosed a combination dosage form of a PPI with an NSAID for treatment and prevention of NSAID-related injury. (Tr. 325:23– 327:1; Tr. 464:11–466:6.) Acceptable PPIs in Depui included omeprazole and esomeprazole, while acceptable NSAIDs included naproxen. (Tr. 326:19–327:1.) Defendants also point to U.S. Patent No. 6,544,556 (the '556 patent) (DTX-1118), which disclosed a combination dosage form of a PPI with an NSAID to prevent NSAID-related injury. ('556 patent at col. 1, lines 7–14.)[17] Specifically, the '556 patent discloses the use of a PPI combined with diclofenac (the same NSAID found in Arthrotec). (Id. at col. 4, lines 51–54; Tr. 1216:17–1219:4.) They also cite U.S. Patent No. 5,204,118 ('118 patent) (DTX-1051), which discloses combination dosage forms of an "[NSAID] or acetaminophen and a histamine receptor blocker

[17] There is some dispute as to whether the '556 patent is prior art. (Dkt. 489-1 at 22 n.4.) The '556 patent issued on April 8, 2003, from a patent application filed on September 11, 2000. Accordingly, it is prior art under former 35 U.S.C. § 102(e), which includes as prior art "a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent." Our finding of nonobviousness, however, does not turn on whether the '556 patent is considered prior art.

and/or a proton pump inhibitor composition." ('118 patent at col. 1, lines 13–16.)

Horizon disputes that a POSA would have been motivated to replace the misoprostol in Arthrotec with a PPI such as esomeprazole. Horizon rejects the notion that a PPI and a synthetic prostaglandin, such as misoprostol, would be seen as interchangeable because they have different mechanisms of action. Misoprostol helps replace prostaglandins, the depletion of which makes the stomach more susceptible to NSAID-related injury. (Tr. 1138:15–1139:4; PTX-292.) In contrast, PPIs act as "acid suppressants" or "acid inhibitors" that do not replace the loss of prostaglandins due to NSAID use. (Tr. 503:16–25; Tr. 1259:20–1260:4.) Dr. Plachetka, the named inventor of the Asserted Patents, similarly explained that "the only thing that a proton pump inhibitor will do is inhibit the secretion of acid . . . , whereas misoprostol will repair or replace the gel coat." (Tr. 40:4-13.) In light of these differences, Horizon argues that a POSA would not have been motivated to swap the two ingredients. (Dkt. 489-1 at 47.)

Horizon argues further that a POSA would not have been motivated to replace the misoprostol in Arthrotec with ***uncoated*** esomeprazole. Although we discuss the prior art related to uncoated PPIs in detail below, Horizon expert Dr. Williams testified that a POSA would not have chosen to replace misoprostol, which is not acid labile, with a PPI that ***is*** acid labile. (Tr. 773:22–774:5; Tr. 774:8-17.) The distinction also matters, in Horizon's view, because

much of the prior art discussing the efficacy of PPIs analyzed enteric coated PPIs. The OMNIUM and ASTRONAUT studies, for example, were conducted using enteric coated PPIs. (Tr. 384:12–386:1.)

The second obviousness theory proffered by Defendants relies on essentially the same references but in a different logical progression. Whereas their first theory is that a POSA would have been motivated to replace the ingredients in a combination drug product (*e.g.*, Arthrotec) with an NSAID/PPI combination, the second theory is that a POSA would have been motivated to take existing NSAID/PPI co-therapies and put them into a combination drug product . (Dkt. 489 at 15–27.) As discussed above, NSAID/PPI co-therapies were known in the prior art. (See, e.g., Depui (DTX-1064); '556 patent (DTX-1118); Tr. 325:23–327:1; Tr. 464:11–466:6.) At the same time, it was understood that administering medications separately "can be difficult to achieve and can be difficult for a patient to faithfully follow." (Tr. 319:17–321:19.) Requiring patients to take multiple tablets per day can lead to patients forgetting or declining to take both tablets. (Tr. 319:17–321:7; Tr. 458:7-23.) Defense expert Dr. Metz testified that a POSA would have sought to address potential compliance issues by combining drug components into a single tablet. (Tr. 321:16-19.) As an example, he highlighted the '843 (Arthrotec) patent, which disclosed that combination tablets

could improve patient compliance. ('843 patent at col. 12, lines 10–14; Tr. 321:24–324:17.)[18]

Defendants explain that the prior art also disclosed combination drug therapies with "coordinated release" (*i.e.*, the sequential release of an acid inhibitor and an NSAID). U.S. Patent No. 6,319,519 ('519 patent) (DTX-1112) discloses a tablet comprised of an NSAID (to treat arthritis pain and inflammation) and misoprostol (to prevent NSAID-related injury). (Tr. 913:7-915:23; '519 patent at col. 1, lines 9–34.) According to the '519 patent, "[i]t has been found experimentally that it is necessary for the prostaglandin to be released before the NSAID so as to protect the stomach from the effects of the NSAID. It is therefore preferable that the NSAID is coated to delay release." ('519 patent at col. 1, lines 21–25.) Horizon expert Dr. Williams conceded at trial that the coordinated release structures described in the '519 patent and the '843 Arthrotec patent are similar to the coordinated release mechanism of the Invention. (Tr. 915:20–917:3; see also Tr. 454:2–457:17.)

(ii) Uncoated PPIs

Horizon's primary response to Defendants' obviousness arguments is that the Invention was

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[18] Defendants also argue that the dependent claims (*e.g.*, claim 52 of the '907 patent) would be
obvious because it was understood that an NSAID in conjunction with a PPI could be used to treat osteoarthritis or rheumatoid arthritis. (Tr. 88:23–89:4; Tr. 333:21–334:2; Tr. 338:10-24.)

nonobvious because it uses an uncoated PPI and the prior art taught away from using uncoated PPIs.[19] (Dkt. 489-1 at 27–43; 45–49.) Horizon argues that it was widely understood—and reflected in the prior art—that PPIs must be enteric coated because they are susceptible to acid degradation in the stomach. Defendants disagree that the prior art taught away from using uncoated PPIs and offered testimony at trial why a POSA would have had a reasonable expectation of success using an uncoated PPI. We summarize below the parties' evidence on these subjects.

Horizon's experts testified that a POSA would not have been motivated to use an uncoated PPI. Dr. Williams explained that, as of the priority date, all commercially available PPIs were formulated with an enteric coating. (Tr. 733:2-13; Tr. 735:8-23; see also Tr. 372:23–373:5.) He testified that PPIs were enteric coated because they are acid labile and dissolve much more quickly in acidic pH environments. (Tr. 733:16–735:1.) In Dr. Williams' view, this understanding was reflected in prior art that affirmatively discouraged the use of non-enteric coated PPIs. (Tr. 737:1-18.) For example, Pilbrant 1985 (PTX-325) evaluated the use of enteric coated and uncoated omeprazole solid dosage formulations, and concluded that the uncoated dosage form was "ruled out in a pilot bioavailability study . . . where it was shown that more than half of the omeprazole in a rapidly dissolving dosage form degrades in the

[19] We use "uncoated PPI" in this section as shorthand to refer to a PPI that does not have a pH- sensitive enteric coating.

stomach." (PTX-435 at 2; Tr. 738:16–740:1.) In contrast, Pilbrant 1985 stated that an enteric coated solid dosage form "offer[ed] the best possibilities." (PTX-435 at 3; Tr. 740:15-22.) Per Dr. Williams, a POSA would conclude from Pilbrant 1985 that a non-enteric coated PPI would not work and would be discouraged from pursuing such a formulation. (Tr. 740:2-14.) Although he did not discuss each in detail, Dr. Williams testified that 25 additional prior art references supported his contention that PPIs must be enteric coated.[20] (Tr. 747:20– 748:12.)

Horizon notes that Defendants' own experts have acknowledged the need to enteric coat PPIs because of their acid lability. (Tr. 502:5-15.) Dr. Metz co-authored an article stating that "[p]roton pump inhibitors are inactivated by gastric acid and thus ***must*** be given as enteric coated granules in gelatin capsules or enteric coated tablets." (PTX- 73 at 8 (emphasis added); Tr. 365:6–369:5.) Dr. Metz testified at trial that it was the "general party line" and belief in the industry that "proton pump inhibitors are inactivated by gastric acid and thus must be given as enteric coated granules in gelatin capsules or enteric coated tablets." (Tr. 369:11-21; Tr. 370:16-20; Tr. 371:16-21.) Dr. Mayersohn

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[20] See (PTX-77 at 3); (PTX-78 at 4); (PTX-79 at 3); (PTX-80 at 2); (PTX-242 at 3); (PTX-243 at 2); (PTX-244 at 2); (PTX-245 at 2); (PTX-246 at 4); (PTX-247 at 9); (PTX-248 at 5); (PTX-249 at 6); (PTX-250 at 2); (PTX-251 at 2); (PTX-252 at 2); (PTX-253 at 3); (PTX-254 at 4); (PTX-255 at 10); (PTX-256 at 2); (PTX-257 at 1); (PTX-258 at 6); (PTX-337 at 5); (PTX-570 at 4–5); (PTX-573 at 5–6); and (DTX-1117 at 13). We recognized at trial that PTX-79 cannot be considered prior art. (Tr. 528:19–529:16.)

likewise testified in a sworn expert declaration in another case that "[b]ecause 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 various stabilizers and coatings, resulting in a drug formulation that has an outer layer (referred to as the 'enteric coat') that protects the PPI from stomach acid." (PTX-434 at 6; Tr. 686:4–689:12.) In light of the prevailing understanding about uncoated PPIs, Horizon argues that a POSA would have understood that using an uncoated PPI in a formulation would fail because of acidic gastric pH levels. (See, e.g., Tr. 737:1-18; 1029:9-22; 1163:10–1164:3.)

Defendants disagree with Horizon's characterization of the prior art, which they see as, at most, expressing a general preference for enteric coated PPIs. (Dkt. 489 at 48.) They criticize Horizon's 25 "teaching away" references that purportedly counsel against using an uncoated PPI on several grounds. Defense expert Dr. Mayersohn explained that one of Horizon's references merely states that omeprazole is acid labile and enteric coated, and does not discuss uncoated PPIs. (Tr. 613:5–614:13 (discussing PTX-256).) Dr. Mayersohn testified that some of the other references were "repetitive and duplicative," (Tr. 611:20-23) while Dr. Kibbe explained that "often the same thing is repeated and repeated in articles because it's easier to do that than to actually test it." (Tr. 527:16-19.) Defendants criticized ten of the references for being AstraZeneca publications, who they argue had an

interest in promoting "the benefits of AstraZeneca's own, patented, enteric coated PPI formulation." (Dkt. 489 at 49; Tr. 939:5–945:4.) Defendants criticized another six references as lacking original research or analysis on the efficacy or usefulness of uncoated PPIs. (Tr. 968:13–970:2.)

Defendants also submitted that a POSA would have been motivated to use uncoated PPIs and would have had a reasonable expectation of success in doing so because: (1) the PPI could be administered with an alkalizing agent to help protect it from stomach acid; (2) the dose of the PPI could be increased to offset acid degradation; (3) the repeated dosing of the PPI would create a "feedback loop" that would increase bioavailability for the uncoated PPI over time; and (4) an uncoated PPI would have certain advantages over an enteric coated PPI.

Alkalizing Agent

Defendants argue that a POSA would have a reasonable expectation of success using an uncoated PPI because the formulation could include an alkalizing agent, such as sodium bicarbonate, that would protect the PPI from degradation by stomach acid. (Dkt. 489 at 43–44.) Dr. Kibbe testified that an alkalizing agent could raise the pH of the stomach around the tablet and protect the PPI from degradation. (Tr. 485:1-16.) He explained that Pilbrant 1985 teaches that an omeprazole-sodium bicarbonate combination could be used to improve bioavailability. (Tr. 489:15-23; PTX-435 at 4–5.)

Other prior art, including U.S. Patent No. 6,489,346 (the '346 patent) (DTX-1117), eventually commercialized as Zegerid, disclosed an omeprazole and sodium bicarbonate formulation. (Tr. 345:1-20; Tr. 483:11–484:10.) Although Horizon submitted the '346 patent as one of its "teaching away" references, Defendants submit that it would have taught a POSA to account for PPI's acid lability by co-administering an alkalizing agent. (Dkt. 489 at 49; Tr. 977:16–980:21.)

Horizon expert Dr. Williams disagreed that sodium bicarbonate could feasibly be added to the formulation to prevent acid degradation. He testified, citing Pilbrant 1993 (PTX-262), that the resulting tablet would be too large because of the amount of sodium bicarbonate needed. (Tr. 758:3–760:16.)[21] Dr. Williams also argued, citing International Patent Publication WO 00/026185 (DTX-1102), that sodium bicarbonate would be incompatible with the enteric coated naproxen also present in the formulation because it could dissolve that enteric coat. (Tr. 753:21–755:16.)

Increased PPI Dosage

Defendants also argue that a POSA would have a reasonable expectation of success using an

[21] Defendants argue that Horizon's "tablet size" arguments do not account for the possibility of multiple dosages nor mechanisms such as the "feedback loop" discussed below that might make smaller amounts of PPI effective. (Dkt. 489 at 44–45.)

uncoated PPI because a POSA could increase the dosage level to account for the PPI's acid lability. Dr. Mayersohn cited Clissold (DTX-1036) for the proposition that about 50% of an uncoated PPI remains bioavailable despite acid degradation. (Tr. 620:7–621:6; DTX-1036 at 19 (citing Pilbrant 1985).) As some of the uncoated PPI remains available to the body (or "bioavailable"), Dr. Mayersohn explained that a POSA could account for acid degradation by increasing the amount of PPI in the formulation—in this case by essentially doubling the dose to account for the PPI's 50% bioavailability. (Tr. 621:23–622:7; Tr. 704:18–705:2.) Dr. Metz likewise testified that the PPI dose could be doubled to account for acid degradation. (Tr. 390:2-6.) Dr. Mayersohn added that a POSA would have further reason to believe that increasing the dosage would be effective because Regårdh (DTX-1029) taught that a comparatively higher percentage of PPI would be bioavailable at higher dosage levels. (Tr. 635:23–636:22.)

Horizon rejects the idea that a POSA would have been motivated to increase the dose of PPI to account for its acid lability. First, Dr. Taft questioned whether the 50% bioavailability figure from Pilbrant 1985 (PTX-432), which explicitly related to suspensions of omeprazole, could be used as a proxy for the bioavailability of a drug in tablet form. (Tr. 1060:5–1061:10.) Dr. Williams added that a subsequent study, Pilbrant 1993 (PTX-262), indicates that as much as 84% of a PPI may be lost

due to acid degradation.[22] (Tr. 778:12–780:7.) Second, even assuming a 50% bioavailability, Dr. Taft testified that a POSA would not have simply doubled the dose to address the acid lability of PPIs. (Tr. 1067:9–1068:3.) On cross-examination, Defendants' experts could not provide any examples of situations where low bioavailability was addressed through doubling the dosage form. (Tr. 393:6-9 (Metz); Tr. 514:4–515:25 (Kibbe); Tr. 692:24–695:10 (Mayersohn).)

PPI Feedback Loop

Defendants also believe that a POSA would have had a reasonable expectation of success using uncoated PPIs because the prior art described a "positive feedback loop" that would increase the bioavailability of an uncoated PPI. As explained by both Dr. Kibbe and Dr. Mayersohn, the feedback loop occurs because the first PPI dose inhibits stomach acid production and raises gastric pH, which consequently causes less acid degradation of the second dose, which further inhibits acid production, and so on. (Tr. 492:25–494:18; Tr. 589:9–590:4; 620:18–627:11; DTX-1396 at 6–7.) Dr. Kibbe pointed to Clissold (DTX-1036) as support for this feedback mechanism. (Tr. 492:25–493:25.) Dr.

[22] Defendants dispute the relevance of the data in Pilbrant 1993 because the study reported the bioavailability of a PPI after a meal and commercially available PPIs, even enteric coated ones, are typically administered with food. (Tr. 964:15–965:21.)

Mayersohn cited Tolman (DTX-1061) as additional evidence of the feedback effect. (Tr. 625:16–627:7.)

Horizon disputes the relevance of Clissold (DTX-1036) and Tolman (DTX-1061), arguing that those references do not assert that an uncoated PPI would increase its own bioavailability over time or reach therapeutically effective levels. (Dkt. 489-1 at 38–39.) Horizon expert Dr. Taft explained that Clissold and Tolman would not provide a POSA with a reasonable expectation of success for an uncoated PPI because those articles evaluated enteric coated or otherwise buffered PPI formulations. (Tr. 1067:9–1068:3.)

Disadvantages of Enteric Coated Formulations

Defendants also submitted evidence that a POSA would have been motivated to use an uncoated PPI because of known disadvantages of enteric coated PPI formulations. (Dkt. 489 at 46–47.) International Patent Pub. No. WO 00/78293 states that "[o]meprazole should preferably not be in contact with the enteric coating" because the enteric coating can cause "discoloration and degradation of omeprazole." (DTX-1105 at 4–5.) On cross-examination, Dr. Williams was presented with U.S. Patent 6,077,541 ('541 patent) (PTX-242) describing how the potential need to provide a protective layer between PPIs and their enteric coating can "increase[] the length of the manufacturing process and the cost of the product." (Tr. 971:24–973:20.) He agreed that one "wouldn't have that problem" if one "ha[d] a delayed release coat that's not pH-

dependent." (Tr. 973:11-16.) The '541 patent also discloses that "[e]nteric coated formulations are expensive and time consuming to manufacture, and requires [sic] elaborate technology and equipment." (Tr. 973:21–974:9.)

2. Secondary Considerations of Non-Obviousness

We also consider the significance and relevance of so-called "secondary considerations" such as commercial success, long felt but unsolved needs, and the failure of others. See AstraZeneca LP v. Breath Ltd., 88 F. Supp. 3d 326, 382 (D.N.J.), aff'd, 603 F. App'x 999 (Fed. Cir. 2015).

(i) Unexpected results

Horizon submits that the nonobviousness of the Invention is evidenced by the fact that its Vimovo product had surprising and unexpected results in treating NSAID-related gastrointestinal injury. Dr. Williams and Dr. Johnson testified that the success of a formulation with an uncoated PPI in Vimovo was an unexpected result. (Tr. 782:24– 783:6; Tr. 1169:16–1170:1.) In designated deposition testimony, Dr. Sostek of AstraZeneca testified that "it was unexpected that a completely unprotected form of a proton pump inhibitor could result in effective acid suppression." (DTX-1396 at 10.) Dr. Johnson also highlighted statements from certain clinical studies involving Vimovo. (Tr. 1170:2-7.) One such study, Goldstein (DTX-1135), noted "a striking and highly statistically significant difference between the patients that received Vimovo"

compared to other formulations, including those who received enteric coated naproxen alone. (Tr. 1170:22–1172:3.) Another publication, Hawkey (DTX-1142) characterized Vimovo by noting that "Impressively—and surprisingly, in view of the instability of PPIs in gastric acid—a clinical trial has shown a reduction . . . in the proportion of patients developing NSAID-associated gastric ulcers on [Vimovo] compared with similar doses of naproxen alone." (DTX-1142 at 3; Tr. 1087:22–1088:10.)

Defendants dispute the relevance of the Goldstein study because it compared Vimovo against formulations ***without*** a PPI component. (Tr. 1170:20–1171:14.) They submit that the study cannot be considered an "unexpected result" because it does not show the effectiveness of Vimovo against the closest prior art, which they assert would be a Naproxen/PPI co-therapy. (Tr. 350:18–354:8; Tr. 641:5–643:17; DTX-1396 at 10; DTX- 1398 at 10–11.)

(ii) Skepticism

Horizon argues that the nonobviousness of the Invention is supported by evidence that there was skepticism that the Invention would work. As with its evidence of unexpected results, Horizon's skepticism evidence at trial focused on the Invention's use of an uncoated PPI. Dr. Plachetka, the inventor, testified that potential marketing partners for Vimovo were skeptical about whether an uncoated PPI would work in the formulation. (Tr. 65:5-22; 68:23–70:9.) In one email from a prospective partner (TAP), an employee asked what steps Pozen had taken to address the degradation of a PPI that

might be predicted from using an uncoated PPI. (PTX-267 at 1.) Dr. Plachetka testified that some TAP employees "didn't believe" the data presented about the formulation and thought it would "never work because everybody knows that [PPIs] have to be enteric coated." (Tr. 66:13–67:23.) In another example, a Pozen employee summarized a call with a potential marketing partner (Purdue) and wrote that Purdue "need[ed] a better understanding of why we do not enteric coat the PPI. They feel this is an 'enigma' vs. all the prior art and they are 'not convinced' it is necessary or beneficial to not enteric coat the PPI." (PTX-085 at 1.) In the same email, the employee asked: "How could all the PPI experts be so wrong for so long?" (PTX-085 at 1; Tr. 796:14–797:18.)

Scientists at AstraZeneca, who had developed the PPIs omeprazole and esomeprazole, similarly appeared to express skepticism regarding the use of an uncoated PPI. (See, e.g., PTX-273; PTX-271; PTX-102; PTX-269.) In one internal email chain, AstraZeneca's Dr. Sostek wrote: "I think it is clear, that the current formulation is NOT optimal from an acid suppression standpoint (because of PPI is degradation [sic] in the stomach), but they characterize it as a good first attempt. It could be difficult to explain to physicians why PPI 'protection' is not necessary for this product unlike all other PPIs." (PTX-273 at 4.) At his deposition, Dr. Sostek explained why he thought it would be difficult to explain to physicians why PPI protection is not necessary for Vimovo:

> Well, for years since 2000 and before, since omeprazole was really first approved in '89, so that at this time was over 25 years. And then by this year, Nexium had been around for five years, Prevacid has been around for 10, 15 years. All of the PPI manufacturers had consistently educated physicians that a critical component of proton pump inhibitors was the enteric coat and that you had to protect the PPI from acid degradation. So I guess that I was saying that in light of all that education effort about the importance of an enteric coat the Pozen platform does not have an enteric coat, and so that might create an educational challenge for physicians.

(DTX-1396 at 9.)

Horizon submitted a number of other examples of skepticism about the use of uncoated PPIs. One Pozen memo recounted a conversation in which a doctor stated he was "of the school" that PPIs need to be enteric coated. (PTX-266 at 1.) Another email from Novartis asked Pozen to "[p]lease explain the rationale for the PPI in a non-enteric coated form (since PPIs are acid labile)." (PTX-268 at 1.) A due diligence assessment by Pozen questioned whether "unprotected esomeprazole 20 mg BID [will] produce sufficient acid suppression to meet primary endpoint of Phase II study." (PTX-271 at 2.) The FDA appeared to express skepticism that an uncoated PPI would be effective, and asked Horizon to "clarify if immediate release or delayed release esomeprazole

will be used" because "[e]someprazole is acid labile…[and] therefore, without a proper delivery system it is not clear if the product will result in an intended pharmacological effect." (PTX-84 at 1; Tr. 789:17-23.)

Defense expert Dr. Mayersohn characterized much of Horizon's skepticism evidence as requests for more information rather than skepticism. (Tr. 650:1–662:16.) Regarding Horizon's AstraZeneca documents, Defendants argue that AstraZeneca was actually concerned about a marketing problem because AstraZeneca had spent years telling physicians that an enteric coating was important. (Dkt. 489-1 at 58; DTX-1396 at 9.) AstraZeneca, as Defendants point out, was the patent holder of a combination of enteric coated esomeprazole with an NSAID and had other patents related to enteric coated esomeprazole. (Tr. 939:5–945:4.) More broadly, Defendants contest the admissibility of Horizon's skepticism evidence on the basis that the documents are from after the priority date. (Dkt. 489 at 56–57.)

(iii) Licensing

Horizon argues in its post-trial brief that the licensing of the '907 and '285 patents by AstraZeneca (and the subsequent acquisition of that license by Horizon) is evidence that the asserted claims are not obvious. (Dkt. 489-1 at 53–54.) Defendants contest the relevance of AstraZeneca's license in view of how quickly AstraZeneca sold the rights to Horizon, and disputes that either license "arose out of recognition and acceptance of the patent." See Stratoflex, Inc. v

Aeroquip Corp., 713 F.2d 1530, 1539 (Fed. Cir. 1983). Defendants also note that many potential marketing partners declined the opportunity to license and develop the invention. (Tr. 65:14–68:12.) Moreover, AstraZeneca's interest may have had incentives to license the product because of its existing esomeprazole product; as Dr. Plachetka explained, AstraZeneca had requested to use its own esomeprazole product in the formulation. (Tr. 74:5-13.)

(iv) Long-felt need

Horizon argues that the prevalence of NSAID-related gastrointestinal injury is additional evidence of non-obviousness. (Dkt. 489-1 at 55.) Horizon expert Dr. Johnson explained that NSAID-induced gastric injury was a significant medical problem at the time of the invention. (Tr. 1118:22–1120:23; PTX-572.) He also testified that various efforts to create safer NSAID therapies (using, *e.g.*, sucralfate, misoprostol, and acid suppression therapies) had not resolved the problem of NSAID-related injuries. (Tr. 1138:4–1139:4.)

Defendants argue that Horizon did not offer any evidence at trial that the Asserted Patents or Vimovo addressed a long-felt but unmet need of reducing the risk of gastric injury associated with long-term NSAID use. Dr. Johnson conceded that he had not opined on whether NSAID-related injuries had declined following the invention. (Tr. 1227:18–1228:18.) Defense expert Dr. Metz testified that the standard of care remains the same today after the release of Vimovo and that he had not seen any

reduction in the incidence or severity of NSAID-induced gastropathy. (Tr. 350:4-15.) Defendants also highlighted designated deposition testimony from Dennis McNamara that Vimovo had not been demonstrated as superior to other available co-therapies. (DTX-1398 at 10–14.)

3. Analysis

We turn now to the overarching inquiry of whether Defendants have demonstrated "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009). Answering that question requires us to address: (1) the level of ordinary skill in pertinent art; (2) the scope and content of prior art; (3) differences between the claims and the prior art; and (4) secondary considerations. See KSR Int'l Co., 550 U.S. at 406.

We note preliminarily that the level of ordinary skill in the art was not a significant area of contention between the parties. The parties submitted proposed definitions of a POSA in the pretrial order:

Horizon's Proposed Definition Dkt. 421 at 10)	Defendants' Proposed definition (Dkt. 421 at 130-31)
A person of ordinary skill in the art for the inventions of the asserted claims is a person with at least a graduate degree in pharmacy, chemistry, chemical engineering, pharmaceutics, or a comparable field, and some relevant pharmaceutical formulation work experience in industry. Other aspects of the claimed subject matter, such as those aspects relating to the amounts of active ingredient in the unit dosage form, would implicate a person skilled in the art of dosage, administration, and intended clinical use and effect of an acid inhibitor. The development of new formulations or dosage forms can require people with different	A person of ordinary skill in the art (POSA) is a pharmaceutical scientist having a Ph.D. degree, or equivalent training or degree, and at least 2 years of practical experience in pharmaceutical formulations. A POSA would have collaborated with a medical doctor having at least 2 years of practical experience treating patients in the gastroenterology field and a pharmacologist / pharmacokineticist having a Ph.D. degree, or equivalent training or degree, and at least 2 years of practical experience in pharmacology and pharmacokinetics. A POSA has a general understanding and knowledge of basic principles of formulation development. A POSA is familiar with the

areas of expertise, including, for example, those with familiarity of the dosage and administration of the relevant active ingredients, as well as those with familiarity or experience in drug formulation.	general strategies, procedures and tools of pharmaceutical formulation development, including pre-formulation studies, formulation screening and optimization, and experimental design. A POSA is also generally familiar with the commonly used textbooks in the field of formulation development, and has a general knowledge of the relevant references and/or printed publications in the field of pharmaceutical formulation.

Witnesses at trial, to the extent they testified about the definition of a POSA, offered largely similar definitions. (See, e.g., Tr. 268:4–269:8; Tr. 444:15-23; Tr. 574:2-8; Tr. 721:8–722:5; Tr. 1028:14-19.) Importantly for our purposes, experts from both sides testified that differences between the proposed definitions of a POSA did not affect their opinion. (See Tr. 270:13-17 (Dr. Metz); Tr. 574:14-20 (Dr. Mayersohn, noting "they're virtually identical descriptions of persons of ordinary skill"); Tr. 723:13-23 (Dr. Williams); Tr. 1144:23–1145:18 (Dr. Johnson).) We will formally adopt Defendants'

definition of a POSA (Tr. 444:13-23), but note that our analysis would be the same under either definition.

The relevant prior art presented by the parties at trial fell broadly into two categories. The first category pertained to drug therapies designed to reduce NSAID-related injury and NSAID/PPI co-therapies. The second pertained to the use and efficacy of coated and uncoated PPIs.[23] We briefly review the key disclosures in the prior art guiding our obviousness analysis.

The '843 (Arthrotec) patent (DTX-1063) disclosed a pharmaceutical composition with an enteric coated NSAID core (*i.e.*, diclofenac or piroxicam) surrounded by a prostaglandin. ('843 patent at col. 12, lines 19–62.) The '519 patent (DTX-1112) disclosed the coordinated release of a prostaglandin and an enteric coated NSAID designed to delay the release of the NSAID in order to protect the stomach. ('519 patent at col. 1, lines 21–30.) The prior art includes studies comparing various treatment options for NSAID-related injuries, including misoprostol, omeprazole, and ranitidine. (DTX-1077; DTX-1069.) Based on these studies, a POSA would have understood that omeprazole compared favorably in at least some ways to

[23] It is undisputed that some features of the Invention were well-known in the prior art, including: (1) use of an NSAID to treat arthritis; (2) use of PPIs to inhibit acid; and (3) use of an enteric coated NSAID. (Tr. 82:13–93:24.)

misoprostol and ranitidine in preventing NSAID-related injuries. (DTX-1080; DTX-1089.) The prior art also disclosed co-therapies that included PPI and NSAID components. (DTX-1051; DTX- 1064; DTX-1118.) Indeed, the '907 patent acknowledges that "others have disclosed strategies for combining" PPIs and NSAIDs for therapeutic purposes. ('907 patent at col. 2, lines 20–27.)

There is much discussion in the prior art on the importance of protecting PPIs because of their acid lability. The '346 patent (DTX-1117) discloses the use of an uncoated PPI together with a buffering agent designed to protect the PPI from acid degradation. ('346 patent at col. 11, lines 13–23.) One review article states that PPIs are "acid-unstable, requiring protection against gastric acidity." (PTX-337 at 5.) U.S. Patent No. 6,013,281 (PTX-573) notes that "it is obvious that a proton pump inhibitor in an oral solid dosage form must be protected from contact with the acidic reacting gastric juice" and that a dosage of PPIs "is best protected from contact with acidic gastric juice by an enteric coating layer." ('281 patent at col. 4, line 63 to col. 5, line 11.) Another reference discloses that 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." (PTX-077 at 3 (emphasis added).)

The prior art also discusses the bioavailability of uncoated omeprazole. Pilbrant 1985 states that a suspension of uncoated PPI had a bioavailability of about 50%. (PTX-435 at 1.) A subsequent study,

Pilbrant 1993 analyzed omeprazole absorption after a meal and indicated that bioavailability might be as low as 16%. (PTX-262 at 7–8.) Clissold cites the 44% bioavailability total from Pilbrant 1985 but also explains that the PPI might increase its own bioavailability over time "by decreasing gastric acid secretion and enhancing the extent of its absorption." (DTX-1036 at 19.) Regårdh offers some evidence that the bioavailability of omeprazole might increase as the dosage amount increases. (DTX-1029 at 10–11.)

The prior art contains at least some support for the notion that the use of an enteric coat in a PPI formulation can have some disadvantages, as the enteric coat itself can degrade the PPI. (DTX-1105; PTX-242.)

We find that the Invention departs from formulations disclosed in the prior art in essentially two ways. First, the Invention differs from other coordinated release drug formulations in the prior art for treating NSAID-related gastric injuries (*e.g.*, the '843 patent) because it used a PPI (*e.g.*, esomeprazole) instead of a prostaglandin (*e.g.*, misoprostol) as the agent to prevent or treat NSAID-related gastric injury. Second, the Invention differs from other therapies in the prior art that used PPIs (including NSAID/PPI co-therapies) by virtue of using an uncoated PPI.

We conclude that Defendants have failed to demonstrate that a POSA would have been motivated to combine the teachings of the prior art

references and would have had a reasonable expectation of success in doing so. Specifically, based on the evidence presented at trial, we conclude that a POSA would not have been motivated to use an uncoated PPI given numerous prior art references reflecting a widely-held understanding that the acid lability of PPIs, particularly in a solid dosage form, would generally require an enteric coating. See KSR Int'l Co., 550 U.S. at 416 (noting "principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious").

Defendants contend that the prior art demonstrated, at most, that enteric coated PPIs were a superior alternative to uncoated PPIs. (Dkt. 489 at 52.) These arguments understate the language used in the prior art when discussing the need to enteric coat PPIs. One reference cited the "obvious" need to protect a PPI from acidic gastric juice, and noted that a PPI is "best protected . . . by an enteric coating layer." (DTX-573 at 5– 6.) Another explained that "PPIs are highly acid labile and hence oral formulations are enteric coated." (PTX-244 at 2.) Pilbrant 1985—a reference heavily relied upon by Defendants to argue that an uncoated PPI might be expected to work—affirmatively "ruled out" the use of uncoated omeprazole given its relatively low bioavailability. (PTX-435 at 2.) Indeed, the Federal Circuit has previously concluded that Pilbrant 1985 "would discourage a [POSA] from pursuing conventional oral dosage forms such as tablets, capsules, or granules with non-enteric coated PPIs,

and thus teaches away from such formulations." Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1355 (Fed. Cir. 2012). Although Defendants' experts argued that a POSA would have been motivated to use an uncoated PPI, prior statements by those same experts undercut the credibility of their testimony. (See, e.g., Tr. 365:6–369:5; Tr. 686:4–689:12.)

In light of the expert testimony and prior art references submitted at trial, we disagree that a POSA would have been motivated to use an uncoated PPI in a new combination drug product. See In re Chapman, 595 F.3d 1330, 1337 (Fed. Cir. 2010) ("A finding that a reference teaches away can preclude a finding that the reference renders a claim obvious.") We acknowledge Defendants' various objections to particular references (Dkt. 489 at 48–50), but conclude that the references in their entirety would have counseled a POSA against the use of an uncoated PPI.

We are not persuaded by Defendants' evidence that a POSA would have had a reasonable expectation that an uncoated PPI would be successful. Defendants base much of their argument on the 44% bioavailability figure from Pilbrant 1985 and the assertion that a POSA would simply double the dosage to account for acid degradation of the PPI. But Pilbrant 1985 itself ***ruled out*** the possibility of using an uncoated PPI given its low bioavailability. (PTX-435 at 2.) Tellingly, in our view, Defendants' experts could not recall examples where a formulator simply increased the dosage to compensate for low bioavailability caused by acid

degradation. (Tr. 393:6-9; Tr. 514:4–515:25; Tr. 692:24–695:10.) And notably, a POSA would be aware that other disclosures, such as Pilbrant 1993, suggest that bioavailability might be even lower than the 44% figure from Pilbrant 1985. (PTX-262 at 7–8.)

Nor are we persuaded by Defendants' contention that a POSA would have had a reasonable expectation of success by virtue of other mechanisms that might serve to increase the bioavailability of uncoated PPI. Although there is some indication from Clissold (DTX-1036) and Tolman (DTX-1061) that there may be a "feedback loop" that might eventually increase the bioavailability of an uncoated PPI, those references did not evaluate whether uncoated PPIs would be effective. The '346 (Zegerid) patent disclosed that an uncoated PPI could be administered with an alkalizing agent such as sodium bicarbonate. But as explained by Horizon's experts, a POSA would have had concerns that the addition of an alkalizing agent would raise new challenges related to tablet size and the possibility that the alkalizing agent would interfere with the enteric coated naproxen also present in the Invention. (Tr. 753:21–760:16.) Indeed, the '346 patent itself describes how sodium bicarbonate can dissolve an enteric coating. ('346 patent at col. 14, lines 32–37.) These drawbacks would have undermined, if not precluded, a POSA's motivation to use an uncoated PPI or any expectation of success in doing so. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1365 (Fed. Cir. 2008) (noting that challenges associated with the inventive

process that "would have prevented one of ordinary skill in this art from traversing the multiple obstacles to easily produce the invention").

The PTAB has similarly rejected the argument that it would have been obvious to use an uncoated PPI in view of Pilbrant 1985. (PTX-351 at 23–26.) Although the PTAB did not analyze all of the references raised at trial, the thrust of the obviousness argument (there made by Defendant DRL) was similar. Consequently, we are mindful that Defendants' evidence must be scrutinized carefully. See Sciele Pharma Inc. v. Lupin Ltd., 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("[I]t may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered.").

Our conclusion is somewhat strengthened by Horizon's evidence of so-called "secondary considerations" of non-obviousness, although we find that the Defendants have failed to satisfy their burden of showing invalidity even without that evidence. For the most part, Horizon's secondary consideration evidence flows from the Invention's use of an uncoated PPI. There is at least some evidence in the record that the success of a formulation with an uncoated PPI was surprising. Indeed, Hawkey explicitly noted that "Impressively—and surprisingly, in view of the instability of PPIs in gastric acid—a clinical trial has shown a reduction…in the proportion of patients developing NSAID-associated gastric ulcers on

[Vimovo] compared with similar doses of naproxen alone." (DTX-1142 at 3.) Defendants reject the relevance of Hawkey, noting that unexpected results "must be shown to be unexpected compared with the closest prior art." In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991). We agree that "naproxen alone" is not the closest prior art, but also note that the reference is commenting on the unexpected result of an uncoated PPI compared, at least implicitly, against PPI formulations in the prior art protected from gastric acid (*i.e.*, through an enteric coat).

Horizon also presented a substantial amount of evidence that industry participants were skeptical that an uncoated PPI would work at all. One potential development partner wrote that they "need[ed] a better understanding of why we do not enteric coat the PPI. They feel this is an 'enigma' vs. all the prior art and they are 'not convinced' it is necessary or beneficial to not enteric coat the PPI…How could all the PPI experts be so wrong for so long?" (PTX-085 at 1.) These documents, as well as others outlined above and presented at trial, evince skepticism that a formulation with an uncoated PPI would work. Defendants object to the applicability of these documents because they post-date the Invention and therefore "fail[] as a matter of law." (Dkt. 489 at 56–57.) See In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (identifying "skepticism of skilled artisans ***before the invention***" as a secondary indicium (emphasis added)). We disagree that controlling case law prohibits our consideration of documents created

after the priority date when evaluating evidence of industry skepticism. While the relevant inquiry may be whether there was skepticism before or at the time of the invention, we see no reason why post-invention documents cannot be considered as evidence of pre-existing industry skepticism. Accordingly, although we may discount the weight of skepticism evidence created some time after the invention, documents evincing longstanding skepticism (*e.g.*, an industry participant asking "[h]ow could all the PPI experts be so wrong for so long?") still support our finding of nonobviousness.[24]

Other secondary indicia cited by Horizon do not similarly support a finding of nonobviousness. We do not find that evidence of "licensing" supports a finding of nonobviousness here, in part because the minimal evidence presented by Horizon does not demonstrate that the "licenses arose out of recognition and acceptance of the patent." Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1539 (Fed. Cir. 1983). Likewise, Horizon did not present evidence at trial that the introduction of Vimovo satisfied a "long-felt, but unmet need" by

[24] Defendants also lodged a standing objection at trial to Horizon's skepticism evidence as inadmissible hearsay, but did not elaborate in their post-trial brief. (Dkt. 489 at 57 (submitting only that Horizon's "vague, after-the-fact, and anecdotal claims derived from hearsay do not salvage the patents").) We deny this objection, but, as noted above, our ultimate conclusion on invalidity would remain the same even without Horizon's evidence of secondary considerations of nonobviousness.

meaningfully reducing the number of injuries associated with NSAID use. (Tr. 1227:18–1228:18) Indeed, Defendants presented unrebutted testimony that the standard of care has remained essentially unchanged. (Tr. 350:4-15.) It is also well-established that filing of an ANDA does not constitute "copying" for obviousness purposes. Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013).

For the reasons above, we conclude that the Defendants have failed to satisfy their evidentiary burden to demonstrate that the Asserted Patents are invalid as obvious.

B. Enablement

Defendants argue that the asserted claims are invalid under 35 U.S.C. § 112 because the '907 and '285 patents do not adequately disclose the utility of using an uncoated PPI. (Dkt. 489 at 69.) They highlight that the patents do not contain any experimental testing data regarding the use of uncoated PPIs, and argue that the inventor's unsupported "suspicion" that the invention would work is insufficient to satisfy the utility prong of enablement. (Id.) Horizon responds that the utility of the invention was self-evident to a POSA and that enablement does not require the disclosure of experimental test results. (Dkt. 489-1 at 67.)

There appears to be no serious dispute between the parties that the Asserted Patents disclose how to make and use the claimed invention. Horizon expert Dr. Williams testified that making the claimed

formulations would be routine. (Tr. 809:24– 819:13.) Defense expert Dr. Mayersohn agreed that the patent specification teaches how to make the claimed tablets. (Tr. 680:18-21.) The patents themselves disclose their intended use. (See, e.g., '907 patent at col. 4, lines 18–27 ("The invention includes methods of treating a patient for pain, inflammation and/or other conditions…Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with osteoarthritis or rheumatoid arthritis….").)

Defendants' specific enablement challenge focuses on whether the patents disclose sufficient evidence to support the Invention's claimed utility for treating various medical conditions. (Dkt. 489-2 at 69–70.) They rely primarily on Rasmusson v. SmithKline Beecham Corp. to argue that the disclosures in the '90 7 and '285 patents are inadequate. 413 F.3d 1318, 1324 (Fed. Cir. 2005). Rasmusson involved an enablement challenge to a patent claiming the use of finasteride to treat prostate cancer. Id. at 1322. The Federal Circuit upheld a finding by the Board of Patent Appeals and Interferences[25] that the claim was not enabled because "a person of ordinary skill in the art would have had no basis…for believing that finasteride could be used to treat prostate cancer in light of the state of the art and in light of [the patentee's] failure

[25] The Board of Patent Appeals and Interferences was replaced by the PTAB under the terms of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

to provide any data to demonstrate the effects of finasteride in treating prostate cancer." Id. The Federal Circuit cited the Board's review of the scientific articles and expert testimony, and noted that the patentee "did not make any contrary showing that a [POSA]…would have recognized that a selective 5αR inhibitor in general, or finasteride in particular, would be effective in treating prostate cancer." Id. at 1324.

The stated utility in the Asserted Patents of using an NSAID and a PPI to treat pain and NSAID-related gastric injury rests on far firmer evidentiary ground than the novel cancer treatment in Rasmusson. Testimony from both sides at trial indicated that a POSA at the time of the invention would have accepted that a combination of an NSAID and a PPI would be effective for treating pain and conditions like arthritis. (Tr. 562:14– 563:4; Tr. 1172:12–1173:5.) Given the understood utility of the invention, we disagree with Defendants that the asserted claims constitute "little more than respectable guess" that must be invalidated under the enablement requirement. Rasmusson, 413 F.3d at 1325. We also do not find that a lack of testing data on the efficacy of uncoated PPIs renders the claims invalid. While it may often be true that "patent applications claiming new methods of treatment are supported by test results," it is also "clear that testing need not be conducted by the inventor." In re '318 Patent Infringement Litig., 583 F.3d 1317, 1324 (Fed. Cir. 2009). Indeed, were testing data required to obtain patents, "the associated costs would prevent many companies

from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue…potential cures." Id. (citing In re Brana, 51 F.3d at 1568). Consequently, we conclude that Defendants have failed to meet their evidentiary burden to show by clear and convincing evidence that the patents should be invalidated for lack of enablement.

C. Written Description (Uncoated PPI)

Defendants mount a separate written description challenge based on the alleged failure of the '907 and '285 patents to adequately describe the use of uncoated PPI. They believe they have caught Horizon in a catch-22:

> According to [Horizon], the claimed formulation is novel because a POSA would not have expected an uncoated PPI to be effective. Against this background, Plaintiffs argue that a POSA reading the asserted patents' formulation recipes would immediately understand that an uncoated PPI is effective— even though the specifications disclose no data, reasoning, or other information in support. But both cannot be true. Fundamentally, because the patents lack any disclosure of an uncoated PPI's efficacy, the claims are either obvious (if the POSA understands that uncoated PPIs work), or lacking description (if the POSA believes uncoated PPIs would not work).

(Dkt. 489 at 69.)

As Defendants point out, the Asserted Patents do not address the efficacy of uncoated PPIs through experimental testing data or other statements in the specification. (Tr. 666:16–677:14; Tr. 1004:16–1005:11.) Instead, Defendants characterize the specification as "parroting claim language," which they view as insufficient given Horizon's position that the prior art had taught away from the use of uncoated PPIs. (Dkt. 489 at 66.)

Horizon responds that the specifications of the Asserted Patents adequately describe the use of uncoated PPIs, and that the law does not require the specification to "present data or an explanation of why the prior art was wrong to refute the teaching the in the prior art." (Dkt. 489-1 at 65.) Instead, Horizon cites Allergan, Inc. v. Sandoz Inc., for the proposition that "[a] claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described." 796 F.3d 1293, 1309 (Fed. Cir. 2015).

Our inquiry is whether the lack of information regarding the efficacy of uncoated PPIs means that the patent specification does not "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad, 598 F.3d at 1351. The '285 patent specification contains various disclosures describing the immediate release of an acid inhibitor

as a component of the invention.[26] For example, the specification describes that "[t]he acid inhibitor is in one or more layers outside of the core which do not contain any NSAID. These layers are not surrounded by an enteric coating and, upon ingestion of the tablet or capsule by a patient, release the acid inhibitor into the patient's stomach." ('285 patent at col. 4, lines 37–41.) This early release of the acid inhibitor is repeatedly described, with the specification similarly disclosing that: "the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen." (Id. at col. 4, lines 45–51; see also id. at col. 5, lines 12–16.) The immediate release of an uncoated acid inhibitor is explicitly distinguished in the specification from enteric coated PPI formulations that delay the absorption of the acid inhibitor: "[t]he effect [of PPIs] may be diminished towards the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours." (Id. at col. 2, lines 3–8.) In contrast, the examples in the specification describe, *e.g.*, the "rapid[] release" of uncoated omeprazole. (Id. at col. 16, lines 33–49.)

Particularly in light of disclosures in the specification describing the immediate release of an

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[26] As noted above, the '285 and '907 patents contain virtually identical specifications and our analysis applies equally to both patents.

uncoated PPI and the potential disadvantages of enteric coated PPI formulations, we conclude that Defendants have not shown by clear and convincing evidence that the Asserted Patents should be invalidated for failing to meet the written description requirement. The lack of experimental testing data or detailed analysis on why an uncoated PPI might prove effective does not require us to find otherwise. We reject, however, Horizon's suggestion that the efficacy of uncoated PPIs need not be described because it is "necessarily inherent" in a formulation. (Dkt. 489-1 at 65.) Horizon relies without elaboration on Allergan, 796 F.3d at 1309, a case which we have previously noted does not provide clear guidance on what qualifies as an inherent property of a formulation nor how that determination bears on the written description analysis. See Helsinn Healthcare S.A. v. Dr. Reddy's Labs., Ltd., No. 12-2867, 2017 WL 631899, at *26 n.43 (D.N.J. Feb. 14, 2017).

V. Conclusion

For the reasons discussed in Section III, we find that the DRL ANDA II Product infringes claims 1, 2, 3, and 4 of the '285 patent and that those claims are not invalid under 35 U.S.C. § 112. For the reasons discussed in Section IV, we find that the claims of the '907 and '285 patents are not invalid under 35 U.S.C. § 103 or § 112. We will file this memorandum opinion under temporary seal and order the parties to submit a proposed form of Judgment in accordance with this opinion.

s/ Mary L. Cooper

MARY L. COOPER
United States District Judge

Dated: July 10, 2017

APPENDIX C

United States District Court
For the District of New Jersey

Civil Action Nos. 3:11-cv-02317-MLC-DEA
and 3:13-cv-00091-MLC-DEA

HORIZON PHARMA, INC. and
POZEN INC.,
Plaintiffs,

vs.

DR. REDDY'S LABORATORIES INC. and
DR. REDDY'S LABORATORIES LTD.,
Defendants.

FINAL JUDGMENT

This is an action for patent infringement having been brought by Plaintiffs Horizon Pharma Inc. and Pozen Inc. (collectively, "Plaintiffs") against Defendants Dr. Reddy's Laboratories, Inc., and Dr. Reddy's Laboratories, Ltd. (collectively, "DRL"), asserting that the products that are the subjects of DRL's Abbreviated New Drug Applications ("ANDAs") No. 202461 and No. 204206 infringe claims of U.S. Patent Nos. 6,926,907 ("'907 patent"), 5,714,504 ("'504 patent"), 6,369,085 ("'085 patent"), 6,875,872 ("'872 patent"), 7,411,070 ("'070 patent"), 7,745,466 ("'466 patent"), and 8,557,285 ("'285 patent").

This matter having been tried before this Court on January 12, 13 and 17-20, 2017, with closing arguments on May 17, 2017, the Court having heard testimony on behalf of Plaintiffs, and DRL regarding DRL's invalidity counterclaims with respect to claims 5, 15, 52 and 53 of the '907 patent and claims 1-4 of the '285 patent, and DRL's noninfringement counterclaims with respect to claims 1-4 of the '285 patent concerning DRL's ANDA No. 204206, the Court having considered the written post-trial submissions of the parties, and the Court having issued its Memorandum Opinion on June 26, 2017 (D.E. No. 493) and Amended Memorandum Opinion on July 10, 2017 ("Amended Opinion") (D.E. No. 497) finding that claims 5, 15, 52 and 53 of the '907 patent and claims 1-4 of the '285 patent are not invalid under 35 U.S.C. §§103 and 112, and finding that claims 1-4 of the '285 patent are infringed by DRL's ANDA No. 204206 under 35 U.S.C. §271(e) (all docket citations refer to Civil Action No. 11-2317);

IT IS ORDERED AND ADJUDGED that this Court has jurisdiction over the Plaintiffs and DRL and the subject matter of this action;

IT IS ORDERED AND ADJUDGED that all claims and counterclaims regarding the '504 patent, the '085 patent, the '872 patent, the '070 patent, and the '466 patent are dismissed with prejudice (*see* D.E. No. 139);

IT IS ORDERED AND ADJUDGED, for the reasons set forth in the Court's Amended Opinion,

that final judgment is entered in favor of Plaintiffs and against DRL on all claims and counterclaims regarding the validity of claims 5, 15, 52, and 53 of the '907 Patent;

IT IS ORDERED AND ADJUDGED, for the reasons set forth in the Court's Amended Opinion, that final judgment is entered in favor of Plaintiffs and against DRL on all claims and counterclaims regarding the validity of claims 1-4 of the '285 Patent;

IT IS ORDERED AND ADJUDGED, pursuant to the Final Pretrial Order regarding Infringement (D.E. No. 421 at 8), that the commercial manufacture, use, offer for sale, sale, or importation of DRL's ANDA 202461 Product (*i.e.,* the generic version of VIMOVO that is the subject of DRL's ANDA No. 202461 submitted under 35 U.S.C. §271(e)(2)(A)) within the United States or administration of DRL's ANDA 202461 Product for the treatment of pain and inflammation according to its prescribing information within the United States would infringe claims 5, 15, 52, and 53 of the '907 Patent and claims 1-4 of the '285 Patent;

IT IS ORDERED AND ADJUDGED, for the reasons set forth in the Court's Amended Opinion, that final judgment is entered in favor of Plaintiffs and against DRL on all claims and counterclaims regarding the infringement of claims 1-4 of the '285 Patent with respect to DRL's ANDA 204206 Product, *i.e.,* the commercial manufacture, use, offer for sale, sale, or importation of DRL's ANDA 204206 Product

(*i.e.,* the generic version of VIMOVO that is the subject of DRL's ANDA No. 204206 submitted under 35 U.S.C. §271(e)(2)(A)) within the United States would infringe claims 1-4 of the '285 Patent;

IT IS ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the FDA of DRL's ANDA No. 202461 shall be a date which is not earlier than the expiration of the '907 Patent, including any patent term extensions and/or adjustments;

IT IS ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the FDA of DRL's ANDA No. 202461 shall be a date which is not earlier than the expiration of the '285 Patent, including any patent term extensions and/or adjustments;

IT IS ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the FDA of DRL's ANDA No. 204206 shall be a date which is not earlier than the expiration of the '285 Patent, including any patent term extensions and/or adjustments;

IT IS ORDERED that, in the event that DRL appeals from this Final Judgment, any motion for attorney fees or costs under Fed. R. Civ. P. 54(d) and L. Civ. R. 54.1- 54.2, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty days after final disposition of any such appeal;

IT IS ORDERED that, in the event that DRL does not appeal from this Final Judgment, any motion for attorney fees or costs under Fed. R. Civ. P. 54(d) and L. Civ. R. 54.1-54.2, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4;

IT IS ORDERED that all pending motions and other outstanding requests for relief not specifically addressed herein are **DENIED**; and

IT IS ORDERED that the Clerk of the Court designate Civil Action Nos. 3:11-cv-02317-MLC-DEA, and 3:13-cv-00091-MLC-DEA as **CLOSED**.

s/ Mary L. Cooper
MARY L. COOPER
United States District Judge

Dated: July 21, 2017

APPENDIX D

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NUVO PHARMACEUTICALS (IRELAND) DESIGNATED ACTIVITY COMPANY, HORIZON MEDICINES LLC,
Plaintiffs-Cross-Appellants

v.

DR. REDDY'S LABORATORIES INC., DR. REDDY'S LABORATORIES, LTD., MYLAN, INC., MYLAN PHARMACEUTICALS INC., MYLAN LABORATORIES LIMITED,
Defendant-Appellants

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,
Defendants-Appellees

2017-2473, 2017-2481, 2017-2484, 2017-2486, 2017-2489, 2017-2491, 2017-2492, 2017-2493

Appeals from the United States District Court for the District of New Jersey in Nos. 3:11-cv-02317-MLC-DEA, 3:13-cv-00091-MLC-DEA, 3:13-cv-04022-MLC-DEA, Judge Mary L. Cooper.

JUDGMENT

THIS CAUSE having been considered, it is

ORDERED AND ADJUDGED:

REVERSED as to 17-2473, 17-2481, 17-2484, 17-2486;
DISMISSED as to 17-2489, 17-2491, 17-2492, 17-2493

ENTERED BY ORDER OF THE COURT

May 15, 2019

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX E

NOTE: This order is nonprecedential.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

NUVO PHARMACEUTICALS (IRELAND) DESIGNATED ACTIVITY COMPANY, HORIZON MEDICINES LLC,
Plaintiffs-Cross-Appellants

v.

DR. REDDY'S LABORATORIES INC., DR. REDDY'S LABORATORIES, LTD., MYLAN, INC., MYLAN PHARMACEUTICALS INC., MYLAN LABORATORIES LIMITED,
Defendant-Appellants

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,
Defendants-Appellees

2017-2473, 2017-2481, 2017-2484, 2017-2486, 2017-2489, 2017-2491, 2017-2492, 2017-2493

Appeals from the United States District Court for the District of New Jersey in Nos. 3:11-cv-02317-MLC-DEA, 3:13-cv-00091-MLC-DEA, 3:13-cv-04022-MLC-DEA, Judge Mary L. Cooper.

ON PETITION FOR REHEARING EN BANC

Before PROST, *Chief Judge*, NEWMAN, LOURIE, CLEVENGER[1], DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, and HUGHES*, *Circuit Judges*.

PER CURIAM.

ORDER

Cross-Appellants Horizon Medicines LLC and Nuvo Pharmaceuticals (Ireland) Designated Activity Company filed a petition for rehearing en banc. A response to the petition was invited by the court and filed by Appellants Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories, Ltd. The petition was first referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

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[1] Circuit Judge Clevenger participated only in the decision on the petition for panel rehearing.

* Circuit Judge Stoll did not participate.

The mandate of the court will issue on August 6, 2019.

FOR THE COURT

JULY 30, 2019
DATE

/S/ PETER R. MARKSTEINER
PETER R. MARKSTEINER
CLERK OF COURT

APPENDIX F

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NUVO PHARMACEUTICALS (IRELAND) DESIGNATED ACTIVITY COMPANY, HORIZON MEDICINES LLC,
Plaintiffs - Cross-Appellants

v.

DR. REDDY'S LABORATORIES INC., DR. REDDY'S LABORATORIES, LTD., MYLAN, INC., MYLAN PHARMACEUTICALS INC., MYLAN LABORATORIES LIMITED,
Defendant - Appellants

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,
Defendants - Appellees

2017-2473, 2017-2481, 2017-2484, 2017-2486, 2017-2489, 2017-2491, 2017-2492, 2017-2493

Appeals from the United States District Court for the District of New Jersey in Nos. 3:11-cv-02317-MLC-DEA, 3:13-cv-00091-MLC-DEA, 3:13-cv-04022-MLC-DEA, Judge Mary L. Cooper.

MANDATE

In accordance with the judgment of this Court, entered May 15, 2019, and pursuant to Rule 41 of the Federal Rules of Appellate Procedure, the formal mandate is hereby issued.

FOR THE COURT

August 6, 2019

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX G

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES PATENT NO. 6,926,907 B2 ENTITLED *"PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS" ISSUED AUGUST 9, 2005*

(54) **PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS**

(75) Inventor: **John R. Plachetka**, Chapel Hill, NC (US)

(73) Assignee: **Pozen Inc.**, Chapel Hill, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 273 days.

(21) Appl. No.: **10/158,216**

(22) Filed: **May 31, 2002**

(65) **Prior Publication Data**
US 2003/0069255 Al Apr. 10, 2003

Related U.S. Application Data

(60) Related U.S. Application Data Provisional application No. 60/294,588, filed on Jun. 1, 2001.

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/24; A61K 9/32; A61K 9/52
(52) **U.S. Cl.**.....**424/472**; 424/457; 424/463; 424/468; 424/474; 424/480; 424/482

(58) **Field of Search**..... 424/457, 463, 424/468, 472, 474, 480, 482, 464, 451

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Primary Examiner-James M. Spear

(74) *Attorney, Agent, or Firm* - Michael A Sanzo; Fitch, Even, Tabin & Flannery

(57) **ABSTRACT**

The present invention is directed to drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The dosage form is designed so that the NSAID is not released until the intragastric pH has been raised to a safe level. The invention also encompasses methods of treating patients by administering this coordinated release, gastroprotective, antiarthritic/analgesic combination unit dosage form to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages.

55 Claims, 2 Drawing Sheets

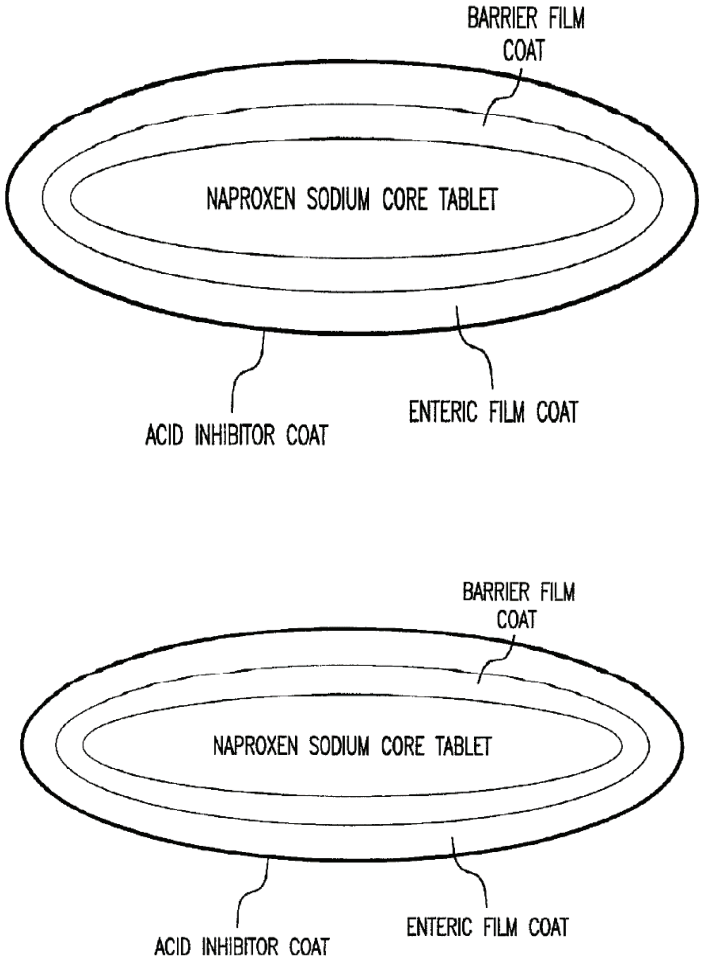

BARRIER FILM COAT
NAPROXEN SODIUM CORE TABLET
ACID INHIBITOR COAT
ENTERIC FILM COAT
BARRIER FILM COAT
NAPROXEN SODIUM CORE TABLET
ACID INHIBITOR COAT
ENTERIC FILM COAT

FIG.1

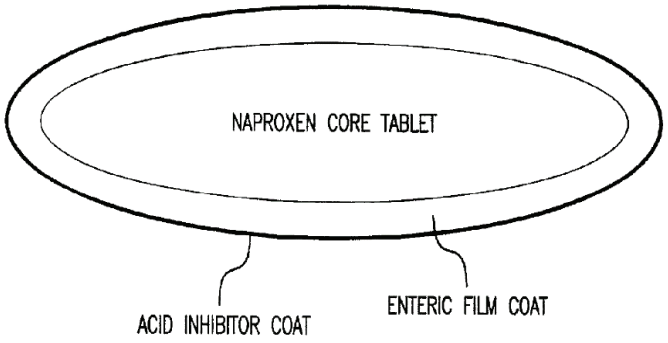

NAPROXEN CORE TABLET
ACID INHIBITOR COAT
ENTERIC FILM COAT

FIG.2

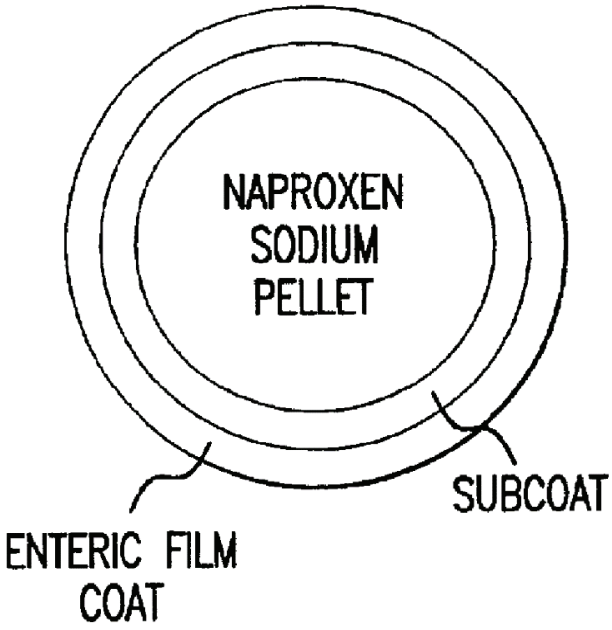

NAPROXEN
SODIUM
PELLET
SUBCOAT
ENTERIC FILM
COAT

FIG.3

PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. provisional application No. 60/294,588, filed on Jun. 1, 2001.

FIELD OF THE INVENTION

The present invention is directed to pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID). These compositions have a reduced likelihood of causing unwanted side effects, especially gastrointestinal side effects, when administered as a treatment for pain, arthritis and other conditions amenable to treatment with NSAIDs.

BACKGROUND OF THE INVENTION

Although non-steroidal anti-inflammatory drugs are widely accepted as effective agents for controlling pain, their administration can lead to the development of gastroduodenal lesions, e.g., ulcers and erosions, in susceptible individuals. It appears that a major factor contributing to the development of these lesions is the presence of acid in the stomach and upper small intestine of patients. This view is supported by clinical studies demonstrating an improvement in NSAID tolerability when patients

are also taking independent doses of acid inhibitors (Dig. Dis. 12:210-222 (1994); Drug Safety 21:503-512 (1999); Aliment. Pharmacol. Ther. 12:135-140 (1998); Am. J. Med. 104(3A):67S-74S (1998); Clin. Ther. 17:1159-1173 (1995)). Other major factors contributing to NSAID-associated gastropathy include a local toxic effect of NSAIDs and inhibition of protective prostaglandins (Can. J. Gastroenterol. 13: 135-142 (1999) and Pract. Drug Safety 21:503-512, (1999)), which may also make some patients more susceptible to the ulcerogenic effects of other noxious stimuli.

In general, more potent and longer lasting acid inhibitors, such as proton pump inhibitors, are thought to be more protective during chronic administration of NSAIDs than shorter acting agents, e.g., histamine H_2 receptor antagonists (H-2 blockers) (N. Eng. J. Med. 338:719-726 (1998);Am. J. Med. 104(3A):56S-61S (1998)). The most likely explanation for this is that gastric pH fluctuates widely throughout the dosing interval with short acting acid inhibitors leaving the mucosa vulnerable for significant periods of time. In particular, the pH is at its lowest point, and hence the mucosa is most vulnerable, at the end of the dosing interval (least amount of acid inhibition) and for some time after the subsequent dose of acid inhibitor. In general, it appears that when a short acting acid inhibitor and an NSAID are administered simultaneously, NSAID-related mucosal damage occurs before the pH of the gastrointestinal tract can be raised and after the acid inhibiting effect of the short acting acid inhibitor dissipates.

Although longer lasting agents, such as proton pump inhibitors (PPIs), usually maintain a consistently higher gastroduodenal pH throughout the day, after several days dosing, their antisecretory effect may be delayed for several hours and may not take full effect for several days (Clin. Pharmacokinet. 20:38-49 (1991)). Their effect may be diminished toward the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from "acid breakthrough" which again leaves them vulnerable to NSAID-associated gastroduodenal damage (Aliment. Pharmacol. Ther. 14:709-714 (2000)). Despite a significant reduction in gastroduodenal lesions with the concomitant administration of a proton pump inhibitor during six months of NSAID therapy, up to 16% of patients still develop ulcers, indicating that there remains substantial room for improvement (N. Eng. J. Med. 338:727-734 (1998)). Thus, the addition of a pH sensitive enteric coating to an NSAID could provide additional protection against gastroduodenal damage not provided by the H2 blocker or PPI alone. In addition, although long acting acid inhibitors may reduce the risk of GI lesions in chronic NSAID users, there are questions about the safety of maintaining an abnormally elevated pH in a patient's GI tract for a prolonged period of time (Scand. J. Gastroenterol. Suppl. 178:85-92 (1990)).

Recognizing the potential benefits of PPIs for the prevention of NSAID-induced gastroduodenal damage, others have disclosed strategies for combining the two active agents for therapeutic purposes. However, these suggestions do not provide for coordinated drug release or for reducing intragastric acid levels to a non-toxic level prior to the release of NSAID (U.S. Pat. Nos. 5,204,118; 5,417,980; 5,466,436; and 5,037,815). In certain cases, suggested means of delivery would expose the gastrointestinal tract to NSAIDs prior to onset of PPI activity (U.S. Pat. No. 6,365,184).

Attempts to develop NSAIDs that are inherently less toxic to the gastrointestinal tract have met with only limited success. For example, the recently developed 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 (JAMA 284:1247-1255 (2000); N. Eng. J. Med. 343:1520-1528 (2000)). In this regard, it appears that even low doses of aspirin will negate most of the benefit relating to lower gastrointestinal lesions. In addition, the COX-2 inhibitors may not be as effective as other NSAIDs at relieving some types of pain and have been associated with significant cardiovascular problems (JADA 131:1729-1737 (2000); SCRIP 2617, pg. 19, Feb. 14, 2001); NY Times, May 22, 2001, pg. C1)).

Other attempts to produce an NSAID therapy with less gastrointestinal toxicity have involved the

concomitant administration of a cytoprotective agent. In 1998, Searle began marketing Arthrotec™ for the treatment of arthritis in patients at risk for developing GI ulcers. This product contains misopristol (a cytoprotective prostaglandin) and the NSAID diclofenac. Although patients administered Arthrotec™ do have a lower risk of developing ulcers, they may experience a number of other serious side effects such as diarrhea, severe cramping and, in the case of pregnant women, potential damage to the fetus.

Another approach has been to produce enteric coated NSAID products. However, even though these have shown modest reductions in gastroduodenal damage in short term studies (Scand. J. Gastroenterol. 20: 239-242 (1985) and Scand. J. Gastroenterol. 25:231-234 (1990)), there is no consistent evidence of a long term benefit during chronic treatment.

Overall, it may be concluded that the risk of inducing GI ulcers is a recognized problem associated with the administration of NSAIDs and that, despite considerable effort, an ideal solution has not yet been found.

SUMMARY OF THE INVENTION

The present invention is based upon the discovery of 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. The method involves the

administration of a single coordinated unit-dose product that combines: a) an agent that actively; raises intragastric pH to levels associated with less risk of NSAID-induced ulcers; and b) an NSAID that is specially formulated to be released in a coordinated way that minimizes the adverse effects of the NSAID on the gastroduodenal mucosa. Either short or long acting acid inhibitors can be effectively used in the dosage forms. This 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.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dosage form suitable for oral administration to a patient. The composition contains an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5, preferably to at least 4, and more preferably to at least 5, when one or more unit dosage forms are administered. The gastric pH should not exceed 7.5 and preferably should not exceed 7.0. The term "acid inhibitor" refers to agents that inhibit gastric acid secretion and increase gastric pH. In contrast to art teaching against the use of H2 blockers for the prevention of NSAID-associated ulcers (N. Eng. J. Med. 340: 1888-1899 (1999)), these agents are preferred compounds in the current invention. Specific, H2 blockers that may be used include cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine or famotidine. The most preferred acid inhibitor is famotidine present in

dosage forms in an amount of between 5 mg and 100 mg. Other agents that may be effectively used include proton pump inhibitors such as omeprazole, esomeprazole, pantoprazole, lansoprazole or rabeprazole.

The pharmaceutical composition also contains a nonsteroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. The NSAID may be a COX-2 inhibitor such as celecoxib rofecoxib meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib: CS-502, JTE-522, L-745,337 or NS398. Alternatively, the NSAID may be aspirin, acetaminophen, ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, nabumetone, or diclofenac. 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. It will be understood that, for the purposes of the present invention, reference to an acid inhibitor, NSAID, or analgesic agent will include all of the common forms of these compounds and, in particular, their pharmaceutically acceptable salts. The amounts of NSAIDs which are therapeutically effective may be lower in the current invention than otherwise found in practice due to potential positive kinetic interaction and NSAID absorption in the presence of an acid inhibitor.

The term "unit dosage form" as used herein 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. A unit dosage form of the present invention preferably provides for coordinated drug release, in a way that elevates gastric pH and reduces the deleterious effects of the NSAID on the gastroduodenal mucosa, i.e., the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen. In a preferred embodiment, the unit dosage form is a multilayer tablet, having an outer layer comprising the acid inhibitor and an inner core which comprises the NSAID. In the most preferred form, coordinated delivery is accomplished by having the inner core surrounded by a polymeric barrier coating that does not dissolve unless the surrounding medium is at a pH of at least 3.5, preferably at least 4 and more preferably, at least 5. Alternatively, a barrier coating may be employed which controls the release of NSAID by time, as opposed to pH, with the rate adjusted so that NSAID is not released until after the pH of the gastrointestinal tract has risen to at least 3.5, preferably at least 4, and more preferably at least 5. Thus, a time-release formulation may be used to prevent the gastric presence of NSAID until mucosal tissue is no longer exposed to the damage enhancing effect of very low pH.

The invention includes methods of treating a patient for pain, inflammation and/or other conditions by administering the pharmaceutical compositions described above. Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with osteoarthritis or rheumatoid arthritis. Other conditions that may be treated

include, but are not limited to: all form of headache, including migraine headache; acute musculoskeletal pain; ankylosing spondylitis; dysmenorrhoea; myalgias; and neuralgias.

In a more general sense, the invention includes methods of treating pain, inflammation and/or other conditions by orally administering an acid inhibitor at a dose effective to raise a patient's gastric pH to at least 3.5, preferably to at least 4 or and more preferably to at least 5. The patient is also administered an NSAID, for example in a coordinated dosage form, that has been coated in a polymer that only dissolves at a pH of least 3.5, preferably at least 4 and, more preferably, 5 or greater or which dissolves at a rate that is slow enough to prevent NSAID release until after the pH has been raised. When acid inhibitor and NSAID are administered in separate doses, e.g., in two separate tablets, they should be given concomitantly (i.e., so that their biological effects overlap) and may be given concurrently, i.e., NSAID is given within one hour after the acid inhibitor. Preferably, the acid inhibitor is an H2 blocker and, in the most preferred embodiment, it is famotidine at a dosage of between 5 mg and 100 mg. Any of the NSAIDs described above may be used in the method but naproxen at a dosage of between 200 and 600 mg is most preferred. It is expected that the inhibitor and analgesic will be typically delivered as part of a single unit dosage form which provides for the coordinated release of therapeutic agents. The most preferred dosage form is a multilayer tablet having an outer layer

comprising an H2 blocker and an inner core comprising an NSAID.

The invention also provides a method for increasing compliance in a patient requiring frequent daily dosing of NSAIDs by providing both an acid inhibitor and NSAID in a single convenient, preferably coordinated, unit dosage form, thereby reducing the number of individual doses to be administered during any given period.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic diagram of a four layer tablet dosage form. There is a naproxen core layer surrounded by a barrier layer. A third, enteric coating, layer delays the release of naproxen sodium until the pH is at a specific level, e.g., above 4. Finally, there is an outer layer that releases an acid inhibitor such as famotidine.

FIG. **2** illustrates a three layer dosage form. An acid inhibitor, e.g., famotidine, is released immediately after ingestion by a patient in order to raise the pH of the gastrointestinal tract to above a specific pH, e.g., above 4. The innermost layer contains naproxen. Thus, the dosage form has a naproxen core, an enteric film coat and an acid inhibitor film coat.

FIG. **3** illustrates a naproxen sodium pellet which contains a subcoat or barrier coat prior to the enteric film coat.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based upon the discovery of improved pharmaceutical compositions for administering NSAIDs to patients. In addition to containing one or more NSAIDs, the compositions include acid inhibitors that are capable of raising the pH of the GI tract of patients. All of the dosage forms are designed for oral delivery and provide for the coordinated release of therapeutic agents, i.e., for the sequential release of acid inhibitor followed by analgesic.

The NSAIDs used in preparations may be either short or long acting. As used herein, the term "long acting" refers to an NSAID having a pharmacokinetic half-life of at least 2 hours, preferably at least 4 hours and more preferably, at least 8-14 hours. In general, its duration of action will equal or exceed about 6-8 hours. Examples of long-acting NSAIDs are: flurbiprofen with a half-life of about 6 hours; ketoprofen with a half-life of about 2 to 4 hours; naproxen or naproxen sodium with half-lives of about 12 to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half-life of about 42 to 50 hours; etodolac with a half-life of about 7 hours; indomethacin with a half-life of about 4 to 6 hours; ketorolac with a half-life of up to about 8-9 hours, nabumetone with a half-life of about 22 to 30 hours; mefenamic acid with a half-life of up to about 4 hours; and piroxicam with a half-life of about 4 to 6 hours. If an NSAID does not naturally have a half-life sufficient to be long acting, it can, if desired, be made

long acting by the way in which it is formulated. For example, NSAIDs such as acetaminophen and aspirin may be formulated in a manner to increase their half-life or duration of action. Methods for making appropriate formulations are well known in the art (see e.g. Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton, Pa. (1980)).

It is expected that a skilled pharmacologist may adjust the amount of drug in a pharmaceutical composition or administered to a patient based upon standard techniques well known in the art. Nevertheless, the following general guidelines are provided:

Indomethacin is particularly useful when contained in tablets or capsules in an amount from about 25 to 75 mg. A typical daily oral dosage of indomethacin is three 25 mg doses taken at intervals during the day. However, daily dosages of up to about 150 mg are useful in some patients.

Aspirin will typically be present in tablets or capsules in an amount of between about 250 mg and 1000 mg. Typical daily dosages will be in an amount ranging from 500 mg to about 10 g.

Ibuprofen may be provided in tablets or capsules of 50, 100, 200, 300, 400, 600, or 800 mg. Daily doses should not exceed 3200 mg. 200 mg-800 mg may be particularly useful when given 3 or 4 times daily.

Flurbiprofen is useful when in tablets at about from 50 to 100 mg. Daily doses of about 100 to 500 mg, and particularly from about 200 to 300 mg, are usually effective.

Ketoprofen is useful when contained in tablets or capsules in an amount of about 25 to 75 mg. Daily doses of from 100 to 500 mg and particularly of about 100 to 300 mg are typical as is about 25 to 50 mg every six to eight hours.

Naproxen is particularly useful when contained in tablets or capsules in an amount of from 250 to 500 mg. For naproxen sodium, tablets of about 275 or about 550 mg are typically used. Initial doses of from 100 to 1250 mg, and particularly 350 to 800 mg are also used, with doses of about 550 mg being generally preferred.

Oxaprozin may be used in tablets or capsules in the range of roughly 200 mg to 1200 mg, with about 600 mg being preferred. Daily doses of 1200 mg have been found to be particularly useful and daily doses should not exceed 1800 mg or 26 mg/kg.

Etodolac is useful when provided in capsules of 200 mg to 300 mg or in tablets of about 400 mg. Useful doses for acute pain are 200-400 mg every six-eight hours, not to exceed 1200 mg/day. Patients weighing less than 60 kg are

advised not to exceed doses of 20 mg/kg. Doses for other uses are also limited to 1200 mg/day in divided doses, particularly 2, 3 or 4 times daily.

Ketorolac is usefully provided in tablets of 1-50 mg, with about 10 mg being typical. Oral doses of up to 40 mg, and particularly 10-30 mg/day have been useful in the alleviation of pain.

Nabumetone may be provided in tablets or capsules of between 500 mg and 750 mg. Daily doses of 1500-2000 mg, after an initial dose of 100 mg, are of particular use.

Mefenamic acid is particularly useful when contained in tablets or capsules of 50 mg to 500 mg, with 250 mg being typical. For acute pain, an initial dosage of 1-1000 mg, and particularly about 500 mg, is useful, although other doses may be required for certain patients.

Lomoxicam is provided in tablets of 4 mg or 8 mg. Useful doses for acute pain are 8 mg or 16 mg daily, and for arthritis are 12 mg daily.

One particular group of long acting NSAIDs that may be used are the cyclooxygenase-2 inhibitors. These include: celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, or NS398. JTE-522, L-745,337 and NS398 as described, inter alia, in Wakatani, et

al. (Jpn. J. Pharmacol. 78:365-371 1998)) and Panara, et al. (Br. J. Pharmacol. 116:2429-2434 1995)). The amount present in a tablet or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example:

Celecoxib may be administered in a tablet or capsule containing from about 100 mg to about 500 mg or, preferably, from about 100 mg to about 200 mg.

Piroxicam may be used in tablets or capsules containing from about 10 to 20 mg.

Rofecoxib will typically be provided in tablets or capsules in an amount of 12.5, 25 or 50 mg. The recommended initial daily dosage for the management of acute pain is 50 mg.

Meloxicam is provided in tablets of 7.5 mg, with a recommended daily dose of 7.5 or 15 mg for the management of osteoarthritis.

Valdecoxib is provided in tablets of 10 or 20 mg, with a recommended daily dose of 10 mg for arthritis or 40 mg for dysmenorrhea.

With respect to acid inhibitors, tablets or capsules may contain anywhere from 1 mg to as much as 1 g. 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, the proton pump inhibitor 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.

Making of Pharmaceutical Preparations

The pharmaceutical compositions of the invention include tablets, dragees, liquids and capsules and can be made in accordance with methods that are standard in the art (see, e.g., Remington's Pharmaceutical Sciences, 16th ed., A Oslo editor, Easton, Pa. (1980)). Drugs and drug combinations will typically be prepared in admixture with conventional excipients. Suitable carriers include, but are not limited to: water; salt solutions; alcohols; gum arabic; vegetable oils; benzyl alcohols; polyethylene glycols; gelatin; carbohydrates such as lactose, amylase or starch; magnesium stearate; talc; silicic acid; paraffin; perfume oil; fatty acid esters; hydroxymethylcellulose; polyvinyl pyrrolidone; etc. The pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents such as: lubricants, preservatives, disintegrants; stabilizers;

wetting agents; emulsifiers; salts; buffers; coloring agents; flavoring agents; or aromatic substances.

Enteric coating layer(s) may be applied onto the core or onto the barrier layer of the core using standard coating techniques. The enteric coating materials may be dissolved or dispersed in organic or aqueous solvents and may include one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethyl-cellulose trimellitate, carboxymethylethylcellulose, cellulose acetate phthalate or other suitable enteric coating polymer(s). The pH at which the enteric coat will dissolve can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of the polymer film can be altered by the ratio of free carboxyl groups to ester groups. Enteric coating layers also contain pharmaceutically acceptable plasticizers such as triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other plasticizers. Additives such as dispersants, colorants, anti-adhering and anti-foaming agents may also be included.

The Making of Tablet Dosage Forms

Preferably, the combination of an acid inhibitor and an NSAlD will be in the form of a bi-or multi-layer tablet. In a bilayer configuration, one portion of the tablet contains the acid inhibitor in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second

portion of the tablet will contain the NSAlD, preferably naproxen, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc. In the most preferred embodiment, the NSAlD layer is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. The naproxen may be granulated by methods such as slugging, low-or high-shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produces tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

EXAMPLES

Example 1

Enteric Coated Naproxen Sodium Core and Famotidine Immediate Release

A schematic diagram of a four layer tablet dosage form is shown in FIG. **1**. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1 % to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium

tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5. The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an unprotected stomach. Methacrylic acid copolymers are used as the enteric coating ingredient, triethyl citrate and dibutyl phthalate are plasticisers, and ammonium hydroxide is used to adjust the pH of the dispersion. The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably the H2 blocker famotidine, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of famotidine in the dosage form will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine within the fourth layer without tablets sticking to the coating pan or to each other during application of the film coat. Other

ingredients may include: plasticisers such as triethyl citrate, dibutyl phthalate, and polyethylene glycol; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

	% W/W	mg/Tablet
Core Tablet Ingredients		
Naproxen sodium, USP	74.074	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.166	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00
Barrier Film Coating Ingredients		
Opadry Clear ® YS-1-7006	5.00	
Purified water USP	95.00	
Total	100.00	
Enteric Coating Dispersion Ingredients		
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	7.30	
Methacrylic Acid Copolymer, NF (Eudragit L-100)	7.30	
Triethyl Citrate, NF	2.95	
Dibutyl Phthalate, NF	1.17	
Ammonium Hydroxide (30%), NF	0.87	

continued

	% W/W	mg/Tablet
Purified water, USP	80.41	
Total	100.00	
Famotidine Coating Dispersion Ingredients		
Famotidine, USP	3.0	
Opadry Clear® (YS-1-7006)	5.0	
Talc, USP	3.0	
Purified Water, USP	89.0	
Total	100.0	

Example 2

Enteric Coated Naproxen Core and Famotidine Immediate Release

FIG. **2** illustrates a three layered dosage form which releases famotidine immediately after ingestion by the patient in order to raise the pH of the gastrointestinal tract to above about 4. The innermost layer contains naproxen uniformly distributed throughout a matrix of pharmaceutically acceptable excipients. These excipients perform specific functions and may serve as binders, disintegrants, or lubricants. A pharmaceutically acceptable enteric coating surrounds the naproxen core. The function of the enteric coat to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the harshly acidic pH of the unprotected stomach. It contains methacrylic

acid copolymers which prevent the release of naproxen in the unprotected stomach. Also included are: triethyl citrate, a plasticiser; simethicone emulsion, an anti-foaming agent; and sodium hydroxide which is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in this example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which raises the pH of the stomach to above 4. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine in the fourth layer without tablets sticking to the coating pan or sticking to each other during application of the film coat. Other ingredients are: plasticisers such as polyethylene glycol 8000; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate;, and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

	% W/W	mg/Tablet
Core Tablet Ingredients		
Naproxen, USP	90.91	500.00
Povidone K-90, USP	2.00	11.00
Starch, USP	2.59	14.25

continued

	% W/W	mg/Tablet
Croscarmellose Sodium, USP	4.00	22.00
Magnesium Stearate, NF	0.50	2.75
Total	100.00	550.00
Purified Water, USP qs		
Enteric Coating Dispersion Ingredients		
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5	
Talc, USP	3.8	
Sodium Hydroxide, NF	0.2	
Triethyl Citrate, NF	1.7	
Simethicone Emulsion, USP	0.02	
Purified Water, USP	79.78	
Total	100.00	
Famotidine Coating Dispersion Ingredients		
Famotidine, USP	3.0	
Opadry Clear ® (YS-1-7006)	5.0	
Talc, USP	3.0	
Purified Water, USP	89.0	
Total	100.0	

Example 3

Naproxen Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen may be used in the present invention. The core tablet of naproxen is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. FIG. 2 shows an example of an appropriate trilayer tablet. In this particular example, naproxen is mixed with a polymeric material, hydroxypropylmethylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extremely acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen until the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropyl-methylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, Pa.) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

	% W/W	mg/Tablet
Core Tablet Ingredients		
Naproxen, USP	94.00	750
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	5.00	39.9

continued

	% W/W	mg/Tablet
Magnesium Stearate, NF	1.00	7.95
Total	100.00	797.85
Enteric Coating Dispersion Ingredients		
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5	
Talc, USP	3.8	
Sodium Hydroxide, NF	0.2	
Triethyl Citrate, NF	1.7	
Simethicone Emulsion, USP	0.02	
Purified Water, USP	79.78	
Total	100.00	
Famotidine Coating Dispersion Ingredients		
Famotidine, USP	2.0	
Opadry Blue® (YS-1-4215)	10.0	
Talc, USP	9.0	
Purified Water, USP	79.0	
Total	100.0	

Example 4

Naproxen and Famotidine Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in film coat from controlled-release naproxen and famotidine may be used in the present invention. The core tablet of naproxen and famotidine is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. FIG. **2** is an example of appropriate trilayer tablet. In this particular example, naproxen and famotidine are mixed with a polymeric material, hydroxypropylmethylcellulose and granulated with water. The granules are dried, milled, and blended with lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen and famotidine is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extremely acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen in the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost later contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropyl-methylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, Pa.) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

	% W/W	mg/Tablet
Core Tablet Ingredients		
Naproxen, USP	88.05	500
Famotidine, USP	3.52	20.0
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	7.03	39.9

continued

	% W/W	mg/Tablet
Magnesium Stearate, NF	1.40	7.95
Total	100.00	567.85
Enteric Coating Dispersion Ingredients		
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5	
Talc, USP	3.8	
Sodium Hydroxide, NF	0.2	
Triethyl Citrate, NF	1.7	
Simethicone Emulsion, USP	0.02	
Purified Water, USP	79.78	
Total	100.00	
Famotidine Coating Dispersion Ingredients		
Famotidine, USP	2.0	
Opadry Blue ® (YS-1-4215)	10.0	
Talc, USP	9.0	
Purified Water, USP	79.0	
Total	100.0	

Example 5

Enteric Coated Naproxen Sodium Core and Pantoprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in FIG. **1**. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1 % to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH may be below 4 such as in an unprotected stomach but it dissolves only when the local pH is above about 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, pantoprazole which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of pantoprazole in the dosage form may vary from 10 mg to 200 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases pantoprazole for absorption. Therefore, pantoprazole releases first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified

water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	% W/W
Opadry Clear ® YS-1-7006	5.00
Purified water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	% W/W
Hydroxypropyl methylcellulose phthalate, NF	5.5
Cetyl alcohol, NF	0.3
Acetone, NF	66.3
Alcohol, NF	27.9
Total	100.00

Hydroxypropylmethylcellulose phthalate and cetyl alcohol are dissolved in a mixture of alcohol and acetone. The solution is then sprayed on to the tablet bed in proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating stopped if the tablets pass the test.

Pantoprazole Film Coating Ingredients	% W/W
Pantoprazole sodium, USP	5.00
Opadry Clear ® YS-1-7006	5.00
Sodium carbonate, NF	1.20
Purified Water, USP	88.80
Total	100.00

Pantoprazole sodium is dissolved in purified water containing sodium carbonate in solution. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until the proper amount of pantoprazole sodium is deposited.

Example 6

Enteric Coated Naproxen Sodium Core and Omeprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in FIG. **1**. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium

tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH is below 4 such as in an unprotected stomach but it dissolves only when the local pH is above 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, omeprazole, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH

of the dispersion. The film coating is thin and rapidly releases omeprazole for absorption. Therefore, omeprazole is released first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	% W/W	Mg/Tablet
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	% W/W
Opadry Clear ® YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until the proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	6.0
Triethyl Citrate, NF	0.6
Talc, USP	3.0
Purified Water, USP	5.0
Isopropyl Alcohol, USP	85.40
Total	100.00

Methacrylic acid copolymer, triethyl citrate, and talc are dissolved in a mixture of isopropyl alcohol and water. The solution is then sprayed on to the tablet bed in a proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating is stopped if the tablets pass the test.

Omeprazole Film Coating Ingredients	% W/W
Omeprazole, USP	5.00
Opadry Clear ® YS-1-7006	5.00
Purified Water, USP	10.00
Isopropyl Alcohol, USP	80.00
Total	100.00

Omeprazole is dissolved in a purified water and isopropyl alcohol mixture. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional

coating pan until proper amount of omeprazole is deposited on the tablets.

Example 7

Naproxen Sodium Delayed Release and Omeprazole Immediate Release Capsule

A coordinated delivery dosage may be used to provide fast release of an acid inhibitor, a proton pump inhibitor, omeprazole which raises the pH of the gastrointestinal tract to above 4, and the delayed release of a non-steroidal anti-inflammatory drug, naproxen sodium. Omeprazole granules modify the pH of the stomach such that the drug readily dissolves and is absorbed in the stomach without significant degradation. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The release of naproxen sodium is delayed by enteric coating.

Omeprazole granules contain an alkalizing excipient such as sodium bicarbonate. Other soluble alkalizing agents such as potassium bicarbonate, sodium carbonate, sodium hydroxide, or their combinations may also be used. The alkalizing agent helps solubilize and protect omeprazole from degradation before its absorption. Sodium lauryl sulfate helps in the wetting of omeprazole. Other surfactants may be used to perform the same function. In the present example, hydroxypropyl methylcellulose helps in granule formation, sodium starch glycolate is a disintegrant, and magnesium

stearate is a lubricant. Other excipients may also be used to perform these functions.

Naproxen sodium pellets as shown in FIG. 3 are prepared by the wet massing technique and the conventional extrusion and spheronization process. The excipients used in the formulation are microcrystalline cellulose, and povidone. The pellets after drying and classification are coated with a protective subcoating containing povidone. Other coating ingredients may also be used such as Opaspray K-1-4210A or Opadry YS-1-7006 (trademarks of Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropyl-methylcellulose 2910 and polyethylene glycol 8000 in a subcoating suspension are also alternatives. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide.

The subcoated pellets are enteric coated using enteric coating polymers. In this example, the enteric coating polymer is methacrylic acid copolymer and the plasticizer is dibutyl phthalate which are dissolved in a mixture of acetone and alcohol. The enteric film does not dissolve in the acidic pH but dissolves when the pH in the gut is above about pH and releases naproxen sodium.

Omeprazole Granules	% W/W	mg/capsule
Omeprazole, USP	12.9	20.00
Sodium Bicarbonate, USP	82.40	127.72

continued

Omeprazole Granules	% W/W	mg/capsule
Hydroxypropyl methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Sodium starch glycolate, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.77
Total	100	100

Hydroxypropylmethylcellulose is dissolved in water, then sodium lauryl sulfate is added and the solution is mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen sodium, USP	86.80	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	11.10	32.00
Povidone (K90), USP	2.10	6.00
Total	100.00	288.00

Povidone is dissolved in water. Naproxen sodium and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is

mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into suitable particle size range.

Subcoat Ingredients	% W/W
Povidone (K29-32), USP	10.00
Alcohol, USP	90.00
Total	100.00

The pellet cores are coated using povidone solution by a conventional coating pan method to a weight gain of 1-2%.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100)	8.20
Diethyl Phthalate, NF	1.70
Acetone, NF	33.30
Isopropyl Alcohol, USP	56.80
Total	100.0

Eudragit L-100 is dissolved in isopropanol and acetone and diethyl phthalate is dissolved. The solution is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process.

Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together

and filled into appropriate size capsules to contain 250 mg naproxen sodium and 20 mg omeprazole per capsule.

Example 8

Naproxen Delayed Release and Omeprazole Immediate Release Capsule

The present Example is directed to a coordinated delivery dosage form containing omeprazole and naproxen. The formulation contains 10 mg omeprazole and uses methylcellulose as a binder and croscarmellose sodium as a disintegrant. Naproxen pellets as shown in FIG. 3 do not need a subcoating layer and are enteric coated with an aqueous dispersion of methacrylic acid copolymer. Optionally, these pellets could be compressed into a core and film coated with an acid inhibitor and thereby form a bilayer tablet.

Omeprazole Granules	% W/W	mg/capsule
Omeprazole, USP	6.45	10.00
Sodium Bicarbonate, USP	88.85	137.71
Methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Croscarmellose sodium, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.78
Total	100	100

Methylcellulose is dissolved in water, then sodium lauryl sulfate is added to the solution and

mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen, USP	76.22	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	21.78	71.44
Povidone (K90), USP	2.00	6.56
Total	100.00	328.00

Povidone is dissolved in water. Naproxen and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into a suitable particle size range.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L30D 30% dispersion)	15.60
Talc, USP	7.60
Triethyl citrate, NF	1.60
Simethicone Emulsion, USP (Silicone antifoam emulsion SE 2)	0.20
Purified Water, USP	74.80

Eudragit 30D is dispersed in purified water and simethicone emulsion. Talc and triethyl citrate are then dispersed. The suspension is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process. Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen and 10 mg omeprazole per capsule.

Example 9

Clinical Study of the Relationship of Gastric pH to NSAlD-induced Gastric Ulcers

Sixty-two subjects were enrolled in a clinical study and randomly assigned to three groups. The following three groups were administered study medication twice daily for five days: (a) 550 mg naproxen sodium (n=10), (b) 40 mg famotidine given with 550 mg of naproxen or famotidine followed 90 minutes later by 550 mg naproxen, (n=39) or (c) 20 mg omeprazole followed by 550 mg naproxen sodium (n=13). Gastric pH was measured hourly beginning at the time of dosing of the final daily dose of study medication and for 8-10 hours thereafter. Subjects had a gastric endoscopy performed at the beginning and on Day 5 prior to the morning dose of study medication to identify gastric and duodenal irritation; no subjects were admitted to the study if gastric irritation was present at the time of initial endoscopy.

Five patients, three (33%) in the naproxen alone group and two (5%) in the famotidine/naproxen group, presented with gastroduodenal ulcers at the end of the study. In the naproxen alone group, the pH was greater than 4 only 4% of the time, and in the famotidine/naproxen group the pH was greater than 4 forty-nine percent of the time during the 8-10 hours following naproxen sodium dosing. Additionally, Lanza grade 3 or 4 damage was present in 28% (n=11) of the subjects receiving famotidine/naproxen sodium, and present 100% (n=10) in the naproxen sodium treatment group. Monitoring of gastric acidity on day 5 indicated that patients with Lanza scores of greater than 2 had integrated gastric acidity of greater than 100 mmol-hr./L. Only 20-40% of patients with integrated gastric acidity of less than 100 mmol-hr/L had gastric pathology, whereas all patients with integrated gastric acidity greater than 100 mmol-hr/L had pathology.

Example 10

Famotidine and Enteric Coated Naproxen Reduce Gastroduodenal Damage Due to NSAlD Therapy

Forty patients are randomized to two groups for a one week study of twice-daily dosing of: 500 mg enteric coated naproxen, and 500 mg enteric coated naproxen preceded by 40 mg famotidine. Endoscopies are conducted on all patients prior to first dosing and on the final day of the study. No subjects have any evidence of gastroduodenal damage at the beginning of the study (at first endoscopy).

At the second endoscopy, Lanza scores for gastroduodenal damage are assessed for all subjects. Subjects in the enteric coated naproxen 500 mg group have a lower incidence of grade 3-4 gastroduodenal damage than subjects previously treated with non-enteric coated naproxen 500 mg. Importantly, subjects administered 500 mg enteric coated naproxen and 40 mg famotidine have substantially lower incidence of grade 3-4 gastroduodenal damage than subjects who had previously taken naproxen alone (either naked or enteric coated) which demonstrates the need for and the value of combining acid inhibition with enteric coating to minimize the gastrointestinal damage of NSAID.

All references cited herein are fully incorporated by reference. Having now fully described the invention, it will be understood by those of skill in the art that the invention may be performed within a wide and equivalent range of conditions, parameters and the like, without affecting the spirit or scope of the invention or any embodiment thereof.

What is claimed is:

1. A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:

(a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;

(b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

and wherein said unit dosage form provides for coordinated release such that:

i) said NSAlD is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAlD from said dosage form unless the pH of the surrounding medium is 3.5 or higher;

ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

2. The pharmaceutical composition of claim **1**, wherein said acid inhibitor is an H2 blocker.

3. The pharmaceutical composition of claim **2**, wherein said H2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

4. The pharmaceutical composition of claim **3**, wherein said H2 blocker is famotidine, present in

said unit dosage form in an amount of between 5 mg and 100 mg.

5. The pharmaceutical composition of claim **1**, wherein said acid inhibitor is a proton pump inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

6. The pharmaceutical composition of claim **5**, wherein said proton pump inhibitor is pantoprazole, present in said unit dosage form in an amount of between 10 mg and 200 mg.

7. The pharmaceutical composition of claim **1**, wherein said NSAID is a cyclooxygenese-2 (COX-2) inhibitor.

8. The pharmaceutical composition of claim **7**, wherein said COX-2 inhibitor is selected from the group consisting of celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

9. The pharmaceutical composition of claim **1**, wherein said NSAlD is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

10. The pharmaceutical composition of claim **9**, wherein said NSAlD is naproxen present in an amount of between 50 mg and 1500 mg.

11. The pharmaceutical composition of claim **10**, wherein said naproxen is present in an amount of between 200 mg and 600 mg.

12. The pharmaceutical composition of claim **1** wherein said unit dosage form is a multilayer tablet comprising a single core and one or more layers outside of said single core, wherein:

i) said NSAID is present in said core;

ii) said coating that does not release said NSAID unless the pH of the surrounding medium is 3.5 or higher surrounds said core; and

iii) said acid inhibitor is in said one more layers outside said core.

13. The pharmaceutical composition of claim **12**, wherein said one or more layers outside of said core do not contain NSAID and are not surrounded by an enteric coating.

14. The pharmaceutical composition of claim **13**, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID and wherein said outer layer of said tablet is surrounded by a non-enteric film coating that releases said acid inhibitor upon ingestion by patient.

15. The pharmaceutical composition of any one of claims **1** or **7-14**, wherein said acid inhibitor is a proton pump inhibitor.

16. The pharmaceutical composition of claim **15**, wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of claim **15**, wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 5 or greater.

18. The pharmaceutical composition of any one of claims **7-14**, wherein said acid inhibitor is an H2 blocker.

19. The pharmaceutical composition of claim **18**, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

20. The pharmaceutical composition of claim **18**, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 5 or greater.

21. The pharmaceutical composition of claim **1**, wherein said unit dosage form is a capsule.

22. A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of any one of claims **1-14**.

23. The method of claim **22**, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

24. A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) orally administering to said patient an NSAID that is coated in a polymer that only dissolves at a pH of 3.5 or greater.

25. The method of claim **24**, wherein said acid inhibitor is an H2 blocker.

26. The method of claim **25**, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

27. The method of claim **26**, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

28. The method of claim **24**, wherein said acid inhibitor is a proton pump inhibitor.

29. The method of claim **28**, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

30. The method of claim **29**, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

31. The method of any one of claims **24-30**, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

32. The method of any one of claims **24-30**, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

33. The method of claim **32**, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

34. The method of claim **33**, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

35. The method of claim **24**, wherein said acid inhibitor and said NSAID are delivered as part of a

single dosage form providing for the coordinated release of therapeutic agents.

36. The method of claim **35**, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

37. A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) concurrently administering to said patient an NSAID that is coated in a polymer that dissolves at a rate such that said NSAID is not released until said gastric pH is at 3.5 or higher.

38. The method of claim **37**, wherein said acid inhibitor is an H2 blocker.

39. The method of claim **38**, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

40. The method of claim **39**, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

41. The method of claim **37**, wherein said acid inhibitor is a proton pump inhibitor.

42. The method of claim **41**, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

43. The method of claim **42**, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

44. The method of any one of claims **37-43**, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522 L-745, 337; and NS398.

45. The method of any one of claims **37-43**, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

46. The method of claim **45**, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

47. The method of claim **46**, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

48. The method of claim **47**, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

49. The method of claim **48**, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

50. A method of improving compliance in patients requiring frequent daily dosages of an acid inhibitor and an NSAID comprising administering said dosages in a coordinated unit dosage form in accordance with claim **1**.

51. A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim **15**.

52. The method of claim **51**, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

53. The pharmaceutical composition of any one of claims **5-11** wherein said unit dosage form is a multilayer tablet comprising a single core and one or more layers outside of said single core, wherein:

i) said NSAID is present in said core;

ii) said coating that does not release said NSAID unless the pH of the surrounding

medium is 3.5 or higher surrounds said core; and

iii) said acid inhibitor is in said one more layers outside said core.

54. The pharmaceutical composition of claim **53**, wherein said one or more layers outside of said core do not contain NSAID and are not surrounded by an enteric coating.

55. The pharmaceutical composition of claim **54**, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID and wherein said outer layer of said tablet is surrounded by a non-enteric film coating that, upon ingestion by a patient, releases said acid inhibitor into the stomach of said patient.

* * * * *

UNITED STATES
PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907 B2 Page 1 of 3
APPLICATION NO.	: 10/158216
DATED	: August 9, 2005
INVENTOR(S)	: John Plachetka

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the first line of claim 1 line 1 in the issued patent, the word "dose" should be --dosage.-- Thus, the correct claim should read as follows:

Col. 20, Claim

1. A pharmaceutical composition in unit dosage form suitable for oral administration to a patient, comprising: (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms; (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms; and wherein said unit dosage form provides for coordinated release such that:

i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher; ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

UNITED STATES
PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907 B2 Page 2 of 3
APPLICATION NO.	: 10/158216
DATED	: August 9, 2005
INVENTOR(S)	: John Plachetka

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 21, Line 1 of claim 16 and 17 should refer to "any one of claims 12-14" and not to "claim 15." In addition, the phrase --wherein said acid inhibitor is a proton pump inhibitor--should be included in 16 and 17. Thus, the claims should read as follows: Col. 21

16. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 5 or greater.

Col. 21, Line 1 of claims 19 and 20 should refer to "any one of claims 12-14" and not to "claim 18." In addition, the phrase --wherein said acid inhibitor is an H2 blocker--should be included in 19 and 20. Thus, the claims should read as

follows:

Col. 21

19. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

UNITED STATES
PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

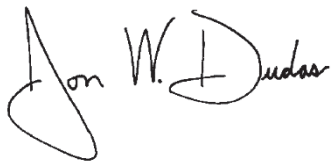
PATENT NO.	: 6,926,907 B2 Page 3 of 3
APPLICATION NO.	: 10/158216
DATED	: August 9, 2005
INVENTOR(S)	: John Plachetka

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 21

20. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier is not released until the pH of the surrounding medium is 5 or greater.

Signed and Sealed this
Twenty-fifth Day of December, 2007



JON W. DUDAS

Director of the United States Patent and Trademark Office

APPENDIX H

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES PATENT NO. 8,557,285 B2 ENTITLED "*PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS" ISSUED OCTOBER 15, 2013*

(54) **PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS**

(75) Inventor: **John R. Plachetka,** Chapel Hill, NC

(73) Assignee: **Pozen Inc**., Chapel Hill, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/215,855**

(22) Filed: **Aug. 23, 2011**

(65) **Prior Publication Data**

US 2012/0064156 A1 Mar. 15, 2012

Related U.S. Application Data

(60) Division of application No. 12/553,804, filed on Sep. 3, 2009, now abandoned, which is a division of application No. 11/129,320, filed on May 16, 2005, now Pat. No. 8,206,741, which is a continuation-in-part of application No. 10/158,216, filed on May 31, 2002, now Pat. No. 6,926,907.

(60) Provisional application No. 60/294,588, filed on Jun. 1, 2001.

(51) **Int. Cl.**

A61K9/22	(2006.01)
A61K9/32	(2006.01)
A61K 9/24	(2006.01)
A61K 9/52	(2006.01)

(52) **U.S. Cl.**

USPC **424/472;** 424/457; 424/463; 424/468; 424/474; 424/482

(58) **Field of Classification Search**

None

See application file for complete search history.

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Ltd's. Invalidity contentions pursuant to L. Pat. R. 3.6(c)," dated Nov. 23, 2011. "*Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. V Lupin Ltd*. and *Lupin Pharmaceuticals, Inc.,* Defendants Lupin Ltd. and Lupin Pharmaceuticals, Inc's Amended Invalidity Contentions Pursuant to L. PAT. R. 3.3 and 3.6(c)," dated Apr. 20, 2012.

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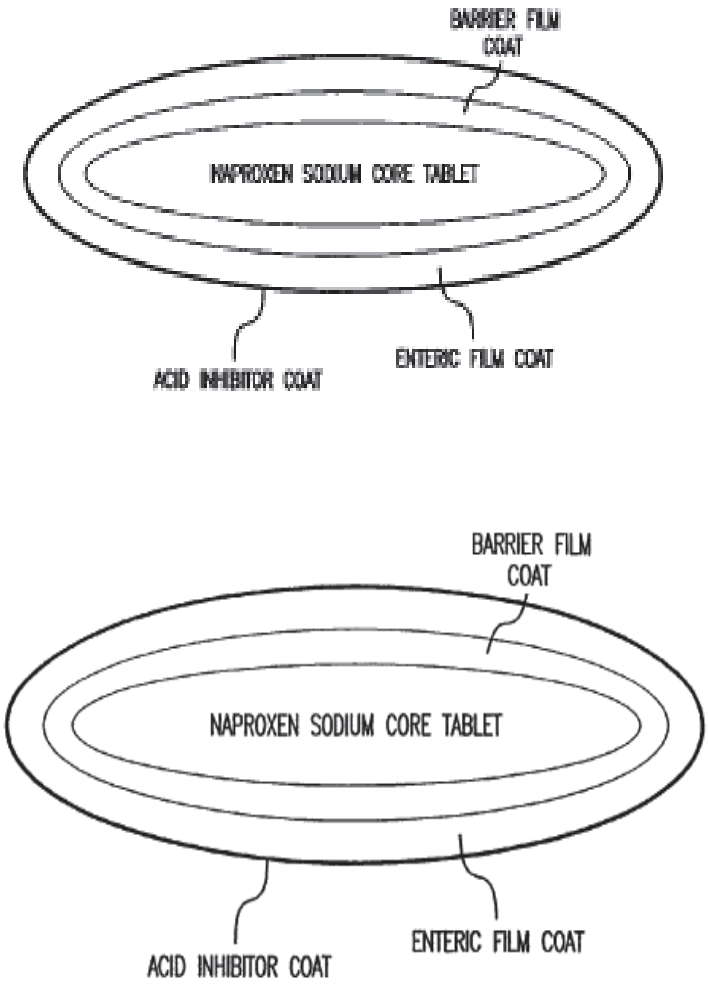
(57) ABSTRACT

The present invention is directed to drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The dosage form is designed so that the NSAID is not released until the intragastric pH has been raised to a safe level. The invention also encompasses methods of treating patients by administering this coordi-nated release, gastroprotective, antiarthritic/anal-gesic combination unit dosage form to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages.

4 Claims, 2 Drawing Sheets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ACID INHIBITOR COAT
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FIG.1

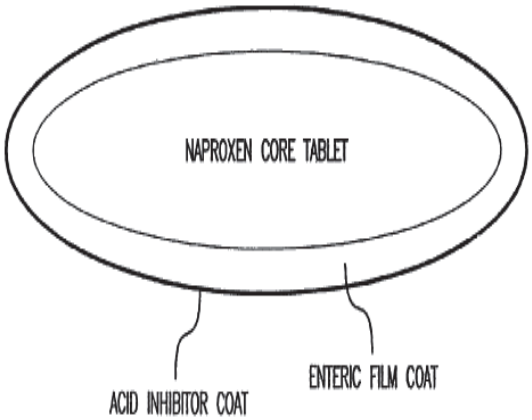
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FIG.2

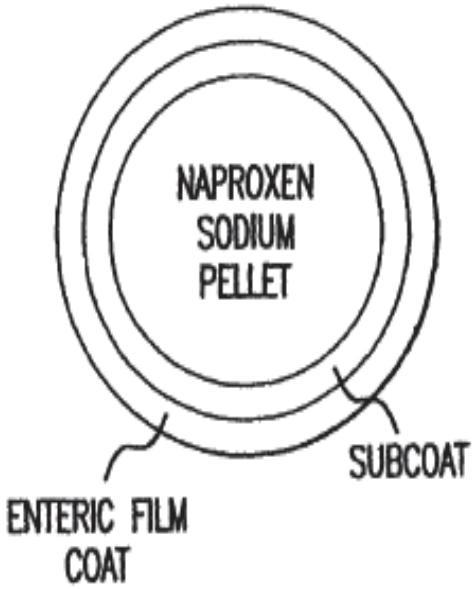

FIG.3

PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a divisional of U.S. application Ser. No. 12/553,804 filed Sep. 3, 2009, now abandoned which is a divisional of U.S. application Ser. No. 11/129,320 filed May 16, 2005, issued as U.S. Pat. No. 8,206,741 on Jun. 26, 2012 which is a continuation-in-part of U.S. application Ser. No. 10/158,216, filed on May 31, 2002, issued as U.S. Pat. No. 6,926,907 on Aug. 9, 2005, which claims the benefit of U.S. provisional application No. 60/294,588, filed on Jun. 1, 2001. The entire contents of all applications are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention is directed to pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID). These compositions have a reduced likelihood of causing unwanted side effects, especially gastrointestinal side effects, when administered as a treatment for pain, arthritis and other conditions amenable to treatment with NSAIDs.

BACKGROUND OF THE INVENTION

Although non-steroidal anti-inflammatory drugs are widely accepted as effective agents for controlling pain, their administration can lead to the development of gastroduodenal lesions, e.g., ulcers and erosions, in susceptible individuals. It appears that a major factor contributing to the development of these lesions is the presence of acid in the stomach and upper small intestine of patients. This view is supported by clinical studies demonstrating an improvement in NSAID tolerability when patients are also taking independent doses of acid inhibitors (*Dig. Dis.* 12:210-222 (1994); *Drug Safety* 21:503-512 (1999); *Aliment. Pharmacol. Ther.* 12:135-140 (1998); *Am. J. Med.* 104(3A):67S-74S (1 998); *Clin. Ther.* 17:1 159-1173 (1995)). Other major factors contributing to NSAID-associated gastropathy include a local toxic effect of NSAIDs and inhibition of protective prostaglandins (*Can. J. Gastro-enterol.* 13:135-142 (1999) and *Pract. Drug Safety* 21:503-512, (1999)), which may also make some patients more susceptible to the ulcerogenic effects of other noxious stimuli.

In general, more potent and longer lasting acid inhibitors, such as proton pump inhibitors, are thought to be more protective during chronic administration of NSAIDs than shorter acting agents, e.g., histamine H_2 receptor antagonists (H-2 blockers) (*N. Eng. J. Med.* 338:719-726 (1998); *Am. J. Med.* 104(3A):56S-61S (1998)). The most likely explanation for this is that gastric pH

fluctuates widely throughout the dosing interval with short acting acid inhibitors leaving the mucosa vulnerable for significant periods of time. In particular, the pH is at its lowest point, and hence the mucosa is most vulnerable, at the end of the dosing interval (least amount of acid inhibition) and for some time after the subsequent dose of acid inhibitor. In general, it appears that when a short acting acid inhibitor and an NSAID are administered simultaneously, NSAID-related mucosal damage occurs before the pH of the gastrointestinal tract can be raised and after the acid inhibiting effect of the short acting acid inhibitor dissipates.

Although longer lasting agents, such as proton pump inhibitors (PPls), usually maintain a consistently higher gastroduodenal pH throughout the day, their antisecretory effect may be delayed for several hours and may not take full effect for several days (*Clin. Pharmacokinet.* 20:38-49 (1991)). Their effect may be diminished toward the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from "acid breakthrough" which again leaves them vulnerable to NSAID-associated gastroduo-denal damage (*Aliment. Pharmacol. Ther.* 14:709-714 (2000)). Despite a significant reduction in gastroduodenal lesions with the concomitant

administration of a proton pump inhibitor during six months of NSAID therapy, up to 16% of patients still develop ulcers, indicating that there remains substantial room for improvement (*N. Eng. J. Med.* 338:727-734 (1998)). Thus, the addition of a pH sensitive enteric coating to an NSAID could provide additional protection against gastroduodenal damage not provided by the H2 blocker or PPI alone. In addition, although long acting acid inhibitors may reduce the risk of GI lesions in chronic NSAID users, there are questions about the safety of maintaining an abnormally elevated pH in a patient's GI tract for a prolonged period of time (*Scand. J. Gastroenterol. Suppl.* 178:85-92 (1990)).

Recognizing the potential benefits of PPIs for the prevention of NSAID-induced gastroduodenal damage, others have disclosed strategies for combining the two active agents for therapeutic purposes. However, these suggestions do not provide for coordinated drug release or for reducing intragastric acid levels to a non-toxic level prior to the release of NSAID (U.S. Pat. No. 5,204,118; U.S. Pat. No. 5,417,980; U.S. Pat. No. 5,466,436; and U.S. Pat. No. 5,037,815). In certain cases, suggested means of delivery would expose the gastrointestinal tract to NSAIDs prior to onset of PPI activity (U.S. Pat. No. 6,365,184).

Attempts to develop NSAIDs that are inherently less toxic to the gastrointestinal tract have met with only limited success. For example, the recently developed 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 (*JAMA* 284:1247-1255 (2000); *N. Eng. J. Med.* 343:1520-1528 (2000)). In this regard, it appears that even low doses of aspirin will negate most of the benefit relating to lower gastrointestinal lesions. In addition, the COX-2 inhibitors may not be as effective as other NSAIDs at relieving some types of pain and have been associated with significant cardiovascular problems (*JADA* 131:1729-1737 (2000); *SCRIP* 2617, pg. 19, Feb. 14, 2001); NY Times, May 22, 2001, pg. C1)).

Other attempts to produce an NSAID therapy with less gastrointestinal toxicity have involved the concomitant administration of a cytoprotective agent. In 1998, Searle began marketing Arthrotec™ for the treatment of arthritis in patients at risk for developing GI ulcers. This product contains misoprostol (a cytoprotective prostaglandin) and the NSAID diclofenac. Although patients administered Arthrotec™ do have a lower risk of developing ulcers, they may experience a number of other serious side effects such as diarrhea, severe cramping and, in the case of pregnant women, potential damage to the fetus.

Another approach has been to produce enteric coated NSAID products. However, even though these have shown modest reductions in gastroduodenal damage in short term studies (*Scand. J. Gastroenterol.* 20: 239-242 (1985) and

Scand. J. Gastroenterol. 25:231-234 (1990)), there is no consistent evidence of a long term benefit during chronic treatment.

Overall, it may be concluded that the risk of inducing GI ulcers is a recognized problem associated with the administration of NSAIDs and that, despite considerable effort, an ideal solution has not yet been found.

SUMMARY OF THE INVENTION

The present invention is based upon the discovery of 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. The method involves the administration of a single, coordinated, unit-dose product that combines: a) an agent that actively raises intragastric pH to levels associated with less risk of NSAID-induced ulcers; and b) an NSAID that is specially formulated to be released in a coordinated way that minimizes the adverse effects of the NSAID on the gastroduodenal mucosa. Either short or long acting acid inhibitors can be effectively used in the dosage forms. This 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.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dosage form suitable for oral administration to a patient. The composition contains an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5, preferably to at least 4, and more preferably to at least 5, when one or more unit dosage forms are administered. The gastric pH should not exceed 7.5 and preferably should not exceed 7.0. The term "acid inhibitor" refers to agents that inhibit gastric acid secretion and increase gastric pH. In contrast to art teaching against the use of H2 blockers for the prevention of NSAID-associated ulcers (*N. Eng. J. Med.* 340:1888-1899 (1999)), these agents are preferred compounds in the current invention. Specific H2 blockers that may be used include cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine or famotidine. The most preferred acid inhibitor is famotidine present in dosage forms in an amount of between 5 mg and 100 mg.

Other preferred agents that may be effectively used as acid inhibitors are the proton pump inhibitors such as omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, pariprazole, leminoprazole and tenatoprazole. Examples of particular proton pump inhibitors include omeprazole, present in unit dosage forms in an amount of between 5 mg and 50 mg; lansoprazole, present in unit dosage forms in an amount of between 5 mg and 150 mg (and preferably at between 5 mg and 30 mg); and pantoprazole, present in unit dosage forms in an

amount of between 10 mg and 200 mg. Recently, a newer class of acid inhibitor has been developed which competes with potassium at the acid pump. The compounds in this class have been referred to as "reversible proton pump inhibitors" or "acid pump antagonists" and may also be used in the present invention. Examples include AZD-0865, AR-H047108, CS-526, pumaprazole, revaprazan and soraprazan (see WO9605177 and WO9605199). Other compounds in this group are H-335/25 (AstraZeneca, Dialog file 128, accession number 020806); Sch-28080 (Schering Plough, Dialog file 128, accession number 009663); Sch-32651 (Schering Plough, Dialog file 128, accession number 006883) and SK&F-96067 (CAS Registry no. 115607-61-9).

The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. The NSAID may be celecoxib, rofecoxib, lumiracoxib, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, NS398, aspirin, acetaminophen (considered to be an NSAID for the purposes of the present invention), ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, meloxicam, piroxicam, droxicam, tenoxicam, nabumetone, diclofenac, meclofenamate, mefenamic acid, diflunisal, sulindac, tolmetin, fenoprofen, suprofen, benoxaprofen, aceclofenac, tolfenamic acid, oxyphenbutazone, azapropazone, and phenylbutazone. 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. It will be understood that, for the purposes of the present invention, reference to an acid inhibitor, NSAID, or analgesic agent will include all of the common forms of these compounds and, in particular, their pharmaceutically acceptable salts. The amounts of NSAIDs which are therapeutically effective may be lower in the current invention than otherwise found in practice due to potential positive kinetic interaction and NSAID absorption in the presence of an acid inhibitor.

Preferably, the pharmaceutical composition of the present invention is in the form of a tablet or capsule that has: (a) the acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5 upon the administration of one or more unit dosage forms; and (b) the non-steroidal anti-inflammatory drug (NSAID) present in an amount effective to reduce or eliminate pain or inflammation in a patient upon administration of one or more of said unit dosage forms. The NSAID in the dosage form should be in a core, preferably a single core when tablets are used, that is surrounded by a coating that does not release NSAID until the pH of the surrounding medium is 3.5 or higher. In the case of capsules, there may be several cores of NSAID, i.e., there may be multiple particles, each being surrounded by a coating that does not release NSAID until the pH of the surrounding medium is 3.5 or higher. The acid inhibitor is in one or more layers outside of the core

which do not contain any NSAID. These layers are not surrounded by an enteric coating and, upon ingestion of the tablet or capsule by a patient, release the acid inhibitor into the patient's stomach.

The term "unit dosage form" as used herein 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. A unit dosage form of the present invention preferably provides for coordinated drug release in a way that elevates gastric pH and reduces the deleterious effects of the NSAID on the gastroduodenal mucosa, i.e., the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen.

In a preferred embodiment, the unit dosage form is a multilayer tablet, having an outer layer comprising the acid inhibitor and an inner core which comprises the NSAID. In the most preferred form, coordinated delivery is accomplished by having the inner core surrounded by a polymeric barrier coating that does not dissolve unless the surrounding medium is at a pH of at least 3.5, preferably at least 4 and more preferably, at least 5. Alternatively, a barrier coating may be employed which controls the release of NSAID by time, as opposed to pH, with the rate adjusted so that NSAID is not released until after the pH of the gastrointestinal tract has risen to at least 3.5, preferably at least 4, and more preferably at least 5. Thus, a time-release formulation may be used to

prevent the gastric presence of NSAID until mucosal tissue is no longer exposed to the damage enhancing effect of very low pH.

One NSAID of special interest in dosage forms is aspirin which not only provides relief from pain and inflammation but may also be used in low doses by patients to reduce the risk of stroke, heart attack and other conditions. Thus, pharmaceutical compositions may contain an acid inhibitor in combination with aspirin in an amount effective, upon the administration of one or more unit dosage forms, to achieve any of these objectives. As with the compositions described above the unit dosage form can be a tablet or capsule in which aspirin is present in a core and is surrounded by a coating that does not release the aspirin until the pH of the surrounding medium is 3.5 or higher. The acid inhibitor is in one or more layers outside the core, which do not include an NSAID, are not surrounded by an enteric coating; and, upon ingestion of the dosage form by a patient, release the acid inhibitor into the patient's stomach. Any of the acid inhibitors described herein may be used in the aspirin-containing dosage foams. In dosage forms designed for providing low dose aspirin therapy to patients, the aspirin should typically be present at 20-200 mg.

The invention includes methods of treating a patient for pain, inflammation and/or other conditions by administering the pharmaceutical compositions described above. Although the method may be used for any condition in which an

NSAID is effective, it is expected that it will be particularly useful in patients with osteoarthritis or rheumatoid arthritis. Other conditions that may be treated include, but are not limited to: all forms of headache, including migraine headache; acute musculoskeletal pain; ankylosing spondylitis; dysmenorrhoea; myalgias; and neuralgias.

In a more general sense, the invention includes methods of treating pain, inflammation and/or other conditions by orally administering an acid inhibitor at a dose effective to raise a patient's gastric pH to at least 3.5, preferably to at least 4 or and more preferably to at least 5. The patient is also administered an NSAID, for example in a coordinated dosage form, that has been coated in a polymer that only dissolves at a pH of at least 3.5, preferably at least 4 and, more preferably, 5 or greater or which dissolves at a rate that is slow enough to prevent NSAID release until after the pH has been raised. When acid inhibitor and NSAID are administered in separate doses, e.g., in two separate tablets, they should be given concomitantly (i.e., so that their biological effects overlap) and may be given concurrently, i.e., NSAID is given within one hour after the acid inhibitor. Preferably, the acid inhibitor is an H2 blocker and, in the most preferred embodiment, it is famotidine at a dosage of between 5 mg and 100 mg. Proton pump inhibitors may also be used and offer advantages in terms of duration of action. Any of the NSAIDs described above may be used in the method but naproxen at a dosage of between 200 and 600 mg is most preferred. It is expected

that the acid inhibitor and analgesic will be typically delivered as part of a single unit dosage form which provides for the coordinated release of therapeutic agents. The most preferred dosage form is a multilayer tablet having an outer layer comprising an H2 blocker or a proton pump inhibitor and an inner core comprising an NSAID.

The invention also provides a method for increasing compliance in a patient requiring frequent daily dosing of NSAIDs by providing both an acid inhibitor and NSAID in a single convenient, preferably coordinated, unit dosage form, thereby reducing the number of individual doses to be administered during any given period.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic diagram of a four layer tablet dosage form. There is a naproxen core layer surrounded by a barrier layer. A third, enteric coating, layer delays the release of naproxen sodium until the pH is at a specific level, e.g., above 4. Finally, there is an outer layer that releases an acid inhibitor such as famotidine.

FIG. **2** illustrates a three layer dosage form. An acid inhibitor, e.g., famotidine, is released immediately after ingestion by a patient in order to raise the pH of the gastrointestinal tract to above a specific pH, e.g., above 4. The innermost layer contains naproxen. Thus, the dosage form has a naproxen core, an enteric film coat and an acid inhibitor film coat.

FIG. **3** illustrates a naproxen sodium pellet which contains a subcoat or barrier coat prior to the enteric film coat.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based upon the discovery of improved pharmaceutical compositions for administering NSAIDs to patients. In addition to containing one or more NSAIDs, the compositions include acid inhibitors that are capable of raising the pH of the GI tract of patients. All of the dosage forms are designed for oral delivery and provide for the coordinated release of therapeutic agents, i.e., for the sequential release of acid inhibitor followed by analgesic.

The NSAIDs used in preparations may be either short or long acting. As used herein, the term "long acting" refers to an NSAID having a pharmacokinetic half-life of at least 2 hours, preferably at least 4 hours and more preferably, at least 8-14 hours. In general, its duration of action will equal or exceed about 6-8 hours. Examples of long-acting NSAIDs are: flurbiprofen with a half-life of about 6 hours; ketoprofen with a half-life of about 2 to 4 hours; naproxen or naproxen sodium with half-lives of about 12 to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half life of about 42 to 50 hours; etodolac with a half-life of about 7 hours; indomethacin with a half-life

of about 4 to 6 hours; ketorolac with a half-life of up to about 8-9 hours, nabumetone with a half-life of about 22 to 30 hours; mefenamic acid with a half-life of up to about 4 hours; and piroxicam with a half-life of about 4 to 6 hours. If an NSAID does not naturally have a half-life sufficient to be long acting, it can, if desired, be made long acting by the way in which it is formulated. For example, NSAIDs such as acetaminophen and aspirin may be formulated in a manner to increase their half-life or duration of action. Methods for making appropriate formulations are well known in the art (see e.g. *Remington's Pharmaceutical Sciences*, 16th ed., A. Oslo editor, Easton, Pa. (1980)).

It is expected that a skilled pharmacologist may adjust the amount of drug in a pharmaceutical composition or administered to a patient based upon standard techniques well known in the art. Nevertheless, the following general guidelines are provided:

Indomethacin is particularly useful when contained in tablets or capsules in an amount from about 25 to 75 mg. A typical daily oral dosage of indomethacin is three 25 mg doses taken at intervals during the day. However, daily dosages of up to about 150 mg are useful in some patients.

Aspirin will typically be present in tablets or capsules in an amount of between about 250 mg and 1000 mg. Typical daily dosages will be in an amount ranging from 500 mg to about 10 g.

However, low dose aspirin present at 20-200 mg (and preferably 40-100 mg) per tablet or capsule may also be used.

Ibuprofen may be provided in tablets or capsules of 50, 100, 200, 300, 400, 600, or 800 mg. Daily doses should not exceed 3200 mg. 200 mg-800 mg may be particularly useful when given 3 or 4 times daily.

Flurbiprofen is useful when in tablets at about from 50 to 100 mg. Daily doses of about 100 to 500 mg, and particularly from about 200 to 300 mg, are usually effective.

Ketoprofen is useful when contained in tablets or capsules in an amount of about 25 to 75 mg. Daily doses of from 100 to 500 mg and particularly of about 100 to 300 mg are typical as is about 25 to 50 mg every six to eight hours.

Naproxen is particularly useful when contained in tablets or capsules in an amount of from 250 to 500 mg. For naproxen sodium, tablets of about 275 or about 550 mg are typically used. Initial doses of from 100 to 1250 mg, and particularly 350 to 800 mg are also used, with doses of about 550 mg being generally preferred.

Oxaprozin may be used in tablets or capsules in the range of roughly 200 mg to 1200 mg, with about 600 mg being preferred. Daily doses of 1200 mg have been found to be particularly

useful and daily doses should not exceed 1800 mg or 26 mg/kg.

Etodolac is useful when provided in capsules of 200 mg to 300 mg or in tablets of about 400 mg. Useful doses for acute pain are 200-400 mg every six-eight hours, not to exceed 1200 mg/day. Patients weighing less than 60 kg are advised not to exceed doses of 20 mg/kg. Doses for other uses are also limited to 1200 mg/day in divided doses, particularly 2, 3 or 4 times daily.

Ketorolac is usefully provided in tablets of 1-50 mg, with about 10 mg being typical. Oral doses of up to 40 mg, and particularly 10-30 mg/day have been useful in the alleviation of pain.

Nabumetone may be provided in tablets or capsules of between 500 mg and 750 mg. Daily doses of 1500-2000 mg, after an initial dose of 100 mg, are of particular use.

Mefenamic acid is particularly useful when contained in tablets or capsules of 50 mg to 500 mg, with 250 mg being typical. For acute pain, an initial dosage of 1-1000 mg, and particularly about 500 mg, is useful, although other doses may be required for certain patients.

Lornoxicam is provided in tablets of 4 mg or 8 mg. Useful doses for acute pain are 8 mg or 16 mg daily, and for arthritis are 12 mg daily.

Other NSAIDs that may be used include: celecoxib, rofecoxib, meloxicam, piroxicam, droxicam, tenoxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, or NS398. JTE-522, L-745,337 and NS398 as described, inter alia, in Wakatani, et al. (*Jpn. J. Pharmacol.* 78:365-371 (1998)) and Panara, et al. (*Br. J. Pharmacol.* 116:2429-2434 (1995)). The amount present in a tablet or administered to a patient will depend upon the particular NSAID being used.

For example:

Celecoxib may be administered in a tablet or capsule containing from about 100 mg to about 500 mg or, preferably, from about 100 mg to about 200 mg.

Piroxicam may be used in tablets or capsules containing from about 10 to 20 mg.

Rofecoxib will typically be provided in tablets or capsules in an amount of 12.5, 25 or 50 mg. The recommended initial daily dosage for the management of acute pain is 50 mg.

Meloxicam is provided in tablets of 7.5 mg, with a recommended daily dose of 7.5 or 15 mg for the management of osteoarthritis.

Valdecoxib is provided in tablets of 10 or 20 mg, with a recommended daily dose of 10 mg for arthritis or 40 mg for dysmenorrhea.

With respect to acid inhibitors, tablets or capsules may contain anywhere from 1 mg to as much as 1 g. 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, the proton pump inhibitor omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 10 or 20 mg being preferred. Other typical amounts are: esomeprazole, 5-100 mg, with about 40 mg being preferred; lansoprazole, 5-150 mg (preferably 5-50 mg), with about 7.5, 15 or 30 mg being most preferred; pantoprazole, 10-200 mg, with about 40 mg being preferred; and rabeprazole, 5-100 mg, with about 20 mg being preferred.

Making of Pharmaceutical Preparations

The pharmaceutical compositions of the invention include tablets, dragees, liquids and capsules and can be made in accordance with methods that are standard in the art (see, e.g., *Remington's Pharmaceutical Sciences*, *16th* ed., A Oslo editor, Easton, Pa. (1980)). Drugs and drug combinations will typically be prepared in admixture with conventional excipients. Suitable carriers include, but are not limited to: water; salt solutions; alcohols; gum arabic; vegetable oils;

benzyl alcohols; polyethylene glycols; gelatin; carbohydrates such as lactose, amylose or starch; magnesium stearate; talc; silicic acid; paraffin; perfume oil; fatty acid esters; hydroxymethyl-cellulose; polyvinyl pyrrolidone; etc. The pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents such as: lubricants, preservatives, disintegrants; stabilizers; wetting agents; emulsifiers; salts; buffers; coloring agents; flavoring agents; or aromatic substances.

Enteric coating layer(s) may be applied onto the core or onto the barrier layer of the core using standard coating techniques. The enteric coating materials may be dissolved or dispersed in organic or aqueous solvents and may include one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose trimellitate, carboxymethylethylcellulose, cellulose acetate phthalate or other suitable enteric coating polymer(s). The pH at which the enteric coat will dissolve can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of the polymer film can be altered by the ratio of free carboxyl groups to ester groups. Enteric coating layers also contain pharmaceutically acceptable plasticizers such as triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other plasticizers. Additives such as dispersants,

colorants, anti-adhering and anti-foaming agents may also be included.

The Making of Tablet Dosage Forms

Preferably, the combination of an acid inhibitor and an NSAID will be in the form of a bi- or multi-layer tablet. In a bilayer configuration, one portion of the tablet contains the acid inhibitor in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second portion of the tablet will contain the NSAID, preferably naproxen, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc. In the most preferred embodiment, the NSAID layer is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. The NSAID may be granulated by methods such as slugging, low- or high-shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produces tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

EXAMPLES

Example 1

Enteric Coated Naproxen Sodium Core and Famotidine Immediate Release

A schematic diagram of a four layer tablet dosage form is shown in FIG. **1**. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5. The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an unprotected stomach. Methacrylic acid copolymers are used as the enteric coating ingredient, triethyl citrate and dibutyl phthalate are plasticizers, and ammonium hydroxide is used to adjust the pH of the dispersion. The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably the H2 blocker famotidine, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of famotidine in the dosage form will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine within the fourth layer without tablets sticking to the coating pan or to each other during application of the film coat. Other ingredients may include: plasticizers such as triethyl citrate, dibutyl phthalate, and polyethylene glycol; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen sodium, USP	74.074	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.166	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Barrier Film Coating Ingredients	% W/W
Opadry Clear ® YS-1-7006	5.00
Purified water USP	95.00
Total	100.00

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	7.30
Methacrylic Acid Copolymer, NF (Eudragit L-100)	7.30
Triethyl Citrate, NF	2.95
Dibutyl Phthalate, NF	1.17
Ammonium Hydroxide (30%), NF	0.87
Purified water, USP	80.41
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	3.0
Opadry Clear ® (YS-1-7006)	5.0
Talc, USP	3.0
Purified Water, USP	89.0
Total	100.0

Example 2

Enteric Coated Naproxen Core and Famotidine Immediate Release

FIG. **2** illustrates a three layered dosage form which releases famotidine immediately after ingestion by the patient in order to raise the pH of the gastrointestinal tract to above about 4. The innermost layer contains naproxen uniformly distributed throughout a matrix of pharmaceutically acceptable excipients. These excipients perform specific functions and may serve as binders, disintegrants, or lubricants. A pharmaceutically acceptable enteric coating surrounds the naproxen core. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the harshly acidic pH of the unprotected stomach. It contains methacrylic acid copolymers which prevent the release of naproxen in the unprotected stomach. Also included are: triethyl citrate, a plasticizer; simethicone emulsion, an anti-foaming agent; and sodium

hydroxide which is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in this example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which raises the pH of the stomach to above 4. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine in the fourth layer without tablets sticking to the coating pan or sticking to each other during application of the film coat. Other ingredients are: plasticizers such as polyethylene glycol 8000; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen, USP	90.91	500.00
Povidone K-90, USP	2.00	11.00
Starch, USP	2.59	14.25
Croscarmellose Sodium, USP	4.00	22.00
Magnesium Stearate, NF	0.50	2.75
Total	100.00	550.00
Purified Water, USP qs		

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	3.0
Opadry Clear ® (YS-1-7006)	5.0
Talc, USP	3.0
Purified Water, USP	89.0
Total	100.0

Example 3

Naproxen Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen may be used in the present invention. The core tablet of naproxen is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. FIG. **2** shows an example of an appropriate trilayer tablet. In this particular

example, naproxen is mixed with a polymeric material, hydroxypropyl-methylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extremely acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen until the pH of the stomach rises. Triethyl citrate is a plasticizer, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropyl-

methylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, Pa.) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticizers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen, USP	94.00	750
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	5.00	39.9
Magnesium Stearate, NF	1.00	7.95
Total	100.00	797.85

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	2.0
Opadry Blue ® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 4

Naproxen and Famotidine Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen and famotidine may be used in the present invention. The core tablet of naproxen and famotidine is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. FIG. **2** is an example of an appropriate trilayer tablet. In this particular example, naproxen and famotidine are mixed with a polymeric material, hydroxypropyl-methylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen and famotidine is film coated with a pharmaceutically acceptable enteric coating. The

function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extremely acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen until the pH of the stomach rises. Triethyl citrate is a plasticizer, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion

The outermost later contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropyl-methylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, Pa.) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticizers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted

to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen, USP	88.05	500
Famotidine, USP	3.52	20.0
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	7.03	39.9
Magnesium Stearate, NF	1.40	7.95
Total	100.00	567.85

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	2.0
Opadry Blue ® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 5

Enteric Coated Naproxen Sodium Core and Pantoprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in FIG. **1**. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH may be below 4 such as in an unprotected stomach but it dissolves only when the local pH is above about 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above 4. In this example, hydroxypropylmethyl-cellulose phthalate is the

enteric coating ingredient, cetyl alcohol is a plasticizer and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, pantoprazole, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of pantoprazole in the dosage form may vary from 10 mg to 200 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticizers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases pantoprazole for absorption. Therefore, pantoprazole releases first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	% W/W	mg/tablet
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	% W/W
Opadry ® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	% W/W
Hydroxypropyl methylcellulose phthalate, NF	5.5
Cetyl alcohol, NF	0.3
Acetone, NF	66.3
Alcohol, USP	27.9
Total	100.00

Hydroxypropylmethylcellulose phthalate and cetyl alcohol are dissolved in a mixture of alcohol and acetone. The solution is then sprayed on to the

tablet bed in proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating stopped if the tablets pass the test.

Pantoprazole Film Coating Ingredients	% W/W
Pantoprazole sodium, USP	5.00
Opadry ® Clear YS-1-7006	5.00
Sodium carbonate, NF	1.20
Purified Water, USP	88.80
Total	100.00

Pantoprazole sodium is dissolved in purified water containing sodium carbonate in solution. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until the proper amount of pantoprazole sodium is deposited.

Example 6

Enteric Coated Naproxen Sodium Core and Omeprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in FIG. **1**. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH is below 4 such as in an unprotected stomach but it dissolves only when the local pH is above 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticizer and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, omeprazole, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of omeprazole in the dosage form

may vary from 5 mg to 50 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticizers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases omeprazole for absorption. Therefore, omeprazole is released first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	% W/W	mg/tablet
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	% W/W
Opadry ® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until the proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	6.0
Triethyl Citrate, NF	0.6
Talc, USP	3.0
Purified Water, USP	5.0
Isopropyl Alcohol, USP	85.40
Total	100.00

Methacrylic acid copolymer, triethyl citrate, and talc are dissolved in a mixture of isopropyl alcohol and water. The solution is then sprayed on to the tablet bed in a proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating is stopped if the tablets pass the test.

Omeprazole Film Coating Ingredients	% W/W
Omeprazole, USP	5.00
Opadry ® Clear YS-1-7006	5.00
Purified Water, USP	10.00
Isopropyl Alcohol, USP	80.00
Total	100.00

Omeprazole is dissolved in a purified water and isopropyl alcohol mixture. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until proper amount of omeprazole is deposited on the tablets.

Example 7

Naproxen Sodium Delayed Release and Omeprazole Immediate Release Capsule

A coordinated delivery dosage may be used to provide fast release of an acid inhibitor, a proton pump inhibitor, omeprazole which raises the pH of the gastrointestinal tract to above 4, and the delayed release of a non-steroidal anti-inflammatory drug, naproxen sodium. Omeprazole granules modify the pH of the stomach such that the drug readily dissolves and is absorbed in the stomach without significant degradation. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The

release of naproxen sodium is delayed by enteric coating.

Omeprazole granules contain an alkalizing excipient such as sodium bicarbonate. Other soluble alkalizing agents such as potassium bicarbonate, sodium carbonate, sodium hydroxide, or their combinations may also be used. The alkalizing agent helps solubilize and protect omeprazole from degradation before its absorption. Sodium lauryl sulfate helps in the wetting of omeprazole. Other surfactants may be used to perform the same function. In the present example, hydroxypropyl methylcellulose helps in granule formation, sodium starch glycolate is a disintegrant, and magnesium stearate is a lubricant. Other excipients may also be used to perform these functions.

Naproxen sodium pellets as shown in FIG. **3** are prepared by the wet massing technique and the conventional extrusion and spheronization process. The excipients used in the formulation are microcrystalline cellulose, and povidone. The pellets after drying and classification are coated with a protective subcoating containing povidone. Other coating ingredients may also be used such as Opaspray K-1-4210A or Opadry YS-1-7006 (trademarks of Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropyl-methylcellulose 2910 and polyethylene glycol 8000 in a subcoating suspension are also alternatives. Other ingredients are, plasticizers such as triethyl

citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide.

The subcoated pellets are enteric coated using enteric coating polymers. In this example, the enteric coating polymer is methacrylic acid copolymer and the plasticizer is dibutyl phthalate which are dissolved in a mixture of acetone and alcohol. The enteric film does not dissolve in the acidic pH but dissolves when the pH in the gut is above about pH 6 and releases naproxen sodium.

mmmOmeprazole Granules	% W/W	mg/capsule
Omeprazole, USP	12.9	20.00
Sodium Bicarbonate, USP	82.40	127.72
Hydroxypropyl methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Sodium starch glycolate, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.77
Total	100	100

Hydroxypropylmethylcellulose is dissolved in water, then sodium lauryl sulfate is added and the solution is mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper

granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen sodium, USP	86.80	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	11.10	32.00
Povidone (K90), USP	2.10	6.00
Total	100.00	288.00

Povidone is dissolved in water. Naproxen sodium and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into suitable particle size range.

Subcoat Ingredients	% W/W
Povidone (K29-32), USP	10.00
Alcohol, USP	90.00
Total	100.00

The pellet cores are coated using povidone solution by a conventional coating pan method to a weight gain of 1-2%.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100)	8.20
Diethyl Phthalate, NF	1.70
Acetone, NF	33.30
Isopropyl Alcohol, USP	56.80
Total	100.0

Eudragit L-100 is dissolved in isopropanol and acetone and diethyl phthalate is dissolved. The solution is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process.

Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen sodium and 20 mg omeprazole per capsule.

Example 8

Naproxen Delayed Release and Omeprazole Immediate Release Capsule

The present Example is directed to a coordinated delivery dosage form containing omeprazole and naproxen. The formulation contains 10 mg omeprazole and uses methylcellulose as a binder and croscarmellose sodium as a disintegrant. Naproxen pellets as shown in FIG. **3** do not need a subcoating layer and

are enteric coated with an aqueous dispersion of methacrylic acid copolymer. Optionally, these pellets could be compressed into a core and film coated with an acid inhibitor and thereby form a bilayer tablet.

Omeprazole Granules	% W/W	mg/capsule
Omeprazole, USP	6.45	10.00
Sodium Bicarbonate, USP	88.85	137.71
Methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Croscarmellose sodium, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.78
Total	100	100

Methylcellulose is dissolved in water, then sodium lauryl sulfate is added to the solution and mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen, USP	76.	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	21.	71.44
Povidone (K90), USP	2.	6.56
Total	100.	328.00

Povidone is dissolved in water. Naproxen and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into a suitable particle size range.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L30D 30% dispersion)	15.60
Talc, USP	7.60
Triethyl citrate, NF	1.60
Simethicone Emulsion, USP (Silicone antifoam emulsion SE 2)	0.20
Purified Water, USP	74.80

Eudragit 30D is dispersed in purified water and simethicone emulsion. Talc and triethyl citrate are then dispersed. The suspension is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process. Omeprazole fast release granules

and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen and 10 mg omeprazole per capsule.

Example 9

Clinical Study of the Relationship of Gastric pH to NSAID-Induced Gastric Ulcers

Sixty-two subjects were enrolled in a clinical study and randomly assigned to three groups. The following three groups were administered study medication twice daily for five days: (a) 550 mg naproxen sodium (n=10), (b) 40 mg famotidine given with 550 mg of naproxen or famotidine followed 90 minutes later by 550 mg naproxen, (n=39) or (c) 20 mg omeprazole followed by 550 mg naproxen sodium (n=13). Gastric pH was measured hourly beginning at the time of dosing of the final daily dose of study medication and for 8-10 hours thereafter. Subjects had a gastric endoscopy performed at the beginning and on Day 5 prior to the morning dose of study medication to identify gastric and duodenal irritation; no subjects were admitted to the study if gastric irritation was present at the time of initial endoscopy.

Five patients, three (33%) in the naproxen alone group and two (5%) in the famotidine/naproxen group, presented with gastroduodenal ulcers at the end of the study. In the naproxen alone group, the pH was greater than

4 only 4% of the time, and in the famotidine/naproxen group the pH was greater than 4 forty-nine percent of the time during the 8-10 hours following naproxen sodium dosing. Additionally, Lanza grade 3 or 4 damage was present in 28% (n=11) of the subjects receiving famotidine/naproxen sodium, and present 100% (n=10) in the naproxen sodium treatment group. Monitoring of gastric acidity on day 5 indicated that patients with Lanza scores of greater than 2 had integrated gastric acidity of greater than 100 mmol-hr./L. Only 20-40% of patients with integrated gastric acidity of less than 100 mmol-hr/L had gastric pathology, whereas all patients with integrated gastric acidity greater than 100 mmol-hr/L had pathology.

Example 10

Famotidine and Enteric Coated Naproxen Reduce Gastroduodenal Damage Due to NSAID Therapy

Thirty-seven patients were randomized to two groups for a one week study of twice-daily dosing of: 500 mg enteric coated naproxen, and 500 mg enteric coated naproxen preceded by 40 mg famotidine. Endoscopies were conducted on all patients prior to first dosing and on the final day of the study. No subjects had evidence of gastroduodenal damage at the beginning of the study (at first endoscopy).

At the second endoscopy, Lanza scores for gastroduodenal damage were assessed for all

subjects. 39% of the subjects in the enteric coated naproxen 500 mg group had grade 3-4 gastroduodenal damage. This is lower than the percentage that would be expected for the administration of 500 mg of non-enteric naproxen based upon previous work. Nevertheless, subjects administered 500 mg enteric coated naproxen and 40 mg famotidine had an even lower incidence of grade 3-4 gastroduodenal damage (26%) than subjects who had previously taken enteric coated naproxen alone which demonstrates the value of combining acid inhibition with enteric coating of NSAID to minimize the gastrointestinal damage.

All references cited herein are fully incorporated by reference. Having now fully described the invention, it will be understood by those of skill in the art that the invention may be performed within a wide and equivalent range of conditions, parameters and the like; without affecting the spirit or scope of the invention or any embodiment thereof.

What is claimed is:

1. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:

(a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and

(b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3 .5 or higher;

wherein said unit dosage form provides for release of said esomeprazole such that 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.

2. The pharmaceutical composition of claim **1**, wherein naproxen is present in said unit dosage form in an amount of 200-600 mg.

3. The pharmaceutical composition of claim **1**, wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.

4. The pharmaceutical composition of claim **1**, wherein naproxen is present in said unit dosage form in an amount of between 200-600 mg and esomeprazole in an amount of from 5 to 100 mg per unit dosage form.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

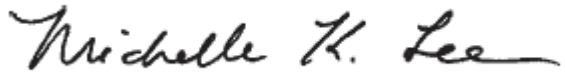
PATENT NO.	: 8,557,285 B2
APPLICATION NO.	: 13/215855
DATED	: October 15, 2013
INVENTOR(S)	: John R. Plachetka

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page

In Item (56) - References Cited, page 2, 58th reference in lefthand column - 6,162,816, delete "210/95" and insert --514/338-- therefor.

Signed and Sealed this
Twenty-fifth Day of February, 2014



Michelle K. Lee
Deputy of the United States Patent and Trademark Office