



DEPARTMENT OF HEALTH & HUMAN SERVICES

JUL 3 2014

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Timothy P. Walbert
Chairman, President, and CEO
Horizon Pharma, Inc.
520 Lake Cook Road, Suite 520
Deerfield, IL 60015

Re: Docket No. FDA-2014-P-0209

Dear Mr. Walbert:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA) by Horizon Pharma, Inc. (Horizon), dated February 3, 2014 (Petition). In the Petition, Horizon asks FDA to take certain actions with regard to any abbreviated new drug application (ANDA) for which Vimovo (naproxen and esomeprazole magnesium) Delayed-Release Tablets (new drug application (NDA) 022511, held by Horizon) is the reference listed drug (RLD).

Specifically, Horizon requests that FDA:

1. Require that any application listing Vimovo as the RLD, which seeks approval for a generic product that employs less than a complete enteric coating around the naproxen component, be supported by either
 - a. pharmacokinetic data sufficient to show that the timing of release of naproxen in the generic product is equivalent to that of Vimovo, or
 - b. data from clinical trials demonstrating that the proposed generic product does not cause more frequent or more severe gastrointestinal adverse events than does Vimovo;
2. If additional clinical trials described above are necessary to support safety of the proposed generic product, require that any such application be filed as a 505(b)(2) application,¹ rather than as an ANDA; and
3. Refuse to approve any currently pending ANDA for such a product, and require the applicant to withdraw its ANDA and resubmit it as a 505(b)(2) application, accompanied by the additional clinical testing described above.

Petition at 2.

¹ An application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)).

We have carefully considered the information submitted in the Petition. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Vimovo

On April 30, 2010, FDA approved an NDA for Vimovo (naproxen and esomeprazole magnesium) Delayed-Release Tablets (NDA 022511, held by Horizon). Vimovo is currently approved for relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and to decrease the risk of developing gastric ulcers in patients at risk of developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers.² Vimovo is available in two strengths: 375 milligrams (mg) of naproxen with 20 mg of esomeprazole, and 500 mg of naproxen with 20 mg of esomeprazole. The 500-mg naproxen/20-mg esomeprazole strength is the RLD.

The active ingredients of Vimovo are naproxen, which is an NSAID with analgesic and antipyretic properties, and esomeprazole magnesium, which is a proton pump inhibitor (PPI) that suppresses gastric acid secretion. Vimovo tablets consist of an enteric-coated naproxen core surrounded by an immediate-release esomeprazole magnesium layer. The enteric coating prevents naproxen from being released when gastric pH is under 5.5.³

The Vimovo application referenced two previously approved NDAs:

- EC-Naprosyn (naproxen) Delayed-Release Tablets (NDA 020067, held by Roche Palo), and
- Nexium (esomeprazole magnesium) Delayed-Release Capsules (NDA 021153, held by AstraZeneca).

EC-Naprosyn is available as enteric-coated tablets containing 375 or 500 mg of naproxen for oral administration. The dissolution of the enteric-coated naproxen tablet is pH-dependent with rapid dissolution above pH level 6. There is no dissolution below pH level 4.⁴ Nexium is available as delayed-release capsules containing 20 or 40 mg of esomeprazole (present as 22.3 mg or 44.5 mg of esomeprazole magnesium trihydrate) in the form of enteric-coated granules⁵ that protect the esomeprazole from being degraded in the stomach's acidic environment.

² See labeling for Vimovo approved on March 27, 2014, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022511s010lbl.pdf.

³ Id. at section 12.1 (Clinical Pharmacology: Mechanism of Action).

⁴ EC-Naprosyn label approved on March 22, 2013, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017581s111,018164s061,018965s020,020067s0181bl.pdf.

⁵ Nexium label approved on March 27, 2014, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021153s046,021957s015,022101s012lbl.pdf.

The Vimovo application was also supported by two clinical studies that were submitted to support the efficacy of Vimovo in reducing the risk of developing NSAID-associated gastric ulcers. The 500-mg naproxen dose of the fixed-combination Vimovo was compared with enteric-coated naproxen in both studies. Both studies showed that Vimovo, given as a 500-mg naproxen/20-mg esomeprazole tablet twice daily, showed a statistically significant reduction in the 6-month cumulative incidence of gastric ulcers, as compared to enteric-coated naproxen given as a 500 mg tablet twice daily.⁶ The approval of the other dose level of Vimovo (375-mg naproxen/20-mg esomeprazole) and approval of the indications for use in treatment of rheumatoid arthritis and ankylosing spondylitis were based on the approval of EC-Naprosyn and bioequivalence (BE) studies between Vimovo and EC-Naprosyn.⁷

B. Statutory and Regulatory Basis for Approving 505(b)(2) Applications and ANDAs

Section 505(b) of the FD&C Act establishes the approval requirements for NDAs. To be approved, an application submitted under 505(b) must, among other things, be supported by well-controlled investigations showing the drug product to be safe and effective.⁸ One pathway under section 505(b) provides for approval of NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference (stand-alone NDA). The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) provided an alternate pathway under section 505(b)(2) for approval of an NDA for which some or all of the safety and efficacy investigations relied upon for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.⁹ Like a stand-alone NDA, a 505(b)(2) application is approved under section 505(c) of the FD&C Act.

The Hatch-Waxman Amendments also provide for submission of ANDAs for approval of generic versions of listed drugs.¹⁰ A listed drug is a drug product with an effective approval under section 505(c).¹¹ The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to repeat the studies conducted to support approval of the listed drug. To rely on such a finding, the ANDA applicant must show that, among other things, its proposed drug product is the same

⁶ Vimovo label approved on March 27, 2014 (supra note 2) at section 14 (Clinical Studies). See also Goldstein JL1, Hochberg MC, Fort JG, Zhang Y, Hwang C, Sostek M. Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone. *Aliment Pharmacol Ther.* 2010 Aug; 32(3):401-413.

⁷ In addition, two clinical studies were conducted to evaluate the efficacy of the 500 mg naproxen component of Vimovo for treating the signs and symptoms of osteoarthritis. The results of these two studies provided sufficient evidence to support the efficacy of Vimovo for the indication of treatment of signs and symptoms of osteoarthritis.

⁸ Section 505(b)(1) of the FD&C Act.

⁹ The Vimovo NDA was itself submitted under section 505(b)(2).

¹⁰ Section 505(j) of the FD&C Act.

¹¹ 21 CFR 314.3(b).

as the listed drug with respect to its active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling, and that the proposed product is bioequivalent to the listed drug.¹²

C. Bioequivalence and ANDAs

The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the FD&C Act's criteria are therapeutically equivalent and may be substituted for each other. A generic drug product is bioequivalent to the RLD "if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient" (section 505(j)(8)(B)(i) of the FD&C Act). FDA regulations at 21 CFR 320.1(e) specify that

*[B]ioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.*¹³

FDA's regulations at 21 CFR 314.94(a)(7) set forth the BE requirements for an ANDA, and the regulations in part 320 (21 CFR Part 320) set forth the procedures for determining BE. The regulations discuss the various methods of establishing BE in general descending order of accuracy, sensitivity, and reproducibility. These methods include pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, comparative clinical trials, and in vitro studies (21 CFR 320.24). In addition, as under section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish [BE]." It is well-accepted that FDA has considerable discretion in determining how the BE requirement is met. FDA's discretion need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs. . . ."¹⁴ Courts have expressly upheld FDA's regulatory implementation of the FD&C Act's BE requirements.¹⁵

Standard BE PK studies are conducted using a two-treatment crossover study design. Single oral doses of the test and reference drugs are administered, and blood or plasma levels of the drug are measured over time. The rate and extent of drug absorption are statistically measured. The relevant PK parameters calculated from these data include the area under the

¹² Section 505(j)(2) of the FD&C Act.

¹³ See also 21 CFR 320.23(b).

¹⁴ *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp 212, 218 (D.D.C. 1996) (quoting *Schering Corp. v. Sullivan*, 782 F. Supp 645, 651 (D.D.C. 1992), vacated as moot sub nom, *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

¹⁵ See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 863-67 (D.D.C. 1994).

plasma concentration versus time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the extent of absorption. Another relevant PK parameter is the maximum or peak drug concentration (C_{max}). C_{max} is used to reflect the rate of absorption.

To establish BE, the calculated 90 percent confidence interval for the log transformed ratio of geometric means for AUC and C_{max} values between the generic product and the RLD should fall entirely within an 80 percent to 125 percent acceptance interval (0.8 to 1.25).¹⁶ The use of an 80 to 125 percent acceptance interval to compare two products with the same active ingredient, dosage form, route of administration, and strength is a scientific judgment about the best statistical practices for BE determinations. It reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients. Because the point estimate of the test/reference ratio lies in the center of the 90 percent confidence interval, the mean of the data is usually close to 100 percent (a test/reference ratio of 1).¹⁷ The PK parameter time to reach maximum concentration (T_{max}) is also a rough indicator of the rate of drug absorption and serves as supportive data in evaluating BE.

For modified-release drug products, FDA may consider an additional PK parameter, lag time.¹⁸ Lag time means the time from administration of a drug product until release and absorption of one or more active ingredients of that product (as reflected by quantifiable plasma concentrations).¹⁹ For example, for an oral delayed-release tablet, the effect of an enteric coating intended to slow release of the active ingredient would be reflected in PK data as the lag time.

D. Product-Specific Bioequivalence Guidance

Under a process set forth in the guidance for industry on *Bioequivalence Recommendations for Specific Products* (BE Recommendation Process Guidance), FDA develops

¹⁶ See FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), Chapter 1.3, "Statistical Criteria for Bioequivalence," available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>; See also FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Revision 1), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹⁷ In general, for the 90 percent BE confidence interval to fall between 0.8 and 1.25, the point estimate should fall within .90 and 1.11.

¹⁸ See, e.g., FDA guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies*, available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf> at 6-7.

¹⁹ See, e.g., description of lag time with regard to delayed-release products in FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Revision 1), *supra* note 16, at 14 (stating "[a]s defined in the USP, delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations)").

recommendations for demonstrating BE of specific products.²⁰ These recommendations are posted on the FDA Drugs guidance Web page²¹ in draft and announced periodically by publication of a notice of availability (NOA) in the *Federal Register*. At any time following the posting of a draft recommendation on the FDA's Web site, a member of the public may submit comments on that draft recommendation by following the instructions listed on the Web site. Following the close of the comment period that is announced in the NOA, FDA considers all comments received and issues either final recommendations or revised draft recommendations for further comment.

In March 2011, FDA issued a draft BE guidance regarding naproxen/esomeprazole magnesium delayed release tablets (the Naproxen/Esomeprazole Draft Guidance).²² This draft guidance provides detailed recommendations for BE studies to applicants submitting ANDAs for which Vimovo is the RLD. The draft guidance recommends conducting two single-dose, two-way, crossover *in vivo* BE studies — one fasting and one fed — with PK endpoints in healthy subjects using 500 mg/EQ 20 mg base strength naproxen/esomeprazole magnesium tablets. *In vivo* studies of the lower strength tablets may be waived if certain conditions are met.

II. DISCUSSION

The Petition requests that any ANDA for a product that lists Vimovo as the RLD and includes a portion of naproxen outside of the enteric-coated core include PK or clinical data beyond that currently recommended in the Naproxen/Esomeprazole Draft Guidance (Petition at 2 and 8). In particular, the Petition asks FDA to require either (1) PK data sufficient to show that the timing of release of the naproxen from such a product is equivalent to that of Vimovo, or (2) clinical trial data demonstrating that the proposed product does not result in more frequent, or more severe, gastrointestinal adverse events than Vimovo (Petition at 2 and 8). Finally, the Petition states that an application supported by such clinical trial data should be required to be submitted under section 505(b)(2) rather than section 505(j) of the FD&C Act.

FDA does not agree that this additional testing should be required. As discussed below, we do not agree with the Petition's claims regarding the clinical significance of the relative timing of the release of esomeprazole and naproxen. Accordingly, we do not believe any testing beyond that recommended in the existing draft BE guidance is necessary either to evaluate BE or to ensure comparable safety. Given that FDA does not agree that such additional testing is necessary, we need not consider whether, if clinical studies were

²⁰ The BE Recommendation Process Guidance is available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

²¹ Available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

²² *Draft Guidance for Esomeprazole Magnesium; Naproxen*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM249220.pdf>.

necessary, an application containing data from such studies would need to be submitted under section 505(b)(2) rather than 505(j) of the FD&C Act.

A. The Petition Fails to Establish that the Release of Esomeprazole Before Naproxen Contributes Materially to the Gastroprotective Effect of Vimovo.

The Petition states that Vimovo has been “specifically formulated to allow esomeprazole (a proton pump inhibitor) to achieve its gastroprotective impact before naproxen is released into the system” (Petition at 5). According to the Petition, “by the time Vimovo begins to release its naproxen, Vimovo’s esomeprazole has already begun to impact gastric pH. This provides a less favorable environment for the development of gastric ulcers” (Petition at 7). In contrast, according to the Petition, “a generic product without all of the naproxen enterically coated would release at least some portion of its naproxen in a less gastroprotective environment, before gastric pH has begun to rise” (Petition at 7). According to the Petition, “a reduction in the enteric coating surrounding the naproxen core could subject patients to significantly increased risk of potentially fatal side-effects” (Petition at 7).

The Petition provides no data (and FDA is not aware of any data) showing that the gastroprotective effect of the esomeprazole is related to or materially enhanced by the fact that in the Vimovo formulation, esomeprazole is released before naproxen. The two clinical trials described in section I.A. of this response do not support the petitioner’s claim that the relative timing of release of esomeprazole and naproxen is clinically meaningful. Rather, they demonstrate that the combination of esomeprazole and naproxen in Vimovo results in a reduced risk of gastric ulcers, compared to naproxen alone. Moreover, FDA’s approval of Vimovo does not reflect a finding as to the clinical significance, if any, of the sequence of release of the active ingredients.²³

In addition, we note two properties of esomeprazole that are inconsistent with the Petition’s hypothesis that Vimovo’s release of esomeprazole before naproxen has a material beneficial effect on the product’s safety profile. First, it takes several days for the esomeprazole in Vimovo to achieve its full PD effect on gastric pH,²⁴ after which this effect plateaus.²⁵ Once

²³ See Vimovo labeling, *supra* note 2; see also Summary Review, NDA No. 022511, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022511Orig1s000SumR.pdf.

²⁴ See, e.g., Miner P, Jr., et al., *Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen/esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label Phase I study in healthy volunteers*, *Aliment Pharmacol Ther* 2010; 32: 414-424 (study data cited in the Petition at 6 and in the Vimovo NDA). In this study of naproxen/esomeprazole magnesium, the antisecretory effect of esomeprazole was assessed on days 1 and 9 and the antisecretory effect on day 9 was significantly greater than on day 1. The mean percent time intragastric pH was greater than 4.0 ranged from 13% to 28% on day 1 (20.5% for Vimovo) and from 41.1% to 76.8% on Day 9 (71.4% for Vimovo).

²⁵ By “plateau” we mean that if the PD effect is compared at the same time each day, the effect reaches a maximum after 4-5 days of dosing. See, e.g., Prilosec labeling approved on March 27, 2014, at p. 21 (Pharmacodynamics Section), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019810s098.022056s014lbl.pdf (“[t]he inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days”).

gastric pH has reached its plateau, it appears that the release of esomeprazole before naproxen would be immaterial. Accordingly, even if there were a safety benefit associated with the release of esomeprazole before naproxen, this advantage would likely apply only to the first few days of administration. But the Petition identifies (at 2) a concern with significant GI adverse events associated with *chronic* NSAID use, not just the first few days of NSAID use. Second, the non-enteric coated esomeprazole in Vimovo must be bioavailable in order to have a beneficial effect on gastric pH. Given that esomeprazole is acid-labile, meaning that it is not stable in acidic environments, its bioavailability is estimated to be only about 50% on the first day of administration for immediate-release esomeprazole formulations (such as Vimovo) as compared to enteric-coated delayed-release esomeprazole products (such as Nexium), which release esomeprazole in a less acidic environment.²⁶ This makes it less plausible that the early release of the esomeprazole in Vimovo somehow enhances the esomeprazole's GI-protective effects even in the first few days of administration.

To the extent that the petitioner claims that the enteric coating of naproxen is responsible for Vimovo's effectiveness,²⁷ we note that there has been considerable debate within the literature regarding whether surrounding NSAIDs in an enteric coating reduces gastric injury or ulceration. Early evidence in the literature suggesting a benefit²⁸ does not seem to be supported by further research, and, as discussed below, subsequent data and analysis suggest that enteric-coated NSAIDs may have similar levels of risk for gastrointestinal injury as do uncoated NSAIDs.

For example, there is evidence that enteric-coated, low-dose aspirin (also an NSAID) has no benefit over uncoated aspirin. One study concluded that "[t]he coating of the active principle in order to spare the stomach does not reduce the risk of upper gastrointestinal complications, neither for the stomach nor for the duodenum."²⁹ Similarly, a meta-analysis of enteric-coated aspirin studies³⁰ concluded that "[n]o clinical benefits in terms of reduction of gastrointestinal bleeding or ulceration with enteric coating have, therefore, been successfully demonstrated, although the endoscopic studies show that potentially these benefits could exist." Studies submitted during the approval of EC-Naprosyn (one of the drug products

²⁶ See, e.g., Clinical Pharmacology and Biopharmaceutics Review(s), NDA No. 022511, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022511Orig1s000ClinPharmR.pdf.

²⁷ For example, after discussing the multifactorial etiology of NSAID-induced damage to the gastric mucosa and the role of locally-present NSAIDs (Petition at 3 and Figure 1), the Petition goes on to state that "[t]he enteric coating of the NSAID in [Vimovo] prevents that exposure," and that "drugs that are not completely enteric coated might lead to . . . increased damage by exposure of the drug in the stomach lumen" (Petition at 3).

²⁸ See, e.g., Hawthorne, AB, Mahida, YR, Cole, AT, and Hawkey, CJ. Aspirin-induced gastric mucosal damage: prevention by enteric coating and relation to prostaglandin synthesis. *Br. J. Clin. Pharmacol.* (1991), 32, 77-83.

²⁹ De Abajo, FJ and García Rodríguez, LA. Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations. *BMC Clin Pharmacol.* (2001) 1: 1. PMC32172.

³⁰ Walker, J, Robinson, J, Stewart, J, and Jacob, S. Does enteric-coated aspirin result in a lower incidence of gastrointestinal complications compared to normal aspirin? *Interact CardioVasc Thorac Surg* (2007) 6 (4): 519-522.

cited in Vimovo's NDA) and discussed on the EC-Naprosyn label include a head-to-head comparison of enteric-coated naproxen vs. non-enteric-coated naproxen. The results of this comparison indicated that EC-Naprosyn and non-enteric-coated Naprosyn showed no significant differences in efficacy or safety and had a similar prevalence of minor GI complaints.³¹ In addition, in long-term open-label trials involving EC-Naprosyn, the rates for clinically-diagnosed peptic ulcers and GI bleeds were similar to what has been historically reported for long-term NSAID use.³² Another researcher notes that "[a]ttempts have been made to produce NSAIDs with reduced gastric irritancy through formulation in slow release of enteric-coated tablets or as prodrugs that require hepatic metabolism to be active. However, the incidence of gastroduodenal ulceration with these drugs is comparable to what is observed with standard NSAIDs."³³

In summary, although FDA agrees that Vimovo has demonstrated a gastroprotective effect, we do not agree that the available data demonstrate that the release of esomeprazole prior to the release of naproxen is material to that effect.

B. The Petition Fails to Establish that the Presence of Any Naproxen Outside an Enteric Coating in ANDA Products Increases the Risk of Adverse Gastrointestinal Effects.

The Petition states that several generic manufacturers have filed ANDAs referencing Vimovo as the RLD, and that Horizon has received notice of one ANDA for a proposed generic product that "contains a measurable amount of naproxen outside of the enteric coating" (Petition at 1). In particular, the Petition states that Horizon received a Paragraph IV notice letter³⁴ from a sponsor of a proposed generic version of Vimovo that described the proposed product as follows:

"A measurable portion of the entire amount of the naproxen (NSAID) in [the ANDA applicant's] proposed product is not surrounded by a coating that prevents release at a pH of less than 3.5 but instead is coated in a polymer that completely dissolves at a much lower pH, and is released at that pH."

Petition at 1-2, footnote 3.

³¹ See EC-Naprosyn label approved on March 22, 2013, at p. 7 (Clinical Studies Section) available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017581s111,018164s061,018965s020,020067s0181b1.pdf (discussing the results of three 6-week, double-blind, multicenter studies with EC-Naprosyn (naproxen) (375 or 500 mg bid, n=385) and Naprosyn (375 or 500 mg bid, n=279) that were conducted comparing the two products and included 355 rheumatoid arthritis and osteoarthritis patients who had a recent history of NSAID-related GI symptoms).

³² Id. (discussing the results of long-term open-label trials involving 553 patients who received EC-Naprosyn (mean length of treatment was 159 days)).

³³ Wallace, J. Nonsteroidal Anti-inflammatory Drugs and Gastroenteropathy: The Second Hundred Years Gastroenterology (1997); 112:1000-1016.

³⁴ Section 505(j)(2)(B) of the Act and 21 CFR 314.94(a)(12)(i)(A)(4) require that the generic drug applicant provide notice to the patent holder and NDA sponsor of any certification made in the ANDA that the patent in question is invalid or will not be infringed by the generic product (known as a "paragraph IV certification").

The Petition states that such an ANDA product “specifically obviates [Vimovo’s] careful design” and would impair the gastroprotective benefits of esomeprazole by “allowing release of a measurable amount of naproxen before the gastroprotective benefits of esomeprazole can take effect” (Petition at 1-2 and 5). The Petition claims that “a reduction in the enteric coating surrounding the naproxen core could subject patients to significantly increased risk of potentially fatal side-effects” (Petition at 7).

FDA does not generally comment on pending ANDAs, including whether a given ANDA has in fact been submitted, and we will not do so in this case.³⁵

Also, for the reasons discussed above in section II.A, even if a proposed generic product referencing Vimovo were to release some amount of naproxen before all of the esomeprazole release had occurred,³⁶ we do not agree with the Petition that there is reason to be concerned, in the abstract, that this could result in materially different gastrointestinal adverse event profiles.

Accordingly, the available data do not lead us to conclude that an ANDA product with any amount of naproxen outside of the enteric-coated core would, for this reason alone, be associated with increased gastrointestinal injury risk compared to Vimovo.

C. Additional Data or Testing Are Not Necessary for Approval of Certain ANDA Products

The Petition states that additional data or testing should be required for any ANDA product that cites Vimovo as the RLD if the product employs less than a complete enteric coating around the naproxen component, and thus may include a portion of naproxen outside the enteric-coated core (Petition at 2 and 8).

In particular, the Petition requests that applications for such products must include either:

- PK data sufficient to show that the timing of release of naproxen in the generic product is equivalent to that of Vimovo, or
- data from clinical trials demonstrating that the proposed generic product does not cause more frequent or more severe gastrointestinal adverse events than does Vimovo.

We disagree. For the reasons discussed in section II.A of this response, we do not agree with the Petition’s claims regarding the clinical significance of the release of esomeprazole before

³⁵ See 21 CFR 314.430(b).

³⁶ We note that if dissolution testing (also discussed in note 37 of this response) shows or predicts early naproxen release from a proposed generic formulation of Vimovo, such a product might not be considered a delayed-release product. In that case, the product would not be approvable as an ANDA to Vimovo because it would not be the same dosage form as Vimovo (unless it was submitted pursuant to an approved suitability petition for a different dosage form). See sections 505(j)(2)(A)(iii) and 505(j)(4)(D)(i) of the FD&C Act and 21 CFR 314.94(a)(6) and 314.127(a)(4)(i).

naproxen. For the reasons discussed in section II.B of this response, we do not agree with the Petition that the presence, in a proposed generic version of Vimovo, of some portion of the naproxen outside the enteric core would result in increased risk of gastrointestinal injury.

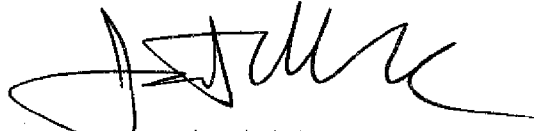
Accordingly, were FDA to receive an ANDA for a generic version of Vimovo that, as the Petition puts it, "includes a portion of naproxen outside of the enteric coated core" (Petition at 8), we would not, solely on that basis, require any testing beyond that recommended in the existing draft BE guidance either to evaluate BE or to ensure comparable safety.³⁷ Given that we do not agree that additional testing would be required, we need not consider whether, if such testing took the form of clinical studies, an application containing data from such studies would need to be submitted under section 505(b)(2) rather than 505(j) of the FD&C Act.

We note that this response addresses the Petition's requests generally. It should not be construed as addressing specific issues raised by any pending 505(j) application, nor does it purport to make any final decisions with respect to any such pending application. Those decisions would be made in the normal course as part of the review process applicable to any such applications.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,



Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

³⁷ As discussed above, we do not believe additional data regarding the relative timing of release of esomeprazole and naproxen should be required simply because a proposed generic version of Vimovo contains some amount of naproxen outside an enteric-coated core. In addition, we expect that compliance with FDA's current BE recommendations would furnish sufficient data to detect any material difference in the relative timing of release of the active ingredients between a proposed generic product and Vimovo. As discussed in section I.C., in evaluating BE for modified-release products, FDA may consider available lag time data. Moreover, if FDA were to conclude that data on relative release is significant for a given ANDA, PK or clinical studies would not be the only potential sources of such data. For instance, information on the relative timing of release of the active ingredients could come from dissolution studies that are already used to test the integrity of the enteric coating of delayed-release products. The current recommendations for dissolution testing of naproxen/esomeprazole magnesium delayed-release tablets can be found on FDA's database of recommended dissolution methods, which is available at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.