

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217186Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 217186

MEETING MINUTES

Impax Laboratories, LLC
Attention: Candis Edwards
Senior Vice President, Specialty Regulatory Affairs
400 Crossing Blvd. Third Floor
Bridgewater NJ 08807

Dear Candis Edwards:¹

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IPX203 (carbidopa and levodopa) extended release capsules 35/140 mg, 52.5/210 mg, 70/280 mg, and 87.5/350 mg.

We also refer to the video conference between representatives of your firm and the FDA on October 4, 2023. The purpose of the meeting was to discuss your June 30, 2023, complete response letter.

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

If you have any questions, please contact Stacy Metz, PharmD, Senior Regulatory Project Manager, at stacy.metz@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laura Jawidzik, MD
Deputy Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹We 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>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: October 4, 2023; 3:00 – 4:00 PM EST
Meeting Location: Videoconference (Zoom)

Application Number: NDA 217186
Product Name: IPX203 (carbidopa/levodopa) extended-release capsules
35/140 mg, 52.5/210 mg, 70/280 mg, and 87.5/350 mg

Indication: Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication

Sponsor Name: Impax Laboratories, LLC
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Emily Freilich, MD
Meeting Recorder: Stacy Metz, PharmD

FDA ATTENDEES

Teresa Buracchio, MD, Director, Office of Neuroscience
Emily Freilich, MD, Director, Division of Neurology 1 (DN1)
Laura Jawidzik, MD, Deputy Director, DN1
Natalie Getzoff, MD, Clinical Team Lead, DN1
Elizabeth Haberfeld, MD, Clinical Reviewer, DN1
Gerald (Dave) Podskalny, DO, MPHS, Clinical Reviewer, DN1
Bilal AbuAsal, PhD, Clinical Pharmacology Team Lead
Yifei Zhang, PhD, Clinical Pharmacology Reviewer
Ramakrishna Samala, PhD, Clinical Pharmacology Reviewer
Eliford Kitabi, QT-IRT
Stacy Metz, PharmD, Senior RPM, DN1

SPONSOR ATTENDEES

Impax Laboratories, LLC

Chintu Patel, Co-CEO, Amneal Pharmaceuticals Inc. (owner of Impax Laboratories, LLC)
Richard D'Souza, PhD, Senior VP, Specialty Pharmaceuticals R & D
Candis Edwards, MS, Senior VP, Specialty Regulatory Affairs and Pharmacovigilance

Hester Visser, MD, PhD, VP, Clinical Development
Stanley Fischer, MD, VP, Medical Affairs
Payal Bhaiya, Senior Director, Project Management
Yvette Wang, Regulatory Affairs Associate III, Specialty Regulatory Affairs

Consultants

(b) (4)

1.0 BACKGROUND

Impax Laboratories, LLC (Impax) has developed IPX203 (carbidopa and levodopa) extended-release capsules, 35 mg/140 mg, 52.5 mg/210mg, 70 mg/280 mg and 87.5 mg/350 mg for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Impax submitted its new drug application NDA 217186 on August 31, 2022, and received a complete response letter on June 30, 2023. Impax has requested this Type A meeting to discuss steps needed to address the deficiencies listed in that complete response letter (CRL).

FDA sent Preliminary Comments to Impax Laboratories, LLC on October 2, 2023.

2.0 DISCUSSION

Question 1:

In its June 30, 2023, CRL, the Agency stated that in the absence of an adequate scientific bridge to Sinemet or Rytary for the safety of the carbidopa component of Crexont, Impax will need to provide long-term safety data from 100 patients with continuous exposure to Crexont for at least 12 months, with a substantial proportion of patients using the highest dose intended for labeling, based on modal dose, to support the safety of Crexont. The Agency also stated, "Your NDA submission contains data for only 67 subjects with 12-month exposure to Crexont at any dose by modal dose..." With respect to the number of subjects, Impax believes that it misinterpreted the Agency's comments related to modal dose calculations in the Agency's March 13, 2023, Information Request discussed in Section 6. Impax has reanalyzed the long-term safety data as presented in Table 1 in Section 10.1, consistent with the Agency's request. The reanalysis presented in Table 1 confirms that 179 patients were exposed to IPX203 for at least 12 months.

Does the Agency agree that the reanalysis of Impax's long-term safety data satisfies the Agency's requirement for long-term safety data from 100 patients with continuous exposure to IPX203 for at least 12 months based on modal dose, to support the safety of IPX203?

FDA Response to Question 1:

We agree that, based on the summary information provided in the meeting package, at least 100 subjects appear to have been exposed to IPX203 at any dose for a minimum of 12 months. You will need to provide justification for the re-calculation of the long-term exposure data in a resubmission. A final determination regarding the adequacy of your long-term exposure data will be a matter of review of at the time of resubmission.

Sponsor's October 3, 2023, Pre-meeting Response (Slide 3)

*The Agency commented that it agrees, based on **summary information** provided in the meeting briefing package, that the reanalysis of Impax's long-term safety data satisfies its requirement for 100 patients with continuous exposure to IPX203 for at least 12 months based on modal dose, to support the safety of IPX203. In addition to the summary information provided in the meeting briefing package, Impax intends to include an additional table detailing the modal dose of each individual subject exposed for at least 12 months in its resubmission.*

Additionally, the resubmission will include the justification for the re-calculation of the long-term exposure data that was presented in the meeting briefing package.

- a) Does the Agency agree that this will be sufficient for a final determination regarding the adequacy of Impax's exposure data?**
- b) If this is not sufficient, does the Agency require Impax to include in its resubmission a re-analysis, based on modal dose, of any of the information provided in the ISS presented in the original NDA?**

Meeting Discussion (Slide 3)

The Agency agreed that the sponsor's approach appears acceptable. On face, the summary data in Section 10.1 of the briefing package suggests there are at least 100 patients with continuous exposure for at least 12 months. However, the adequacy of the data will be a matter of review. In the resubmission, the sponsor should include an explanation of any differences between the 12-month exposure data that were in the original NDA (July 2022), the April 2023 response to the Agency's Information Request (IR), and the briefing package.

Reanalysis of all of the data in the original Integrated Summary of Safety (ISS), such as adverse events, laboratory findings, and vital signs is not needed.

Question 2a:

In the June 30, 2023, CRL, the Agency stated that Impax will need to provide long-term safety data "...with a substantial proportion of patients using the highest dose intended for labeling based on modal dose to support the safety of Crexont." Impax notes that CD/LD treatment in PD is very individualized, and subjects take a wide range of doses based on their clinical needs. For example, Table 1 in Section 10.1 indicates that

patients who were exposed for at least 12 months took 24 different modal doses during treatment to achieve their clinical response. As discussed in Section 10.2, it would be highly unlikely in a clinical study with CD/LD to have a substantial proportion of patients taking the highest dose intended for labeling, which is 2400 mg LD. Impax proposes utilizing the highest modal dose range, rather than the highest dose, to assess the safety of IPX203. Using this approach, Impax believes that the data from the 45 patients exposed at the highest modal dose range represents a substantial proportion of patients to support the long-term safety of IPX203.

Does the Agency agree with Impax’s proposal to utilize the highest modal dose range instead of “...the highest dose intended for labeling...” to provide long-term safety data for IPX203 from a substantial proportion of patients?

FDA Response to Question 2a:

Your approach to use a modal dose range appears reasonable to support the long-term safety of the carbidopa component of IPX203 in the absence of an adequate scientific bridge to the referenced products. However, whether this approach supports labeling for the maximum dose you have proposed (b) (4) would be a matter of review. We recommend that in a resubmission, you include a discussion of how the reanalysis altered the calculation of modal doses, any differences between the exposures in the resubmission and exposures based on the revised datasets submitted to the NDA on April 3, 2023, and any impact these recalculations may have on efficacy. The adequacy of the revised exposure data will be a matter of review.

Sponsor’s October 3, 2023, Pre-meeting Response (Slide 4)

The Agency recommended that Impax’s resubmission include a discussion on how the reanalysis altered the calculation of modal doses. Impax interprets the Agency’s use of the term “reanalysis” to refer to its calculation of the highest modal dose range.

- a) *Does the Agency agree with Impax’s interpretation of the term “reanalysis”?*
- b) *Since the calculation of highest modal dose range was based on modal doses, Impax would like clarification from the Agency regarding its comment asking how the reanalysis altered the calculation of modal doses.*

Meeting Discussion (Slide 4):

The Agency stated that the term “reanalysis” refers to the differences between the data submitted in the April 2023 IR response (e.g., 67 subjects with 12-month exposure by modal daily dose) and the data in Table 1 of the meeting package (179 subjects with 12-month exposure to IPX203), in particular for the proposed maximum dose. The sponsor agreed to provide clarification of the differences.

The Agency noted that using the dose strengths proposed for marketing, it is not possible to achieve the proposed maximum daily dose of IPX203 proposed in the labeling (b) (4). The Agency recommended that the sponsor revise the label to include a dose that is achievable, such as (b) (4) levodopa.

Sponsor's October 3, 2023, Pre-meeting Response (Slide 5)

The Agency recommended that Impax's resubmission include a discussion on "... any impact these recalculations may have on efficacy." The reanalysis presented in the meeting briefing package consisted of IPX203 exposure for at least 12 months, based on modal dose, to ensure an adequate number of patients for safety evaluation. However, efficacy was based on Study IPX203-B16-02 where IPX203 was compared with IR CD/LD during a 13-week double blind period.

Can the Agency please clarify its comment regarding "impact on efficacy"?

Meeting Discussion (Slide 5):

The Agency stated that whether there are sufficient long-term safety data to support the proposed maximum daily dose of (b) (4) will be a matter of review. The Agency also explained that based on the determination of the highest dose for which there are adequate safety data, the Agency may perform sensitivity analyses on the primary efficacy endpoint in support of lower doses.

Question 2b:

Does the Agency agree that the 45 patients exposed to IPX203 at the highest modal dose range satisfies the Agency's requirement for long-term safety data in a substantial proportion of patients?

FDA Response to Question 2b:

See the response to Question 2a.

Sponsor's October 3, 2023, Pre-meeting Response

See 2a discussion.

Meeting Discussion:

See discussion of Question 2a.

Question 3:

As discussed in Section 10.3, CD has a long history of use without documented cardiac toxicity. Based on the numerous studies demonstrating the tolerability and lack of QTc prolongation of single doses of CD up to 225 mg, total daily doses of greater than 600 mg (up to 1260 mg) daily in Impax's Phase 3 trials, and 600 mg daily reported in the literature, Impax believes that there is no risk of QTc prolongation associated with the proposed maximum dose of CD in IPX203. In addition, Impax believes it has provided long-term safety data from an adequate number of patients in its Phase 3 clinical trials to establish a scientific bridge to the listed drug.

Based on Impax's Phase 2 and Phase 3 QTc data, and published literature, Impax believes that there is no risk of QTc prolongation associated with the proposed

maximum dose of CD in IPX203. Additionally, Impax believes it has provided long-term safety data from an adequate number of patients in its Phase 3 clinical trials to establish a scientific bridge to the listed drug. Does the Agency agree?

FDA Response to Question 3:

No, we do not agree. Per ICH E14 section 1.3, you will need to conduct a thorough QT study to adequately assess the QT effects of IPX203 because the new formulation results in significantly higher carbidopa exposure (i.e., C_{max} and AUC) compared to the referenced drugs. Routine QT assessment conducted in Phase 2 and 3 studies is not sufficient to characterize the QTc effects of IPX203. The results of the thorough QT study should be included in a future resubmission.

Sponsor's October 3, 2023, Pre-meeting Response (Slide 6, 7, 8 and 9)

Impax agrees to conduct a TQT study. Impax proposes

(b) (4)

(b) (4)

Does the Agency agree with this proposal?

Meeting Discussion (Slide 6, 7, 8 and 9):

- The Agency did not agree with the sponsor's proposal

(b) (4)

(b) (4)

because there

are similar drugs already approved for the same indication. The Agency also noted that it is not practical (b) (4)

- The Agency recommended that the sponsor provide a comparison of exposures (i.e., simulated steady state C_{max} of the maximum recommended doses of IPX203 under both fed and fasting conditions versus that observed at the maximum recommended dose for Sinemet) as a context to the design of the TQT study.
- The sponsor inquired whether repeating Study B16-05 to demonstrate that IPX203 is bioequivalent to Sinemet would satisfy the bridging requirements. The Agency noted that repeating this study will be unlikely to result in different results. The Agency further clarified that the PK comparison to establish the bridge should be done by comparing the exposure of the highest proposed dosing regimen with highest approved dosing regimen at steady state.

Sponsor's October 3, 2023, Pre-meeting Response (Slide 10):

Impax acknowledges the Agency's comment and agrees to conduct a TQT study. Impax seeks Agency guidance on the following aspects with regards to the conduct of the TQT study:

Impax proposes conducting a 2-part study. The first part will be a lead-in study to evaluate the tolerability and PK of carbidopa doses greater than 200 mg. The results of the first part will inform the selection of the suprathreshold dose to be used in the second part of the study, the formal QT study.

Impax proposes to perform a 3-sequence single dose cross over study to assess the effects of a suprathreshold dose of IPX203 on cardiac repolarization and other ECG parameters. The three treatment sequences will be:

- Placebo
- Moxifloxacin 400mg PO as a positive control
- Suprathreshold dose of CD as determined in Part 1 of the study

a) *Does the Agency agree that the study can be conducted on CD alone without the inclusion of LD?*

b) *Does the Agency agree with Impax's study approach?*

Meeting Discussion (Slide 10):

The Agency stated that, on face, the proposal to conduct a TQT study with carbidopa alone is reasonable. The Agency recommended that the sponsor submit a full TQT study protocol to the IND. The protocol should include the study design, a statistical plan, and the rationale and justification for conducting the study with CD alone. The sponsor was advised that the review by the QT-IRT would take a minimum of 2 to 3 weeks.

3.0 OTHER IMPORTANT MEETING INFORMATION

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 guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.² 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.³

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).⁴ 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).⁵

² <https://www.fda.gov/media/86340/download>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ 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>.

⁵ <http://www.regulations.gov>

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)).

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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

Action Item/Description	Owner	Date
Sponsor to provide protocol for QT-IRT review.	Sponsor	Submission Received October 18, 2023

6.0 ATTACHMENTS AND HANDOUTS

On October 3, 2023, the sponsor provided a response document (slides). Those responses have been incorporated within these minutes and are also attached at the end of this document.

10 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK
11/03/2023 03:09:51 PM



IND 122793

MEETING MINUTES

Impax Laboratories, LLC
Attention: Pamela Fitzpatrick, MS
Director, Specialty Regulatory Affairs
50 Horseblock Road
Brookhaven, NY 11719

Dear Ms. Fitzpatrick:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IPX203 (carbidopa-levodopa extended-release capsules).

We also refer to the telecon between representatives of your firm and the FDA on March 8, 2022. The purpose of the meeting was to obtain feedback on your proposed NDA submission for IPX203.

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

If you have any questions, please contact Stacy Metz, PharmD, Senior Regulatory Project Manager, at stacy.metz@fda.hhs.gov.

Sincerely,
{See appended electronic signature page}

Teresa Buracchio, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹We 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>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: March 8, 2022; 2:00 - 3:00 PM EST
Meeting Location: Teleconference

Application Number: IND 122793
Product Name: IPX203 (carbidopa-levodopa extended-release capsules)

Indication: Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Sponsor Name: Impax Laboratories, LLC
Regulatory Pathway: 505(b)(2)

Meeting Chair: Teresa Buracchio, MD, Director Division of Neurology 1
Meeting Recorder: Stacy Metz, PharmD, Senior RPM

FDA ATTENDEES

Teresa Buracchio, MD, Director
Laura Jawidzik, MD, Deputy Director (Acting)
Sally Yasuda, MS, PharmD, Safety Team Lead
Tracy Peters, PharmD, Associate Director for Labeling
Natalie Getzoff, MD, Clinical Team Lead
Kenneth Bergmann, MD, Clinical Reviewer
Ami Mankodi, MD, Clinical Reviewer
Bilal AbuAsal, PhD, Clinical Pharmacology Team Lead
Poonam Delvadia, PhD, Clinical Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Lead
Sharon Yan, PhD, Statistical Reviewer
Luann Mckinney, DVM, Nonclinical Reviewer
Stacy Metz, PharmD, Senior RPM

SPONSOR ATTENDEES

Impax

Richard D'Souza, PhD, Senior VP, Specialty Pharmaceuticals R&D
Candis Edwards, MS, Senior VP, Regulatory Affairs and Pharmacovigilance
Hester Visser, MD, PhD, VP, Clinical Development
Anita Kumar, M Pharm, MS, VP, Pharmaceutical Research and Development

Pamela Fitzpatrick, MS, MBA, Director, Specialty Regulatory Affairs
Roshan Tiwari, PhD, Senior Manager Clinical Development, R&D Specialty Pharma
Arlin Frias-Medina, MS, Director, Regulatory Affairs Clinical

Consultants



1.0 BACKGROUND

Impax has entered phase 3 development and has included top line results for its pivotal efficacy study IPX203-B16-02, entitled “A Randomized Controlled Study to Compare the Safety and Efficacy of IPX203 with Immediate Release Carbidopa-Levodopa in Parkinson’s Disease Patients with Motor Fluctuations” in this meeting package. An open-label extension safety study, IPX203-B16-03, is currently ongoing.

Impax anticipates submitting its NDA for IPX203 in the second quarter of 2022. At this point in development, Impax is requesting a pre-NDA meeting to obtain feedback on the proposed IPX203 NDA submission.

FDA sent Preliminary Comments to Impax on March 4, 2022.

2.0 DISCUSSION

2.1. Regulatory NDA Questions

Question 1:

Impax proposes to submit an NDA for IPX203 (carbidopa-levodopa extended-release capsules) via the 505(b)(2) NDA pathway relying on the prior finding of safety and efficacy of carbidopa-levodopa products for Sinemet (NDA 017555), Sinemet CR (NDA 019856), and Rytary® NDA 203312 (carbidopa and levodopa extended-release capsules), which is owned by Impax in combination with the Phase 3 double-blind study (IPX203-B16-02) and open-label safety study (IPX203-B16-03) results demonstrating the safety and efficacy of IPX203 in patients with Parkinson’s disease.

Does the Agency agree that a 505(b)2 NDA pathway relying on NDA 017555, NDA 019856 and NDA 203312 as Listed Drug is acceptable?

FDA Response to Question 1:

A 505(b)(2) application would be an acceptable approach, at this time, based on the information provided. While the Agency typically does not advise a sponsor on the

selection of a particular listed drug or drugs that may be relied upon to support approval of a proposed product, your proposal to rely on Sinemet and Sinemet CR appears acceptable. Additionally, your proposal to reference information in your Rytary NDA is acceptable as well.

Meeting Discussion:

None.

Question 2:

As discussed in Section 10.2, most FDA approved CD/LD formulations have a broad indication which includes treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. Impax believes that the safety and efficacy of IPX203 in PD patients has been established and provides support for the following general indication in line with other FDA approved CD/LD products:

Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Does the Agency agree that the proposed indication is acceptable to be included in IPX203 Prescribing Information?

FDA Response to Question 2:

On face, the proposed indication appears reasonable; however, the final indication for IPX203 will be determined during review of the NDA application.

Meeting Discussion:

None.

Question 3:

A detailed description of the proposed Table of Contents (excluding Module 3 CMC) for the IPX203 NDA is provided in Section 10.3. Impax notes that the Module 3 Table of Contents was provided in the Pre- NDA CMC meeting briefing package (November 24, 2021, Seq 0234).

Does the Agency agree with Impax's proposed TOC for the IPX203 NDA (excluding Module 3 CMC)?

FDA Response to Question 3:

The NDA submission should follow technical specifications as presented in the eCTD Technical Conformance Guide to ensure that information is easily located within the electronic submission.² The Comprehensive Table of Contents Headings and Hierarchy

² <https://www.fda.gov/media/93818/download>

for the eCTD is available to guide you.³ Note that because this is a comprehensive listing, not all headings are necessarily applicable to all submissions.

Meeting Discussion:

None.

2.2. Nonclinical Questions

Question 4a:

Impax established a pharmacokinetic bridge to Rytary (carbidopa and levodopa) extended-release capsules, Sinemet (carbidopa and levodopa) Tablets and Sinemet CR (carbidopa levodopa) Sustained-Release Tablets as the Listed Drugs for IPX203's nonclinical safety data. Pharmacokinetic data from a comparative clinical pharmacokinetic study with IPX203 and the Listed Drugs and reliance on relative bioavailability revealed that the systemic exposure of levodopa and carbidopa from IPX203 was similar to the Listed Drugs. In addition, the results from Impax's clinical development program have shown that there were no new safety issues identified with IPX203 as compared to currently approved CD/LD drug products. Supporting information can be found in Section 10.4.

There were no new impurities above the threshold for identification based on the Maximum Daily Dose (MDD) of (b) (4) LD. All inactive ingredients comply with the FDA's IID (Inactive Ingredient Database) allowable limits. Impax notes that the MDD of (b) (4) LD was included in the IPX203-B16-02 study protocol which was subject to a Special Protocol Assessment (SPA) and agreed to on October 13, 2017.

Does the Agency agree that, in the absence of new safety issues identified with IPX203 as compared to currently approved CD/LD drug products, no further nonclinical studies are required?

FDA Response to Question 4a:

If an adequate bridge has been established to the intended listed drugs and there are no issues such as impurities or excipients, additional nonclinical studies should not be needed to support your NDA.

Meeting Discussion:

None.

Question 4b:

Can the Agency confirm that the proposed MDD of (b) (4) LD is acceptable?

³ <https://www.fda.gov/media/76444/download>

FDA Response to Question 4b:

The acceptability of the proposed MDD will depend on the adequacy of the pharmacokinetic (PK) bridging to the MDD of the highest approved daily dosing regimen for the reference product and the actual MDD tested in the pivotal clinical study.

Please see the responses to Questions 7a, 7b, and 9 below regarding the safety data needed to support your proposed doses.

Meeting Discussion:

None.

Question 5:

Impax proposes to rely on the Agency's previous findings of the safety and effectiveness of the carbidopa-levodopa products Sinemet (NDA 017555), Sinemet CR (NDA 019856) and Rytary (carbidopa and levodopa) extended-release capsules, (NDA 203312) as found in the FDA-approved product labeling. Impax proposes including any new relevant information in the IPX203 NDA. The NDA will not contain previously submitted information. Supporting information is provided in Section 10.5.

Does the Agency agree with Impax's proposal to only include new relevant non-clinical information and not to include previously submitted information in the NDA?

FDA Response to Question 5:

All supporting information should be submitted to the NDA.

Meeting Discussion:

None.

2.3. Clinical Pharmacology Questions

Question 6a:

In Study IPX203-B16-06, the dose proportionality was established for all 4 strengths of IPX203 for both carbidopa and levodopa for all primary pharmacokinetic parameters. Bioequivalence was also established for IPX203 35-140 mg manufactured at two different sites. Supporting information is provided in Section 10.6.

Does the Agency agree that the data from study IPX203-B16-06 supports the establishment of dose proportionality for all 4 strengths of IPX203?

FDA Response to Question 6a:

Your conclusion on dose proportionality of all four proposed strengths of IPX203 for both carbidopa and levodopa appears to be supported by the provided data in the briefing package. However, the adequacy of the IPX203-B16-06 study data will be matter of NDA review.

Meeting Discussion:

None.

Question 6b:

Does the Agency agree that the data from study IPX203-B16-06 establishes bioequivalence for IPX203 capsules manufactured at the two different sites?

FDA Response to Question 6b:

Your conclusion on establishment of bioequivalence of IPX203 manufactured at two sites for both carbidopa and levodopa appears to be supported by the data provided in the briefing package. However, the adequacy of the IPX203-B16-06 study to establish a PK bridge between the two sites will be matter of review.

Meeting Discussion:

None.

Question 7a:

The exposure of LD from IPX203 based on AUC relative to Rytary (Study IPX203-B14-02) and to Sinemet and Sinemet CR (Study IPX203-B16-05) was approximately 112%, 99% and 110%, respectively. The exposure to LD from IPX203 as measured by Cmax relative to Rytary, Sinemet and Sinemet CR was approximately 103%, 36% and 79%, respectively. The exposure of CD from IPX203 based on AUC relative to Rytary (Study IPX203-B14-02) and to Sinemet and Sinemet CR (Study IPX203-B16-05) was 196%, 123% and 157%, respectively. The exposure to CD from IPX203 as measured by Cmax relative to Rytary, Sinemet and Sinemet CR was approximately 237%, 120% and 156%, respectively. Supporting information is provided in Section 10.7.

Does the Agency agree that study IPX203-B14-02 and IPX203-B16-05 demonstrated a safety bridge between IPX203 and the Listed Drugs Rytary, Sinemet, and Sinemet CR, and that based on the results of this study Impax can rely on the Prescribing Information of the Listed Drugs?

FDA Response to Question 7a:

No, we do not agree. In order to rely on the FDA's finding of safety on the listed drug(s) to establish the safety of your product, the exposure of levodopa/carbidopa (Cmax and AUC) at the highest proposed regimen at steady state for the test product should be equal to or less than the exposure of the highest approved dosing regimen. Based on our analysis, exposures of carbidopa for proposed MDD of your product is expected to be higher than the exposure of carbidopa for the highest approved dosing regimen of the reference products. It is not clear to us how are you planning to justify the higher exposures of carbidopa of your product compared to reference product at the highest proposed regimen.

Please provide the distribution of dosing for patients in the completed pivotal and ongoing extension studies for discussion at the meeting. Also, see response to Question 9.

Meeting Discussion:

See summary of meeting discussion of Question 7b below.

Question 7b:

Does the Agency agree that the data from study IPX203-B16-05 demonstrates comparable bioavailability of IPX203 relative to the Listed Drugs Sinemet and Sinemet CR?

FDA Response to Question 7b:

No, we do not agree. The dose-normalized AUC of the proposed and reference products appear comparable for levodopa when compared to Sinemet IR and is slightly higher when compared to Sinemet CR. However, carbidopa exposure and bioavailability seem to be much higher for your product when compared to listed drugs (Sinemet, Sinemet CR). See response to Questions 4b, 7a, and 9.

Meeting Discussion:

The Sponsor mentioned that relative bioavailability data for the proposed product comparing to listed drugs were based on dose normalization. The Agency clarified that the dose normalization should be done for the products based on their corresponding highest approved and proposed dose. The Agency commented that internal analysis of the exposure of carbidopa (C_{max} and AUC) at the highest dose of (b) (4) of the proposed drug product is higher than the exposure of carbidopa at the highest approved regimen of listed drugs. The Agency emphasized that to establish a bridge of the proposed drug product to the listed drugs(s), the exposure of levodopa/carbidopa (C_{max} and AUC) at the highest proposed regimen at steady state for the proposed drug product should be equal to or less than the exposure of the highest approved dosing regimen. The Agency recommended that the sponsor conduct a pharmacokinetic (PK) simulation to compare the exposure at the highest proposed regimen of the proposed drug product versus the highest approved dosing regimen of the listed product(s) they plan to use as a reference.

The sponsor also presented a comparison of exposure of the proposed product versus (b) (4) based on information available in summary basis of approval (SBOA), labeling, and literature. The sponsor proposed referencing (b) (4) as a listed drug in addition to Sinemet IR. The Agency recommended that if (b) (4) will be used as a listed drug, a study would need to be conducted to establish the bridge. The Agency also advised the sponsor to conduct a simulation to confirm that (b) (4) is the most appropriate reference product to establish the bridge.

The Sponsor further asked, if a PK bridge is not possible, could the proposed highest dose of carbidopa ((b) (4)) be supported by clinical safety data. The Agency

recommended that the exposure for chronic use in patients with Parkinson's disease should include a minimum number of 100 patients treated for one year with at least 50% of patients using the highest dose intended for labeling. The Agency stated that based on the information provided, it was unclear if the number of patients receiving the highest dose of carbidopa ((b) (4)) met the recommended exposures for a safety database and requested that the sponsor provide updated information on distribution of patients by carbidopa dose and duration of exposure in the completed Phase 3 trial and ongoing open-label extension study. The Agency further stated that it would be willing to review the updated information and provide advice on the Sponsor's proposal to rely on clinical safety data to establish a bridge.

The Sponsor also asked if, in the absence of a PK bridge, there is a nonclinical approach to provide a safety bridge to the listed drugs. The Agency responded that the team would discuss and respond back to the sponsor.

Impax Post Meeting Note:

On March 14, 2022, the sponsor provided an updated table of CD dose level and length of exposure from Studies IPX203-B16-02 and IPX203-B16-03 for the Agency's review. This table showed that 169 patients were exposed to IPX203 for at least 12 months with 76 patients exposed at the highest dosage range of CD (>400 mg).

Subsequent to the FDA teleconference, Impax internally discussed a proposal to reduce the maximum recommended daily dose (MRDD) of IPX203 to (b) (4) CD/LD in order to further assure the safety of its proposed drug product and to improve the risk/benefit assessment. Impax requests that the Agency consider the proposal to potentially reduce the MRDD of CD. Impax considers that the human clinical safety data, with a reduced MRDD of CD will establish an adequate safety bridge.

Impax requests that the Agency provide its comments on this proposal in the final meeting minutes.

FDA Post Meeting Response

The Agency acknowledges the sponsor's updated CD exposure data and we note that the exposure of (b) (4) of CD in IPX203 will likely still be greater than the exposure of CD at the highest approved regimen of listed drugs. The adequacy of the safety data from 76 patients who received 400 mg or greater of IPX203 for at least 1 year to support safety will be a matter of review.

The adequacy of the reduced dose to support efficacy will also be a review issue.

Regarding the ability of nonclinical data to provide a bridge for safety to listed drugs, nonclinical studies cannot be used as a substitute for adequate clinical safety data.

Question 8a:

Impax conducted study IPX203-B16-04 “Effect of food on the pharmacokinetics of IPX203” to assess the effect of a standardized high-fat meal on the pharmacokinetics of IPX203 and to characterize the pharmacokinetics of IPX203 after sprinkling the capsule contents on applesauce as a representative soft food. Supporting information is provided in Section 10.8. Based on the results of this study, Impax proposes recommend dosing with or without food condition in the Dosing and Administration section of the IPX203 Prescribing Information.

Does the Agency agree that the data from study IPX203-B16-04 demonstrates the effect of a standardized high-fat, high-calorie meal on the pharmacokinetics of IPX203?

FDA Response to Question 8a:

Based on information provided in the briefing package, Study IPX203-B16-04 appears to characterize the PK of IPX203 in the presence of high fat, high-calorie meal. However, the adequacy of the food effect study will be a matter of NDA review. Note that if the final to-be-marketed formulation is different from clinical trial formulation evaluated in pivotal registration trial, you should discuss with the Agency the potential need for additional PK bridging and food effect study(ies).

Meeting Discussion:

None.

Question 8b:

Does the Agency agree that the data from study IPX203-B16-04 characterizes the pharmacokinetics of IPX203 after sprinkling the capsule contents on applesauce?

FDA Response to Question 8b:

Based on information provided in the briefing package, Study IPX203-B16-04 appears to characterize the PK of IPX203 after sprinkling the capsule contents on applesauce. However, the adequacy of the study will be a matter of review.

Meeting Discussion:

None.

Question 8c:

Does the Agency agree with the dosing recommendation of with or without food in the IPX203 Prescribing Information?

FDA Response to Question 8c:

The dosing recommendation with regards to food is a matter of review and may also rely on the dosing instructions with regards to food in the pivotal registration trial.

Meeting Discussion:

None.

2.4. Clinical Question

Question 9:

As noted in the February 27, 2017 End of Phase 2 Meeting Minutes, Impax's agreed upon development plan for IPX203 included the following Phase 3 studies:

- Efficacy double blind clinical Phase 3 study in PD patients with motor fluctuations (IPX203-B16-02)
- Open-label extension Phase 3 study (IPX203-B16-03) in PD patients with motor fluctuations

Impax has received top line results for the IPX203-B16-02 study which met its primary endpoint. The Open-label extension study IPX203-B16-03 is currently ongoing. Supporting information is provided in Section 10.9.

Does that Agency agree that the clinical study data from the IPX203-B16-02 efficacy study in combination with the long- term safety exposure data (from study IPX203 B16-02 and IPX203 B16-03) is adequate to support the submission of Impax's 505(b)(2) NDA for IPX203 and that no additional data is required?

FDA Response to Question 9:

On face, it appears that Studies B16-02 and B16-03 may be adequate to support submission of your NDA. The adequacy of the data will be a matter of review at the time of the NDA submission. However, see prior concerns regarding safety outlined in the responses to Questions 7a and 7b.

In general, the minimum number of exposures required for evaluation of a drug intended for chronic use is 100 patients treated for one year with at least 50% of patients using the highest dose intended for labeling. Please note that the number of subjects is just one aspect of the necessary safety evaluation of IPX203, especially in the setting of higher carbidopa exposures with IPX203 than with the reference product.

You should submit all data for the entire safety population (i.e., all persons receiving at least one dose of IPX203 in the development program) using the November 30, 2021, cut-off date. (The cut-off date should be adjusted as needed so that the submitted data is current up to a date approximately 6 months prior to the NDA submission.)

As stated in the October 12, 2021, Type C Guidance letter, your safety database must be complete at the time of NDA submission. The 120-day safety update should only add data from ongoing studies generated after the cut-off date for the initial NDA submission.

Please also refer to the additional advice given to you in the Type C Guidance letter dated October 12, 2021, regarding the presentation of the safety database in your application.

Meeting Discussion:

None.

3.0 OTHER IMPORTANT MEETING INFORMATION

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*.⁴ 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.⁵

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

⁴ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁵ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

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 Information⁶ and Pregnancy and Lactation Labeling Final Rule⁷ 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.

⁶ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁷ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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)				

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.⁸ and the guidance for industry, *Identification of Manufacturing Establishments in*

⁸ <https://www.fda.gov/media/84223/download>
 U.S. Food and Drug Administration
 Silver Spring, MD 20993
www.fda.gov

*Applications Submitted to CBER and CDER Questions and Answers*⁹. 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.

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).¹⁰ 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).¹¹

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)).

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.

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

¹⁰ 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>.

¹¹ <http://www.regulations.gov>

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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>

(3) Example: NDA YYYYYY "TRADENAME"	Previous finding of safety for Carcinogenicity, labeling section B
(4)	

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications 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 ORA investigators who conduct those inspections. 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 the submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

None.

6.0 ATTACHMENTS AND HANDOUTS

On March 7, 2022, the sponsor provided a response document (slides). During the March 8, 2022, telecon the sponsor informed FDA that those slides had been revised. The revised slides are attached at the end of this document.

18 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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04/08/2022 03:44:58 PM



IND 122793

MEETING MINUTES

Impax Laboratories, Inc.
Attention: Michelle Landolfi, PhD
Senior Director, Regulatory Affairs
31047 Genstar Road
Hayward, CA 94544

Dear Dr. Landolfi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IPX203 (levodopa and carbidopa)

We also refer to the meeting between representatives of your firm and the FDA on February 8, 2017. The purpose of the meeting was to discuss your Phase 3 development plan.

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 Jack Dan, RPh, Regulatory Project Manager at (240) 402-6940.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: February 8, 2017, 10:00am-11:00am
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: 122793
Product Name: IPX203 (levodopa and carbidopa)
Indication: Parkinson's disease
Sponsor/Applicant Name: Impax Laboratories, Inc.

Meeting Chair: Billy Dunn, MD
Meeting Recorder: Jack Dan, RPh

FDA ATTENDEES

Billy Dunn, MD, Director, Division of Neurology Products (DNP)
Eric Bastings, MD, Deputy Director, DNP
Gerald Podskalny, DO, MPHS Clinical Team Leader, DNP
Kenneth Bergmann, MD, Clinical Reviewer, DNP
Laura Jawidzik, MD, Clinical Reviewer, DNP
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader, DNP
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer, DNP
Luann Mckinney, DVM, Nonclinical Reviewer, DNP
Kun Jin, PhD, Biostatistics Team Leader, DNP
Junshan Qiu, PhD, Biostatistics Reviewer, DNP
Susan Daugherty, Regulatory Health Project Manager, DNP
Michelle Mathers, Regulatory Health Project Manager, DNP
Jack Dan, Regulatory Health Project Manager, DNP

SPONSOR ATTENDEES

Suneel Gupta, PhD, Chief Scientific Officer
Scott Bowersox, PhD, Senior Director, Toxicology
Aravind Mittur, PhD, Director, Clinical Pharmacology
Nishit B. Modi, PhD, Vice President, Clinical Pharmacology
Robert Rubens, MD, MBA, Senior Director, Clinical Development
Phillip Dinh, PhD, Director, Statistics
Sarita Khanna, PhD, Senior Director, Biostatistics
Michelle Landolfi, PhD, Senior Director, Regulatory Affairs

Itrat Harrold, PhD, Senior Associate, Regulatory Affairs

1.0 BACKGROUND

On October 22, 2014, Impax Laboratories, Inc., submitted an Investigational New Drug Application for IPX 203 (levodopa and carbidopa) for the treatment of Parkinson's disease.

Impax Laboratories, Inc. requested a Chemistry, Manufacturing and Controls (CMC) meeting on November 21, 2016.

The purpose of this meeting is to gain agreement on the Phase 3 development plan, and to obtain feedback on Phase 3 protocols. Impax Laboratories, Inc., also seeks agreement on whether the proposed nonclinical and clinical development programs are adequate to support an NDA for IPX203.

FDA sent Preliminary Comments to Impax Laboratories on February 3, 2017.

2.0 DISCUSSION

Pharmacology/Toxicology

Question 1: Does the Division agree that given the extensive nonclinical and clinical safety of CD and LD the approach outlined in [Section 7](#) is acceptable and that no additional nonclinical studies are necessary?

FDA Response to Question 1:

See response to Question 2.

Meeting Discussion:

None

Question 2: Does the Division agree that no nonclinical studies are required to qualify the excipients in the IPX203 formulation at the levels listed for the anticipated MDD?

FDA Response to Question 2:

Based on the information provided, the excipients and maximum levels of each in IPX203 appear acceptable. No additional nonclinical studies will be needed for IPX203 unless safety issues arise (e.g., impurities) that require nonclinical safety assessment.

Meeting Discussion:

None

Clinical Pharmacology and Biopharmaceutics

Question 3: Does Division concur that the studies outlined in [Section 8.1](#) represent an adequate biopharmaceutics and clinical pharmacology program for an NDA of IPX203?

FDA Response to Question 3:

On face, the proposed clinical pharmacology program seems adequate to begin review of the NDA; however, you will need to conduct an in-vitro alcohol dose dumping study for the extended release product.

Meeting Discussion:

FDA advised the applicant to submit the results of the in vitro alcohol dose dumping studies for the review.

Question 4: Impax believes that the single and multiple dose PK/pharmacodynamic data generated in PD patients are important to potential prescribing physicians for their understanding of the product characteristics and dosing. Does the Division agree

(b) (4) ?

FDA Response to Question 4:

It is premature to discuss labeling language at this stage. We recommend that you submit your rationale for the proposed labeling language in the NDA submission.

Please provide your justification for the dosing of the reference and the test drug product in the proposed phase 3 study (i.e., unit dose conversion between the immediate release and extended release products). It appears that the extended release product may have to be used up to 4 times a day, similar to the immediate release product. However, the extended release product has more than 3 fold higher unit dose of levodopa than the immediate release product. Please clarify.

Meeting Discussion:

The applicant proposed the use of individual unit dose conversion from IR CD LD to the extended release formulation for IPX203. According to the proposed dosing regimen, the total daily dose will be different for the two drug products. The dosing frequency can be different for patients in the same dosing cohort. The sponsor clarified that it is planning to use this design for dose conversion because the health care provider does not use total daily dose for dose conversion and prefers to use a single unit dose conversion. The sponsor also clarified that the OFF time symptoms can be better controlled if they ensure higher concentrations after dosing with a particular unit dose. The sponsor mentioned that it will provide the dosing frequency data after the end of the trial to compare the total daily dosing.

FDA noted that it would be difficult to convert patients on a unit dose basis because patients may take IR CD LD 6 times a day or more and only take IPX203 3-4 times a day. A simple one-to-one unit dose conversion may not adequately inform dose conversion. Many patients will need to change their daily dosing frequency during conversion from IR CD LD to IPX203. Information on how to change dosing frequency would not be addressed by unit dose conversion.

Question 5: Does the Division agree with the overall design, including the IR CD-LD dose adjustment (3 weeks) and IPX203 dose conversion (4 weeks) periods and the proposed 13-week double-blind maintenance phase?

FDA Response to Question 5:

The meeting package and draft protocol do not include sufficient detail to agree to the overall study design.

You should use the pharmacokinetic (PK) and pharmacodynamic information from the ongoing multiple dose PK study in patients with advanced PD to support the initial dose conversion plan and the dosing interval for Study IPX203-B16-02.

Although the 13-week blinded treatment phase is acceptable, it is likely that some patients will require further dose adjustment for increased dyskinesia or increasing “OFF time” after randomization. The anticipated 7 or 8 hour dose interval noted in the protocol may leave some patients with significant OFF periods requiring rescue medication. You should describe your plan for managing patients who need rescue medication or dose reduction post-randomization and the plan to analyze the data from these patients. This information is needed to evaluate the design of Study IPX203-B16-02.

Please also see our response to Question #9.

Meeting Discussion:

The sponsor discussed the rationale for initial dose conversion from IR CD LD to IPX203 and explained that Table 2 in the protocol is based upon the initial PK findings of the Phase 2 studies.

FDA noted that the initial titration period of IPX203 serves as an enrichment of the PD population intended for the trial and it is important for the sponsor to describe dropouts, adverse events, and treatment failures occurring during this period in detail.

FDA indicated concern that dose conversion using the preliminary PK findings of IPX203 C_{max} and AUC taken together might result in increased dyskinesia and/or inability to support QID dosing. (FDA pointed out the discrepancy in the protocol where the text suggests QID dosing while Table 2 indicates dosing at a 7 to 8 hour interval). There is concern that, should a shorter dosing interval be needed for control of PD symptoms, this could result in a greater total daily dose of IPX203 than Table 2 suggests.

FDA raised concern that the protocol does not address rescue medication and further medication adjustment during the blinded period. The sponsor confirmed that it plans to discontinue all patients who require dose adjustment after randomization (Visit 4). This would create informative missing data. FDA noted that if post-randomization dose increases are not allowed under the protocol, a patient needing a fourth or fifth daily dose would be discontinued from the study. The sponsor indicated its belief that this would not be a problem, based upon its experience with the Rytary Phase 3 trials. The multiple dose Phase 2 study in PD patients are similar to those anticipated in the Phase 3 trial; the final analysis of the data will inform the Phase 3 protocol’s final dosing considerations. FDA asked the sponsor to collect detailed information regarding reason for discontinuation in all patients who discontinue after randomization. Patients should not simply be reported as “discontinued” or “withdrawn”.

Question 6: Does the Division agree with the proposed patient population and study entry criteria?

FDA Response to Question 6:

The inclusion and exclusion criteria for Study IPX203-B16-02 are acceptable.

Meeting Discussion:

None

Question 7: Does the Division have other suggestions or comments regarding this IPX203-B16-02 Phase 3 protocol?

FDA Response to Question 7:

Please see our response to Question 5.

Meeting Discussion:

None

Question 8: It is estimated that approximately 300 of the completers in Study IPX203-B16-02 will enter the 9-month OLE Study IPX203-B16-03. Does the Division agree that this proposed OLE study would provide an adequate long-term patient safety database to support an NDA filing as a 505(b)(2) application?

FDA Response to Question 8:

On face, this would be acceptable unless unexpected safety findings are identified that require further testing, or the daily exposure to carbidopa or levodopa exceeds the exposure for the reference product. The determination of the adequacy of the safety database is subject to review.

Meeting Discussion:

None

Biostatistics

With respect to the proposed Phase 3 Study IPX203-B16-02:

Question 9: Does the Division agree with the primary and key secondary endpoints?

FDA Response to Question 9:

We recommend that you use the change from baseline in “ON” time without troublesome dyskinesia as your primary efficacy outcome.

A global rating such as the PGI-C would not be needed to support the clinical meaning of the change “ON” time without troublesome dyskinesia.

Meeting Discussion:

FDA noted that the benefit for “ON time without troublesome dyskinesia” is interpreted more easily in the patient diaries. The benefit from a reduction in “OFF” time can be offset by an increase in troublesome dyskinesia or by increasing sleep time without increasing “ON time”. These other factors need to be carefully recorded and then calculated from the patient diaries. (FDA notes that sleep time must be recorded using the patient diaries, not in a separate sleep scale.)

Following the meeting, the sponsor communicated by letter (February 13, 2017) their intent to use “change from baseline in “ON time without troublesome dyskinesia” as the primary efficacy outcome”.

Question 10: Does the Division agree with the statistical analyses proposed in the protocol, acknowledging that a more formal Statistical Analysis Plan will be submitted at a later date?

FDA Response to Question 10:

We have the following preliminary comments on the statistical analyses:

1. You should consider a modified intent treat population as the primary efficacy analysis population. Subjects should have a valid baseline and at least one post baseline measurement.

Meeting Discussion:

The sponsor’s response seems reasonable.

2. You should consider Visit 4 as baseline right before randomization.

Meeting Discussion:

The sponsor stated in the meeting (and reiterated in the February 13 letter to FDA) that “Visit 4 is not a true baseline because the subjects have already received study drug intervention by the time of this visit. The open-label treatment/titration periods may introduce bias due to the additional medical care and attention the subject receives during these periods.”

FDA indicated that Visit 4 is the appropriate baseline for comparison. The use of Visit 1 as baseline would compare IPX203 and IR CD LD to the patient’s previous pre-study treatment “OFF” time. The inference drawn from the comparison using Visit 1 as the baseline is unclear. The use of Visit 1 as the baseline only provides an indirect comparison of IPX203 to IR CD LD by comparison of “OFF” time on their pre-study treatment. This comparison may show IPX203 is superior to IR CD LD compared to each patients previous pre-study treatment (not optimized) for Parkinson’s disease, but only in patients successfully converted to an optimized regimen of IR CD LD and then to an optimized IPX203 regimen.

The sponsor noted that the sensitivity analysis for the study in advanced Parkinson’s disease for Rytary (IPX066-B09-02) showed that the pre-randomization baseline comparison led to the same efficacy conclusion as the Visit 1 baseline comparison.

3. You need a pooling plan for this analysis to handle the case in which there is a center with subjects in only one group.

Meeting Discussion:

The sponsor's response seems reasonable. FDA will review the details in the statistical analysis plan (SAP). FDA recommends the sponsor submit the SAP as soon as possible to allow enough time to review the SAP and, if needed, provide comments.

4. Per the description of efficacy analysis population, the last observation carried forward (LOCF) method may result in carrying over the baseline values and you should consider other methods instead.

Meeting Discussion:

The sponsor proposed using an MMRM; however, FDA commented that it does not consider informative censoring cases. The sponsor should plan to include additional sensitivity analyses. FDA advised the sponsor not to design a trial with an expectation that the dropout rate will be low.

5. Please propose subgroup analyses with respect to age, gender, and race.

Meeting Discussion:

Subgroup analyses are required by regulation and are described in 21 CFR 314.50 (d)(5).

Question 11: Does the Division agree with the proposed imputation methods to handle missing data?

FDA Response to Question 11:

See our response to Question 10.

Meeting Discussion:

None

Question 12: Does the Division agree with the sensitivity analyses proposed for the primary and key secondary endpoints?

FDA Response to Question 12:

Your proposed sensitivity analysis plan is not broad enough. In general, sensitivity analyses should be performed to inform deviation from model assumptions such as normality and missing data mechanism assumed in the primary efficacy analysis such as not missing at random analyses.

Meeting Discussion:

The sponsor proposed using a MMRM. As noted earlier, it does not consider informative censoring cases. The sponsor should plan to include additional sensitivity analyses. FDA will review the details in the statistical analysis plan (SAP). FDA recommends the sponsor submit the SAP as soon as possible to allow enough time to review the SAP and, if needed, provide comments.

Question 13: Does the Division agree with the proposed plan to adjust for multiplicity with the use of the proposed hierarchy? If the Division agrees with this plan and if the NDA is approved, does the Division also agree that the primary and key secondary endpoint results are appropriate to be included as part of the final product package label?

FDA Response to Question 13:

The multiple testing procedures seem fine. Please see our response to Question 9 with regard to study endpoints. The primary endpoint and the key secondary measured should be included in a single, ordered hierarchy. The testing procedure should start with the primary endpoint, followed by the key secondary endpoint in order.

Meeting Discussion:

The discussion for Question 13 was covered under Question 9.

Administrative/Regulatory

Question 14: Does the Division agree that the proposed development program is sufficient to support a 505(b)(2) NDA for the proposed indication (“treatment of Parkinson’s disease, postencephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication”)?

FDA Response to Question 14:

On face, it appears that your proposed plan would support an indication for the treatment of advanced Parkinson’s disease, but a final decision on its adequacy is subject to FDA review of the actual application.

A global indication for the treatment of symptoms of Parkinson’s disease (PD) usually requires adequate and well-controlled trials supporting its use in both early and advanced PD. The currently proposed protocol would only support the latter indication.

In your NDA submission for this 505(b)(2) application, list specifically the sections and information in the labeling for each listed drug upon which you intend to rely.

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 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. For additional information for sponsors considering the submission of an application through the 505(b)(2) pathway, please see the information in the **505(b)(2) REGULATORY PATHWAY** section of 3.0 of this document.

Meeting Discussion:

None

Question 15: Parkinson’s disease is an adult degenerative neurologic disease that is virtually never seen in the pediatric population. The indication for IPX203 has “extremely limited

applicability to pediatric patients because the pathophysiology or disease occurs for the most part in adult populations” (FDA Guidance 2005). Therefore, necessary studies are impossible or highly impracticable (FD&C, as amended by Pediatric Research Equity Act (PREA), section 505B(a)(4)(A)(i)). Does the Division agree that a full waiver for PREA requirements can be granted for IPX203 for the proposed indication?

FDA Response to Question 15:

Your proposal to submit an iPSP with the intention of requesting a full waiver from PREA requirements is reasonable. The request for full waiver from PREA requirements would be submitted in the NDA. Please see the PREA Requirements section below, regarding the submission of an iPSP.

Meeting Discussion:

None

Question 16: Does the FDA agree that an Environmental Assessment is not required for IPX203?

FDA Response to Question 16:

Refer to CMC meeting response to question #4 from January 19, 2017.

Meeting Discussion:

Refer any comments to Dahlia Woody, Project Manager for CMC.

3.0 OTHER IMPORTANT INFORMATION

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 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.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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 at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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 interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

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)).

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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>

4.	

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.

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).

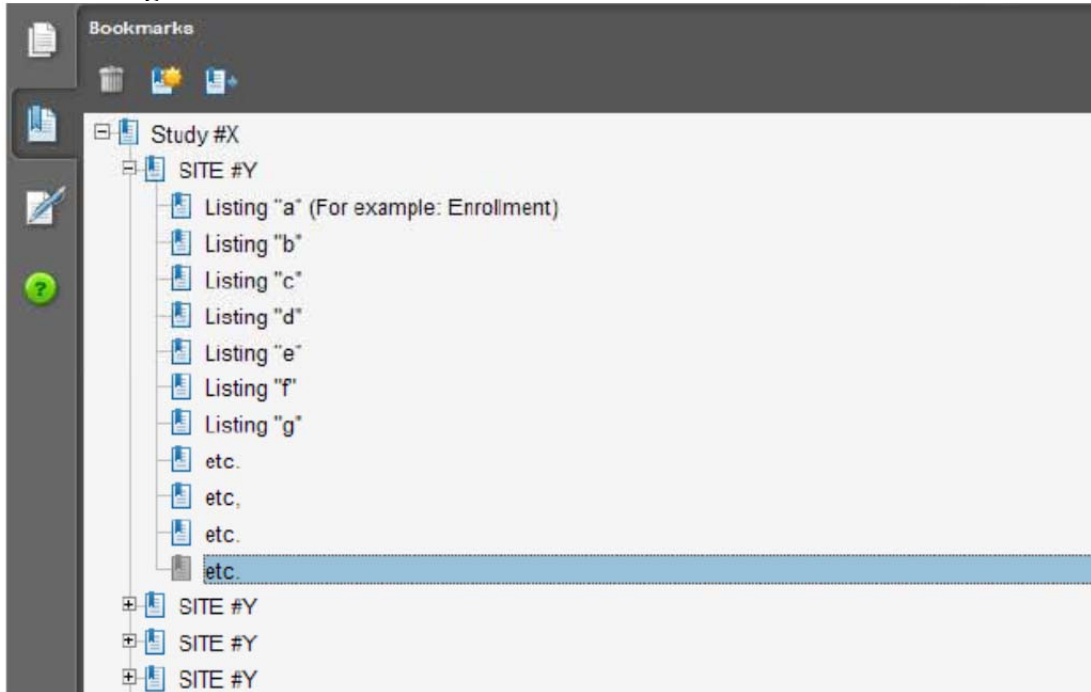
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - 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.

Attachment 1 Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

- C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

5.0 ACTION ITEMS

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Action Item/Description	Owner	Due Date
[Insert action item with a brief description, if applicable]	FDA	[Insert date]
[Insert action item with a brief description, if applicable]	Sponsor	[Insert date]

6.0 ATTACHMENTS AND HANDOUTS

19 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
02/27/2017