APPLICATION NUMBER:

209589Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
PIND 101738

Ferring Pharmaceuticals Inc.
Attention: Erik Thygesen
Director of US Regulatory Affairs
100 Interpace Parkway
Parsippany, NJ 07054

Dear Mr. Thygesen:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Prepopik (sodium picosulfate, magnesium oxide, citric acid).

We also refer to the meeting between representatives of your firm and the FDA on May 17, 2016. The purpose of the meeting was to discuss an agreement on whether the provided data are appropriate for filing of the NDA including the specific items needed to support the biowaiver.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-7295.

Sincerely,

Cheronda Cherry-France, R.N., B.S.N., M.H.A.
LCDR/USPHS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 17, 2016 at 9:00AM-10:00AM (EST)
Meeting Location: White Oak Building #22, Conference Room #1311

Application Number: 101738
Product Name: Prepopik
Indication: Bowel prep
Sponsor/Applicant Name: Ferring Pharmaceuticals Inc.

Meeting Chair: Jessica Lee, M.D., Medical Reviewer, Team Lead, DGIEP
Meeting Recorder: LCDR Cheronda Cherry-France, R.N., B.S.N., M.H.A

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joette Meyer, Pharm.D. Associate Director for Labeling, DGIEP
Jessica J. Lee, M.D., M.M.Sc., Medical Reviewer, Team Lead, DGIEP
Charles McQueen, M.D., Medical Reviewer, DGIEP
Tamal Chakraborti, PhD, Nonclinical Reviewer
Sue-Chih Lee, Ph.D., Team Leader, Division of Clinical Pharmacology III
Steven, Li, Ph.D., Clinical Pharmacology Reviewer
Andrejus Parfionovas, Ph.D., Statistical Reviewer, Division of Biometrics III
Maria R. Walsh, R.N., M.S., Associate Director for Regulatory Affairs, Office of Drug Evaluation III
Hamid Shafiei, Ph.D., Drug Product Reviewer, Division of New Drug Products II, Office of New Drug Products, Office of Pharmaceutical Quality
Tien-Mien Chen, Ph.D., Acting Biopharmaceutics Lead, Division of Biopharmaceutics (DB)/Office of New Drug Product (ONDP)/OPQ
Vidula Kolhatkar, Biopharmaceutics Reviewer, DB/ONDP/OPQ
1.0 BACKGROUND

PREPOPIK® NDA #202535 (sodium picosulfate, magnesium oxide, citric acid) powder for oral solution was approved on July 16, 2012. Ferring Pharmaceuticals Inc. has developed a ready to use pre-mixed oral solution dosage form of the same active ingredients to eliminate the mixing step to ensure administration of proper dosage and provide more convenience to the patients. This exact formulation has not yet been submitted for approval in any country.

The purpose of the meeting is to reach an agreement on whether the provided data is adequate for the filing of the NDA, including the specific items needed to support the biowaiver.

On March 17, 2016, the FDA granted Ferring Pharmaceuticals Inc. a face-to-face Pre-NDA meeting.

FDA sent Preliminary Comments to Ferring Pharmaceuticals Inc. on May 13, 2016, and Ferring responded to those comments May 16, 2016.

2.0 DISCUSSION

Questions from Ferring Pharmaceuticals Inc. (Ferring) are in plain text. Responses from the FDA are in bold text. Meeting discussions are in italics.

Introductory Comment:
Please be advised that your proposed NDA will be a 505(b)(2) application because it will cross-reference NDA 202535, a 505(b)(2) application that relied on published literature.

2.1 REGULATORY QUESTIONS

Question 1: Does the Agency agree with the plan for filing of the New Drug Application based on a request for a biowaiver (no clinical data for this formulation to be provided); with no refuse to file based on lack of clinical data?

FDA Response to Question 1:
We agree that lack of clinical data in your NDA submission would not be a filing issue, since you plan to submit the NDA based on a request for a biowaiver. However, if we determine that the data submitted in the NDA are not adequate to support granting a biowaiver during the course of the NDA review, one or more clinical studies will be required to support the safety and efficacy of the proposed formulation and the submitted NDA will not be approved.

We remind you that if a biowaiver request cannot be granted for the new pre-mixed oral solution formulation based on our review of the NDA, we do not consider PK to be a viable approach for establishing bioequivalence. You will need to conduct additional clinical studies to demonstrate comparable efficacy and safety of the new formulation; PK should be measured as part of the safety assessments.

**Meeting Discussion Question #1:**
Ferring acknowledged that if the biowavier is not granted FDA requires a clinical study and PK could not be used to demonstrate bioequivalence.

**Question 2:** Does the Agency agree with the list of CMC, nonclinical, and biopharmaceutics information that will be included in the NDA as well as the plans to reference the PREPOPIK NDA #202535 as listed in the meeting package?

**FDA Response to Question 2:**
No, we do not agree as we recommend additional items to be included in your NDA submission. See our responses to Questions 5 and 9.

**Meeting Discussion Question #2:**
No discussion occurred.

**Question 3:** Does the Agency agree to the proposed package insert relative to PREPOPIK NDA #202535 (revised with the new composition and elimination of the mixing steps and the warning in section 5.8 about direct ingestion), with the understanding that final labelling is subject to review?

**FDA Response to Question 3:**
If you will continue to market the powder for oral suspension in addition to the premixed oral solution, we recommend that both formulations share a common Prescribing Information (PI). We discourage sponsors from creating separate PIs for different dosage forms of the same product unless there is a compelling reason to do so. Having one PI allows the prescriber access to a comprehensive overview of the strengths, indications, dosage forms, etc. available for the active moiety. In addition, one document allows for easier updating by the sponsor when new information becomes available.

We agree with your plan to update the label to conform to the Pregnancy and Lactation Labeling Rule (PLLR) format. We remind you that conversion to PLLR is required for all new NDA submissions.
Meeting Discussion Question #3:
See the attached slides for Ferring’s rationale to have two separate PIs for the two products. FDA continues to recommend that Ferring submit one PI for both the marketed powder for oral solution and the proposed new premixed oral solution, as they contain the same active ingredients (sodium picosulfate, magnesium oxide, and anhydrous citric acid).

DGIEP does not review proprietary names, but referred the sponsor to the Guidance of Industry – Best Practices in Developing Proprietary Names for Drugs. DGIEP recommends that Ferring discuss with OSE/DMEPA their rationale for not using the same proprietary name for two formulations with the same active ingredients and why a distinct proprietary name for the new formulation will not cause a potential safety risk.

DGIEP does not believe differing instructions for use between the two formulations is a compelling reason for having two distinct PIs. DGIEP provided several examples of products with two formulations that share a PI with differing instructions for preparation and administration.

- Prilosec delayed-release capsules and oral suspension: [http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022056s018lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022056s018lbl.pdf)
- Orfadin capsules and oral suspension: [http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206356s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206356s000lbl.pdf)
- Emend capsules and oral suspension: [http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207865lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207865lbl.pdf)

DGIEP recommended that Ferring consider developing an Instructions for Use (IFU) document, separate from the Medication Guide, to provide patients with clear instructions for use. Ferring was advised to refer to the IFUs for the above 3 products.

DGIEP also stated that differing warnings and precautions between the two formulations can be addressed in a combined PI. For example, the following Warning and Precaution pertains to the inactive ingredient glycerol, which is found in the Orfadin oral suspension but is not present in the Orfadin oral capsules:

5.3 Risk of Adverse Reactions Due to Glycerol Content of ORFADIN Oral Suspension
Oral doses of glycerol of 10 grams or more have been reported to cause headache, upset stomach and diarrhea. ORFADIN oral suspension contains 500 mg/mL of glycerol. Patients receiving more than 20 mL of ORFADIN oral suspension (10 grams glycerol) as a single dose are at increased risk of these adverse reactions. Consider switching patients who are unable to tolerate the oral suspension to ORFADIN capsules.

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**Question 4:** Does the Agency require a new safety update of the PREPOPIK powder for oral solution NDA #202535 (from the cutoff date in the last safety update) which will be referenced in the new NDA for the pre-mixed oral solution product?

**FDA Response to Question 4:**
We acknowledge that you will not have any clinical safety data on the new pre-mixed oral solution, and you intend to cross-reference safety updates submitted under NDA 202535. We recommend that you also include in your NDA submission any new safety data on PREPOPIK powder for oral solution that have not been already submitted under NDA 202535.

**Meeting Discussion Question #4:**
No discussion occurred.

2.2 QUALITY

**Question 5:** Does the Agency agree the CMC plan is adequate for filing of the New Drug Application?

**FDA Response to Question 5:**
Overall, your plan appears to be acceptable. However, for your drug substances, in addition to cross-referencing information from three DMFs, at minimum include “General Information” (3.2.S.1) and “Specification” (3.2.S.4.1) for each drug substance. We agree with your proposal to include the full new CMC section for the drug product in Module 3 of the NDA submission.

**Meeting Discussion Question #5:**
No discussion occurred.

**Question 6:** Does the Agency agree to file the NDA in accordance with ICH Q1C based on six-months stability data from three registration stability batches and additional 12-months supporting stability data from the development batches?

**FDA Response to Question 6:**

Additionally, you are required to conduct compatibility studies to demonstrate that there are no chemical interactions between the active and inactive pharmaceutical ingredients that could adversely affect the impurity profile and stability of the proposed formulation.

**Meeting Discussion Question #6:**
See the attached slides for stability data that Ferring intends to include in the NDA submission. FDA informed Ferring that the NDA submission must include 12 months of long-term stability data on registration batches and/or batches of the to-be-marketed formulation with a minimum of [redacted] of the commercial manufacturing.

2.3 NON-CLINICAL

**Question 7:** Does the Agency agree that based on the present nonclinical information from the PREPOPIK NDA #202535 and the nonclinical information for the inactive ingredients provided in the meeting package no additional nonclinical studies/evaluations are needed for filing of the New Drug Application?

**FDA Response to Question 7:**
Nonclinical information from the PREPOPIK powder for oral solution NDA #202535 and the nonclinical information for the inactive ingredients provided in the meeting package appear to be adequate for the filing of the NDA.

**Meeting Discussion Question #7:**
No discussion occurred.

**Question 8:** Does the Agency agree the plan for impurity qualification is adequate for filing of the New Drug Application?

**FDA Response to Question 8:**
Yes. Your plan for impurity qualification appears to be adequate for the filing of the NDA.

**Meeting Discussion Question #8:**
No discussion occurred.

2.4 BIOPHARMACEUTICS

**Question 9a:** Does the Agency agree the absorption/permeability data in the meeting package are adequate to support the biowaiver for filing of the New Drug Application?

**FDA Response to Question 9a:**
The absorption/permeability data submitted in the meeting package appear adequate to support the filing of the NDA. However, the acceptability of the submitted data to support the biowaiver is a review issue.

In your NDA submission, include justification that any differences in the inactive ingredients will not affect absorption, or systemic or local availability of the proposed drug product. You may include literature references and/or your study reports to support your justification. This justification should include (but not limited to) the following:

1) We acknowledge the permeability data included in the meeting package. However, in your permeability study reports you have used atenolol as low permeability marker. Per

Meeting Discussion Question #9a(1):
Ferring agreed to include in the NDA submission the justification to support why atenolol has been chosen as the reference compound and provide data supporting its use including the validation data.

Ferring noted that the BCS guidance is for immediate-release solid oral dosage forms only, and inquired if there is anything in particular in this guidance that could be utilized to support the biowaiver for the oral solution. FDA stated that the BCS guidance for oral solid dosage forms does not apply to the proposed product. Only the in vitro permeability study for testing drug substance in aqueous phase is applicable.

Post-meeting comment:
In the data provided in your meeting package, you used atenolol as a low permeability marker. We intended to direct you to the in vitro permeability study, in particular model drugs suggested for use in establishing suitability of a permeability method. As stated in the revised BCS guidance 2015, atenolol is a moderate permeability marker.

2) We note that for permeability studies, you have selected 20% dilution of the proposed pre-mixed oral solution. Provide study reports, justification and/or literature report that permeability for the proposed pre-mixed oral solution and reconstituted PREPOPIK powder for oral solution will be comparable under all relevant dilution conditions.

Meeting Discussion Question #9a(2):
Ferring indicated that the 20% dilution condition was selected to ensure the cells are viable in the permeability experiments. Ferring intends to provide literature to support comparable permeability under all relevant dilution conditions. FDA reiterated that Ferring should include all relevant data and justification in the NDA submission; however, acceptability of the data to support the biowaiver is a review issue.

3) In your NDA submission, include a detailed report of the experiments conducted to assess precipitation of the proposed pre-mixed oral solution and reconstituted PREPOPIK powder for oral solution at pH range of [____] (b) (4).

Meeting Discussion Question #9a(3):
Ferring will include the requested information in the NDA.

4) Provide the composition of the simulated gastric fluid and simulated intestinal fluid used to evaluate osmolality of the pre-mixed oral solution and PREPOPIK powder for oral solution (reconstituted) after dilution (described in Table 22 in the meeting package).
**Meeting Discussion Question #9a(4):**
Ferring will include the requested information in the NDA.

5) The stimulant laxative, sodium picosulfate, is hydrolyzed by colonic bacteria to form an active metabolite: bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM, which acts directly on the colonic mucosa to stimulate colonic peristalsis. Provide data and/or justification that the inactive ingredients in the proposed product will not affect this process.

**Meeting Discussion Question #9a(5):**
Ferring intends to include a justification in the NDA to support the lack of clinically relevant changes in colonic bacteria applicable to the formation of the active metabolite BHPM. Ferring also proposes to conduct an in vivo rat study to measure formation of the active metabolite and the laxative effect for both formulations. FDA stated that Ferring’s approach seems reasonable.

6) Your proposed product contains high amount of malic acid and sodium hydroxide. Provide literature references and/or study results to support that the new additions, especially \text{[redacted]} grams of malic acid and \text{[redacted]} grams of sodium hydroxide, will not affect the \textit{in vivo} performance of the drug.

**Meeting Discussion Question #9a(6):**
See the attached slides for Ferring’s proposed justification plan to support that malic acid and sodium included in the proposed formulation have no impact on the \textit{in vivo} performance of the drug. FDA stated that although Ferring’s approach seems reasonable, the acceptability of the justification will be a review issue. FDA requested to include information about how malic acid and sodium hydroxide \text{[redacted]} in the proposed product. It would also be helpful to provide data to support that malic acid is absorbed in small intestine before reaching the colon. Ferring also agreed to provide FDA with the amounts of malic acid and sodium in the proposed product and how they compare to clear liquids mentioned in the justification (e.g., chicken broth, apple juice, Gatorade).

7) Develop a complete plan to demonstrate that the interaction of inactive ingredients will not affect product performance.

**Meeting Discussion Question #9a(7):**
Ferring proposed a complete plan that will include the following studies:

- comparative solubility study under relevant physiological pH
- comparative permeability study (magnesium, picosulfate)
- \textit{in vivo} rat study to measure formation of the metabolite and the laxative effect for both formulations (under Question #9a(5))
- comparative osmolality study
- comparative sodium study

FDA stated that the proposed approach seems reasonable; however, acceptability of the submitted data to support the biowaiver is a review issue that will be determined based on the totality of the information provided in the NDA submission.
Please note that the final decision on the acceptability of the biowaiver will be made based on totality of the provided information.

**Question 9b:** Does the Agency agree the comparative electrolyte and osmolality data and rationale for any significant differences in the meeting package are adequate to support the biowaiver for filing of the New Drug Application?

**FDA Response to Question 9b:**
The comparative electrolyte and osmolality data submitted in the meeting package appear adequate to support the filing of the NDA. However, the acceptability of the submitted data to support the biowaiver is a review issue. Please also see response to Question 9(a) above.

**Meeting Discussion Question #9b:**
No discussion occurred.

**Question #10:** Does the Agency agree with the conclusion above that bioequivalence is considered self-evident, subject to review of the full reports to be submitted with new NDA?

**FDA Response to Question 10:**
No, we cannot agree at this time that bioequivalence is considered self-evident because your pre-mixed oral solution contains inactive ingredients that may significantly affect absorption or systemic or local availability. This issue will be addressed during the course of the NDA review. Please see our responses to Questions 9(a) and 9(b).

**Meeting Discussion Question #10:**
FDA will communicate review issues with Ferring as they arise during the course of the NDA review. However, it is unlikely that the review team will be able to make determination regarding the acceptability of the biowaiver and the need for a clinical study until after the midcycle meeting.

### 3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric
plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.


### 4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/) and [Pregnancy and Lactation Labeling Final Rule](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm360507.pdf) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* ([http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf)).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.
5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

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<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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Corresponding names and titles of onsite contact:

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<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
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6.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.
List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature

<table>
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<tr>
<th>Source of information (e.g., published literature, name of listed drug)</th>
<th>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</th>
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<tr>
<td>1. Example: Published literature</td>
<td>Nonclinical toxicology</td>
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<td>2. Example: NDA XXXXXX “TRADENAME”</td>
<td>Previous finding of effectiveness for indication X</td>
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<td>3. Example: NDA YYYYY “TRADENAME”</td>
<td>Previous finding of safety for Carcinogenicity, labeling section XXX</td>
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Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

7.0 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator’s site address or contact information since the time of the clinical investigator’s participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site
1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:
III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

8.0 ISSUES REQUIRING FURTHER DISCUSSION
None

9.0 ACTION ITEMS
None

10.0 ATTACHMENTS AND HANDOUTS
Ferring Pharmaceuticals Inc.’s PowerPoint Presentation will be attached.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHERONDA L CHERRY-FRANCE
05/25/2016