

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203312Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203312

SUPPL #

HFD # 120

Trade Name Rytary

Generic Name carbidopa/levodopa extended release capsules (IPX066)

Applicant Name Impax Laboratories

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17555 Sinemet                      19856 Sinemet CR

NDA# 21485 Stalevo                      17830 Lodosyn

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III      THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

IPX066-B09-03  
IPX066-B08-05  
IPX066-B09-02  
IPX066-B09-06

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 (B09-03)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2 (B08-05)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3 (B09-02)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4 (B09-06)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 (B09-03)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
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Investigation #2 (B08-05)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3 (B09-02)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4 (B09-06)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

IPX066-B09-03	IPX066-B08-05
IPX066-B09-02	IPX066-B09-06

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 (IPX066-B009-03)

IND # 102887      YES       ! NO   
! Explain:

Investigation #2 (IPX066-B08-05)

IND # 102887      YES       ! NO   
! Explain:

Investigation #2 (IPX066-B09-02)

IND # 102887      YES       ! NO   
! Explain:

Investigation #2 (IPX066-B09-06)

IND # 102887      YES       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1      !  
!  
YES       ! NO   
Explain:      ! Explain:

Investigation #2      !  
!  
YES       ! NO   
Explain:      ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES       NO

If yes, explain:

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Name of person completing form: Tracy Peters, PharmD  
Title: Senior Regulatory Project Manager  
Date: 12/19/14

Name of Office/Division Director signing form: Eric Bastings, MD  
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TRACY J PETERS  
12/19/2014

ERIC P BASTINGS  
12/19/2014

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 203312 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DNP PDUFA Goal Date: 01/09/15 Stamp Date: 04/09/14

Proprietary Name: Rytary

Established/Generic Name: carbidopa/levodopa extended release

Dosage Form: capsules

Applicant/Sponsor: Impax Laboratories, Inc

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) N/A
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Treatment of (b)(4) Parkinson's disease (b)(4), postencephalitic parkinsonism and (b)(4) parkinsonism (b)(4) may follow injury to the nervous system by carbon monoxide intoxication (b)(4) or manganese intoxication

**Indication 1:** treatment of (b)(4) Parkinson's disease (b)(4)

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): \_\_\_\_\_

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** Treatment of <sup>(b) (4)</sup> postencephalatic parkinsonism and <sup>(b) (4)</sup> parkinsonism which may follow <sup>(b) (4)</sup> carbon monoxide intoxication <sup>(b) (4)</sup> or manganese intoxication**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

 Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

N203312  
IPX066 (carbidopa/levodopa ER capsules)

**Pediatric Full Waiver Justification**

**Background:**

Product: Rytary (under review)

Indication: treatment of (b) (4) Parkinson's Disease (b) (4), post-encephalitic parkinsonism and (b) (4) parkonsism (b) (4) may follow injury to the nervous system by carbon monoxide intoxication (b) (4) or manganese intoxication

**Sponsor's Justification for Waiver Request:**

Parkinson's disease is a progressive neurological disorder. According to the National Institute of Neurological Disorders and Stroke, the average age of onset is about 60. Both prevalence and incidence increase with advancing age; the rates are very low in people under 40 and rise among people in their 70s and 80s. The prevalence and incidence of Parkinson's disease in the pediatric population is sufficiently low that accurate estimates are not available. Thus IPX066 for the treatment of Parkinson's disease is consistent with FDA guidance ("How to Comply with the Pediatric Research Equity Act; September 2005) on waivers insofar as the indication has extremely limited applicability to pediatric patients because the pathophysiology of the diseases occur for the most part in the adult population. Additionally, Parkinson's disease is included in a list of indications potentially eligible for a waiver found in Attachment A of that guidance.

**The Division's Justification for a Waiver Request:**

The application is relying upon listed drugs Sinemet, Sinemet CR, Lodosyn, and Stalevo. Sinemet and Sinemet CR are approved for the exact same indication(s), and we have not required studies of the pediatric population for those drugs.

Parkinson's disease appears in the list of Adult-Related Conditions that do not occur in pediatrics and qualifies for a waiver. In addition, the number and location of children with post-encephalitic parkinsonism (not reported since 1940) and symptomatic parkinsonism following carbon monoxide intoxication or manganese intoxication are too small and geographically dispersed to feasibly study.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TRACY J PETERS  
01/08/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203312 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: RYTARY Established/Proper Name: carbidopa/levodopa extended release Dosage Form: oral capsules		Applicant: Impax Laboratories Agent for Applicant (if applicable):
RPM: Tracy Peters		Division: Division of Neurology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: 01/07/15</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>1-9-2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None    CR: 01-18-2013
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 3: New dosage form  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: Complete Response 01/18/13 Approval 01/07/15
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**Labeling**

❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	<u>Letter</u> <a href="#">10/30/14</a> <u>(first cycle: 04/12/12)</u> <u>Review</u> <a href="#">10/20/14</a> <u>(first cycle: 04/12/12,08/13/12, 12/18/12)</u>
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 12/05/14 DMEPA: <input checked="" type="checkbox"/> <a href="#">10/01/14</a> <u>(first cycle: 07/11/12, 09/17/12, 10/31/12, 12/18/12, 01/08/13)</u> DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 09/17/12 and 09/29/12 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Other: <input type="checkbox"/> None

**Administrative / Regulatory Documents**

<ul style="list-style-type: none"> <li>❖ RPM Filing Review<sup>4</sup>/Memo of Filing Meeting (<i>indicate date of each review</i>)</li> <li>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</li> </ul>	<p>05/15/12</p> <p><input checked="" type="checkbox"/> 08/06/14 (first cycle: 09/17/12)</p>
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<p><input checked="" type="checkbox"/> Included 12/19/22</p>
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (checked 12/5/14)</p>
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not an AP action</p>
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>08/08/12</u> If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	<p>Information Requests: 03/06/12, 06/01/12, 08/07/12, 08/20/12, 10/31/12</p> <p>Letters: SPA Agreement: SPA 1 and 2 (12/5/08, 02/27/09); SPA No Agreement: SPA 3 and 4 (03/20/09, 08/07/09); Ack NDA (1/3/12); Filing Communication (3/1/12); Ack Resubmission (4/22/14), Extension (10/4/12, 09/15/14)</p>
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	<p>NAI OSI 07/24/12 OSI Memo 04/18/12</p>
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> 04/07/14</p>
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> CMC: 07/21/11 Clinical: 08/30/11</p>
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> 09/19/08</p>
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<p><input type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<p>SPA-Type A (05/07/09)</p>

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input type="checkbox"/> <u>No AC meeting</u>
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> <u>None</u>
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> First Cycle: 01/18/13 Resubmission: 01/07/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> First Cycle: 01/18/13 Resubmission: 12/23/14
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> 12/17/14 (1996-1 and 1996-2)
<b>Clinical</b>	
❖ Clinical Reviews • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> <u>No separate review</u>
• Clinical review(s) ( <i>indicate date for each review</i> )	Filing Review: 05/14/12 Primary Review: 01/18/13, 12/22/14
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input type="checkbox"/> <u>None</u>
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical review dated January 18, 2013, section 3.3  Clinical review dated December 22, 2014, section 3.3
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> <u>None</u>
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> <u>N/A</u>
❖ Risk Management • REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> ) • REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> ) • Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input type="checkbox"/> <u>None</u>
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> Review: 08/29/12 Letters: 08/09/12, 07/24/12
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> <u>None</u>	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> <u>None</u>	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> <u>No separate review</u>
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> <u>No separate review</u>
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> <u>08/13/12</u>

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> <u>No separate review</u>
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> <u>No separate review</u>
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> <u>Filing Review: 04/25/12</u> <u>Primary Review: 11/19/12</u>
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> <u>None requested</u>
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> <u>No separate review</u>
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> <u>12/6/12</u>
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> <u>09/26/12</u>
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> <u>None</u>
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> <u>No carc</u>
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> <u>None</u> <u>Included in P/T review, page</u>
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> <u>None requested</u>
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> <u>No separate review</u>
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> <u>No separate review</u>
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> <u>CMC</u> <u>Filing Review: 01/24/12</u> <u>First Cycle: 08/28/12, 01/18/13</u> <u>Resubmission: 11/05/14, 12/23/14</u>  <u>Biopharmaceutics</u> <u>Filing Review: 02/10/12</u> <u>First Cycle: 08/26/12</u> <u>Resubmission: 11/05/14</u>
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> <u>Not needed</u>
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> <u>None</u>
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> <u>Categorical Exclusion</u> <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	<u>08/28/12 (CMC review p.208)</u>
<input type="checkbox"/> <u>Review &amp; FONSI</u> <i>(indicate date of review)</i>	
<input type="checkbox"/> <u>Review &amp; Environmental Impact Statement</u> <i>(indicate date of each review)</i>	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup></i> )  <b>CMC final review dated 12/23/14 includes facilities inspections final acceptable recommendation.</b>	Date completed: 12/23/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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TRACY J PETERS  
01/12/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 203312

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Impax Laboratories, Inc.  
30831 Huntwood Avenue  
Hayward, CA 94544

ATTENTION: Michael R. Marsman, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Marsman:

Please refer to your New Drug Application (NDA) dated December 20, 2011, received December 21, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Carbidopa and Levodopa Extended-Release Capsules, 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, and 61.25 mg/245 mg.

We also refer to your correspondence, dated and received August 22, 2014, requesting review of your proposed proprietary name, Rytary.

We have completed our review of the proposed proprietary name, Rytary and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your August 22, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Tracy Peters, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
10/30/2014



NDA 203312

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Impax Laboratories, Inc.  
Attention: Michael Marsman, PharmD  
Vice President, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Marsman:

Please refer to your New Drug Application (NDA) resubmission dated and received April 9, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rytary (IPX066; carbidopa-levodopa extended-release capsules) 23.75-95 mg, 36.25-145 mg, 48.75-195mg, 61.25-245 mg.

On August 29, 2014, we received your August 29, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 9, 2015.

If you have any questions, call Tracy Peters, Regulatory Project Manager, at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, M.D.  
Acting Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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WILLIAM H Dunn  
09/15/2014



NDA 203312

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Impax Laboratories, Inc.  
Attention: Michael Marsman, PharmD  
Vice President, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Marsman:

We acknowledge receipt on April 9, 2014, of your April 9, 2014, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rytary (IPX066; carbidopa-levodopa extended-release capsules) 23.75-95 mg, 36.25-145 mg, 48.75-195mg, 61.25-245 mg.

We consider this a complete, class 2 response to our action letter dated January 18, 2013. Therefore, the user fee goal date is October 9, 2014.

If you have any questions, call me at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Tracy Peters, PharmD  
Senior Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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TRACY J PETERS  
04/22/2014



NDA 203312

**MEETING MINUTES**

Impax Laboratories, Inc.  
Attention: Michael Marsman, PharmD  
Vice President, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Marsman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rytary (IPX066; carbidopa-levodopa extended-release capsules).

We also refer to the teleconference between representatives of your firm and the FDA on April 7, 2014. The purpose of the meeting was to discuss the content, format and classification of the resubmission for NDA 203312.

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

If you have any questions, call Tracy Peters, Regulatory Project Manager at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy 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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A  
**Meeting Category:** End of Review

**Meeting Date:** April 7, 2014  
**Meeting Time:** 3:00-4:00pm EST  
**Meeting Format:** Teleconference

**Application Number:** 203312  
**Product Name:** Rytary (IPX066; carbidopa-levodopa extended-release capsules)  
**Indication:** Parkinson's Disease  
**Sponsor/Applicant Name:** Impax Laboratories, Inc.

**Meeting Chair:** Eric Bastings, MD  
**Meeting Recorder:** Tracy Peters, PharmD

**FDA ATTENDEES**

Eric Bastings, MD, Deputy Director, Division of Neurology Products  
Gerald David Podskalny, D.O., MPHS, Clinical Team Leader  
Kenneth Bergmann, M.D., Clinical Reviewer  
LuAnn McKinney, Ph.D., Pharmacologist  
Martha Heimann, Ph.D., Supervisory Chemist, CMC  
Charles Jewel, Ph.D., CMC reviewer  
Christina Capacci-Daniel, Ph.D., Consumer Safety Officer, Division of Good Manufacturing Practice Assessment (DGMPA)  
Dennis Lin, PharmD Candidate, Intern  
Tracy Peters, PharmD, Senior Regulatory Project Manager

**SPONSOR ATTENDEES**

Suneel Gupta, Ph.D., Chief Scientific Officer  
Sarita Khanna, Ph.D., Senior Director, Biostatistics,  
Sherron Kell, M.D., MPH, Vice President, Clinical Development  
Michael Marsman, PharmD, Vice President, Regulatory Affairs

## 1.0 BACKGROUND

On December 20, 2011, Impax Laboratories submitted a new drug application for IPX066 (Rytary). The application was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and it was proposed that the dosing and side effect profiles were more favorable due to the pharmacokinetic differences from the listed drugs. IPX066 (Rytary) is an extended release capsule formulation of carbidopa-levodopa developed for the (b) (4) treatment of adult patients with (b) (4) Parkinson's disease (b) (4), post-encephalitic parkinsonism and symptomatic parkinsonism (b) (4) may follow injury to the nervous system by carbon monoxide intoxication (b) (4) or manganese intoxication. On January 18, 2013, the Division issues a Complete Response letter which described deficiencies in the Hayward, CA manufacturing facility as the basis for the decision. On February 25, 2014, a Memorandum was relayed to Impax Laboratories from the Office of Regulatory Affairs, San Francisco District Office (through the Division of Good Manufacturing Practice Assessment), which stated that Impax had adequately addressed the inspectional deficiencies at this site, as related to NDA 203312 only. Subsequent to that notification, Impax submitted a meeting request on March 6, 2014, to discuss the resubmission of NDA 203312.

The Agency's preliminary responses to the questions presented in the meeting package were electronically sent to the sponsor on Friday, April 4, 2014. After receiving the preliminary comments, the sponsor determined that a face-to-face meeting was no longer necessary and requested that the meeting format be changed to a teleconference. Listed below is an account of the sponsor's questions, the Agency's preliminary responses, and the discussion that took place during the meeting.

## 2. DISCUSSION

### **Question 1:**

*The CRL states that a Safety Update including any new safety data for IPX066 be included in the NDA resubmission and provides requirements for how such data should be presented and integrated. Impax has prepared a Safety Update as specified in the CRL and a detailed description is included in the meeting briefing package.*

*Does the Division agree that the proposed format and content of the Safety Update meets FDA requirements for resubmission of the NDA? If not, what changes are required?*

### **FDA Response to Question 1:**

Your proposal for review of the safety information is, on face, acceptable. For the new information from the B11-01 trial, in addition to usual narratives for deaths, nonfatal SAEs, and AEs resulting in a subject leaving the trial, include narratives for any patient who left due to "withdrawn consent."

Please update the individual trial results and the ISS to include both the analyses submitted by you and those previously requested by the Division. The ISS update should include a discussion of the results in total at the time of resubmission (not just a summary of the changes from the

time of the NDA complete response letter and the 120 day update). Submit safety information tables giving numbers of events submitted in the NDA, 120-day update, new since the 120-day update, and a row total for all events submitted. Separate any adverse events in studies involving healthy volunteers from that of the PD population.

New draft guidances have been published which suggest the preferred format for electronic dataset submission. These are available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>.

Safety data from individual studies and trials submitted to the Division for review should be MedDRA compliant and they should follow the format of your previous safety dataset submissions. Data submitted for review must be reliable, transparent, and traceable.

You should provide updated totals for Case Report Tabulations and Listings and an updated line-listing table with hyperlinks to the narratives.

We encourage you to contact the CDER Study Data Standards group at the FDA for any technical questions you may have about the electronic format and compatibility for data submission ([cder-edata@fda.hhs.gov](mailto:cder-edata@fda.hhs.gov)).

**Discussion:**

**The Sponsor's resubmission will include studies in the original NDA submission, and four additional studies previously submitted to the IND: two completed pK studies, one open label, and one ongoing open label extension study. The Sponsor confirmed they have not generated new controlled study data since the NDA submission. The updated safety datasets included in the resubmission should follow the same format used in the NDA and 120-day update. This will facilitate analysis of the sequential ISS datasets submitted to the NDA. Full copies of completed study reports submitted to the IND should be included in the NDA resubmission. The updated ISS tables should include revised Exposure and Adverse Event figures that show the number of patients by the dose and duration of their exposure. For adverse events, the sponsor should list the number of patients for each of the three columns listed below. The sponsor should submit the results in three columns, the results submitted in the original NDA and 120-day update, since the 120-day update and new row totals for all updated exposure/adverse events submitted for the entire NDA. The Sponsor confirmed they plan to continue open-label study 11-01 beyond the date for the NDA resubmission.**

**Question 2:**

*The IPX066 stability data sets already presented in the NDA are extended to the durations listed in Table 1 of the briefing document. For Hayward Registration and Supporting lots, each "Lot" is a series of capsule lots encompassing <sup>(b)</sup><sub>(4)</sub> different package configurations (various capsule*

*strengths, container size, and container count); please refer to 3.2.P.8.2 and 3.2.P.8.3 for complete descriptions. For the Taiwan Registration lots, each "Lot" is a similar series, encompassing<sup>(b) (4)</sup> different package configurations.*

*Does the Division agree with the presentation of the additional stability data on IPX066?*

**FDA Response to Question 2:**

This is acceptable. We will assign expiration dating for the drug product configurations based on review of the data submitted in the application.

**Discussion:**

**None.**

**Question 3:**

*Prior to issuance of the CRL, Impax and the Division discussed a postmarketing requirement for certain nonclinical studies relating to<sup>(b) (4)</sup> used in IPX066 capsules, and Impax proposed a timetable for agreement on protocols and conduct of the studies. This timetable has been updated as described in the briefing document.*

*Does the Division agree with the proposed studies and timetable? If not, what changes does the Division propose?*

**FDA Response to Question 3:**

It is premature to comment on the new dates that you have proposed for the PMR milestones. We do note your letter dated December 7, 2012, received December 10, 2012, stating agreement to PMR milestone dates. A resubmission of the Rytary (N203312) application should include proposed PMR milestone dates that have a similar relationship to the potential approval date as those submitted previously. In addition, we expect the study titles to be submitted exactly as they are listed below. We also note that if there is an approval of the application, these studies will be *requirements* under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act and not classified as *commitments*.

**Post Marketing Requirement #1:**

Six-month oral toxicology study of methacrylic acid copolymer,<sup>(b) (4)</sup> in rat. The methacrylic acid copolymer,<sup>(b) (4)</sup> should be the same as the excipient in the to-be-marketed product.

**Post Marketing Requirement #2:**

Oral absorption study of radiolabeled methacrylic acid copolymer,<sup>(b) (4)</sup> in rat. The methacrylic acid copolymer,<sup>(b) (4)</sup> should be the same as the excipient in the to-be-marketed product.

**Discussion:**

**None.**

**Question 4:**

*In addition to the Safety Update, stability update, and postmarketing requirements described above, Impax proposes to include revised labeling, including SPL format, and updated patent information in the resubmission.*

*Does the Division agree that the information described above constitutes a complete response to the CRL and is adequate for resubmission and continued review of the NDA? If not, what additional information and / or actions are required?*

**FDA Response to Question 4:**

The determination of whether your submission constitutes a Complete Response is a matter for review. It will also depend on the outcome of your facilities inspections and the recommendation from the FDA Office of Compliance.

We refer to your amendment dated January 16, 2013, and received January 17, 2013, which includes your proposed revisions to the Prescribing Information based on our communication dated January 16, 2013. You should include this version, as appended to this Preliminary Meeting Comments document, in your resubmission. If you have any additional edits that are not included in the appended Prescribing Information, they will need to be included in tracked changes based on the attached document.

**Discussion:**

**The Agency recommended submitting only one version of the Prescribing Information that includes all of the tracked changes from the January 16, 2013, version (as appended to the preliminary responses) and any additional edits in tracked changes.**

**Question 5:**

*Based on the resubmission information described in this briefing document, Impax believes that the resubmission meets the standards for a Class 1 resubmission as described in the Guidance for Industry, Classifying Resubmissions in Response to Action Letters.*

*Does the Division agree?*

**FDA Response to Question 5:**

NDA 203312 (Rytary) does not meet the criteria for Class 1 resubmission designation. As an evaluation of the manufacturing facilities is required, this will be a Class 2 resubmission.

Previous discussions between Impax and the CDER Office of Compliance addressed deficiencies found during the first review and inspection cycle. Comments provided to Impax on February 25, 2014, were “made to facilitate future resubmission and review, and inspection in support of this NDA.” A current and satisfactory evaluation of the manufacturing facilities listed in the resubmission is required before this application may be approved.

**Discussion:**

**The Sponsor agreed that they will submit a list of all manufacturing facilities and responsibilities. They stated it was their understanding that all of the facilities were now in compliance and inspections pursuant to the resubmission of NDA 203312 would not be required. The Agency confirmed that the manufacturing facilities will need to be assessed, and therefore, the resubmission will be considered a Class 2.**

**3.0 ADDITIONAL INFORMATION: 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.				

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

**5.0 ACTION ITEMS**

None.

**6.0 ATTACHMENTS AND HANDOUTS**

**Labeling: Prescribing Information from January 16, 2013.**

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

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/s/  
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ERIC P BASTINGS  
04/11/2014



NDA 203312

**MEETING REQUEST GRANTED**

Impax Laboratories, Inc.  
Attention: Michael Marsman, PharmD  
Vice President, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Marsman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rytary (IPX066; carbidopa-levodopa extended-release capsules).

We also refer to your March 6, 2014, correspondence requesting a meeting to discuss content and timing of the resubmission of the new drug application. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

**Date:** Monday, April 7, 2014  
**Time:** 3:00-4:00pm EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1313  
Silver Spring, Maryland 20903

**Invited CDER Participants:**

Billy Dunn, MD, Acting Director, Division of Neurology Products  
Eric Bastings, MD, Deputy Director, Division of Neurology Products  
Mahesh Ramanadham, LCDR, U.S. Public Health Service, Acting Branch Chief  
New Drug Manufacturing Assessment Branch  
Division of Good Manufacturing Practice Assessment (DGMPA)  
Christina Capacci-Daniel, PhD, Consumer Safety Officer, DGMPA  
Olen Stephens, PhD, ONDQA Acting Branch Chief  
Martha Heimann, PhD, Supervisory Chemist, CMC  
Charles Jewel, PhD, Chemist  
Gerald David Podskalny, DO, MPHS, Clinical Team Leader  
Kenneth Bergmann, MD, Clinical Reviewer  
Lois Freed, PhD, Supervisory Pharmacologist  
LuAnn McKinney, PhD, Pharmacologist  
Alice Hughes, MD, Deputy Director for Safety  
Sally Yasuda, PhD, Lead Pharmacologist, Safety Team Leader  
Kelly Ngan, PharmD, Safety Regulatory Project Manager  
Tracy Peters, PharmD, Senior Regulatory Project Manager

Please e-mail me any updates to your attendees at Tracy.Peters@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Tracy Peters, 301-796-2953.

We note receipt of the background information with your March 6, 2014, meeting request. Submit 15 desk copies of the background information for the meeting to me as soon as possible at the following address:

Tracy Peters, PharmD  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 4117  
10903 New Hampshire Avenue  
Silver Spring, Maryland  
*Use zip code **20903** if shipping via United States Postal Service (USPS).*  
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Tracy Peters, PharmD  
Senior Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Foreign Visitor Data Request Form

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	April 7, 2014 at 3:00pm EST
MEETING ENDING DATE AND TIME	April 7, 2014 at 4:00pm EST
PURPOSE OF MEETING	Type A
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	10903 New Hampshire Avenue Silver Spring, Maryland 20903  White Oak Building 22, Conference Room: 1313
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Tracy Peters, PharmD Senior Regulatory Project Manager WO Bld 22, Room 4117 Office phone: 301-796-2953

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/s/  
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TRACY J PETERS  
03/07/2014

**From:** Peters, Tracy  
**To:** ["Jeff Mulchahey"](#)  
**Subject:** PMR modification  
**Date:** Thursday, December 06, 2012 3:16:00 PM

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Hi Jeff,

Based on further internal discussion regarding the PMRs for Rytary, we have some modifications regarding the species and duration of the tox study:

We acknowledge that during our recent teleconference (12/4/2012) we indicated that one of the two planned nonclinical PMRs would be for a 6-week toxicity study of (b) (4) in mouse. However, after having reviewed the available data and summaries, we believe that in order to definitively assess the potential for this excipient to induced thyroid (or other systemic) toxicity, we would need to have a 6-month toxicity study in rat. The thyroid findings in the 6-week mouse study were described as "slight" at 600 and 1500 mg/kg/day. Those in the rabbit study were characterized as "definite" or "distinct" only at the highest dose tested (1500 mg/kg). In contrast, the thyroid findings in the original (high-dose) 6-month study in rat were described as indicating "definite" and "extensive" activation, particularly in males, even at the lowest dose tested (200 mg/kg/day). Although 6 weeks of dosing might be sufficient, data from a study of less than 6 months duration are not available in rat.

Therefore, we ask that you provide the following dates for a **6-month** oral toxicity study of (b) (4) in rat:

Final protocol submission date:

Study completion date:

Final study report submission date:

Kind regards,  
Tracy

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TRACY J PETERS  
12/06/2012

**From:** Peters, Tracy  
**To:** [Jeff Mulchahey](#)  
**Subject:** Rytary carton/container DMEPA comments  
**Date:** Wednesday, October 31, 2012 11:55:00 AM

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Hello Jeff,

Please see the following comments from our review team regarding Rytary's carton and container. Please respond with the carton/container revisions by November 8th.

**Review of the revised container labels and carton labeling determined that not all of our previous recommendations were implemented by the Applicant. Furthermore, we identified additional vulnerability that can lead to medication errors. DMEPA recommends the following recommendations be implemented prior to approval of this application:**

**A. Container Labels and Carton Labeling (Retail and Professional Samples)**

**1. Revise statements that appear in all upper case to title case to improve readability. For example, revise the statement "PROFESSIONAL SAMPLE – NOT FOR SALE" to read "Professional sample – Not for sale."**

**B. Carton Labeling (Retail, all strengths)**

**1. On the panels containing the strength statement, increase the font size of the strength statement and the size of the color highlighting block for increased prominence.**

**If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.**

Kind regards,  
**Tracy Peters, PharmD**  
Regulatory Project Manager  
Food and Drug Administration  
CDER/Division of Neurology Products  
Bld. 22, Room 4369  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Office: 301-796-2953  
Fax: 301-796-9842  
Email: [Tracy.J.Peters@fda.hhs.gov](mailto:Tracy.J.Peters@fda.hhs.gov)

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TRACY J PETERS  
10/31/2012



NDA 203312

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Impax Laboratories, Inc.  
Attention: Jeff Mulchahey  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Mr. Mulchahey:

Please refer to your December 21, 2011 New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rytary (IPX066; carbidopa-levodopa extended-release capsules) 23.75-95 mg, 36.25-145 mg, 48.75-195 mg, 61.25-245 mg.

On October 2, 2012, we received your September 28, 2012 solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 21, 2013.

In addition, we are establishing a new timeline for communicating postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate, if necessary, any postmarketing requirement/commitment requests by December 21, 2012.

In your document entitled [REDACTED] <sup>(b) (4)</sup> provided in this amendment, you stated that, according to the manufacturer of the copolymer, “re-evaluation of findings” from the high-dose 6-month oral toxicity study in rats “led to the conclusion that there were documentation deficiencies which restricted the validity of this study.” Please provide additional information on these deficiencies and their impact on study validity in a manner that allows substantive review, no later than November 1, 2012.

If you have any questions, call Tracy Peters, Regulatory Project Manager, at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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RUSSELL G KATZ  
10/04/2012

## David, Jeannie C

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**From:** David, Jeannie C  
**Sent:** Monday, August 20, 2012 11:48 AM  
**To:** 'Jeff Mulchahey'  
**Cc:** Suneel Gupta; Daven Mody; Lynn Hansen; Bouie, Teshara; Peters, Tracy  
**Subject:** RE: NDA 203312 CMC t-con Follow Up  
**Attachments:** NDA 203312 IPX066 Sprinkled on (b)(4).docx

Hi Jeff,

In reference to your August 16, 2012, and August 17, 2012, emails below, we have the following responses:

- 1) *There is no need to provide a "new" section 3.2.P.5.6 - Justification of Specifications.*
- 2) *All specifications including fill weights should be updated in the application as soon as possible. Your updates should include all agreements from our August 7, 2012, teleconference discussion (e.g. 12 months intermediate storage conditions for stability studies on first three commercial batches, etc.). Stability proposals should be updated to include the TA dissolution.*
- 3) *For issues related to expiration dating, we will complete our evaluation of the submitted data and assign an expiration date based on our review. Our determination will be communicated in the action letter or remain pending, depending on the action.*
- 4) *For issues related to the sprinkled capsule content on (b)(4), we will review the new information you have provided. Our determination on the use of capsule contents in food will be communicated during the labeling discussions.*

Please let us know if there are any further questions.

Best regards,

Jeannie

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**From:** Jeff Mulchahey [mailto:jmulchahey@impaxlabs.com]  
**Sent:** Friday, August 17, 2012 1:35 PM  
**To:** David, Jeannie C  
**Cc:** Peters, Tracy; Bouie, Teshara; Suneel Gupta; Daven Mody; Lynn Hansen  
**Subject:** RE: NDA 203312 CMC t-con Follow Up

Hi Jeannie,

Attached is a description of our current thinking on the performance of the IPX066 formulation when allowed to sit after being sprinkled on (b)(4) and the stability of the drug substances when sprinkled (b)(4). As you'll see in the document, we believe the NDA contains information which addresses the concerns expressed by the CMC reviewers during our 07 August teleconference. We're sending this as part of our discussion on the subject and would appreciate some feedback as to the what the next steps should be. I imagine that the first step is for the reviewers to evaluate our comments. If the reasoning is acceptable then we'll talk about a formal submission to the NDA. If not, then we'll want further discussion/clarification of the issues, the current data, or data which might need to be generated.

Thanks, and have a great weekend.

Jeff

Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
IMPAX Pharmaceuticals,  
A Division of IMPAX Laboratories, Inc.  
31047 Genstar Road  
Hayward, California 94544  
USA  
Phone: +1-510-240-6426  
Fax: +1-510-240-6113  
E-mail: [jmulchahey@impaxlabs.com](mailto:jmulchahey@impaxlabs.com)  
[www.impaxlabs.com](http://www.impaxlabs.com)

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**From:** Jeff Mulchahey [<mailto:jmulchahey@impaxlabs.com>]  
**Sent:** Thursday, August 16, 2012 4:26 PM  
**To:** David, Jeannie C; Peters, Tracy  
**Cc:** Lynn Hansen; Suneel Gupta; Daven Mody; Lynn Hansen  
**Subject:** RE: NDA 203312 CMC t-con Follow Up

Hi Jeannie,

We have a procedural question around updating the NDA with the revised specifications. Obviously the specification change impacts several documents within the application and we will be updating these. Our procedural question is whether the materials we submitted as S-0014 and S-0017 are sufficient documentation of the specification justification, or do we need to provide a "new" section 3.2.P.5.6 – Justification of Specifications? Also, as we're endeavoring to complete all of our CMC comments to the Agency questions in the upcoming sequence, was the revised expiry dating proposed in S-0014 (FDA Comment 5 and our response) and the revised in process fill weights (also S-0014, FDA Comment 1 and our response) accepted? If so, we'll update section 3.2.P.8.1 - Stability Summary and Conclusions and the Master Batch Records, respectively, to reflect these at this time.

Thanks in advance,

Jeff

Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
IMPAX Pharmaceuticals,  
A Division of IMPAX Laboratories, Inc.  
31047 Genstar Road  
Hayward, California 94544  
USA  
Phone: +1-510-240-6426  
Fax: +1-510-240-6113  
E-mail: [jmulchahey@impaxlabs.com](mailto:jmulchahey@impaxlabs.com)  
[www.impaxlabs.com](http://www.impaxlabs.com)

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**From:** David, Jeannie C [<mailto:Jeannie.David@fda.hhs.gov>]  
**Sent:** Thursday, August 16, 2012 7:42 AM  
**To:** Jeff Mulchahey  
**Cc:** Suneel Gupta; Daven Mody; Lynn Hansen; Bouie, Teshara; Peters, Tracy; Suneel Gupta; Daven Mody; Lynn Hansen  
**Subject:** RE: NDA 203312 CMC t-con Follow Up  
Thank you for your confirmation, Jeff.  
We look forward to the submission.  
Best regards,  
Jeannie

Jeannie David, M.S.  
Regulatory Health Project Manager  
Food and Drug Administration

Phone: (301) 796-4247

**From:** Jeff Mulchahey [mailto:jmulchahey@impaxlabs.com]

**Sent:** Thursday, August 16, 2012 10:39 AM

**To:** David, Jeannie C

**Cc:** Suneel Gupta; Daven Mody; Lynn Hansen; Bouie, Teshara; Peters, Tracy; Suneel Gupta; Daven Mody; Lynn Hansen

**Subject:** RE: NDA 203312 CMC t-con Follow Up

Hi Jeannie,

Thank you for sending this. I'm glad we're able to finalize these specifications. As you requested, we will formalize the agreed specifications with updated specification pages ASAP. I'll let you know the exact timeline later today. Also, we agreed at the t-con that we would provide additional information by this Friday (tomorrow) around proposed stability testing of IPX066 when sprinkled on (b) (4). We're working on that and will have it to you tomorrow.

Best regards,

Jeff

Jeff Mulchahey, PhD

Senior Director, Regulatory Affairs

IMPAX Pharmaceuticals,

A Division of IMPAX Laboratories, Inc.

31047 Genstar Road

Hayward, California 94544

USA

Phone: +1-510-240-6426

Fax: +1-510-240-6113

E-mail: [jmulchahey@impaxlabs.com](mailto:jmulchahey@impaxlabs.com)

[www.impaxlabs.com](http://www.impaxlabs.com)

**From:** David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]

**Sent:** Thursday, August 16, 2012 7:14 AM

**To:** Jeff Mulchahey

**Cc:** Suneel Gupta; Daven Mody; Lynn Hansen; Bouie, Teshara; Peters, Tracy

**Subject:** RE: NDA 203312 CMC t-con Follow Up

**Importance:** High

Hi Jeff,

We have the following Biopharmaceutics comments:

*The following dissolution method and dissolution acceptance criteria are deemed acceptable for Carbidopa+Levodopa fixed dose combination (FDC) extended release (ER) capsules, 23.75/95mg, 36.25/145mg, 48.75/195mg, and 61.25/245 mg :*

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
Basket/75 rpm	Medium A (Acid phase): SGF (without enzyme) for 120 min then switch to Medium B (Buffer phase): Phosphate buffer 50 mM pH 7.0 for 240 min.	900 mL for all Strength except 500 mL for the Lower strength	Levodopa % Dissolved 30 min: (b) (4) % 120 min: (b) (4) % 180 min: (b) (4) % 360 min: $\geq$ (b) (4) % Cardidopa % Dissolved 30 min: (b) (4) % 120 min: (b) (4) % 180 min: (b) (4) % 360 min: $\geq$ (b) (4) % Tartaric Acid % Dissolved 30 min: $\leq$ (b) (4) % 180 min: (b) (4) % 360 min: $\geq$ (b) (4) %

*Revise the dissolutions specifications accordingly and submit an updated sheet of specifications reflecting these changes ASAP.*

*We also acknowledge the changes made to the dissolution acceptance criteria for the individual components which are deemed acceptable as follows:*

(b) (4)	Dissolution Method (Medium)	Dissolution Time Point (min)	Acceptance Criteria		
			Mean % CD Dissolved	Mean % LD Dissolved	Mean % TA Dissolved
			Revised	Revised	Revised
(b) (4)	T066DS (SGF)				(b) (4)
	T066DS (SGF for (b) (4) then pH 7)				
	T066DS (SGF for (b) (4) then pH 7)				
	T066DS (SGF fo (b) (4) then pH 7)				

Regards,

Jeannie

Jeannie David, M.S.  
 Regulatory Health Project Manager  
 Food and Drug Administration  
 Phone: (301) 796-4247

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**From:** Jeff Mulchahey [mailto:jmulchahey@impaxlabs.com]  
**Sent:** Friday, August 10, 2012 2:11 PM  
**To:** Peters, Tracy; Bouie, Teshara; David, Jeannie C  
**Cc:** Suneel Gupta; Daven Mody; Lynn Hansen  
**Subject:** NDA 203312 CMC t-con Follow Up

Hi Tracy, Teshara and Jeannie,  
 Thank all of you and the CMC review team for a very productive t-con Tuesday concerning the proposed dissolution specifications and IVIVC for IPX066. During the call Impax agreed to provide additional information linking the proposed tartaric acid dissolution specification at (b) (4) min (i.e. (b) (4)%) and TR0006 by today. Attached is a pdf document which should clarify our rationale for the proposed specification and the relationship to the data in TR0006.  
 It was also agreed during the call that the team would review this information and decide if the proposed specification was acceptable or if additional discussion would be required. Additionally, we will delay submitting updated specifications in eCTD to the NDA until those specifications are agreed upon. Therefore we will wait to update the affected sections of the NDA until we have a response from the CMC review team.  
 In the meantime, we will submit the attached document as Quality/Information to the NDA through the electronic portal next week unless you advise otherwise.

Have a great weekend,  
Jeff  
Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
IMPAX Pharmaceuticals,  
A Division of IMPAX Laboratories, Inc.  
31047 Genstar Road  
Hayward, California 94544  
USA  
Phone: +1-510-240-6426  
Fax: +1-510-240-6113  
E-mail: [jmulchahey@impaxlabs.com](mailto:jmulchahey@impaxlabs.com)  
[www.impaxlabs.com](http://www.impaxlabs.com)

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/s/  
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JEANNIE C DAVID  
08/20/2012

**From:** Peters, Tracy  
**To:** ["Jeff Mulchahey"](#)  
**Subject:** Carton/Container Comments (IPX066)  
**Date:** Tuesday, August 07, 2012 11:39:00 AM  
**Attachments:** [DMEPAcomments.doc](#)

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Hi Jeff,

I have comments from the review team that I would like to relay to you regarding the carton and container that was submitted with the application for IPX066. Please address the issues that are presented in these comments and resubmit the carton/container labeling by August 21st.

**Thank you,**  
**Tracy**

A. Container Label (All bottle sizes)

1. All four strengths use (b) (4) color blocking to highlight the strength, which (b) (4)

2. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and has a prominence commensurate with the prominence with which the proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).

3. As currently presented, the "Rx Only" statement is separated from the other information on the label by a surrounding (b) (4)

4. Revise the presentation of the active ingredients from (b) (4) to read "carbidopa and levodopa."

5. Add the finished dosage form of the product as follows: (carbidopa and levodopa) extended-release capsules.

6. Relocate the NDC to appear in the top third portion of the label per 21 CFR 207.35(b)(3)(i), and increase the readability by presenting the NDC in a horizontal orientation.

7. The proposed proprietary name (b) (4) should be replaced with the name Rytary. Additionally, revise the proprietary name from all upper case (RYTARY) to title case (Rytary) to improve readability.

8. The symbol '- ' is used on the side panel, which should be substituted with its intended meaning. Revise the statement 'Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).' to read 'Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)' to improve clarity.

9. (b) (4)  
(b) (4)

10. Decrease the size of the Impax logo and consider moving it to the side panel since it competes with the prominence of the proprietary name, established name, and strength.

11. Remove the net quantity statement “XX capsules” found on the side panel since this is redundant.

B. Carton Labeling

1. See Recommendations A.1 through A.8

2. Revise the statement [REDACTED] (b) (4) on the principal display panel to read “(b) (4) Bottles, Each Bottle Contains 25 Capsules” for clarity.

3. Remove the statement [REDACTED] (b) (4) from the back panel since this is redundant.

4. [REDACTED] (b) (4)  
[REDACTED] (b) (4)

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

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TRACY J PETERS  
08/07/2012



NDA 203312

**INFORMATION REQUEST**

Impax Laboratories, Inc.  
Attention: Jeff Mulchahey  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Haywood, CA 94544

Dear Mr. Mulchahey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carbidopa-Levodopa Extended Release Capsules.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1. The following dissolution acceptance criteria are recommended for your proposed product:

Time Point	Recommended Acceptance Criteria
	<b>Levodopa % dissolved</b>
<b>30</b>	(b) (4)
<b>120</b>	(b) (4)
<b>180</b>	(b) (4)
<b>360</b>	(b) (4) 0%
	<b>Cardidopa% dissolved</b>
<b>30</b>	(b) (4)
<b>120</b>	(b) (4)
<b>180</b>	(b) (4)
<b>360</b>	(b) (4) 0%

The recommended acceptance criteria at the 30 min time point is based on the ranges of mean release for pivotal clinical and stability batches. The recommended acceptance criteria at other time points is based on the mean dissolution (b) (4) variation from pivotal clinical and stability batches. Additionally, evaluate the impact of this change in dissolution acceptance criteria on the current proposed limits for the parameters given below. Justify current limits or tighten if necessary the following:

- component specification limits
- [REDACTED] (b) (4)
- PARs for all relevant process parameters

Justify and/or revise the limits for the above parameters if needed. Include additional data if necessary, or reference the best supporting data.

Revise the drug release specifications accordingly and submit an updated sheet of specifications. Also provide updated versions of component specifications, fill weight limits and PARs as necessary.

2. It is noted that you did not propose to implement dissolution testing for the tartaric acid component as part of your product specifications, which is not acceptable. You need to implement dissolution testing for tartaric acid at release and stability testing. Submit the following information:
  - Dissolution method development report for tartaric acid
  - Dissolution profile data from the pivotal clinical and stability batches. These data are needed for setting the dissolution acceptance criteria (i.e., specification-sampling time point and specification value) for this component of your proposed product.
3. We acknowledge your response and clarifications provided on submission dated 03/30/12. However, the FDA reiterates the non-acceptability of your proposed IVIVC for the reasons stated in the 74-day letter.
4. The suitability of proposed [REDACTED] (b) (4) as administration vehicles for your proposed drug product should be assessed by demonstrating that stability and release of the drug are preserved in the selected foods. Furthermore, the selected [REDACTED] (b) (4) should also provide the necessary taste masking so that they are found palatable and are suitable for ingestion by the target patient population. Submit primary batch stability data in your NDA from these studies after mixing in the food matrix held for a period of time to cover the in-use period. It is recommended that you perform this stability testing on primary stability batches as a part of the formal stability studies at initial and final time points and at 12 months or the last time point for which data will be available. At a minimum, include testing for Assay and impurities. If this has not already been done for the initial time point of the primary stability batches, it can be done as part of the stability commitment on the confirmation commitment batches.
5. The Agency does not find your proposal for expiration dating adequate for the drug product. Expiration dating begins with the [REDACTED] (b) (4). In addition, [REDACTED] (u) (4). (e.g., it appears you did this for [REDACTED] (b) (4) degradation in long term stability). Provide a new proposal for expiration dating,

supported by data, considering these points. Refer to ICH Quality Guidelines Q1E Evaluation of Stability Data.

6. Your comparability protocol to switch mixers in the future for the commercial manufacturing process of component (b) (4) is not accepted. (b) (4)

To make this change, it is recommended that you review the appropriate scale-up and post-approval guidance for modified-release oral dosage forms from the Agency, and after you have determined the appropriate level of change, report the change supported by appropriate data using the reporting strategy required for the change (e.g., annual report, pre-approval supplement, etc.). Alternatively you may consult the FDA draft guidance for industry; Comparability Protocols - Chemistry, Manufacturing, and Controls Information, February 2003, and provide the information suggested.

7. Include accelerated (or intermediate if accelerated conditions are not appropriate) storage conditions in addition to the long term storage conditions for your commitment to stability testing for the first three commercial batches of each capsule.
8. Include tartaric acid levels in stability testing, since we are recommending tartaric acid dissolution testing on stability.
9. Since you have designated two methods for tartaric acid testing, specify the designated regulatory method for finished capsules and for in-process and component testing.
10. The PAR for (b) (4) time in Component (b) (4) manufacture indicates a range of (b) (4) minutes. (b) (4) time does not appear to have been tested so change this PAR according to the studied range.
11. Referring to your Stage (b) (4) Monitoring plan, notification of all changes, including changes to process parameters, should be provided in accordance with 21CFR 314.70

12. (b) (4)

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief

Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH K SOOD  
06/01/2012



NDA 203312

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Impax Laboratories, Inc.  
30831 Huntwood Avenue  
Hayward, CA 94544

ATTENTION: Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs

Dear Dr. Mulchahey:

Please refer to your New Drug Application (NDA) dated December 20, 2011, received December 21, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for carbidopa and levodopa extended-release capsules, 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, and 61.25 mg/245 mg.

We also refer to:

- Your correspondence submitted on January 16, 2012, received January 17, 2012, requesting review of your proposed proprietary name, (b) (4).
- Your proprietary name amendment, submitted on February 10, 2012, received on February 14, 2012, updating dosing and frequency of administration information for your product.
- The teleconference held March 30, 2012, between representatives of Impax Laboratories, Inc, and the Division of Medication Errors Prevention and Analysis.
- Your correspondence submitted April 4, 2012, received April 5, 2012, amending your Request for Proprietary Name review to change the proposed proprietary name to Rytary.

We have completed our review of the proposed proprietary name, Rytary, and have concluded that it is acceptable. If **any** of the proposed product characteristics as stated in your January 16, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

Rytary will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Tracy Peters at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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LAURIE A KELLEY  
04/11/2012

CAROL A HOLQUIST  
04/12/2012

**From:** [Peters, Tracy](#)  
**To:** ["Jeff Mulchahey"](#)  
**Subject:** IPX066 Information Request  
**Date:** Tuesday, March 06, 2012 12:04:00 PM  
**Attachments:** [IPX066.InformationRequest.doc](#)

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Hello Jeff,

We are reviewing your NDA submission (N203312) for IPX066 and have some information requests and comments to relay to you. Please see the document below. If you could please confirm that you have received this correspondence and provide an estimated time-frame for which we can anticipate the responses (except the labeling request, for which a response date of March 27th has been requested). To assist in expediting the delivery of the information to the review team, please submit the responses by email to me, followed by a formal submission to the NDA.

Thank you in advance for your assistance.

Kind regards,

**Tracy Peters, PharmD**

Regulatory Project Manager  
Food and Drug Administration  
CDER/Division of Neurology Products  
Bld. 22, Room 4369  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Office: 301-796-2953  
Fax: 301-796-9842  
Email: [Tracy.J.Peters@fda.hhs.gov](mailto:Tracy.J.Peters@fda.hhs.gov)

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical:

In Section 2.3 of your proposed product label, you recommend dose adjustments for patients converting from carbidopa/levodopa/entacapone and from carbidopa/levodopa sustained release to IPX066 (TRADE NAME). Please provide a justification and the PK/PD data with the analyses that support these recommendations.

Clinical Pharmacology:

In the NDA you state that the IPX066 formulation used in the pivotal Phase II and III clinical trials, and in the primary registration and site qualification stability studies intended for commercial manufacture, were the same except for the capsule size and color. However, we can not identify which clinical trials used the formulation manufactured in Taiwan except for the BE study (IPX066-B10-01). Please clearly identify the clinical trials that used IPX066 formulation manufactured in Taiwan.

Pharmacometrics:

You based the dose conversion information described in your proposed label on PK/PD data from IPX066-B09-02. However, the PK/PD data from this study that supports your rationale for the proposed dose conversion was not submitted with the NDA. We need the PK/PD data and analysis report for IPX066-B09-02 to complete our review.

Biopharmaceutics:

1. Your proposed in vitro-in vitro correlation (IVIVC) is not acceptable for the following reasons:

- The formulations used in the construction of the proposed (IVIVC) do not meet the requirements of being at least 10% different in terms of the *in vitro* and *in vivo* performance (refer to IVIVC guidance for industry). (b) (4)

(b) (4)  
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(b) (4)

- It appears that the *in vitro* dissolution and the *in vivo* BA batches used in the construction and validation of the IVIVC are different.
- There is not a rank order between the trend in dissolution profiles and the trend *in vivo* exposure for the batches used in the construction and validation of the IVIVC

- The deconvolution step considered the mean concentration time profiles instead of the individual concentration time profiles. It is a common practice to use the individual values to take into consideration the inter-subject variability.
2. Since the IVIVC is not acceptable at this time, you need to revise your proposed dissolution acceptance criteria based on the mean *in vitro* performance of batches used in pivotal clinical studies and batches under stability testing.
    - Submit the complete dissolution profile data (raw data, mean values, and SD) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values).
  3. Submit the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
    - Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, *in vitro* dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product.

Labeling:

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. There is redundancy of information in the Highlights (HL). Information about the concomitant use with dopamine agonists, MAO inhibitors, anticholinergics is repeated in the Dosage and Administration section and the Drug Interactions section.
2. Several cross-references in the HL are incorrect (e.g., there is no information about hypersensitivity to carbidopa or levodopa in Section 11).
3. The product title line in the HL is under review. At this time we recommend the following product title line: TRADENAME (carbidopa and levadopa) extended-release capsules, for oral use.
4. Include the four digit year that the FDA initially approved the combination of active ingredients in the HL.

5. If a product belongs to an established pharmacologic class, the following statement is required in HL: [(Drug Product) is a (name of class) indicated for (indication(s))]. Identify the established pharmacologic class for the drug at: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
6. It is unclear whether there is a known serious hypersensitivity to the excipients of your proposed product. If this is theoretical, it should be not be a contraindication.
7. For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. A general link to a company’s website cannot be used to meet the requirement to have adverse reactions reporting contact information in HL. Either remove the reference to the general website or include a specific website dedicated to reporting adverse reactions. Furthermore, we recommend that you use a toll free number.
8.  (b) (4)
9. A placeholder for the revision date, presented as “Revised: MM/YYYY or Month, Year”, must appear at the end of HL. The revision date is the month/year of application or supplement approval. The date should be revised when submitting new labeling and the month should be in sentence case; not all upper case.
10. The section headings and subheadings in the TOC must match the headings and subheadings in the FPI. For example in Section 7.2, the titles in the TOC and FPI are not consistent.
11. The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1). When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)

12. If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”
13. A horizontal line must separate the TOC and FPI.
14. Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events”, should be avoided.
15. For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

During our preliminary review of your submitted labeling, we have identified the following major labeling content issues:

1. Your proposed Dosage and Administration section is not consistent with the 2010 *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* guidance. It is not an effective communication of important dosage and administration instructions to prescribers. See this guidance at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>
2. The 2011 *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biologic Products — Content and Format* Guidance states that each subsection in the Warnings and Precautions “should accurately characterize the risk.” Subsections including “5.1 General”, “5.2 Laboratory Tests”, “5.4 CNS Effects”, “5.7 Special Population” are not consistent with this guidance. See this guidance at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>

3. According to 21 CFR 201.57c(8), the Drug Interactions section should only include “clinically significant interactions” and “details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.” Your proposed label is not consistent with this regulation.
4. Your proposed  <sup>(b) (4)</sup> section may not be clear to prescribers. We recommend you revise this section, using command language, and include subsections for each individual concept.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

We request that you resubmit labeling that addresses these issues by March 27, 2012. The resubmitted labeling will be used for further labeling discussions.

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/s/  
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TRACY J PETERS  
03/06/2012



NDA 203312

**FILING COMMUNICATION**

Impax Laboratories, Inc.  
Attention: Jeff Mulchahey  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Mr. Mulchahey:

Please refer to your New Drug Application (NDA) dated and received December 21, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for IPX066 (carbidopa-levodopa extended-release capsules) 23.75-95 mg, 36.25-145 mg, 48.75-195 mg, 61.25-245 mg. We also refer to your amendments dated January 17, 2012 and February 6, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 21, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 28, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed

promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Tracy Peters, Regulatory Project Manager, at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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RUSSELL G KATZ  
03/01/2012



NDA 203312

**NDA ACKNOWLEDGMENT**

Impax Laboratories, Inc.  
Attention: Jeff Mulchahey  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Mr. Mulchahey:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: IPX066 (carbidopa-levodopa extended-release capsules) 23.75-95 mg, 36.25-145 mg, 48.75-195 mg, 61.25-245 mg

Date of Application: December 21, 2011

Date of Receipt: December 21, 2011

Our Reference Number: NDA 203,312

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 19, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neurology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/Development/ApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Tracy Peters, Regulatory Project Manager, at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Tracy Peters, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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TRACY J PETERS  
01/03/2012



IND 102,887

**MEETING MINUTES**

IMPAX Laboratories, Inc.  
Attention: Jeff Mulchahey, Ph.D.  
Senior Director, Regulatory Affairs  
31047 Genstar Road  
Hayward, CA 94544

Dear Dr. Mulchahey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IPX066 (carbidopa-levodopa extended release capsules).

We also refer to the meeting between representatives of your firm and the FDA on August 30, 2011. The purpose of the meeting was to discuss the content and structure of an NDA submission for IPX066.

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 Tracy Peters, Regulatory Project Manager at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, M.D.  
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**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** August 30, 2011 (9:00 AM – 10:00 AM)  
**Meeting Location:** CDER White Oak Campus  
Building 22, Room 1311

**Application Number:** IND 102887  
**Product Name:** IPX066 (Carbidopa-Levodopa Extended-Release Capsules)  
**Indication:** (b) (4) Parkinson's Disease, postencephalatic parkinsonism, and (b) (4) parkinsonism following carbon monoxide (b) (4) or manganese intoxication  
**Sponsor/Applicant Name:** IMPAX Laboratories, Inc.

**Meeting Chair:** Russell Katz, M.D.  
**Meeting Requestor:** Jeff Mulchahey, Ph.D.  
**Meeting Recorder:** Tracy Peters, PharmD

**FDA ATTENDEES**

Russell Katz, M.D., Director, Division of Neurology Products  
Gerald David Podskalny, D.O., Clinical Team Leader  
Anne Constantino, M.D., Clinical Reviewer  
Kun Jin, Ph.D., Biostatistics Team Leader  
Sharon Yan, Ph.D., Statistical Reviewer  
Ta-Chen Wu, Ph.D., Senior Clinical Pharmacologist  
Xinning Yang, Ph.D., Clinical Pharmacology Reviewer  
Zachary Oleszczuk, DMEPA Reviewer  
Cathy Miller, DMEPA Reviewer  
Robbin Nighswander, R.Ph., Supervisory Regulatory Project Manager  
Tracy Peters, PharmD, Regulatory Project Manager

**SPONSOR ATTENDEES**

Suneel Gupta, Ph.D. Chief Scientific Officer, Impax Pharmaceuticals  
Ann Hsu, Ph.D. Vice President, Clinical Research, Impax Pharmaceuticals  
Sherron Kell, M.D., MPH Vice President, Clinical Development, Impax Pharmaceuticals  
Sarita Khanna, Ph.D. Senior Director, Biostatistics, Impax Pharmaceuticals  
Mary Martinson Ph.D. Acting Head, Global Neurosciences Therapeutic  
Group, GlaxoSmithKline  
Nishit Modi, Ph.D. Vice President, Clinical Pharmacology, Impax Pharmaceuticals  
Daven Mody, PharmD Director, Regulatory Affairs, Impax Pharmaceuticals  
Jeff Mulchahey, Ph.D. Senior Director, Regulatory Affairs, Impax Pharmaceuticals  
Martin O'Connell, Ph.D. Vice President, Statistics and Data Management,  
Impax Pharmaceuticals  
Tom Thompson, M.D. Clinical Director, Neurosciences Medicines

## 1.0 BACKGROUND

In a letter dated April 5, 2011, IMPAX Laboratories, Inc. requested a Type B Meeting to discuss the submission of an NDA for IPX066 (carbidopa-levodopa extended release capsules), including the type and scope of data to be included in the application. A separate meeting to discuss Chemistry, Manufacturing and Control topics took place on July 21, 2011.

## 2.0 DISCUSSION

### 2.1 Regulatory/General Questions

**Question 1:** Impax proposes to submit an NDA for IPX066 (carbidopa-levodopa extended release capsules) via the 505(b)(2) path relying on the prior finding of safety and efficacy of carbidopa-levodopa products for Sinemet (NDA 017-555), Sinemet CR (NDA 19-856) and Stalevo (NDA 21-485) in combination with clinical trial results demonstrating the safety and efficacy of IPX066 in patients with Parkinson's disease. Does the Agency agree with this approach?

**FDA Response to Question 1:** 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 October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" 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 challenging 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 is scientifically appropriate.

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 that drug and eligible for approval under section 505(j) of the act, we may 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 ANDA that cites the duplicate product as the reference listed drug.

**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), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 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.**

**On page 13 of your briefing document, you indicate that the nonclinical sections of your application will draw on over 30 years of experience with CD-LD products and the extensive nonclinical information available on these products (e.g., Summary Basis of Approvals and package inserts for SINEMET, SINEMET CR, LODOSYN and STALEVO as well as from the published literature). This statement suggests that you are proposing to reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries for support of safety and/or efficacy. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.**

***Discussion:** The Sponsor requested guidance regarding the amount of information they should include from published reports and the product label(s) in their review of the Summary Basis of Approval(s). The FDA explained that the 505(b)(2) application regulations allow the Sponsor to rely on the fact of approval and relevant studies that have been completed and described in the labels or in published reports for other carbidopa-levodopa products. There is no need to provide a detailed review of published clinical data for the reference drug(s) in your 505(b)(2) application. This may also be true with the non-clinical requirement but the non-clinical team will respond to this question as a post-meeting comment.*

***Nonclinical Post-Meeting Comments***

*You should discuss and provide copies of any recent published literature on levodopa/carbidopa that might have an impact on labeling for your product, or indicate that there is none. An overall summary of the nonclinical data on levodopa/carbidopa is not needed.*

**Question 2:** Impax proposes to submit safety information from IPX066-B09-03, an open label extension study at the time of NDA filing with additional safety information to be submitted in a 120 day safety update. Our current expectations are an NDA filing in December 2011 and a data cutoff for filing of 30 June 2011. Approximately 600 subjects have enrolled and data available as of the cutoff date will be included in the NDA. Additional information will be provided in the 120 day safety update. Does the Agency agree with this proposal?

**FDA Response to Question 2:** Yes, please include a tabular presentation of safety data in a manner that facilitates comparison between the events reported in each segment of the safety submission and for the total number of events. The columns should include the safety data at the time of original NDA submission, new events from the NDA submission up to the 120-day safety update and total number of events that included the events reported in the NDA submission and the 120-day

**update. The ISS should be updated with the additional information and any change in the company's results and conclusions concerning IPX066. This should include adverse reaction data, premature patient withdrawals and exposure tables. Please provide patient exposure data by dose and duration of exposure that are non-overlapping and that will clearly define the duration of exposure.**

**Discussion:** *There was no further discussion.*

**Question 2b:** A complete report on the double blind portion of IPX066-B09-06 (Part I) will be included in the NDA. From Part I of the study 74 subjects have enrolled into the 6 month open label extension (Part II). The safety data available as of July 21, 2011 for Part II of the study is very sparse (1 early termination and 7 AEs on 4 subjects). Given the limited safety information as of the data cutoff date only listings will be submitted in NDA. Complete data from the 6 month safety extension will be included in the 120 day safety update. Does the Agency agree with this proposal?

**FDA Response to Question 2b:** **The Statistical Analysis Plan section (p.153) in the pre-meeting package indicates Impax will submit data from at least 350 patients with 6 months and 150 patients completing 1 year of continuous exposure to clinical relevant dosages of IPX066 in the NDA. The data included in the submission must be sufficient to support filing and review. Narrative summaries for the patients, who have died, experienced adverse events leading to discontinuation or other serious adverse events (if requested) are required for filing.**

**Discussion:** *There was no further discussion.*

**Question 3:** Multiple studies have been conducted in healthy subjects during formulation development stage. These studies are referenced in Section 5.3.1.1 entitled "Bioavailability Study Reports". As these formulations were experimental formulations and not the final IPX066 formulation, Impax proposes to provide synopsis reports for these studies. Since these studies did not include the final IPX066 formulation we propose to report PK results of these studies and not to include these studies as part of the integration of studies in healthy subjects for the ISS. Does the Agency agree with this proposal?

**FDA Response to Question 3:** **The NDA submission should include the data from the Bioavailability studies within in a separate data pool. The safety experience should also be discussed separately in the ISS.**

**Discussion:** *Early BA studies explored several different formulations of IPX066 that were different from the final formulation used in the clinical safety and efficacy trials. Approximately 75 healthy volunteers received one of several earlier formulations of IPX066 in these BA studies. Both parties agreed that the ISS should include safety data from BA studies that used the same formulation used in the clinical trials that will support the safety and efficacy in the NDA.*

**Question 4:** Impax plans to include clinical study reports for Study IPX066-B09-01 “Effect of Food on Pharmacokinetics of IPX066” and Study IPX066-B09-04 “Effect of Alcohol on IPX066” in Module 5 Section 5.3.1.2. Does the Agency agree with this proposal?

**FDA Response to Question 4:** Yes.

**Discussion:** *There was no further discussion.*

## 2.2 Clinical Pharmacology Questions

**Question 5:** Does the Agency agree that the clinical pharmacology and biopharmaceutics program meet the Agency’s requirements for a 505(b)(2) filing and appear adequate to support approval of this product?

**FDA Response to Question 5:** We generally agree, though the acceptability will depend on review at the NDA stage. We notice that only the tablet containing 195 mg of levodopa instead of the highest dosage strength (245 mg levodopa) was evaluated in the *in vivo* alcohol dumping study. Please provide a justification in the NDA for not studying the highest strength and whether the result can be extrapolated to the highest strength.

**Discussion:**

*The Sponsor believes that the highest strength capsule (245 mg levodopa content) given with ethanol would be poorly tolerated in healthy volunteers unaccustomed to levodopa. They based their opinion on the results of the current alcohol induced dose-dumping study where the 195-mg strength was used and only 18 of the 27 subjects enrolled, completed the study. The sponsor believes that the results obtained with the 195-mg strength are applicable to the 245-mg strength considering the linear PK profile of IPX066, and they will provide justification in the NDA to support the use of the 195 mg levodopa strength capsule in the *in vivo* alcohol dumping study.*

## 2.3 Non-Clinical Development Questions

**Question 6:** Impax has concluded from the results of the clinical development program that no new safety issues have been identified with IPX066 as compared to currently approved CD-LD products and no new impurities above the threshold for identification have been noted in the IPX066 formulation. Therefore and as discussed at the EOP2 meeting, no additional non-clinical safety studies are required. Does the Agency continue to agree that no additional non-clinical studies are required if the review of the application corroborates the lack of new safety signals?

**FDA Response to Question 6:** If no safety issues are identified following review of the data, no additional nonclinical studies would be required.

**Discussion:** *There was no further discussion.*

## 2.4 Clinical Development Questions

**Question 7:** Based on the summary information presented and pending data review does the Agency agree that the placebo controlled double blind clinical study in early PD patients (IPX066-B08-05) and an active comparator (Sinemet) controlled double blind study in advanced PD patients (IPX066-B09-02) have demonstrated the safety and efficacy of IPX066 in early and advanced PD patients, respectively, and that the trials may support the naïve and advanced PD indication as agreed at the EOP2 meeting?

**FDA Response to Question 7:** **In principle, the trials may support indications for levodopa naïve and advanced PD indication as agreed upon in the EOP2 meeting, however the final decision will depend on the Agency's review of information and data in the NDA.**

**Discussion:** *There was no further discussion.*

**Question 8:** Impax understands that the Division of Neurology Products has recently implemented a new policy requiring prospective assessments for suicidality in all clinical trials for all drugs with central nervous system activity at every visit and in every phase of development. Our studies to date (Phase I: B08-08, B08-09, B08-10, B09-01, B09-04, B10-01; Phase 2: B08-11; Phase 3 B08-05, B09-02, B09-03, B09-06) have not included an instrument to assess suicidality. For these studies, we are proposing a retrospective search of the IPX066 safety database in the ISS that would use a list of suicide keywords. This keyword list would contain text description contained in any of the following text strings: attempt, cut, gas, hang, hung, jump, mutilat, overdos, shoot, slash, suic, poison, firearm, suff, asphyx, self, accid, death, burn, drown, gun, immolat, monoxid, tox, lacerat, injur, and die. Given the long experience with the active ingredient and this 505 (b) (2) submission, is this search for suicidality behavior necessary? If yes, is the approach and list acceptable for identifying suicidal behavior in the studies that will be included in the IPX066 NDA submission?

**FDA Response to Question 8:** **Our recommendations for the analysis of adverse event data for terms related to suicidality are in Appendix 1 at the end of our Preliminary Responses.**

**Discussion:** *The Sponsor generally agrees with FDA recommendations on the analysis of adverse events related to suicidality. They plan a retrospective analysis of suicidality using adverse event data from placebo controlled trials but they request guidance on whether they should include data from active comparator studies that used a crossover design. The Agency agreed that data from crossover trials could be confounded by period and sequence effects and should be excluded from the planned suicidality analysis.*

**Question 9:** IMPAX will submit the SDTM data sets following the current guidelines. However, Impax plans to submit the analysis data sets in the traditional format (FDA Guidance for Industry January 1999). As a sample, a copy of our SDTM and Analysis data (for Protocol IPX066-B08-05) is included on electronic media. Are these formats for SDTM and Analysis data set acceptable?

**FDA Response to Question 9:** Some variables appear to be redundant or the differences among similar variables are not clear. For example, ARM (description of planned arm) and TRTP (planned treatment), both character variables, are confusing. Similarly, visit name and analysis visit sound confusing as well. Some variables are not labeled clearly. For example, EXSTRAT (Stratum assignment) and SVSEQ (sequence number) need further explanation for what these variables are. Please make sure all variables are labeled clearly for their use and distinction.

For “End of Study” visit, we prefer that you have a flag for the last visit while the subject is on study. If a subject withdrew from the study, the entries after withdrawal should be entered as missing “.” instead of carrying forward previous values.

All SAS programs for analysis of primary and secondary endpoints need to be submitted with clear label of what program is about.

**Discussion:** *The Sponsor will address the redundancy or differences among similar variables in the NDA. The Sponsor requested clarification regarding the method they plan to use to flag the End of Study visit in the datasets and the company’s planned sensitivity analyses for the effects of missing visits. The Agency’s statistical reviewer is willing to provide comments on the presentation of the End of Study visit flag and general comments regarding the sponsor’s planned sensitivity analyses prior to submission of the NDA.*

**Question 10:** The outline and organization for Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) is presented in Section 10. Does the Agency agree with the proposed outline for information to be included in the ISS and ISE?

**FDA Response to Question 10:** Preliminary FDA Response:  
In general, we find the organization of the ISS and ISE to be acceptable. We recommend that your safety dataset submission be organized into the following:

- Pool 1a: Placebo controlled studies for early PD which includes the following study:**
- IPX066-B08-05 A placebo controlled study of early Parkinson’s subjects. This study evaluated the 3 different fixed doses of IPX066 with placebo.

**Pool 1b: All active controlled studies in advanced PD which includes the following studies:**

- **IPX-066-B09-02** An active controlled (IR CD-LD) study in advanced PD subjects
- **IPX-066-B09-06 (part 1)** A crossover study that compares IPX066 with a combination of CD-LD and entacapone.

**Pool 1c: Combined data from Pool 1a and 1b**

**Pool 2a: Uncontrolled, open label safety trials and trial extensions in early PD subjects**

- **IPX066-B09-03: Includes subjects who completed IPX066-B08-05.**

**Pool 2b: Open label extension study in advanced PD subjects includes the following studies:**

- **IPX066-B08-11**
- **IPX066-B09-02**
- **IPX-066-B09-06 (part 2)**

**Pool 2c: Safety data from all open label trials involving LD naïve and advanced PD patients and all open label extensions of placebo-controlled trials (pools 2a plus pool 2b).**

**Data from trials involving healthy volunteers should be contained in a separate data pool.**

***Discussion:*** *The Sponsor generally agrees to the Agency's response. However, they propose submitting data from IPX-066-B09-06 (part 2) separate from pooled data in the ISS since data from only a few patients (n=74) will be available at the time of NDA submission. The safety data from all available patients will be incorporated into Pools 2b and 2c at the time of the 120-day safety update.*

***Question 11:*** Impax intends to provide an interim summary report for Protocol B09-03, an ongoing, open label follow up trial of subjects completing Protocols B08-05, B08-011, and B09-02. Using a data cutoff of 30 June 2011, safety data from this portion of the trial will be reported. The data from B09-03 and the previous trials will also be combined to assess long term use with IPX066.

Impax intends to provide the data unique to Protocol B09-03 in SDTM. The combined study data will be provided in traditional analysis data sets (FDA Guidance for Industry January 1999). Does the agency have any issues with this approach for ongoing studies?

***FDA Response to Question 11:*** **Impax may provide an interim summary report for Protocol B09-03 in traditional analysis datasets. The Safety Database must include data for patients meeting the exposure criteria for the number of patients (excluding healthy volunteers) exposed and the duration of exposure described in our response**

**to question 2b. You can report safety data from this portion of the trial but for NDA filing purposes, the safety data needs to be complete.**

**Discussion:** *There was no further discussion.*

**Question 12:** Impax has completed the clinical development of IPX066. The safety and efficacy of IPX066 has been demonstrated in a phase II study in patients with advanced PD (Study IPX066-B08-11) and in 2 phase III studies in patients with early and advanced PD (Studies IPX066-B08-05 and IPX066-B09-02, respectively). Two additional phase III studies, an open label extension of previous Phase II and III IPX066 studies and a comparison of IPPX066 to carbidopa-levodopa-entacapone, are ongoing at the present time and will be reported in the NDA. The IPX066 clinical pharmacology program has defined the pharmacokinetics of IPX066 in the PD patient population. Studies in (b) (4) IPX066 compared with Sinemet, Sinemet CR, and Stalevo, have investigated the effect of a high fat meal on the PK of IPX066 capsule and evaluate the effect on sprinkling capsule contents onto (b) (4), have investigated the effect of 240 mL of 0%, 5%, 20%, and 40% v/v alcohol on the IPX066 capsule formulation, have demonstrated the dose proportionality of IPX066 dosage strengths, and have demonstrated bioequivalence of IPX066 manufactured at Impax facilities in Hayward, USA and in Jhunan, Taiwan.

The proposed indication for IPX066 is taken from currently approved CD-LD products: "IPX066 is indicated (b) (4) the treatment of (b) (4) Parkinson's disease (b) (4), post-encephalatic parkinsonism, and (b) (4) parkinsonism (b) (4) may follow injury to the nervous system by carbon monoxide (b) (4) or manganese intoxication."

Does the Agency agree that the IPX066 clinical development program (clinical pharmacology and phase III trials) is adequate to support an NDA filing and approval, pending data review?

**FDA Response to Question 12:** **In principle the data will appear to be sufficient for NDA filing, however, the final decision regarding the acceptability of the NDA for filing, the agency's finding of safety and effectiveness and wording of the indication (if approved), can only be decided after the Agency completes its review of the NDA.**

**Discussion:** *There was no further discussion.*

**Question 13:** Given the extensive history of CD-LD use in PD, Impax proposes a REMS for IPX066 consisting of a Medication Guide to patients describing the unique attributes of the product with an emphasis on differences in dosing between IPX066 and other CD-LD products. Does the Agency agree that a Medication Guide is adequate as a REMS for IPX066?

**FDA Response to Question 13:** **We do not expect a REMS will be required for this application.**

**Discussion:** *There was no further discussion.*

**Question 14:** Can the Agency confirm the eligibility of IPX066 for a waiver of pediatric requirements on the basis of its intended use in PD?

**FDA Response to Question 14:** **The Division will support a waiver from the requirement to conduct pediatric studies to PeRC but the NDA must include a waiver request and your justification stating why you believe Pediatric studies are not feasible in this population.**

**Discussion:** *There was no further discussion.*

## **Appendix 1**

### **Suicidality Analysis**

#### **Search for “Possibly Suicide-Related” Adverse Events and Preparation of Narrative Summaries**

##### **Time Frame for “Possibly Suicide-Related” Adverse Events**

This search should be strictly limited to adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. Adverse events should not be included if they occurred prior to randomization or more than 1 day after discontinuing from randomized treatment. The end of trials with a tapering period should be set to be at the beginning of the tapering period. Events occurring more than 1 day after discontinuing from randomized treatment should be excluded even if discontinuation occurred before the nominal endpoint of the trial. For example, if a patient either discontinued of his own volition or was asked to discontinue by the investigator after 2 weeks of randomized treatment in a trial of 8 weeks duration, and the patient then experienced a “possibly suicide related” adverse event 2 days after stopping, that event should not be included.

##### **Search Strategies for “Possibly Suicide-Related” Adverse Events**

The following search strategies should be employed to identify adverse events of possible interest:

- Any events coded to preferred terms that include the text strings “suic” or “overdos,” including all events coded as “accidental overdose” should be included.
- Regardless of the preferred term to which the verbatim term is mapped, all verbatim terms should be searched for the following text strings: “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-”, “overdos-”, “self damag-”, “self harm”, “self inflict”, “self injur-”, “shoot”, “slash”, “suic-”, “poison”, “asphyxiation”, “suffocation”, “firearm” should be included.

Note: Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string “cut” might identify the word “acute”). These terms might be characterized, as “false positives” in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

<u>Study # Patient # Treatment Assignment</u>	<u>Term in Which Text String</u>
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### Occurred

The patients in this table will have as many rows as they have potential events.

- All deaths and other serious adverse events (SAEs) should be included.
- All adverse events coded as “accidental injury” should be included.

### Preparation of Narrative Summaries for “Possibly Suicide-Related” Adverse Events

A complete set of narrative summaries should be prepared and collected for all “possibly suicide-related” adverse events. In some cases, narratives will have already been prepared, e.g., deaths and SAEs. In other cases, however, you will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. You should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

- Patient ID number
- Trial number
- Treatment group
- Dose at time of event (mg)
- Recent dose change – elaborate on timing and amount of dose change
- Sex
- Age
- Diagnosis
- History of suicidal thoughts
- History of suicide attempt
- History of self harm
- Adverse event Preferred term
- Adverse event Verbatim term
- Serious adverse event (y/n)
- Number of days on drug at time of event
- Treatment was discontinued following event (y/n)
- Patient had an emergency department visit and was discharged (y/n)
- Patient was hospitalized (y/n)
- Patient died (y/n) – if yes, elaborate on cause of death
- Associated treatment emergent adverse events
- Concurrent psychosocial stressors
- Psychiatric co-morbidities
- Concomitant medications
- Other pertinent information (e.g., family history of psychiatric disorders)

### **Other relevant information for preparing narrative summaries:**

-Patients may be identified as having events of interest in one or more of the above searches, and they may have more than one event of interest. In no case, however, should there be more than one narrative summary per patient. In cases where there is more than one event for a given patient, each different event should be clearly demarcated in the narrative.

-Only events occurring during the “exposure window” defined as during the double-blind phase (including the first day after abrupt discontinuation or the first day of taper, if tapering is utilized) should be included in the narrative summary, i.e., do not include any pre-randomization events or events occurring more than 1 day after stopping randomized treatment or during the tapering period.

-Do not exclude events of interest on the basis of your judgment that they might not represent “treatment-emergent” events; we feel this judgment is too difficult to make and we prefer to simply include all potentially relevant events, regardless of whether or not similar thoughts or behaviors may have occurred prior to treatment.

### **Classification of “Possibly Suicide-Related” Adverse Events**

Once the narrative summaries for “possibly suicide-related” adverse events are prepared and collected, we ask that you accomplish a rational classification of these events using the approach that was well-characterized by the Columbia group for the pediatric suicidality narratives. This approach was described in detail by Dr. Kelly Posner at the September 13 and 14, 2004 advisory committee meeting. The details are provided in her slides for that meeting (available on FDA’s website), in the transcript for that meeting, and in other reviews, etc. pertinent to pediatric suicidality and available on FDA’s website at the following URLs:

- Slides [http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1\\_06\\_FDA-Posner.ppt](http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt)
- Briefing Document, transcripts, etc.  
<http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>

### **The categories of interest from FDA’s standpoint are as follows:**

Suicide attempt (code 1)  
Preparatory acts toward imminent suicidal behavior (code 2)  
Self-injurious behavior, intent unknown (code 3)  
Suicidal ideation (code 4)  
Not enough information (code 5)  
Self-injurious behavior, no suicidal intent (code 6)  
Other: accident; psychiatric; medical (code 7)

Those individuals who classify the narratives must have the appropriate expertise and training to

accomplish this task.

Prior to their rational classification, the narratives must be blinded to details that might bias their assessments. The details of appropriate blinding of the narratives can also be obtained in the transcript from the advisory committee meeting referred to above, and the materials available on FDA’s website pertinent to that meeting. We request that you block out the following information that could reveal treatment assignment:

Identifying patient information, identity of study drug, and patient's randomized drug assignment Page 5

- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial
- All years with the exception of years in remote history
- Study drug start and stop dates (month, day, and year)
- All medications, both prescription and non-prescription, whether taken before, during, or after the study; non-pharmaceutical substances (e.g., alcohol, tobacco) should not be blocked out
- Names of medications involved in overdoses; the number of pills consumed should not be blocked out
- Indications for medications started during or after the study
- Indications for study drug

Decided on an approach to accomplishing the task of blinding and classifying the narratives.

**Data Submission to DNDP**

In order to perform additional analyses investigating the relationship between exposure to AEDs and “suicide-related” adverse events in adults and the pediatric population, we would appreciate your submitting the following variables as outlined in the next table. Note that we are requesting information from placebo (and “low dose-placebo”) controlled trials only. We expect that you will provide us with a completed dataset.

Variable name	Type	Description	Coding notes
SOURCE	Character	First few letters of your drug name	
INDICATION	Character	Disease being studied in trial	E.g., epilepsy- adjunctive, epilepsy- monotherapy, bipolar disorder, migraine, etc.
TRIAL	Character	Trial ID	
CTPID	Character	Patient ID within each trial	
UNIQUEID	Character	A unique ID for every patient	Composed of “TRIAL” and “CTPID” joined in that order with no intervening punctuation or dashes
AGE	Numeric	Patient age	In years

AGECAT	Numeric	Age category	1=5-11 2=12-17 3=18-24 y 4=25-64 y 5=65 y or more
GENDER	Numeric	Patient gender	1=female 2=male

Variable name	Type	Description	Coding notes
RACE	Numeric	Patient race	1=White Caucasian 2=African-American 3=Hispanic 4=Asian 5=Other . = Missing
SETTING	Numeric	Setting of trial	1=inpatient 2=outpatient 3=both
LOCATION	Numeric	Location of trial	1=North America 2=Non-North America
TXARM	Numeric	Randomized treatment	1=drug 2=placebo 3=active control 4=low dose-placebo No missing values are allowed in this variable.
TXLOW	Character	Name of drug used as low dose-placebo	Leave patients in other treatment arms blank
TXACTIVE	Character	Name of drug used as active control	Leave patients in other treatment arms blank
EVENT	Numeric	This variable contains the code for the first suicidality event. If a patient had more than one event in the desired "exposure window", then the most severe event should be listed. Severity is decided based on the following order of codes 1>2>4>3>5	0=no event 1=suicide attempt 2=preparatory acts toward imminent suicidal behavior 3=self-injurious behavior, intent unknown 4=suicidal ideation 5=not enough information No missing values are allowed in this variable.

EVENTDAY	Numeric	The number of days to the first suicidal event counting from the day of the first dose.	for patients without events, this variable should contain days until end of trial or until premature discontinuation for patients with more than one event, this variable should contain days until the most severe event that is listed under the variable "EVENT"
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Variable name	Type	Description	Coding notes
			No missing values are allowed in this variable.
DISCONT	Numeric	The patient discontinued before the end of the controlled portion of the trial	0=No 1=Yes No missing values are allowed in this variable

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUSSELL G KATZ  
09/28/2011



IND 102,887

**MEETING MINUTES**

IMPAX Laboratories, Inc.  
Attention: Jeff Mulchahey, Ph.D.  
Senior Director, Regulatory Affairs  
31047 Genstar Road  
Hayward, CA 94544

Dear Dr. Mulchahey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IPX066.

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2011. The purpose of the meeting was to discuss the CMC content of the NDA expected to be filed before the end of 2011.

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

If you have any questions, call me at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Teshara G. Bouie, MSA, OTR/L  
CDR, USPHS, Regulatory Health Project Manager  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** July 21, 2011; 11:00 a.m. – 12:00 p.m.  
**Meeting Location:** FDA White Oak Campus

**Application Number:** IND 102,887  
**Product Name:** IPX066  
**Indication:** Parkinson's disease  
**Sponsor/Applicant Name:** IMPAX Laboratories, Inc.

**Meeting Chair:** Ramesh Sood, Ph.D.  
**Meeting Recorder:** Teshara G. Bouie

**FDA ATTENDEES**

Office of New Drug Quality Assessment

Ramesh Sood, Ph.D., Branch Chief  
Martha Heimann, Ph.D., CMC Lead  
Akm Khairuzzaman, Ph.D., CMC Reviewer  
Tien Mien Chen, Ph.D., Biopharmaceutics Reviewer  
Teshara G. Bouie, Regulatory Health Project Manager

**SPONSOR ATTENDEES**

Suneel Gupta, Ph.D. CSO  
Jim Kou, Ph.D. Director, Product Development  
Steve Fields, Ph.D. Director, Analytical Sciences  
Jeff Mulchahey, Ph.D. Senior Director, Regulatory Affairs  
Lynn Hansen, RAC. Manager, Regulatory Affairs  
Prachi Shah, M.B.S., RAC. Regulatory Affairs Associate

## 1.0 BACKGROUND

IND 102,887 is proposed for the treatment of Parkinson's disease. On May 13, 2011, the sponsor submitted a type B meeting request to discuss the CMC content of the NDA expected to be filed before the end of 2011. Background materials were received June 20, 2011. Preliminary meeting responses were sent to the sponsor on July 19, 2011.

## 2. DISCUSSION

### *Question 1:*

Impax plans to include information about two suppliers for each of the two drug substances in IPX066 in the NDA (i.e. CD from (b) (4) and (b) (4); LD from (b) (4) and (b) (4)). We propose to combine common elements of each drug substance (e.g. structure, CAS number) into a single presentation (one CTD section 3.2.S.1 General Information and 3.2.S.5 Reference Standards for each drug substance) to avoid redundancy in the drug substance sections of the application. Unique aspects of each drug substance (e.g. CTD sections describing Manufacture, Characterization, Control, Container and Stability; 3.2.S.2, 3.2.S.3, 3.2.S.4, 3.2.S.6 and 3.2.S.7) will be presented by supplier within the sections on that drug substance. Does the Agency agree with this proposal?

### ***FDA Preliminary Response:***

*For general chemistry information, you can combine the common elements of each drug substance (e.g. structure, CAS number) into a single presentation in CTD section 3.2.S.1. of the NDA submission. However, you also need to provide all the DMF reference numbers for each drug substance from every vendor that you intend to purchase. The relevant DMFs should contain all the CMC information and these details are subject to review. We also would like to remind you that we expect to see single unified acceptance criteria for each drug substance in the NDA irrespective of the various sources.*

Meeting Discussion: The Agency reiterated that the submission should have a single set of API acceptance criteria for each API component. The Agency understands there may be different process impurities in the API from each source. The non-applicable tests based on the source of the API can be noted in the specification through appropriate footnotes.

### *Question 2:*

The specifications planned for the commercial product are listed in Table 3. The numerical limits will be reviewed and possibly revised for the NDA submission based on additional stability and manufacturing data that are obtained prior to submission. Rationale and justifications for the specifications are presented in Section 8 and 9.

a. Does the Agency agree that the list of Test Attributes adequately controls the IPX066 (extended release CD-LD) drug product?

**FDA Preliminary Response:**

The details of the specification and their numerical limits are subject to review once NDA is submitted. We have noticed that one of the components (component (b) (4)) in your multi-particulate extended release system is tartaric acid which is a functional excipient. (b) (4)

Therefore, we suggest that you include the content uniformity of the tartaric acid in your product specification.

You should either include microbiological test with limit or justify why a such test is not necessary for this product.

**Meeting Discussion:**

The Sponsor explained how the tartaric acid (b) (4) proposed to conduct an assay test as a quantitative control for tartaric acid in the drug product. The agency agreed upon this proposal and advised that Impax should re-evaluate clinical lots to evaluate the influence of tartaric acid on bioavailability then propose a specification. The Agency also agreed that Impax can provide the tartaric acid finished product release data by day 120.

b. Is the Agency willing to consider a dissolution specification of up to (b) (4) time points?

**FDA Preliminary Response:**

As per FDA's Guidance for Industry entitled, "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations", Section B.1. Setting Dissolution Specifications Without an IVIVC (p.16-17),

- A width greater than  $\pm 10\%$  is allowed when there is a significant number of batches that will not be able to meet the specifications of the  $\pm 10\%$  range (a total width 20%). In this instance, a range of the mean value  $\pm 12.5\%$  (a total width 25%) will be permitted.

If you propose a mean value (b) (4)%, you should provide data from an in vivo BE study showing that the lots on the upper (mean (b) (4)%) and lower (mean (b) (4)%) limits (a total width of (b) (4)%) of the specifications are bioequivalent.

Alternatively, in the presence of an acceptable (b) (4) IVIVC, the mean predicted  $C_{max}$  and AUCs from the dissolution profiles using the IVIVC will permit deviations from the  $\pm 10\%$  range, but these deviations should not be greater than  $\pm 20\%$ .

Finally, the adequacy of the proposed dissolution methodology and specifications will be determined when the NDA is submitted for review (from Biopharmaceutics).

**Meeting Discussion:** No further discussion at the meeting.

*Question 3:*

Impax manufactured the six (6) site qualification stability lots in the quantities of bulk capsules that were agreed to by the Agency (Agency letter of 18 October 2010). Impax proposes to take representative samples from across the bulk capsule batch that will then be packaged for the bottle stability study, (b) (4) (see Section 6.3). Does the Agency agree that this proposed site qualification packaging plan will be acceptable for the purpose of the Taiwan site qualification?

***FDA Preliminary Response:***

*We agree that only the representative samples from across the bulk capsule batches will be packaged for the bottle stability studies.* (b) (4)

*We would like to remind you that using the principles described in the FDA guidance for industry (SUPAC-MR: Modified Release Solid Oral Dosage Forms, September 1997) this change is considered as a level 3 manufacturing site change and therefore three (3) batches with three months accelerated stability data along with the long terms stability data is required for your site qualification.*

**Meeting Discussion:** (b) (4)

Sampling occurs within a batch. There are 6 site qualification lots on stability. They will sample each bulk capsule lot separately.

*Question 4:*

The registration stability plan for IPX066 agreed to by the Agency contains 20 separate stability studies. Impax plans to include in the NDA data through the 12-month time point on 15 of those studies, and through the 9-month time point on the last 5 studies. Impax plans to provide an update to the stability in the 120-day safety update that will include the 12-month time point on the last 5 studies.

- Does the agency agree that stability information can be updated in the 120-day safety update?

***FDA Preliminary Response: Yes.***

**Meeting Discussion:** No further discussion at the meeting.

- Impax desires (b) (4) month expiry dating at the time of approval based on ongoing registration stability protocols which will include 24-months data (available November-December 2012). Does the agency agree that extension of the expiry dating can be made based on acceptable stability data to be reported in the NDA annual report?

***FDA Preliminary Response: Yes.***

**Meeting Discussion:** No further discussion at the meeting.

*Question 5:*

Impax proposes commercial packaging in 25-, 100- and 240-count bottles using materials as used in the product stability program. The bottle package parameters for the proposed commercial counts and for the registration stability study are described in Section 10. This program will also include changing the lowest count bottle in the Taiwan Site Qualification lot stability studies from (b) (4) 25-count. Does the Agency agree that the proposed configurations are adequately bracketed by the current stability program?

***FDA Preliminary Response:*** *Yes.*

Meeting Discussion: No further discussion at the meeting.

*Question 6:*

Regarding the Taiwan site qualification proposal of 11 June 2010, Impax requests clarifications and agreement on the following points discussed in the Agency's response letter of 18 October 2010.

- a. Impax release and stability testing of dissolution for clinical and registration lots has consisted of two acid-phase time points (30 and 120 min) and seven neutral pH time points (from 140 to 360 min, including 4- and 6-hour time points). In the dissolution comparison testing (f2 comparison) for the Taiwan site, Impax proposed and the Agency agreed to time points of 1, 2, 4 and 6 hours. Impax proposes to change the (b) (4) time point to 30 min in the f2 comparison to be consistent with the data acquired during development; this change will also provide a more stringent challenge for the immediate release portion of the formulation. Does the Agency agree with this proposal?

***FDA Preliminary Response:***

*Yes, your proposal appears acceptable to change the dissolution time point of (b) (4) to 30 min for better characterizing the immediate release portion of the formulation. Again, the adequacy of the proposed dissolution methodology and specifications will be determined when the NDA is submitted for review.*

Meeting Discussion: No further discussion at the meeting.

1. Impax has conducted in vitro dissolution and in vivo PK studies using IPX066 supplies manufactured in Hayward to demonstrate the absence of dose dumping in the presence of alcohol. In addition, Impax has conducted a clinical study (IPX066-B10-01) which demonstrated the bioequivalence of IPX066 supplies manufactured in Hayward and Jhunan. Does the Agency agree that the in vitro and/or in vivo studies evaluating the effect of alcohol do not need to be repeated with supplies manufactured in Jhunan?

***FDA Preliminary Response:***

*Yes, we agree that repetition is not necessary. Please submit the study results of the in vitro alcohol dose-dumping and the in vivo alcohol dose-dumping human PK studies completed to the NDA for review.*

Meeting Discussion: No further discussion at the meeting.

- b. In accordance with the SUPAC guidance for Modified Release Dosage Forms (FDA Guidance for SUPAC-MR), the dissolution comparison between sites for this product would only require testing under the intended commercial test method conditions (which are 2 hours in acid, followed by 4 hours in pH 7 buffer) and comparison of the results, rather than the dissolution tests in three different media pH as indicated in the Agency response letter. Does the Agency agree?

***FDA Preliminary Response:***

*Yes, we agree. Under SUPAC guidance for Modified Release Dosage Forms, the dissolution comparison between sites for this product would require testing under the intended commercial test method conditions.*

*As indicated in the Agency Response Letter dated October 18, 2011, the request for three media evaluation is to remind you to include this information as a part of the Dissolution Development Report in the NDA.*

Meeting Discussion: No further discussion at the meeting.

- c. Impax is initiating the packaged capsule stability program using storage conditions as agreed upon by the Agency, with the exception that the intermediate stability condition 30°C/65%RH will be tested and the (b) (4) °C/ (b) (4) %RH condition will not be tested. The rationale for this proposed change is discussed in Section 6.2. Does the Agency agree with the proposed change?

***FDA Preliminary Response: Yes.***

Meeting Discussion:

- d. As discussed in Question 6, the lowest bottle count has been changed from (b) (4) to 25 (c. f. Question 5). Does the agency agree with this change?

***FDA Preliminary Response: Yes.***

Meeting Discussion: No further discussion at the meeting.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

### **4.0 ACTION ITEMS**

None.

### **5.0 ATTACHMENTS AND HANDOUTS**

None.

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*{See appended electronic signature page}*

Teshara G. Bouie  
Regulatory Health Project Manager  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Branch I, Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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TESHARA G BOUIE  
08/26/2011

RAMESH K SOOD  
08/26/2011



IND 102,887

**SPECIAL PROTOCOL ASSESSMENT –  
NO AGREEMENT**

IMPAX Laboratories, Inc.  
Attention: Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
31047 Genstar Road  
Hayward, CA 94544

Dear Dr. Mulchahey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for IPX066, Carbidopa-Levodopa Extended Release Capsules.

We also refer to your June 23, 2009 request, received on June 24, 2009, for a special protocol assessment of a clinical protocol (Protocol IPX066-B09-02, "A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson's Disease.")

We note that this protocol includes revisions discussed in our March 20, 2009 Special Protocol Assessment (SPA) letter for Protocol IPX066-B08-06 and feedback from the Division discussed at the May 7, 2009 meeting and from the June 4, 2009 meeting minutes.

We have completed our review and, based on the information submitted, do not agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission.

We also have the following responses to your questions raised in your June 23, 2009, submission.

1. Does the Division agree with the revised study design which deletes the carbidopa-levodopa + entacapone comparator arm?

FDA Response: Yes, we agree with the simplification of the trial design which will greatly facilitate performance of the trial and interpretation of the results. However, the design has features that still make it difficult to interpret the trial results based on the primary outcome alone. The reliability of the primary outcome will depend greatly upon

patient compliance with keeping complete and timely diary entries in accordance with the protocol. Extensive efforts to improve the validation and reliability of patient diary data may be reassuring but ultimately the quality of patient diary data would not be known until the data is reviewed by the agency. The number of dropouts and the impact of different methods of imputation are also unknown. There is also no optimal time-point in the current trial design to consider as the appropriate “Baseline” for analysis. The trial design proposed in the SPA is unique and the Division can not rely on past experience to conclude that the current statistical plan will provide a reliable estimate of the efficacy of IPX066. Because of the uncertainty regarding the selection of the most appropriate “Baseline” value for analysis of the primary endpoint, the results of the primary endpoint must be supported by positive although not necessarily statistically significant, findings for the secondary outcomes. The trial you have proposed may well provide evidence to support a claim of effectiveness. Nevertheless, at this point in time, we cannot agree prospectively to accept the results of the primary outcome without consideration of the potential flaws in the design.

2. Does the Division agree with the statistical analyses described in the revised protocol?

FDA Response: A sensitivity analysis adjusting for the primary outcome with Baseline defined as the end of the IR CD-LD adjustment period (near the end of Week 3) is needed to support a robust positive effect of IXP066.

3. Does the Division agree with the proposed use of the m-MIDI and associated severity scales in the proposed trial?

FDA Response: Yes.

4. Does the Division agree that the subject population as defined by the Inclusion and Exclusion criteria appropriately enrolls patients with advanced Parkinson’s disease?

FDA Response: Yes.

5. Does the division agree that a positive result in the proposed protocol would satisfy the requirement to demonstrate a clinical benefit of IPX066 in patients with advanced Parkinson’s disease?

FDA Response: Yes but analysis of the secondary outcomes should support a positive finding for the primary endpoint. The Division holds this opinion because of the well known difficulties collecting Parkinson’s diary data, which you have chosen as the primary endpoint for this SPA. In addition, please see our answer to question 1.

In addition, we have the following comment.

- There is no secondary outcome that provides a general assessment of the patient's functional ability or the extent of disability except on scales limited to the effects of PD. This limits the ability to estimate and document the severity of adverse events and confirm the overall efficacy outcome.

If you choose to submit a revised protocol, it should address all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*). This meeting would be limited to discussion of this protocol.

If you have any questions, call Stacy Metz, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- IND 102887	----- ORIG 1	----- IMPAX LABORATORIES INC	----- IPX066, Carbidopa-Levodopa Extended Release Capsules

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/s/  
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RUSSELL G KATZ  
08/07/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 102,887

IMPAX Laboratories, Inc.  
Attention: Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
31047 Genstar Road  
Hayward, CA 94544

Dear Dr. Mulchahey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IPX066 Carbidopa-Levodopa Extended Release Capsules.

We also refer to the meeting between representatives of your firm and the FDA on May 7, 2009. The purpose of the meeting was to discuss the Division's Special Protocol Assessment (SPA) responses to your protocol and questions from our March 20, 2009 SPA letter.

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

If you have any questions, contact Stacy Metz, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Date and Time:** May 7, 2009  
**Meeting Type:** Type A  
**Meeting Category:** SPA Responses  
**Meeting Location:** White Oak Bldg #22, Room 1311  
**Application Number:** IND 102,887  
**Product Name:** IPX066  
**Received Briefing Package:** April 21, 2009  
**Sponsor Name:** Impax Laboratories Inc.  
**Meeting Requestor:** Jeff Mulchahey, PhD  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Stacy Metz, Pharm.D.  
**Meeting Attendees:**

**FDA Attendees**

Russell Katz, M.D., Director  
Gerald (Dave) Podskalny, M.D., Clinical Team Leader  
John Marler, M.D., Clinical Reviewer  
Sharon Yan, PhD, Biostatistics Reviewer  
Stacy Metz, Pharm.D, Regulatory Project Manager

**External Attendees**

Suneel Gupta, PhD, Chief Scientific Officer  
Ann Hsu, PhD, Vice President, Clinical Research  
Sherron Kell, MD, M.P.H, Vice President, Clinical Development  
Nishit Modi, PhD, Vice President, Clinical Pharmacology  
Jeff Mulchahey, PhD, Senior Director, Regulatory Affairs  
Martin O'Connell, PhD, Vice President, Statistics and Data Management.

**1.0 BACKGROUND**

In a letter dated April 6, 2009, IMPAX Laboratories Incorporated requested a Type A meeting for IND 102,887 to discuss our Special Protocol Assessment (SPA) responses to your protocol and questions from our March 20, 2009 SPA letter. The Division's

preliminary responses to the questions posed in the background package were electronically mailed to you on May 7, 2009.

## 2.0 DISCUSSION

Question 1:

Does the Division agree that the proposed use of riboflavin would adequately blind subjects to the possible discoloration of urine by entacapone?

### **Preliminary FDA Response:**

**The plan to administer riboflavin to all patients enrolled in the clinical trial is acceptable to the agency. However, you should consult with the specific regulatory authority requesting the comparison of IXP066 to entacapone and levodopa plus a decarboxylase inhibitor. Can you confirm that there are no known interactions between any of the drug products administered in the proposed trial and riboflavin?**

*Meeting Discussion:*

*You have confirmed and will document that there are no known interactions with riboflavin and any of the components of the drug product.*

Question 2:

If the proposed blinding to entacapone treatment is acceptable, does the Division agree that the study design will allow the use of the CD-LD + entacapone arm as a comparator to IPX066?

### **Preliminary FDA Response:**

**The addition of riboflavin to help maintain the integrity of the blind for patients receiving entacapone is acceptable. An alternate method would be to use an independent rater to collect data for the trial outcome measures.**

**The results of the proposed trial would not be sufficient to support a claim of superiority or non-inferiority of IPX066 compared to the combination of carbidopa/levodopa/entacapone. Effectiveness and not superiority/non-inferiority is the primary goal of the proposed study. Claims based on results of secondary endpoints must meet the Division's criteria to be included in the product label.**

**Typically, secondary endpoints can only be included in the label if the type I error rate is controlled by correcting for multiple comparisons. In addition, study results that are included in the product label (even in the clinical trials section) must be replicated in a supporting study.**

*Meeting Discussion:*

*All agreed that the focus of the proposed trial was to evaluate the effectiveness of IPX066 without any intention to claim superiority to any other treatment.*

Question 3:

IMPAX proposes to use a commercially available riboflavin product in a non-blinded manner. Does the Division agree with this plan?

**Preliminary FDA Response:**

**No, patients could defeat the blind by being selectively non-compliant with riboflavin. Riboflavin must be encapsulated in the same manner as the other study medications. Please identify the product and source for the commercially available riboflavin that will be used in the drug trial.**

*Meeting Discussion:*

*You asked whether the Agency requires data on pharmacokinetics, dissolution, and bioavailability for OTC vitamin supplements used for the purpose of blinding. Since the meeting, the Division has determined that there is no requirement for PK that we know of if the only purpose of the riboflavin is to blind the study.*

Question 4:

Does the Division agree with the proposed imputation and handling of missing data?

**Preliminary FDA Response:**

**Clinical**

**The primary endpoint must be percent of awake off time per 24 hour period.**

**Valid patient diaries should contain no more than 2 hours (four 30-minute periods) of missing entries (total) per 24-hour diary. If a 24-hour diary contains more than 2 hours of missing data the diary should not be considered valid. Valid diaries for the**

**3 consecutive days should be averaged with respect to the percent off time and used as the primary outcome variable. The following method for calculating the percent of awake off time should be followed:**

- **If only 2 of the 3 24-hour diaries are valid then the percentage of awake off time should be averaged over those 2 days to calculate the primary endpoint.**
- **If only 1 of the daily diaries is valid then it will be used to calculate the primary endpoint.**
- **If there are no valid patient diaries for a particular visit then the data will be considered missing and the imputation rules would apply. Information from the last post-randomization visit where valid diary data was available would be carried forward (imputed) for the current visit.**
- **If there are missing entries in time slots (less than 2 hours per day), the proposed imputation method could be used.**
- **For sensitivity analyses, the proposed WOCF and worst case scenario can be used for subjects who drop out before any scheduled post-randomization visits.**

*Meeting Discussion:*

*A secondary analysis excluding patients with no diary entries after randomization could be done as a part of a sensitivity analysis of different methods of accounting for drop-outs.*

*Post Meeting Discussion:*

*In summary, the primary analysis will be intent-to-treat including a value from every patient randomized. The primary outcome measure will be the 20-week percent of awake off time per 24 hour period as recorded in the patient diary. If the 20 week diary entry is missing or not valid as described above, the most recent (last) valid diary entry obtained from the patient after randomization will be used. If there are no valid diary entries obtained after randomization for a particular patient, an average value based on the other patients will be imputed for week 20. This average value will be the average of all 20-week valid (imputed and actual) values from the combined patient population of the two treatment groups: carbidopa-levodopa IR alone without entacapone and IPX066. In weighing the evidence of effectiveness, the Agency will consider the number of imputed values, the number of dropouts, and the robustness of any drug effect seen in the sensitivity analysis. Large amounts of missing or imputed data or a lack of robustness of any effect for different methods of imputation could cast doubt on the results of the primary analysis.*

Question 5:

Does the Division agree that the revisions to the statistical analyses adequately address the Division's earlier comments?

**Preliminary FDA Response:**

**Please see comments for Question 4. Please submit an SAS code for the primary analysis model.**

*Meeting Discussion:*

*No further discussion at the meeting.*

Question 6:

Does the Division agree the currently proposed production of the Sinemet CD-LD comparator?

**Preliminary FDA Response:**

**Clinical**

**You describe the Sinemet product manufactured by Bristol-Meyers Squibb (BMS) in your discussion of the blinded comparator medication, but you do not explicitly state that the BMS product will be used to make the active comparator. Will you use the BMS Sinemet product to produce the CD-LD active comparator?**

*Meeting Discussion:*

*The BMS product manufactured in England will be used as the comparator. The Agency finds this acceptable.*

Question 7:

Does the Division agree with the proposed use of the QUIP?

**Preliminary FDA Response:**

**The Modified Minnesota Impulsive Disorders Interview (mMIDI), described by Weintraub D, et al., should be used to monitor for incident Impulse Control**

**Disorder (ICD). The mMIDI captures more detailed information concerning symptom severity than the QUIP, (Weintraub D, et al.,) which only devotes 2 items with (Yes/No) dichotomous responses to each ICD domain. The mMIDI should be measured at baseline, Visit 4 (beginning of maintenance), Visit 10 and Visit7 or early discontinuation.**

*Meeting Discussion:*

*The mMIDI will be used as described above.*

Question 8:

Does the Division agree with IMPAX responses to the Divisions comments?

**Preliminary FDA Response:**

**If you have additional specific questions relating to this SPA, you should raise them at the May 7th meeting.**

**This protocol uses a complex dosing regimen with potential for medication errors or errors while dispensing study related medication. The study requires participants to take a different amount of four different, blinded study medications. The Division is focused on the comparison between IPX066 and CD-LD. If a substantial number of participants are noncompliant with any of the study medications, become unblinded to any of the study medications or commit medication errors, the study results may be impossible to interpret.**

*Meeting Discussion:*

*You will consider simplifying the study design as well as implementing procedures to improve patient compliance with the complex study drug dosing described in the protocol. With a primary outcome that is patient-reported, a low dropout rate, a high rate of patient compliance with the drug regimen, and the completeness of the data will be especially important.*

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 102887

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IMPAX LABORATORIES  
INC

-----  
IPX066, Carbidopa-Levodopa Extended  
Release Capsules

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ERIC P BASTINGS on behalf of RUSSELL G KATZ  
06/04/2009



IND 102,887

**SPECIAL PROTOCOL ASSESSMENT –  
NO AGREEMENT**

IMPAX Laboratories, Inc.  
Attention: Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Mulchahey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for IPX066, Carbidopa-Levodopa Extended Release Capsules.

We also refer to your February 3, 2009 request, received February 4, 2009, for a special protocol assessment of a clinical protocol (Protocol IPX066-B08-06, “A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson’s Disease Subjects.”)

We note that this protocol includes feedback from the Division discussed at the September 19, 2008 meeting and from the October 14, 2008 meeting minutes.

We have completed our review and, based on the information submitted, have determined that the design and planned analysis of your study do not adequately address the objectives necessary to support a regulatory submission.

We also have the following responses to your questions raised in your February 3, 2009 submission.

1. Does the Division agree that the proposed study design is appropriate to support a claim of efficacy in advanced PD?

FDA Response: Your proposed study could support a claim of efficacy for IPX066 in advanced PD. Blinding the patients in the entacapone arm of the study will be extremely difficult and the data in that arm are unlikely to be appropriate for use to support an efficacy claim. All patients who are randomized to either placebo or IPX066 would have to be considered “evaluable” and included in the final intent-to-treat analysis.

2. Does the Division agree with the use of “off” time calculated from subject diaries as the primary outcome measure?

FDA response: Reduced “off” time has previously been accepted as evidence of effectiveness for approved Parkinson drugs. We prefer that you use percent of “off” time during waking hours instead of “off” time to adjust for the difference of waking time among subjects. You should also include total “off” time expressed in hours included as a secondary outcome variable. Because of the subjectivity of the patient diary as a clinical measure, secondary analyses will need to corroborate the primary analysis. Also, the protocol gives the patient a choice of a wide range of days in which to fill out the diary. The proposed analysis does not use all of the diary data.

3. Does the Division agree with the statistical analysis methodology proposed in the protocol, including the interim analysis plan?

FDA response: You need to add details of calculations of “off” time. We recommend that you take the average of the last 2 diary days for Week 20 as the “off” time for Week 20. The average percent of “off” time should represent the total “off” time for the 2 days divided by total awake time for the 2 days.

You did not provide statistical methodology for the primary analysis in your protocol. The protocol should specify the analysis model and the primary comparison, which should be the IPX066 group versus the placebo group.

You need to add details of handling of missing data. Imputation of missing diary data needs to be proposed. You must also define the maximum amount of missing data allowed in each 24-hour diary in order for the diary to be considered valid. Subjects may drop out at the beginning of the study when dose adjustments are allowed. We recommend that you add a sensitivity analysis for the primary efficacy endpoint under a worst case scenario for subjects who discontinue the study before reaching their stable doses. In addition, to account for any reciprocal increase in dyskinesias as “off” time decreases, analyses of “on with/without troublesome dyskinesias” should be added to your protocol and statistical analysis plan. Results of these analyses in addition to the primary analysis will all be critical elements in determining whether the study is successful or not.

4. Assuming the results of the interim analysis are robust and the stopping rule is met, would these complete results (about n=60 per treatment arm) and positive results from Protocol IPX066-B08-05 in early PD patients support an NDA filing? Results from the remaining subjects would be submitted during the review process.

FDA response: You did not provide a rationale for conducting the interim analysis. Based on your previous experience and power calculation, it is unlikely that the treatment difference will reach the statistical significance of (b) (4) from the interim data. We strongly recommend that you not conduct the interim analysis and allow the study to complete as planned.

5. IMPAX intends for Protocol IPX066-B08-06 also to be filed in support of a European Marketing Authorization. The EMEA may place different emphasis on endpoints or may request additional endpoints. However, IMPAX will report the results of all analyses to the Division at the time of the NDA filing. Does the Division agree with this approach?

FDA response: Yes. There should only be one protocol with one statistical analysis plan; i.e. prospective plans for statistical analyses for submission to both agencies should be in the one final trial protocol. The data for these variables must be submitted to the agency as well.

6. Does the Division agree with the proposed plan to produce blinded comparators for the clinical supply?

FDA response: Yes. The plan seems reasonable.

In addition, we have the following comments.

- The concurrent open-label extension study is not described in sufficient detail to determine whether it will be conducted in a manner that provides maximum information on drug safety and does not interfere with the randomized trial.
- The single version of MedDRA to be used for each of the clinical studies must be specified. Use of a single version facilitates combining safety data from all the trials.
- You should describe your plan to perform the multi-dose pK study to evaluate drug accumulation late in the day that we requested September 19, 2009.
- Your protocol must include a method to monitor for treatment emergent impulse control disorders (ICD); the modified Minnesota Impulsive Disorders Interview (mMIDI) and/or SCID have been used for this purpose. The division recommended that treatment emergent ICD should be studied as a separate safety endpoint. The Agency has implemented class label language regarding a potential increased risk for melanoma and ICDs in patients taking medication used to treat PD. If approved, the label for IPX066 would be required to contain the same class label language.

Furthermore, we ask that you clarify the following concerns.

- There are no restrictions in the selection criteria that correspond to some of the prohibitions in the section on concomitant medications on page 26 of 130.
- It is unclear in the protocol section on concomitant medications why the use of anti-psychotics (presumably including neuroleptics) to treat conditions other than psychosis is allowed but neuroleptics are prohibited when they are given to treat psychosis.
- The reason for prohibiting the use of anticonvulsants is not stated in the protocol.

- In the protocol, it is mentioned in the summary of the analysis for efficacy on page 7 of 130 that there will be strata for dopamine agonists; however, this stratification is not consistently mentioned in the plans for randomization elsewhere in the document.
- On page 12 of 130 in the proposed trial, it is not clear which components of the UPDRS will be done in the “on” and “off” states.
- On page 30 of 130 the reasons listed for early discontinuation (drop-out) will not provide sufficient information to determine the cause of discontinuation. For example, “protocol violation” is given as a reason for early discontinuation and “replacement”.
- “Physician decision” is not sufficient as an explanation of discontinuation.
- Please define the degree of noncompliance that would result in a subject being discontinued for this reason.
- You must submit detailed narratives for all subjects who withdrew from the trial because of an adverse event.
- It is not clear what “replacement” refers to in the title of the section. With intent-to-treat analysis, patients should not be “replaced”.

If you choose to submit a revised protocol, it should address all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*). This meeting would be limited to discussion of this protocol.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 102887

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IMPAX LABORATORIES  
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IPX066, Carbidopa-Levodopa Extended  
Release Capsules

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RUSSELL G KATZ  
03/20/2009



IND 102,887

**SPECIAL PROTOCOL – AGREEMENT**

IMPAX Laboratories, Inc.  
Attention: Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Mulchahey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for IPX066, Carbidopa-Levodopa Extended Release Capsules.

We also refer to your January 8, 2009 request, received January 12, 2009, which contains a special protocol assessment of a clinical protocol (Protocol IPX066-B08-05, “A Placebo-Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson’s Disease.”) We also refer to your February 6, 2009 amendment, received February 9, 2009, which contains a corrected version of Protocol IPX066-B08-05.

We note that this protocol includes revisions discussed in our December 5, 2008 letter.

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act (see *Guidance for Industry; Special Protocol Assessment*).

We also have the following responses to your questions raised in your January 8, 2009 and February 6, 2009 submissions.

1. Do the revisions and clarifications of the statistical analysis portion of the protocol adequately address the Division’s concerns?

FDA Response: Yes.

2. Does the Division agree that the successful completion of the amended protocol, defined as a demonstration of efficacy of IPX066 on the primary endpoint vs. placebo and safety results consistent with currently approved carbodopa-levodopa products, would support approval of IPX066 for use in early Parkinson's disease?

FDA Response: Yes, we agree.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 102887

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IMPAX LABORATORIES  
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IPX066, Carbidopa-Levodopa Extended  
Release Capsules

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RUSSELL G KATZ  
02/27/2009



IND 102,887

IMPAX Laboratories, Inc.  
Attention: Jeff Mulchahey, PhD  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Mulchahey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IPX066, Carbidopa-Levodopa Extended Release Capsules.

We also refer to your October 21, 2008, request for a special clinical protocol assessment, received October 22, 2008. The protocol is titled "A Placebo-Controlled Study to Evaluate the Safety and Efficacy of IPX066 in subjects With Parkinson's Disease."

We have completed our review and, based on the information submitted, have the following responses to your questions.

*1. Does the Division agree that the proposed inclusion and exclusion criteria, which would enroll early Parkinson's disease (PD) patients and allow MAO-B inhibitors, anticholinergic agents and amantadine while excluding dopamine agonists, are appropriate to support a claim of efficacy in early PD?*

Yes, provided the proposed further analysis includes examining the potential effect of concomitant PD medications by class on the efficacy variables, if the stratum by treatment interaction is at least marginally significant ( $p \leq 0.1$ ).

*2. Does the Division agree with the proposed IPX066 doses to be studied in this trial?*

The doses chosen for testing are acceptable.

*3. Does the Division agree with the use of the Unified Parkinson's Disease Rating Scale (UPDRS) as the primary outcome measure? IPX066-B08-05 proposes the UPDRS as an outcome measure rather than the recently developed Movement Disorder Society's (MDS)-UPDRS.*

We have no objection to using the UPDRS instead of the MDS-UPDRS.

*4. Does the Division agree with the statistical analysis methodology proposed in the protocol?*

We recommend that you keep the effect of stratum in the model regardless of its significance since the effect is important and randomization is stratified by it. It is unclear how multiple comparisons will be corrected for determining a therapeutic effect for the various dosage arms. That is, we are uncertain as to whether or not the Fisher's LSD is to be applied to primary endpoint and/or secondary endpoints. This needs clarification. Moreover, you imply that multiple comparisons of secondary endpoints will be performed. This leads us to believe that you may be planning on including secondary endpoints in the label. The labeling of secondary endpoints requires that you fulfill a number of critical criteria, one of which is replication, which is not possible considering you are performing a single study. Other criteria also may not be fulfilled: e.g. the secondary endpoints must be in a different domain from the primary endpoint.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the *Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products*). This meeting would be limited to discussion of this protocol.

If you have any questions, call Stacy Metz, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

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IND 102887

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IMPAX LABORATORIES  
INC

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IPX066, Carbidopa-Levodopa Extended  
Release Capsules

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/s/  
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RUSSELL G KATZ

12/05/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 102,887

Impax Laboratories, Inc.  
Attention: Jeff Mulchahey, Ph.D.  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Dr. Mulchahey:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IPX066 (carbidopa – levodopa extended-release capsules).

We also refer to the meeting between representatives of your firm and the FDA on September 19, 2008. The purpose of the meeting was to discuss your development plan for IPX066.

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

If you have any questions, contact Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION

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MEMORANDUM OF MEETING MINUTES

**Meeting Date and Time:** September 19, 2008  
**Meeting Type:** Type B  
**Meeting Category:** Pre-Phase 3  
**Meeting Location:** White Oak Bldg #22, Room 1315  
**Application Number:** IND 102,887  
**Product Name:** IPX066 (carbidopa/levodopa extended-release capsules)  
**Received Briefing Package** August 20, 2008  
**Sponsor Name:** Impax Labs  
**Meeting Requestor:** Jeff Mulchahey, Ph.D.  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Susan Daugherty  
**Meeting Attendees:**

**FDA Attendees**

Division of Neurology Products (DNP)

Russell Katz, M.D., Director  
Norman Hershkowitz, M.D., Ph.D., Medical Team Leader  
Gerald Podskalny, D.O., Medical Reviewer (via telephone)  
Martin Rusinowitz, M.D., Medical Reviewer  
Susan Daugherty, Regulatory Project Manager

Division of Pharmaceutical Evaluation

Veneeta Tandon, Ph.D., Clinical Pharmacology Team Leader  
Sripal Mada, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics II

Kun Jin, Ph.D., Biometrics Team Leader

Division of Pre-Marketing Assessment I

Ramesh Sood, Ph.D., Branch Chief  
Chhagen Tele, Ph.D., Chemistry Reviewer

Division of Medication Error Prevention and Analysis (DMEPA)

Kristina Arnwine, Pharm. D, Team Leader  
Lori Cantin, Safety Evaluator

**External Attendees**Impax Labs

Ann Hsu, Ph.D., Vice President, Clinical Research

Jeff Mulchahey, Ph.D., Senior Director, Regulatory Affairs

Suneel Gupta, Ph.D., Chief Scientific Officer

Nishit Modi, Ph.D. Vice President, Clinical Pharmacology

 (b) (4), Biostatistics Consultant (b) (4), Clinical Development Consultant**1.0 BACKGROUND**

On July 3, 2008, Impax Labs submitted IND 102,887 for carbidopa/levodopa extended-release capsules indicated to treat Parkinson's disease. In a letter dated August 5, 2008, Impax Labs requested a pre-Phase 3 meeting to discuss their development plan for IPX066. The Division's preliminary responses to the questions posed in the background package were electronically mailed to the Sponsor on September 18, 2008.

**2.0 DISCUSSION**CLINICAL

## Question 1:

At our 08 April 2008 meeting with the Division, two potential development paths for a non-bioequivalent CD-LD ER product were suggested. Accordingly, we have prepared protocols to address each path for our new product:

Path #1: A placebo-controlled trial of IPX066 in LD-naïve Parkinson's patients (protocol IPX066-B08-05) to establish the efficacy of IPX066.

**Preliminary FDA Response:****Path #1 - Additional Information Needed**

**Please confirm which of the (b) (4) prototype IPX066 formulations  is being developed as the investigational drug product? The Sponsor's data suggests IPX066 (b) (4) was considered to be the best to bring forward in development, is this true?**

**What capsule strengths does Impax plan to develop for marketing aside from the possibility of the  mg LD component?**

Path#1

- Is the proposed placebo-controlled trial in LD naïve patients demonstrating clinical benefit sufficient for approval?

- Are there elements of the proposed study which could be strengthened?

**Preliminary FDA Response:****Path #1 (both questions answered together)**

- **The study design is a flexible design using novel dose strengths of a non-bioequivalent formulation of CD/LD ER a flexible dose design seems less likely to give the Sponsor and the agency adequate dose response information. The B08-05 study (LD naive subjects) may be more appropriately studied in a fixed dose trial.**
- **The flexible dose design may contribute to unblinding of the study site personnel who may be able to determine treatment assignment by observing subjects who have a clinical response to lower doses or adverse reactions to higher doses of study medication compared to subjects on placebo who are more likely to titrate up to the maximum dose of study medication and not experience symptomatic improvement or adverse reactions.**

Path #2: An active-controlled (superiority) trial comparing IPX066 with Sinemet® CR in LD-experienced Parkinson's patients (protocol IPX066-B08-06). This trial would also serve to establish conversion recommendations and to assess the degree of interchangeability of the two CR formulations.

**Preliminary FDA Response:****Path#2-Additional Information Needed**

- **Exclusion criteria #3 appears to be missing in the study protocol or just mis-numbered?**
- **The Sponsor must describe the method used to calculate the average LD dose that will be administered in the form of Sinemet CR and IPX066 during part 2 of the study.**

**The trial design optimizes therapy in PD patients who are all given IPX066 in Part I of the study, then in part 2 the protocol reads:**

**“Depending on the randomized treatment, subjects will take IPX066 and Sinemet CR placebo OR IPX066 placebo and Sinemet CR according to the dose and dosing intervals established during Part I. Based on similar average LD concentrations between the two formulations, subjects will be instructed to take identical number of capsules from the assigned IPX066 and Sinemet CR bottle(s).”**

- **The Sponsor should present multiple dose pK data from patients with Advanced PD because IPX066 may exacerbate motor fluctuations (i.e. increased dyskinesia) cause by LD accumulation later in the day.**

#### Path #2 Questions

- Would the comparative trial versus Sinemet® CR in LD-experienced Parkinson's disease patients demonstrating clinical benefit over current CD-LD ER products be sufficient for approval?
- Are there elements of the proposed study which could be strengthened?

#### **Preliminary FDA Response:**

#### **Path #2 (both questions answered together).**

**The Division believes that the current trial design for study IPX066-B08-06 can not be used demonstrate superiority of IPX066 over CD/LD ER. Although, the current trial design may demonstrate effectiveness of IPX066 in PD it does not equally compare the optimal treatment with IPX066 to optimal treatment with CD/LD ER.**

- **If a superiority claim is intended the trials design should be modified to evaluate the potential superiority of IPX066 in improving a PD clinical primary endpoint versus optimal treatment with CD/LD ER. Moreover, a second trial would likely be required if such a claim is intended.**
- **The Sponsor must choose one method of analysis the ANOVA or ANCOVA of the primary endpoint and designate it as the primary analysis upon which an efficacy claim will be based. Additional sensitivity or exploratory analysis can be conducted but it will not be considered the primary method for determining the primary efficacy endpoint.**
- **If the change in the % of the awake off hours is selected as the primary efficacy variable, then one of the secondary endpoints must include a comparison of the change from baseline of the number of awake hours (or minutes) subjects spend in the off state for each treatment group.**
- **The Sponsor must describe in detail the method they plan use to calculate the change in the % of off time.**

**Question 2:**

Does the Division agree that the clinical program agreed to in Question 1 is sufficient for approval of IPX066 for the same indication as other CD-LD products (i.e. for treatment of (b) (4) Parkinson's disease (b) (4), postencephalatic parkinsonism, and (b) (4) parkinsonism (b) (4) may follow injury to the nervous system by carbon monoxide intoxication (b) (4) or manganese intoxication)?

**Preliminary FDA Response:**

The Division anticipates IPX066 would be approved for same indications as the marketed CD/LD products unless there was new evidence to suggest a need to modify the indications for IPX066.

***Meeting Discussion- Clinical:******The Sponsor clarified the following:***

- *The proposed dosage strengths, in mg of levodopa, are 95mg, 145 mg, 195mg, and 245mg.*
- *They plan to develop formulation (b) (4) because of its bioavailability.*
- *They are not seeking a superiority claim.*

*The Division said that a demonstration of superiority to Sinemet CR is not needed for approval of an effectiveness claim.*

*Hypothetically, in lieu of any efficacy trials, the Division noted that the Sponsor may wish to argue that efficacy would be expected if the Sponsor can demonstrate thier formulation, at the proposed doses, result in plasma levels within a bracketed range of plasma concentrations as those produced by Sinemet CR and IR formulations, when used in dosages according to the label. Approval based upon this strategy, with no efficacy trials, would, however, be a high hurdle. Alternatively, the Sponsor would have to demonstrate equivalent exposures with Sinemet CR (AUC, C<sub>max</sub> and C<sub>min</sub>).*

*The division noted that a single efficacy trial will provide adequate infortion for approval, but may result only in an indication for the studied population (i.e. early or late PD).*

*The Sponsor asked whether Early or late PD should be studied. The Division noted that early PD trials are easier to interpret. The Division indicated that a single trial (in either early or late PD) might be adequate; and in lieu of the second trial the Sponsor may use the proposed bracketing approach for the remaining form of PD (early or late). The Division noted that their proposed trials should be adequate for demonstrating efficacy, but the Sponsor should submit their protocol as a Special Protocol Assessment (SPA).*

*The Sponsor expressed concern regarding the ability to bridge doses with Sinemet CR because of the IR component in IPX066. The division noted they will research the label. The Sponsor may wish to do the same, but the following*

*information is now being provided. The approved product label for Sinemet CR<sup>®</sup>, marketed by Bristol-Myers Squibb (October 6 2006 version) includes data regarding the bioavailability of both Sinemet CR and Sinemet 25/100 (IR) at steady state. Information regarding the initial Sinemet CR dose and dose conversion from Sinemet (IR) to Sinemet CR is included in the "Dosing and Administration" section. In addition, there are numerous peer reviewed journal articles published in the late 1980s and early 1990s regarding the PK profile and plasma concentrations of Sinemet CR-4. These studies should be helpful when the sponsor considers the feasibility of conducting bridging studies between IPX066 and the marketed CL/LD products.*

*The Division suggested that the Sponsor design their early PD trial with 3 dose arms expressed in equivalent doses of standard CD/LD (50mg TID, 100mg TID, and 200 mg TID) and 1 placebo arm. The Division recommends the duration of the trial be 3 months. Whether or not long term safety data are needed will depend upon the range of plasma levels for IPX066.*

*FDA Post-Meeting Clarification: The 50 mg LD dose would be considered a titration dose but the 100 mg and 200 mg doses are target doses for the proposed 3 arm trial. An intermediate dose between 100 mg and 200 mg (LD component) would be the third target dose for (active treatment arms) in the trial in addition to a placebo arm.*

*The Sponsor noted that they will define the endpoints for the second trial in the protocol. They asked if a second effectiveness trial would be acceptable if they chose not to utilize a bracketed approach, and whether both trials would be needed for a global PD claim. The Division said that conducting a second trial in lieu of the bracketing approach would be acceptable for an effectiveness claim. The Division is open to an argument as to whether both trials would be needed for a global PD claim.*

*The Division told the Sponsor that, for a superiority claim, they would need to show replication and have a fair comparator. The proposed protocol is not sufficient for demonstrating a superiority claim. Moreover, the expected superiority claim would be a more rapid time to onset. That is considered a week superiority claim.*

## CLINICAL PHARMACOLOGY

Question 3:

Does the Division agree with the proposed clinical pharmacology development program?

### **Preliminary FDA Response:**

**The Sponsor's overall Clinical Pharmacology program is not acceptable. The Division has the following recommendations for the clinical pharmacology**

**program for IPX066:**

- The rationale for using (b) (4) mg IPX066 capsules in the single dose relative BE study is not clear. Ideally a fasting study comparing the ER product at the highest strength (i.e. (b) (4) mg) as a single dose should be compared to the IR reference. Including both Sinemet and Sinemet CR arm is acceptable in this study.
- It is also not clear why the strengths proposed in the Clinical Pharmacology and CMC sections are different from those proposed to be studied in the Pivotal Phase III studies. Appropriate strengths should be evaluated in the Clinical Pharmacology program.
- A steady-state study on the highest strength of IPX066 compared to Sinemet should also be conducted.
- It also recommended that the Sponsor take sparse samples in the efficacy studie(s) in order to characterize pharmacokinetic differences of IPX066 in the elderly population compared to the younger subjects.

The Sponsor's proposal for conducting a food effect study on the highest strength and the dose proportionality study are acceptable.

***Meeting Discussion:***

*The Sponsor proposes to conduct the steady state pharmacokinetic study with IPX066 compared to Sinemet in a cohort of patients with more intense sampling that would also characterize the pharmacokinetic differences of IPX066 in the elderly population compared to the younger subjects, rather than conducting the steady state study in healthy subjects and taking sparse samples from the efficacy studies to evaluate the pharmacokinetic differences in the elderly and the young patients. The Division indicated that the Sponsor's proposal was acceptable and that they should ensure that the IPX066 and the Sinemet populations are comparable in order to adequately interpret the results.*

**NONCLINICAL DEVELOPMENT****Question 4:**

The IPX066 program will be developed based on the assumption that the NDA can be filed as a 505(b)(2) application with the Sinemet and Sinemet CR products as the Reference Listed Drugs. Does the Agency agree that this is acceptable and that no additional nonclinical studies are required?

**Preliminary FDA Response:**

**Yes, unless issues arise during development (e.g., changes in the impurity profile) that would require additional nonclinical data.**

*There was no discussion of the response to this question at the meeting.*

**CHEMISTRY, MANUFACTURING AND CONTROLS**

Question 5:

Does the Division agree with our proposed scale up plan summarized in CMC Table 3?

**Preliminary FDA Response:**

**Yes, your proposed scale-up plan for the drug product is reasonable. Provide details of changes made to the manufacturing process to allow for the scale-up including an assessment of the impact of these changes in the NDA. Provide adequate information demonstrating physical and chemical comparability to qualify two proposed commercial manufacturing sites for each, CD and LD drug substances from each vendor in the NDA. Include proposal for the qualification of two manufacturing sites of each drug substance in the NDA. Provide drug substance (CD and LD) manufacturing site information, analytical methods used for the tests, and the batch analysis of the batches used for clinical and primary stability drug product batches. Provide comparison and rationale of the differences if any in analytical methods in tabular form. Include validation of the analytical test methods at the time of NDA submission.**

*There was no discussion of the response to this question at the meeting.*

Question 6:

Does the Division agree with our proposed bracketing plan summarized in CMC Table 4?

**Preliminary FDA Response:**

**Yes, your bracketing plan appears generally acceptable. Are the tests methods and specifications limits same in stability studies as those used for release testing?**

*Meeting Discussion:*

*The Division said that the response to this question does not apply if four strengths are used.*

Question 7:

Does the Division agree with our scale up batch size?

**Preliminary FDA Response:**

**Yes, your scale-up batch size is acceptable.**

*There was no discussion of the response to this question at the meeting.*

Question 8:

Does the Division agree with the proposed testing procedures and methods for IPX066 ER Sprinkle Capsule?

**Preliminary FDA Response:**

**Yes, your proposed testing procedures and methods for IPX066 ER capsule are**

**reasonable at this time. However, your proposed identification acceptance criterion for drug product specification is determined using an HPLC method. Identification solely by retention time is not regarded as being specific (refer ICH Q6A: Test procedures and acceptance Criteria for New Drug Substances and Drug Products). Include a specific identification test (e.g., Infrared spectroscopy/TLC) as part of the drug product specification. The acceptability of the ultimate specification limits will be subject of the NDA review.**

*Meeting Discussion:*

*The Sponsor will either include a microbial limit test and acceptance limit for the drug product or provide justification for not including it.*

Question 9:

Does the Division agree the proposed specification for (b) (4)?

**Preliminary FDA Response:**

**The proposed limit for (b) (4) will be evaluated during the review of your application based on the information provided in the submission. If you propose to rely on human exposure to (b) (4) resulting from administration of other approved drugs (i.e., levodopa or methyldopa), you should provide a comparison of the maximum total daily intake of (b) (4) from your product with the systemic exposure to (b) (4) resulting from administration of the approved drug(s) at the recommended doses.**

*There was no discussion of the response to this question at the meeting.*

Question 10:

Are additional *in vitro* studies required to characterize the performance of this ER sprinkle formulation?

**Preliminary FDA Response:**

**Not at this time**

*There was no discussion of the response to this question at the meeting.*

REGULATORY

Question 11:

Are there any additional actions the Division requires for approval of IPX066 via the 505(b)(2) path?

**Preliminary FDA Response:**

**None are presently obvious, but this does not mean other issues will not be uncovered in the process of development. If the Sponsor has any specific issues these should re discussed at the meeting.**

*There was no discussion of the response to this question at the meeting.*

***Additional Meeting Discussion:***

***The Sponsor's proposed program seems to have addressed the Division's concerns regarding nomenclature/naming issues and safety. The Division noted that the Sponsor would need to show both the carbidopa and levodopa doses in labeling.***

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

**4.0 ACTION ITEMS**

The Sponsor will submit a Special Protocol Assessment for their proposed Phase 3 study.

**5.0 ATTACHMENTS AND HANDOUTS**

None.

Linked Applications

Sponsor Name

Drug Name

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IND 102887

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IMPAX LABORATORIES  
INC

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IPX066, Carbidopa-Levodopa Extended  
Release Capsules

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/s/  
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RUSSELL G KATZ

10/14/2008