CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215152Orig1s000
215153Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 143190
IND 144399

MEETING MINUTES

Phathom Pharmaceuticals, Inc.
Attention: Nancianne Knipfer, PhD, RAC
Senior Director, Regulatory Affairs
2150 East Lake Cook Road
Suite 800
Buffalo Grove, IL 60089

Dear Dr. Knipfer:

Please refer to your investigational new drug applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for:

IND 143190: Vonoprazan/amoxicillin/clarithromycin
IND 144399: Vonoprazan/amoxicillin

We also refer to the teleconference between representatives of your firm and the FDA on November 10, 2020. The purpose of the Pre-NDA meeting was to discuss the content of the nonclinical and clinical sections required to support the submission of New Drug Applications (NDAs) for vonoprazan used in combination with amoxicillin/clarithromycin and vonoprazan used in combination with amoxicillin for the treatment of *Helicobacter pylori* infection.

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 Eva Zuffova, Regulatory Project Manager, at 301-796-0697.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 10, 2020; 11:00 AM – 12:00 PM
Meeting Location: Teleconference

Application Numbers/ Product Names: IND 143190: Vonoprazan/amoxicillin/clarithromycin
IND 144399: Vonoprazan/amoxicillin

Indication: Treatment of *H. pylori* infection
Sponsor Name: Phathom Pharmaceuticals, Inc.

Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Eva Zuffova, PhD, MS

FDA ATTENDEES

Division of Anti-Infectives (Division)

Adebowale Abimbola, PhD	Associate Director for Labeling
Carmen DeBellas, PharmD, RPh	Chief, Project Management Staff
Maureen Dillon-Parker, MS, RAC	Director, Project Management Staff
Mayurika Ghosh, MD	Clinical Reviewer
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Karen Higgins, ScD	Statistical Team Leader
Dmitri Iarikov, MD, PhD	Deputy Director
Dorota Matecka, PhD	Product Quality Team Leader
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Jason Moore, PharmD	Clinical Pharmacology Reviewer
Sumathi Nambiar, MD, MPH	Director
Leah Rosenfeld, PhD	Pharmacology/Toxicology Reviewer
Thomas Smith, MD	Clinical Team Leader
Ursula Waack, PhD	Microbiology Reviewer
Grace Yan Danielsen, PhD	Clinical Pharmacology Team Leader
Eva Zuffova, MS, PhD	Regulatory Health Project Manager
Jie Cong, PhD	Statistical Reviewer
Sheel Shah, PharmD, RPh	Regulatory Health Project Manager

Office of Regulatory Policy

Katherine Schumann, MS	Deputy Director, Division of Regulatory Policy

Division of Medication Error Prevention and Analysis

Deborah Myers, RPh, MBA	Safety Evaluator
Nicholas Miles, PharmD	Regulatory Health Project Manager

Division of Gastroenterology

Laura Finkelstein, MD	Clinical Reviewer
Maureen Dewey, MPH	Regulatory Health Project Manager
Min Kang, PhD	Biopharmaceutics Reviewer
Mathew Kowalik, MD	Clinical Team Leader

SPONSOR ATTENDEES

Phathom Pharmaceuticals, Inc.

Maria Buckley, Vice President	Clinical Operations
Esha Desai, Director	Regulatory Affairs
Thomas Harris, RPh	Head of Regulatory Affairs, CMC, R&D Quality/Systems and Biostatistics
Barbara Hunt, MS	Senior Director, Biostatistics
Nancianne Knipfer, PhD, RAC	Senior Director, Regulatory Affairs
Aditya Kohli, PhD	Chief Business Officer
Eckhard Leifke, MD	Chief Medical Officer
Azmi Nabulsi, MD	Chief Operating Officer and Head of Research and Development
Neila Smith, MD	Vice President Patient Safety
Roger Ulrich, PhD	Chief Scientific Officer

1.0 BACKGROUND

The purpose of the meeting was to discuss the content of the nonclinical and clinical sections required to support the registration of NDAs for the treatment of *H. pylori* infection; (b) (4) vonoprazan used in combination with amoxicillin and clarithromycin (convenience package), and vonoprazan used in combination with amoxicillin (convenience package).

The Sponsor, Phathom, submitted a request for a meeting on September 1, 2020. A meeting background package with specific **Questions** for the Agency was submitted on October 10, 2020. The Division of Anti-Infectives (Division) sent preliminary comments via email on November 5, 2020 noted below as **FDA Response** (Attachment 1). On November 7, 2020, the Sponsor submitted responses to FDA preliminary comments (Attachment 2) and communicated that they would like to discuss questions 12, 23, 26, and 28 (possibly questions 17 and 31). On November 9, 2020, the Sponsor provided a sample Council for International Organizations of Medical Sciences (CIOMS) form

(Attachment 3), and slides to be presented at the meeting (Attachment 4). The discussion that took place during the meeting is captured under ***Meeting Discussion***.

Only the Questions/Responses discussed at the meeting are captured below. See **Attachment 2** for the complete set of Questions/Responses.

2.0 DISCUSSION

Question 12: The case report forms from the Takeda studies conducted in Japan will require translation. Therefore, does the Agency agree with this approach to limit the number of case report forms and narratives to those from the *H pylori* studies?

FDA Response to Question 12: We do not agree. 21 CFR 314.50(f)(2) requires that CRFs be submitted for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not.

In addition, provide narrative for all deaths (all studies) and narratives for the SAEs for studies Hp-301 and CCT-401. Provide a sample of the Council for International Organizations of Medical Sciences (CIOMS) form for SAEs from study TAK-438/CCT-401.

The above information will be needed for the safety review of the NDA.

***Meeting Discussion**: Based on the sample CIOMS form and Sponsor's response to the preliminary comment, the Division agreed that the Sponsor can provide the following in the NDA:*

- *CIOMS forms in lieu of narratives for deaths and other serious adverse events from all studies*
- *Narratives for Treatment Emergent Adverse Events (TEAE) leading to premature discontinuation from all studies*
- *Narratives for Adverse Events of Special Interest (AESI) from studies CCT-401 and HP-301*
- *CRFs for deaths from all studies*
- *CRFs for TEAEs leading to premature discontinuation from all non-Japanese studies*
- *CRFs for TEAEs leading to premature discontinuation from study CCT-401*
- *CRFs for SAEs for studies CCT-401 and HP-301*
- *CRFs for AESI for studies CCT-401 and HP-301*

The Division also agreed to grant the Sponsor a waiver for providing the CRFs for all Japanese studies (except study CCT-401). The Sponsor agreed to provide the CRFs for the remaining Japanese studies (except study CCT-401) if requested during the review of the NDA.

Question 17: Does the Agency agree to the proposed plan for handling data due to the COVID-19 pandemic?

FDA Response to Question 17: We recommend against excluding subjects without test-of-cure data due to COVID-19. These patients should be considered as treatment failures in the primary efficacy analysis. Other missing data imputation methods can be considered in the sensitivity analyses. Late IBT results due to COVID-19 are acceptable.

***Meeting Discussion**: The Division agreed to engage in future discussions if the pandemic worsens and further impacts the study conduct due to COVID-19.*

Question 23: Does the Agency agree the convenience pack NDAs can be filed under section 505(b)(2)?

FDA Response to Question 23: In general, we agree with your proposal to submit NDAs for the two convenience packs (vonoprazan and amoxicillin; vonoprazan, amoxicillin, and clarithromycin) under the 505(b)(2) pathway. The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on NDA 050459 (AMOXIL) for the NDA for vonoprazan and amoxicillin and both NDA 050459 (AMOXIL) and NDA 050662 (BIAXIN) for the NDA for vonoprazan, amoxicillin, and clarithromycin generally appears acceptable.

We remind you that 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. Absence of a bridge between a proposed drug product and the reference drug product to demonstrate that reliance is scientifically justified may be a refuse to file issue for a 505(b)(2) NDA (see CDER's Manual of Policies and Procedures 6025.4, Good Review Practice: Refuse to File).

We note that both AMOXIL and BIAXIN are discontinued from marketing. If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) and intend to support the scientific appropriateness of reliance through a comparative bioavailability study, it is recommended you use the ANDA product designated as the reference standard in the Orange Book to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

So that we can provide feedback on your proposed bridge to each relied upon listed drug prior to NDA submission, we strongly recommend that you clarify the source of amoxicillin and/or clarithromycin drug product for each convenience pack NDA. You

should also explain your proposed bridge between each of those drugs products and the relied-upon listed drugs you have identified for each proposed NDA.

Please see additional information regarding 505(b)(2) applications below under **ADDITIONAL APPLICATION INFORMATION**.

***Meeting Discussion**: The Sponsor confirmed that Biaxin was listed as the reference listed drug in the clarithromycin Abbreviated New Drug Application (ANDA 065136) and Amoxil was listed as the reference listed drug in the amoxicillin ANDA (064076). They also stated that although Biaxin and Amoxil are discontinued, the NDAs were not discontinued or withdrawn for safety or efficacy reasons. Based on this information, the Sponsor proposed to submit a letter of cross-reference to the Sandoz ANDAs in the NDAs and asked if this was an acceptable bridging strategy for these NDAs. FDA agreed with the proposed bridging strategy.*

Question 26: Should Phathom proceed to submit requests for a QIDP designation for each of these potential NDAs? If yes, Phathom proposes to file a letter cross-referencing the prior justification submitted in June 2019. Will this be acceptable?

FDA Response to Question 26: (b) (4) For purposes of the QIDP comments, these are specific to NDA 215152 (convenience package vonoprazan/amoxicillin/clarithromycin) and NDA 215153 (convenience package vonoprazan/amoxicillin).

(b) (4)

You should proceed to submit new requests for QIDP to the respective INDs 143190 and 144399 to reflect the final proposed dosage form(s) for each NDA. These submissions should identify the package configuration, dosage form for all products to be included in the convenience package and the proposed indication.

***Meeting Discussion:** Based on the Division's preliminary response regarding QIDP designation, the Sponsor described their revised plan for the NDAs. They stated that they would* (b) (4) *submit NDAs 215152 and 215153 for the two respective convenience packs. The primary NDA will be*

the vonoprazan/amoxicillin/clarithromycin NDA (NDA 215152). The vonoprazan/amoxicillin NDA (NDA 215153) will be the secondary NDA and will include a cross reference to NDA 215152. The Sponsor also agreed to submit new QIDP designation requests to INDs 143190 and 144399 to include the use of amoxicillin capsules [redacted] (b) (4) *The Division agreed with the Sponsor's plans.*

Question 28: Does the Agency agree with the rolling review submission strategy?

FDA Response to Question 28: [redacted] (b) (4) A product must be designated as Fast Track (or Breakthrough) in order to be eligible for rolling review. Please see FDA Response to Question 27.

***Meeting Discussion**: The Sponsor would like to submit portions of NDA 215152 for vonoprazan tablets co-packaged with amoxicillin and clarithromycin on the same schedules provided in their pre-NDA briefing package. The Division stated that their preference is to receive a complete submission for review. However, they would accept the Sponsor's proposed rolling review submission strategy and plan for vonoprazan/amoxicillin/ clarithromycin NDA (NDA 215152). The Division also clarified that the review clock would not start until the final portion of the NDA is submitted. The Sponsor plans to submit a request to the IND for the rolling review of NDA 215152 early next year. They also confirmed that they would not be submitting vonoprazan/amoxicillin NDA (NDA 215153) for a rolling review.*

Question 31: [redacted] (b) (4)

(b) (4)

[redacted]

POST-MEETING FOLLOW UP QUESTION AND COMMENTS

[Note: Question 14 is a follow-up to the original Question 14; see Preliminary Comments (Attached) for original question and Division response.]

Question 14: Phathom would like to confirm with the Agency if it would be acceptable to add QT prolongation as AESI for only the HP-301 and CCT-401 studies. As noted by the Agency clarithromycin is associated with QT prolongation and HP-301 and CCT-401 are the 2 key studies which include a combination treatment arm with clarithromycin.

FDA Response: Your proposal is acceptable.

(b) (4)

[redacted]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application(s) was discussed. The Sponsor plans to submit NDA 215152 for vonoprazan/amoxicillin/clarithromycin as the primary NDA; NDA 215153 for vonoprazan/amoxicillin will include a cross-reference to NDA 215152, as well as Modules 1, 2 (CMC) and 3.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the applications.

- Major components of the applications are expected to be submitted with the original application(s) and are not subject to agreement for late submission. You stated you intend to submit complete applications and therefore, there are no agreements for late submission of application components.

In addition, we note that a Chemistry, Manufacturing, and Controls pre-submission meeting will be held on January 7, 2021. We refer to this meeting for any additional agreements that may have been reached.

4.0 ACTION ITEM

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	December 10, 2020

5.0 ATTACHMENTS

- Attachment 1: Division preliminary comments, dated November 5, 2020
- Attachment 2: Sponsor response to FDA preliminary comments, dated November 7, 2020
- Attachment 3: Sponsor sample CIOMS form, dated November 9, 2020
- Attachment 4: Sponsor slide presentation, dated November 9, 2020

IND 143190
IND 144399

MEETING PRELIMINARY COMMENTS

Phathom Pharmaceuticals, Inc.
Attention: Nancianne Knipfer, PhD, RAC
Senior Director, Regulatory Affairs
2150 East Lake Cook Road
Suite 800
Buffalo Grove, IL 60089

Dear Dr. Knipfer:

Please refer to your investigational new drug applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for:

IND 143190: Vonoprazan/Amoxicillin/Clarithromycin
IND 144399: Vonoprazan/Amoxicillin

We also refer to your September 1, 2020, correspondence, received September 1, 2020, requesting a pre-NDA meeting to discuss the content of complete nonclinical and clinical sections required to support the submission of New Drug Applications for vonoprazan used in combination with amoxicillin/clarithromycin and vonoprazan used in combination with amoxicillin, submitted as convenience packs, for the treatment of *Helicobacter pylori* infection.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 301-796-0697.

Sincerely,

{See appended electronic signature page}

Eva Zuffova, MS, PhD
Regulatory Project Manager
Anti-Infectives Group 1
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 10, 2020; 11:00 AM – 12:00 PM

Meeting Location: Teleconference

Application Numbers/ Product Names: IND 143190: Vonoprazan/Amoxicillin/Clarithromycin
IND 144399: Vonoprazan/Amoxicillin

Indication: Treatment of *H. pylori* infection

Sponsor Name: Phathom Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

CDER Participants (tentative):
Adebowale Abimbola, PhD, Associate Director for Labeling
Carmen DeBellas, PharmD, RPh, Chief, Project Management Staff
Maureen Dillon-Parker, MS, RAC, Director, Project Management Staff
John Farley, MD, MPH, Director, Office of Infectious Diseases
Mayurika Ghosh, MD, Clinical Reviewer
Avery Goodwin, PhD, Clinical Microbiology Team Leader
Karen Higgins, ScD, Statistical Team Leader
Dmitri Iarikov, MD, PhD, Deputy Director, Division of Anti-Infectives (DAI)
Dorota Matecka, PhD, Product Quality Team Leader
Terry Miller, PhD, Pharmacology/Toxicology Team Leader
Jason Moore, PharmD, Clinical Pharmacology Reviewer
Sumathi Nambiar, MD, MPH, Director, DAI
Leah Rosenfeld, PhD, Pharmacology/Toxicology Reviewer
Katherine Schumann, MS, Deputy Director, Division of Regulatory Policy
Thomas Smith, MD, Clinical Team Leader
Ursula Wack, PhD, Microbiology Reviewer
Grace Yan, PhD, Clinical Pharmacology Team Leader
Eva Zuffova, MS, PhD, Regulatory Health Project Manager

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 10, 2020; 11:00 AM – 12:00 PM between Phathom Pharmaceuticals,

Inc. and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On September 1, 2020, the Sponsor, Phathom Pharmaceuticals, Inc., requested a meeting to discuss the content of complete nonclinical and clinical sections required to support the registration of (b) (4) NDAs for the treatment of *H. pylori* infection; (b) (4) vonoprazan used in combination with amoxicillin and clarithromycin (convenience package), and vonoprazan used in combination with amoxicillin (convenience package).

Note: The comments in this document are specific to the (b) (4) NDAs planned for submission to the Division of Anti-Infectives for the indication of treatment of *H. pylori* infection. (b) (4)

2.0 DISCUSSION

NONCLINICAL DEVELOPMENT PROGRAM

Question 1: Does the Agency agree no further evaluation of MATE1 and OCT1 is necessary?

FDA Response to Question 1: Based on the provided summary of in vitro study results, we agree that no further evaluation of MATE1 and OCT1 is necessary. This finding will be reassessed upon NDA submission.

Question 2a: Does the Agency have any further questions regarding the response submitted on 09 March 2020?

FDA Response to Question 2a: Our comments to your responses submitted March 9, 2020 are as follows:

NONCLINICAL: Agency Comment 6

Please provide complete historical control data on fetal findings for the rat EFD study (Study No. TAK-438-00172). Please include data from both the animal vendor and laboratory conducting the study for the relevant years. Please include information on both the fetal and litter incidence for all malformations and variations available in the historical control data.

The Agency clarified on 31 October 2019 that they were referring to Study TAK-438/00135 and that they were looking for historical data from both the animal vendor and the contract lab from the time immediately preceding or following the study.

Phathom Response
The Agency has requested historical control data from the study "Effects of TAK-438 on Embryo-Fetal Development in Rats" (Report A. TAK-438/00135, Study No. 06-424/TE), and historical control data from Test Facility and Animal Vendor, which includes all malformations (external, visceral, and skeletal) and litter and fetal incidences.
In Report TAK-438/00135, Annex 2 lists Historical Data: External Findings in Fetuses for the Test Facility. It should be noted that in Annex 2 (pages 92-93), the correct values for 05-079/TE No. of Fetuses examined is n=263 and No. of animals is n=19, rather than n=274 and n=20, respectively. Historical control data is not available for the Animal Supplier. However, Ema M., *et al.* 2014, includes historical control data (fetal incidence only available) in Japanese testing facilities between 2001-2010 (Table Supplement S10: years 2000-2010) [1].

FDA Follow-up Comment: We appreciate the correction to the report and the reference provided. In examining developmental studies, the unit of comparison used by FDA is the litter (as opposed to the fetus). It would be helpful for our review if you are able to provide the historical data presented on a litter incidence as well as on a per fetus basis.

Thank you for providing a published reference; however, we are not sure the relevance of the data cited to the testing facility you used for the relevant years. Additionally, the data in the cited article provided does not allow us to make an appropriate per litter comparison, and so we will continue to use both the concurrent control and the requested historical data for the testing facility as the basis of comparison for malformations.

NONCLINICAL: Agency Comment 7
If you have tissues or slides of the fetuses from the low dose group (3 mg/kg/day) from Study no. TAK-438-00172 available for evaluation, we recommend that malformation (external, visceral, and skeletal) and variation data from that group be collected, reviewed and submitted to your IND.

The Agency clarified on 31 October 2019 that they are requesting data for the 30 mg/kg/day group in Study TAK-438/00135.

Phathom Response
The Agency recommends evaluation of fetuses in the low dose 30 mg/kg/day group from the study: Effects of TAK-438 on Embryo-Fetal Development in Rats (Report TAK-438/00135, Study No. 06-424/TE, completed June 19, 2007). Treatment-related malformations were noted in the high dose (300 mg/kg/day) group including 42 fetuses from 16 litters with specific cardiovascular malformations (membranous ventricular septal defect and/or malpositioned subclavian artery) and 2 fetuses from 2 litters with tail and anus defects (1 also with short trunk). Reduced fetal weights were also seen at this dose. There were no treatment-related findings in fetuses in the 30 or 100 mg/kg/day dose groups. The no-observed-adverse-effect-level (NOAEL) for developmental toxicity was 100 mg/kg/day. In the mid-dose group (100 mg/kg/day), only a single fetus (1 of 144 evaluated in 20 litters) showed a visceral malformation (Interrupted Aortic Arch). This was not considered treatment related by the Study Director because it occurred as an isolated, low incidence (0.7%) finding with no dose-dependency (i.e., no aortic arch defects at the high dose). Additionally, there were no skeletal malformations, no effects on fetal body weight and no other signs of developmental toxicity at this dose. Although no historical control data were included in the report for visceral malformations, aortic arch defects have been reported as a background finding in this strain of rat, during the time frame in which study was conducted, at a similar incidence as occurred in the 100 mg/kg/day group (absent or interrupted aortic arch, maximum incidence 0.8-1.32%) as reported by Ema *et al*. 2014, Table Supplement S10: years 2000-2010 [1]. Based on this information, Phathom agrees with the interpretation in the original study report; therefore, additional evaluation of low dose group fetuses is not considered warranted.

FDA Follow-up Comment: We also note the cardiovascular fetal malformations in litters in the high dose group as well as tail and anus defects. In the 100 mg/kg dose group, there was one litter with a fetus that had an interrupted aortic arch. An interrupted aortic arch is a rare and serious malformation. We disagree that it can be concluded that the interrupted aortic arch is necessarily unrelated to the membranous septal defects as both are cardiovascular system effects. In the absence of historical data from the laboratory conducting the study presented on a per litter basis, we are also unable to conclude that the interrupted aortic arch is not a related manifestation of vonoprazan's toxicity. Without the visceral malformation data from the low dose group, we are unable to determine the NOAEL for this study. We reiterate our recommendation that the low dose fetuses be examined if they are available.

NONCLINICAL: Agency Comment 8
Please provide your justification for the length of administration of the test articles to males for the premating period in the fertility study (Study No. TAK-438-00172). The males used for the fertility study were treated daily starting 14 days before mating. ICH S5B states, "For detection of effects not detectable by histopathology of male reproductive organs and sperm analysis, mating with females after a premating

treatment of 4 weeks has been shown to be at least as efficient as mating after a longer duration of treatment (2 weeks may be acceptable in some cases). However, when 2 weeks treatment period is selected, more convincing justification should be provided."

Phathom Response (Comment 8)
Per ICH S5B guidance "Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility", a premating treatment interval of 2 weeks for males in the fertility study (Study No. TAK-438-00172) is acceptable if no effects have been found in the repeat-dose toxicity studies of at least 2 weeks duration. In the 2-week (Study No. TAK-438-00049, non-GLP) and 4-week (Study No. TAK-438-00085.003A, GLP) repeat-dose toxicity studies in Sprague-Dawley rats, there were no treatment-related findings at any vonoprazan dose level administered on gross pathology or histopathologic examination. These examinations included male reproductive organ weights [testes, prostate, and seminal vesicles* (*4-week study)], and histopathologic examination of testes, prostate, epididymides, and seminal vesicles. There were no remarkable or vonoprazan treatment-related findings on examination and therefore, it was considered acceptable to dose male rats for a 2-weeks premating interval in the fertility study.

FDA Follow-up Comment: In your NDA, provide your justification for only dosing for 2-weeks. We also encourage you to submit any sperm analysis available from the studies.

Question 2b: Does the Agency agree that the existing nonclinical development program is complete and adequate to support review of the planned NDAs?

FDA Response to Question 2b: The types, species, and durations of studies listed in your proposal are consistent with those that we would expect for a marketing application. We reiterate our previous comment that additional nonclinical combination toxicity studies with complete toxicokinetic and histopathologic assessments may be recommended to assess any unexpected toxicities or pharmacokinetic interactions encountered in your HP-301 Phase 3 study findings with vonoprazan in combination with amoxicillin with or without clarithromycin. The acceptability of the studies will be determined during the review. Plan to submit all the final nonclinical study reports that you intend to support the marketing application to this NDA.

Please note that additional nonclinical studies with complete toxicokinetic and histopathologic assessments may be required to explore any unexpected toxicities encountered during clinical development, or to qualify any novel impurities, degradants, or excipients detected in your clinical formulation.

CLINICAL DEVELOPMENT PROGRAM

Question 3: Does the Agency agree with the plan for updating the popPK model and Ethnic Bridging Report?

FDA Response to Question 3: We agree with the plan for updating the population PK model and the Ethnic Bridging Report.

We recommend that you submit the following information regarding the population PK, exposure-response, and PK/PD datasets in the NDA:

- The PK and PK/PD analysis/parameter datasets in .xpt format for Phase 1 to Phase 3 studies (data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets; the flag for exclusion should be clearly explained in the define.pdf file);
- The NONMEM control streams of the base and final models for population PK analyses;
- The codes (R, SAS, etc.) for PK/PD analyses;
- The output files for the final population PK and PK/PD models if applicable; the standard model diagnostic plots, tables with parameter estimates, and a description of the clinical application of modeling results;

Include a USUBJID (unique subject ID) column to all the population PK and PK/PD datasets so that we can relate these datasets to the corresponding clinical analysis datasets.

Question 4: Phathom proposes to submit Module 2.7.3 SCE in lieu of the Integrated Summary of Efficacy required per 21 Code of Federal Regulations (CFR) 314.50 (d)(5)(v). Does the Agency agree with Phathom's proposal and the contents of SCE?

FDA Response to Question 4: We recommend against pooling data from HP-301 and CCT-401 due to the difference in dosage and duration.

Question 5: Does the Agency agree with the proposed change to the amoxicillin breakpoint?

FDA Response to Question 5 : Currently, the FDA does not recognize amoxicillin breakpoints for *H. pylori*. However, the Agency recognizes that there are different resistance rates to amoxicillin in the literature and we understand that there may be a correlation between an amoxicillin MIC of >0.125 mcg/mL and treatment outcome. However, the differences in the in vitro susceptibility methods in determining *H. pylori* MICs may be a contributing factor in determining the prevalence of amoxicillin

resistance in *H. pylori*. Therefore, the impact of amoxicillin MIC in the context *H. pylori* treatment will be assessed during the NDA review.

Question 6: Does the Agency agree with the plan to not submit datasets to the ECG Warehouse?

FDA Response to Question 6: We encourage you to submit ECG data to the ECG Warehouse regardless of the study outcome. Additionally, we have the following comments for you to consider when preparing your submission:

1) We recommend using predose (e.g., 0 hours) data in each study period as the baseline for QTc assessment. The current baseline based on Day -1 for all 4 periods is not appropriate to derive the proper placebo adjusted and baseline adjusted ΔΔQTc as the same baseline will be cancelled out for the same subject. You should use the pre-dose baseline for each period in your derivations of ΔQTc, ΔΔQTc and as a baseline covariate in your analyses, where appropriate.
2) We recommend you perform appropriate multiplicity adjustment (e.g., Bonferroni) in the assay sensitivity assessment.
3) When you submit your QT evaluation report, please include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinaryreview-team-cardiac-safety-studies-formerly-qt-irt).
4) For each study included in your QT evaluation report, submit the related digital ECGs with annotations in electronic format (XML) following the HL7 annotated ECG (aECG) standard to the ECG warehouse (www.ecgwarehouse.com). Scan paper ECGs into PDF and submit to FDA only if digital ones are not available.
5) FDA is currently testing our capability to receive aECG HL7 files directly through the FDA electronic submission gateway. If you would like to volunteer to test this capability, you are welcome to perform an additional submission of the aECG HL7 files directly through FDA electronic submission gateway. We recommend placing the aECG file in an aecg folder under the misc folder (e.g., m5 -> datasets -> [study-id] -> misc -> aecg).

Question 7: Does the Agency agree with this approach for translations of the CSR appendices?

FDA Response to Question 7: The body of the clinical study report body for Study CCT-401 should be in English. The approach for translations of the CSR appendices is acceptable.

The documents with English translation should be complete, accurate, and include the name, address, and a brief statement of the qualifications of the person making the translation. Translation of literature or other material in a foreign language is to be accompanied by copies of the original publication.

Question 8: Does the Agency agree with not translating these fields in the Subject Data Listings or datasets?

FDA Response to Question 8: We do not agree. We recommend that you translate the Site Name/Department Name in English to facilitate inspections if needed.

During our safety review, we will be reviewing the details of certain individual cases to determine whether the event was coded to the correct preferred term. The assessment of causality for specific adverse events depends on comparisons of event rates between treatment groups, and the numerator of these rate calculations includes events coded to the same preferred term. If an investigator used a verbatim term incorrectly when recording the event in the case report form, or there was incorrect coding to the preferred term, the rate calculations may be erroneous. Therefore, we recommend that you submit English translations of the verbatim terms and populate the datasets. Please submit the coding dictionary and version used for mapping investigator verbatim terms to preferred terms for each Phase 2 and 3 clinical study supporting your application.

Provide case narratives and case report forms for patients with adverse events of special interest. Provide a table with eCTD links (or dataset) that contains a list of all subjects for whom you submit a narrative or CRF. Provide the location of this table, and relevant hyperlink, in the Reviewer's Guide.

In your NDA, submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population. Provide the location of this statement, and relevant hyperlink, in the Reviewer's Guide.

Question 9: Does the Agency agree that the two bioequivalence studies undertaken in Japan (Study TAK-438ASA-1001; Study TAK-438 ODT-1001) as well as Study Vonoprazan-4006 can be excluded?

FDA Response to Question 9: We agree.

Question 10: Does the Agency agree with the sponsor's approach for references?

FDA Response to Question 10: We agree.

Question 11: Phathom proposes to submit Module 2.7.4 SCS in lieu of the Integrated Summary of Safety required per 21 CFR 314.50 (d)(5)(vi). Does the Agency agree with the proposal and planned analysis, including the pooling strategy?

FDA Response to Question 11: It is acceptable to submit Module 2.7.4 SCS in lieu of the Integrated Summary of Safety.

It is important to get an accurate incidence rate of adverse events, therefore we recommend that you not pool studies that enrolled subjects with *H. pylori* infection who were treated with eradication therapy with vonoprazan or lansoprazole in combination with antibacterial drugs, unless they were of similar design, that is, similar in dose, duration, choice of control, methods of ascertainment, and population. It is reasonable to pool studies with short term (8 weeks) treatment with vonoprazan, lansoprazole or esomeprazole or placebo and have a separate pool of studies in other indications with long-term treatment with vonoprazan or lansoprazole. It is also possible that different populations may have different vulnerabilities to a drug, and therefore, different risk profiles, therefore provide analysis for exposure duration and assess for time-dependent events.

Question 12: The case report forms from the Takeda studies conducted in Japan will require translation. Therefore, does the Agency agree with this approach to limit the number of case report forms and narratives to those from the *H pylori* studies?

FDA Response to Question 12: We do not agree. 21 CFR 314.50(f)(2) requires that CRFs be submitted for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not.

In addition, provide narrative for all deaths (all studies) and narratives for the SAEs for studies Hp-301 and CCT-401.

Provide a sample of the Council for International Organizations of Medical Sciences (CIOMS) form for SAEs from study TAK-438/CCT-401.

The above information will be needed for the safety review of the NDA.

Question 13: Does the Agency agree with the plan for the 120-day safety update report?

FDA Response to Question 13: We agree.

Question 14: Does the Agency agree that these AESI are adequate and appropriate for inclusion?

FDA Response to Question 14: Consider including QT prolongation as an AESI, since clarithromycin is associated with prolongation of the QT interval and infrequent cases of arrhythmia. Also, add hypersensitivity to the list of AESI.

Question 15: Does the Agency agree with Phathom's approach for submitting the CDISC datasets?

FDA Response to Question 15: Your plan sounds reasonable but further comments will be provided upon review of the datasets. We recommend that you provide a random sample of the datasets so we can provide feedback.

Question 16: Does the Agency agree with the plan for data listing and for dataset submission for the BIMO inspections?

FDA Response to Question 16: We agree. 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 https://www.fda.gov/media/85061/download for structure and format of the submission.

Question 17: Does the Agency agree to the proposed plan for handling data due to the COVID-19 pandemic?

FDA Response to Question 17: We recommend against excluding subjects without test-of-cure data due to COVID-19. These patients should be considered as treatment failures in the primary efficacy analysis. Other missing data imputation methods can be considered in the sensitivity analyses. Late IBT results due to COVID-19 are acceptable.

Question 18: Does the Agency agree that a regional participation cap is no longer necessary?

FDA Response to Question 18: We agree that a regional participation cap is no longer necessary.

Question 19: Does the Agency agree a routine post-marketing pharmacovigilance strategy for vonoprazan is appropriate?

FDA Response to Question 19: It is reasonable based on the information you have provided in the briefing package; however, the determination of postmarketing pharmacovigilance strategy will depend on the safety signals identified during the NDA review.

Question 20: Does the Agency agree to Phathom's approach for labeling short-term and long-term safety information?

FDA Response to Question 20: We agree.

Question 21: Does the Agency agree to align the convenience pack labeling to the reference AMOXIL® and BIAXIN® labels (and where applicable to the OMECLAMOX-PAK®, TALICA® labels and/or Sandoz labels)?

FDA Response to Question 21: Yes, we agree that you can rely on FDA's findings of safety and effectiveness for AMOXIL and BIAXIN as reflected in the approved labeling for the products, consistent with your proposal to submit your convenience pack NDAs under the 505(b)(2) pathway (see also the response to Question 23 below).

We do not agree that you should align your proposed labeling with any other listed drug, such as OMECLAMOX-PAK or TALICIA, unless you identify such drugs as relied-upon listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54 and meet all regulatory requirements for a 505(b)(2) application with respect to them.

Question 22: Does the Agency agree with the proposal for submitting Financial Disclosure Certification?

FDA Response to Question 22: Since CCT-401 is a covered study, you are required to submit the financial disclosure certifications. However, if you are unable to obtain this information from the investigator, you must submit documentation of your efforts to obtain this information with due diligence from the investigator and certification that you have acted with due diligence to obtain the information but were unable to do so and stating the reason(s).

Question 23: Does the Agency agree the convenience pack NDAs can be filed under section 505(b)(2)?

FDA Response to Question 23: In general, we agree with your proposal to submit NDAs for the two convenience packs (vonoprazan and amoxicillin; vonoprazan, amoxicillin, and clarithromycin) under the 505(b)(2) pathway. The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on NDA 050459 (AMOXIL) for the NDA for vonoprazan and amoxicillin and both NDA 050459 (AMOXIL) and NDA 050662 (BIAXIN) for the NDA for vonoprazan, amoxicillin, and clarithromycin generally appears acceptable.

We remind you that 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. Absence of a bridge between a proposed drug product and the reference drug product to demonstrate that reliance is scientifically justified may be a refuse to file issue for a 505(b)(2) NDA (see CDER's Manual of Policies and Procedures 6025.4, Good Review Practice: Refuse to File).

We note that both AMOXIL and BIAXIN are discontinued from marketing. If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) and intend to support the scientific appropriateness of reliance through a comparative bioavailability study, it is recommended you use the ANDA product designated as the reference standard in the Orange Book to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

So that we can provide feedback on your proposed bridge to each relied upon listed drug prior to NDA submission, we strongly recommend that you clarify the source of amoxicillin and/or clarithromycin drug product for each convenience pack NDA. You should also explain your proposed bridge between each of those drugs products and the relied-upon listed drugs you have identified for each proposed NDA.

Please see additional information regarding 505(b)(2) applications below under **ADDITIONAL APPLICATION INFORMATION**.

Question 24: Does the Agency agree with this approach for the convenience pack NDAs?

FDA Response to Question 24: We agree with your approach to submission of the convenience pack NDAs.

Question 25: Does the Agency agree with the proposed user fee payments?

FDA Response to Question 25: For information regarding user fee payments please contact the FDA User Fee Office at 301-796-1203 or userfees@fda,gov.

Question 26: Should Phathom proceed to submit requests for a QIDP designation for each of these potential NDAs? If yes, Phathom proposes to file a letter cross-referencing the prior justification submitted in June 2019. Will this be acceptable?

FDA Response to Question 26: (b) (4) For purposes of the QIDP comments, these are specific to NDA 215152 (convenience package vonoprazan/amoxicillin/clarithromycin) and NDA 215153 (convenience package vonoprazan/amoxicillin).

(b) (4)

(b) (4)

You should proceed to submit new requests for QIDP to the respective INDs 143190 and 144399 to reflect the final proposed dosage form(s) for each NDA. These submissions should identify the package configuration, dosage form for all products to be included in the convenience package and the proposed indication.

Question 27: Does the Agency agree with Phathom's understanding of how to apply the Fast Track Designation and Priority Review?

FDA Response to Question 27: If submitted at the same time, priority review would apply to the applications designated as QIDP. If an application does not have QIDP designation, the application will have to meet the standards for priority review outside of QIDP.

(b) (4)

Question 28: Does the Agency agree with the rolling review submission strategy?

FDA Response to Question 28: (b) (4) A product must be designated as Fast Track (or Breakthrough) in order to be eligible for rolling review. Please see FDA Response to Question 27.

Question 29: (b) (4)

(b) (4)

Question 30: Does the Agency agree that the agreed iPSPs apply to (b) (4) NDAs?

FDA Response to Question 30: We have reviewed our records and it does not appear that you have an agreed to iPSP for (b) (4) for the treatment of *H. pylori*. An agreed to iPSP is required prior to submission of an NDA. See **PREA REQUIREMENTS** below under **ADDITIONAL APPLICATION INFORMATION**.

Question 31: (b) (4)

ADDITIONAL COMMENTS

Clinical Pharmacology

1. In previous communications, we have noted the need for further characterization of the time-dependent inhibition of vonoprazan against CYP2B6 and CYP2C19. If your proposed study VONO-101 demonstrates a significant inhibition effect of vonoprazan on the metabolism of midazolam, we recommend that you further evaluate the inhibition effect of vonoprazan on CYP2B6 and CYP2C19.
2. In your NDA submission, clarify the formulation of vonoprazan used in each study and whether the studied formulation is the final to-be-marketed formulation.
3. We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers

through the use of text attributes, tables, and figures as outlined in the above guidance.

4. We recommend you submit all pharmacokinetic (PK) and/or pharmacodynamic (PD) bioanalytical method validation reports and bioanalytical study reports for PK and/or PD assessments used in clinical studies. In addition, we recommend you submit tables summarizing the bioanalytical methods and the life-cycle information using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document (https://go.usa.gov/xVsdJ) and submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

Clinical

Please submit investigator qualifications in English and a copy of the approved foreign labeling in English.

3.0 ADDITIONAL APPLICATION INFORMATION

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).[1] 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 interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[2]

If you intend to submit a 505(b)(2) application that relies for approval 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 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. by trade name(s)).

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] http://www.regulations.gov

If you intend to rely 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*

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.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 16, 2020 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of

any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[3]

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-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP 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.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.

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

[3] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

Information and Pregnancy and Lactation Labeling Final Rule 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design

differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in

eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[4]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

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.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

[4] http://www.fda.gov/ectd
[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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