

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203312Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

TO: OFFICE OF NEUROLOGY PRODUCTS
FROM: CHARLES JEWELL, CMC REVIEWER, BRANCH 1, DIVISION 1, ONDQA
SUBJECT: REVIEW OF NDA 203312 (RYTARY; IMPAX LABORATORIES; (CARBIDOPA AND LEVODOPA) EXTENDED RELEASE CAPSULES; CMC OVERALL APPROVAL RECOMMENDATION
DATE: DECEMBER 23, 2014
CC: TRACY PETERS, RPM
DAVE PODSKALNY, CDTL

*****Recommendation and Conclusion on Approvability*****

This application is recommended for APPROVAL from the CMC perspective. Since our preliminary recommendation entered on 11/5/2014, the ONDQA Biopharmaceutics reviewer (Sandra Suarez) has submitted her approval recommendation (11/6/2014). The CDER Office of Compliance (Reviewer: Christina Capacci-Daniel via Ebern Dobbin) has entered the OVERALL ACCEPTABLE recommendation covering the cGMP status for all manufacturing sites on 12/23/2014.

The following statement regarding the assignment of the expiration dating period for the drug product should be communicated to the applicant in the approval letter:

The Agency has assigned an expiration dating period of 30 months for each strength of the Rytary (IPX066; carbidopa-levodopa extended-release capsules) drug product in the described packaging configurations. The 30 month expiration dating period begins with the [REDACTED] (b) (4). No extension period is granted for hold time of components or bulk capsules.

ONDQA Biopharmaceutics Recommendation Captured from the Review in Panorama 11/6/2014

RECOMMENDATION:

The dissolution information included in Amendment-0047 dated Aug 29, 2014, supports the approval of the proposed manufacturing equipment change.

From the Biopharmaceutics perspective the Resubmission of NDA 203-312 for Carbidopa+Levodopa (23.75/95mg, 36.25/145mg, 48.75/195mg, and 61.25/245 mg) fixed dose combination (FDC) extended release (ER) capsules is recommended for APPROVAL.

Sandra Suarez -A

Digitally signed by Sandra Suarez -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sandra Suarez -A,
0.9.2342.19200300.100.1.1=1300147809
Date: 2014.11.05 13:21:45 -05'00'

Sandra Suarez Sharp, Ph. D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes -S

Digitally signed by Angelica Dorantes -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300070843, cn=Angelica Dorantes -S
Date: 2014.11.05 13:28:03 -05'00'

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: PSeo;

CMC REVIEW OF NDA 203312 AFTER COMPLETE RESPONSE

CDER Office of Compliance Overall Site Recommendation Captured from Panorama 12/23/2014

The screenshot shows a Firefox browser window displaying a task page in the Panorama system. The browser's address bar shows the URL: `panorama.fda.gov/attask/taskView.cmd?ID=5425ca0b00cc922aa1d7e240f1ba92bf`. The page title is "Overall Manufacturing Inspection Recommendation". The breadcrumb navigation is "ATTask Home > Search Results > Project > Parent Task > Task". The user is identified as "Charles Jewell".

The main content area displays the following information:

- Task Details** | **Task Data** | Open Issues | More ▾
- Facility Inspection - Overall Application Recommendation**
- Facility Inspection - Overall Application Recommendation
- Approve**
- Facility Inspection - Overall Application Re-evaluation Date
- 7/26/16**

At the bottom of the browser window, there is a Firefox notification: "Firefox automatically sends some data to Mozilla so that we can improve your experience." and a "Choose What I Share" button.

CMC REVIEW OF NDA 203312 AFTER COMPLETE RESONSE

MEMORANDUM

TO: OFFICE OF NEUROLOGY PRODUCTS
FROM: CHARLES JEWELL, CMC REVIEWER, BRANCH 1, DIVISION 1, ONDQA
SUBJECT: REVIEW OF NDA 203312 (RYTARY; IMPAX LABORATORIES; (CARBIDOPA AND LEVODOPA) EXTENDED RELEASE CAPSULES; CMC APPROVAL RECOMMENDATION; PENDING COMPLIANCE AND BIOPHARM
DATE: NOVEMBER 5, 2014
CC: TRACY PETERS, RPM
 DAVE PODSKALNY, CDTL

Documents Covered Under This Review

Resubmission/Class 2; Form 3674	04/09/2014	DARRTS SDN 40 - Resubmission after Complete Response; updated stability data
Quality/Response to IR	04/11/2014	DARRTS SDN 41 - Clarification of Manufacturing and Testing Site Duties
Quality/Response to IR	06/11/2014	DARRTS SDN 44 - Update to clarify more manufacturing site details
Quality Information	07/03/2014	DARRTS SDN 45 - Corrections to sections to eliminate reference to Hayward, CA manufacturing site, which has been withdrawn
Quality Information	08/29/2014	DARRTS SDN 47 - Data and information to support the replacement of the (b) (4) with the (u) (4)

*****Background for this Response to Complete Response from CMC Perspective*****

- A complete response was issued to NDA 203312 on **January 18, 2013** due to un-satisfactory resolution of deficiencies identified in the inspections at the Hayward, CA manufacturing site. Even though the Applicant had withdrawn the Hayward manufacturing site from the application, the approval of the application depended on critical manufacturing data generated at the Hayward facility. The Agency required resolution of the identified deficiencies. An inspection was ongoing that occurred during **January 8, 2013** and lasted until **February 28, 2013**.
- The Office of Compliance (Christina Capacci-Daniel, Consumer Safety Office through Mahesh Ramanadham, Acting Branch Chief) sent a memorandum to the Applicant dated **February 25, 2014** indicating that responses to the inspection related deficiencies had adequately addressed inspectional deficiencies observed during the inspections at the Hayward, CA facility. Recommendations were given with regard to a future resubmission of the application.
- A Type A meeting with the Applicant was held **April 7, 2014** (Telecon). In this meeting, it was communicated to the Applicant that further inspections were required. The Agency agreed to accept extended duration stability data generated from the Hayward site, and that expiration dating would be determined from the review of this data.
- On **April 9, 2014**, the Applicant resubmitted the application. From the CMC perspective this included a stability update for the drug product. This included updates to 36 months for Hayward lot 1, 30 months for Hayward lots 2, 3, 4 and 5 and 24 months for the Taiwan site qualification lots. Minor revisions were made to

CMC REVIEW OF NDA 203312 AFTER COMPLETE RESONSE

the commercial bottle labeling and packaging. Drug product includes the following (100-count and 240-count bottles of each strength for marketing; 25-count bottles of professional samples):

- 23.75 mg / 95 mg (120 cc bottles for 100-count; 200 cc bottles for 240-count)
- 36.25 mg / 145 mg (120 cc bottles for 100-count; 250 cc bottles for 240-count)
- 48.75 mg / 195 mg (200 cc bottles for 100-count; 400 cc bottles for 240-count)
- 61.25 mg / 245 mg (200 cc bottles for 100-count; 500 cc bottles for 240-count)

- On **July 21-26, 2014**, an inspection at the Taiwan manufacturing site was completed. The validation of the (b) (4) equipment (b) (4) was deficient. The sponsor responded with an amendment on **August 29, 2014**. In this amendment they updated their manufacturing information to indicate that only the (b) (4) (an (b) (4) not covered in the original submission) would be used in the commercial production of Rytary. (b) (4)

The (b) (4) (u) (4) was unable to do this. Although the studies in the application justifying their (b) (4) were deemed adequate by the CMC reviewer, the validation of the (b) (4) at the Taiwan manufacturing site was not found acceptable by the Agency's inspection team. This amendment was considered a major amendment and extended the review clock by three months.

- This change includes an updated portion to section 3.2.P.3.3 Description of Manufacturing Process with Process controls. It also includes undated versions of the Master Batch Records for each strength.
- Section 3.2.P.2.3 Manufacturing Process and Controls is updated to include a section for the (b) (4).
- Section 3.2.P.5.4 Batch Analysis for (b) (4) is provided covering Content Uniformity and Dissolution of levodopa, carbidopa and tartaric acid. This is provided for all four dosage strengths. These studies were conducted during **October through December 2012** at the Taiwan site. (b) (4)

*****Recommendation and Conclusion on Approvability*****

This application is recommended for approval from the CMC perspective, pending an overall acceptable recommendation from the CDER Office of Compliance, based on inspection-related issues. It is also pending an approval recommendation from the Biopharmaceutics Reviewer. In the event this application receives an approval rating from all review disciplines, it should be communicated to the applicant that the expiration dating period granted by the Agency based on review of the updated stability information for all drug product configurations proposed for commercialization is 30 months. The applicant should be reminded that the expiration period begins with the (b) (4), no extension is granted for hold time of components or bulk capsules.

***** Review Details *****

Review of Manufacturing Process Development for the (b) (4)

In the original application, process development was presented for the (b) (4).

In this amendment the development was presented for the (u) (4)

CMC REVIEW OF NDA 203312 AFTER COMPLETE RESONSE

supports the applicant's recommendation for 30 months expiration dating from the time of (b) (4) [redacted]. The Agency is not assigning an extension to long term stability because of pre-stability studies covering component storage time and bulk finished capsule storage time. The 30 month expiration dating period begins with the date of the (b) (4) [redacted].

To: Memo-to-File

From: Charles Jewell, Ph.D. - CMC Reviewer for this application

Subject: NDA 203312 - Recommendation to issue a Complete Response from a CMC Perspective

Date: 18-Jan-2013

This memo refers to the following reviews already in DARRTS:

- Review-Quality-03(General Review); Jewell, Charles F.; 8/28/2012 (Main CMC Review)
- Review-Quality-03(General Review); Suarez, Sandra.; 8/26/2012 (Main Biopharmaceutics Review)

This memo refers to the following amendments submitted to the application:

- NDA 203312 SDN 34 (Quality Response to IR; Updated Specifications); 1/9/2013
- NDA 203312 SDN 33 (Labeling/Package Insert Draft); 1/8/2013
- NDA 203312 SDN 32 (Labeling/Container - Carton Draft); 12/28/2012
- NDA 203312 SDN 30 (Quality Information; Withdrawal of Hayward, CA site); 12/7/2012

Review Summary

Since the previous CMC related reviews for overall CMC issues and biopharmaceutical issues were filed in August 2012, the applicant updated the drug product and capsule specifications to include specific company and strength related markings to appear on the finished capsules. These modifications were also put in the proposed labeling provided with the application. The applicant also requested the withdrawal of the Hayward, CA site as a commercial manufacturing site. This was one of two sites listed for the manufacture, release testing and stability testing of drug product. The applicant was concerned that an outstanding warning letter for this site (still unresolved) would prevent approval for this application. Because of this, all drug product will be manufactured, release tested and stability tested at the Jhunan, Taiwan site.

From the establishment evaluation perspective, the Office of Compliance has provided an overall not acceptable decision (WITHHOLD) for the application. An ongoing inspection at the applicant's Hayward, CA site revealed that the applicant still continues to perform testing operations in support of the commercial manufacturing at a site that they requested to be withdrawn from the application. Satisfactory resolution of the deficiencies identified in recent inspections and regulatory meetings have not been verified and are required before this application may be approved. Accordingly, this NDA is recommended for a complete response from a CMC perspective.

In the August 2012 CMC review; I commented that we would be assigning an expiration dating period of [REDACTED] (b) (4). This judgment will need to be reassessed once recent deficiencies found at the Hayward, California site are resolved. These deficiencies render suspect the method validation studies and registration stability data for the drug product, as contained in the application.

Review Notes

Final Establishment Evaluation Report

Reviewer Comments: As discussed in the above summary, the overall recommendation for this application is WITHHOLD, due to the stated deficiencies at the Hayward, California site.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	NDA 203312/000	Action Goal:	
Stamp Date:	21-DEC-2011	District Goal:	22-AUG-2012
Regulatory:	21-JAN-2013		
Applicant:	IMPAX LABS INC 30831 HUNTWOOD AVE HAYWARD, CA 94544	Brand Name:	Rytary
Priority:	5	Estab. Name:	
Org. Code:	120	Generic Name:	IPX066 (carbidopa-levodopa extended rele
		Product Number; Dosage Form; Ingredient; Strengths	
			001; CAPSULE, EXTENDED RELEASE; CARBIDOPA; 23.75MG 001; CAPSULE, EXTENDED RELEASE; LEVODOPA; 95MG 002; CAPSULE, EXTENDED RELEASE; CARBIDOPA; 36.25MG 002; CAPSULE, EXTENDED RELEASE; LEVODOPA; 145MG 003; CAPSULE, EXTENDED RELEASE; CARBIDOPA; 48.75MG 003; CAPSULE, EXTENDED RELEASE; LEVODOPA; 195MG 004; CAPSULE, EXTENDED RELEASE; CARBIDOPA; 61.25MG 004; CAPSULE, EXTENDED RELEASE; LEVODOPA; 245MG

Application Comment:

FDA Contacts:	T. BOUIE	Project Manager	3017961649
	C. JEWELL	Review Chemist	3017964232
	M. HEIMANN	Team Leader	3017961678

Overall Recommendation:	WITHHOLD	on 18-JAN-2013	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 05-OCT-2012	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: MANUFACTURER, LOT RELEASE TESTING, STABILITY TESTING.
 (b) (4)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-JAN-2012				JEWELLC
SUBMITTED TO DO SITE WILL BE 3 MONTHS OVERDUE FOR INSPECTION BY PDUFA DATE.	16-FEB-2012	GMP Inspection			SMITHDE
ASSIGNED INSPECTION TO IB	16-FEB-2012	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	24-JUL-2012		(b) (4)		IRIVERA
INSPECTION PERFORMED See EIR in TURBO	(b) (4)		(b) (4)		Rachel.Harrington
DO RECOMMENDATION	10-NOV-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	23-NOV-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: DRUG SUBSTANCE MANUFACTURE, LOT RELEASE TESTING, STABILITY TESTING (on (b) (4) ()
3017961649)
Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-JAN-2012				JEWELLC
OC RECOMMENDATION	10-JAN-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER
 Establishment Comment: DRUG SUBSTANCE MANUFACTURER. LOT RELEASE TESTING, STABILITY TESTING (on (b) (4))
 3017961649)
 Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-JAN-2012				JEWELLC
OC RECOMMENDATION	10-JAN-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 2954383 FEI: 3004182921
 IMPAX LABORATORIES
 31153 SAN ANTONIO STREET
 HAYWARD, CA 94544

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURE LOT RELEASE TESTING, STABILITY TESTING (on 06-JAN-2012 by T. BOUIE (3017961649))
Profile: CAPSULES EXTENDED RELEASE **OAI Status:** OAI ALERT

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-JAN-2012				JEWELLC
SUBMITTED TO DO CTR NOT COVERED ON PREVIOUS INSPECTION	10-JAN-2012	GMP Inspection			INYARDA
ASSIGNED INSPECTION TO IB	11-JAN-2012	Product Specific			WMILLAR
DO RECOMMENDATION WL F/U INSPECTION CONDUCTED IN FEB/MAR 2012. 483 ISSUED. REGULATORY MEETING WITH FIRM CONDUCTED ON 12-JUN-2012. WL CLOSE-OUT LETTER WILL NOT BE ISSUED UNTIL RE-INSPECTION.	24-AUG-2012			WITHHOLD REGULATORY ACTION TAKEN AND/OR	WMILLAR
OC RECOMMENDATION FIRM REMAINS OAI	26-SEP-2012			WITHHOLD WARNING LETTER ISSUED	GODWINF
SUBMITTED TO DO PLEASE COVER THIS ON THE EI PLANNED IN THE NEXT FEW WEEKS PER EMIAL FROM UDUAK	05-OCT-2012	Product Specific			SMITHDE
ASSIGNED INSPECTION TO IB	15-OCT-2012	Product Specific			LDESOUZA
EIR RECEIVED BY OC	15-JAN-2013				SMITHDE
DO RECOMMENDATION PER SCSO INOKON EMAIL ON 1/15/13: 1)THERE WERE UNIDENTIFIED IMPURITIES (DEGREDAATION) IN THE BULK HOLD STUDY AND STABILITY STUDIES; 2)FOLLOW-UP TO DATA INTEGRITY HAS NOT YET DETERMINED THAT THE FIRM HAS STOPPED TRIAL INJECTIONS DURING ANALYSIS; & 3)THERE IS NO DATA ON BULK HOLD STUDIES.	16-JAN-2013			WITHHOLD OTHER/NOT ELSEWHERE CATEGORIZE	LDESOUZA
OC RECOMMENDATION PLEASE NOTE THE EIR FROM THE MOST RECENT INSPECTION WAS NOT AVAILABLE FOR FULL REVIEW AS THE INSPECTION IS ONGOING. BASED ON THE CGMP DEFICIENCIES NOTED IN PREVIOUS INSPECTIONS LEADING TO AN UNACCEPTABLE CGMP STATUS, OMPQ/DGMPA CONCURS WITH SAN-DO'S WITHHOLD RECOMMENDATION FOR NDA 203-312. FURTHER ASSESSMENT OF THE PRODUCT-SPECIFIC DEFICIENCIES NOTED DURING THE ONGOING INSPECTION WILL CONTINUE TO BE DISCUSSED WITH SAN-DO AND CDER/OPS/ONDQA. FOR MORE DETAILS PLEASE SEE THE CONCURRENCE MEMO IN CMS.	18-JAN-2013			WITHHOLD DISTRICT RECOMMENDATION EIR REVIEW-CONCUR W/DISTRICT WARNING LETTER ISSUED	SMITHDE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** **FEI:** 3007184570
 IMPAX LABORATORIES (TAIWAN) INC.
 NO 1, KE DONG 3RD RD
 JHUNAN, MIAO-LI COUNTY, , TAIWAN, PROVINCE OF CHINA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURER, LOT RELEASE TESTING, STABILITY TESTING. (on 09-JAN-2012 by T. BOUIE ())
 3017961649)
Profile: CAPSULES EXTENDED RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-JAN-2012				JEWELLC
SUBMITTED TO DO NEW PROFILE	10-JAN-2012	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	21-JAN-2012	Product Specific			PHILPYE
INSPECTION SCHEDULED	30-MAY-2012		26-JUL-2012		PHILPYE
INSPECTION PERFORMED	26-JUL-2012		26-JUL-2012		Tom.Limchumroon
<p>This is a comprehensive pre-approval and cGMP Establishment Inspection (EI) of a foreign finished oral dosage pharmaceutical manufacturer relating to FDA review of NDA 203312, IPX066 carbidopa-levodopa extended release capsules and (b) (4) submitted by Impax Pharmaceuticals, Inc. (USA). The inspection was initiated through DFI per FACTS assignment # (b) (4). This inspection was conducted in accordance with CPGM 7356.002, Drug Manufacturing Inspections and CPGM 7346.832 Pre-Approval Inspection (PAI). This inspection covered Quality, Facilities and Equipment, Production, Materials, and Laboratory Control systems. Profile Class CTR and TCM were covered. PAC Code covered for this inspection is 46832, 52832, and 56002.</p> <p>The previous inspection was conducted 06/2009 and classified as VAI. A 7-item FDA-483 for the following: (b) (4) program are incomplete, laboratory control test procedures are incomplete, equipment cleaning procedures incomplete, batch record not adequate to fully control variability, investigation are incomplete, and written procedures not followed. The current inspection followed up on these items and the firm had corrected these previous deficiencies and they appeared to be acceptable.</p> <p>Impax Laboratories (Taiwan) is wholly owned subsidiary of Impax Laboratories, Inc. (USA). Impax TW is a R&D and Manufacturing Facility of finished solid oral dosage pharmaceutical product manufacturer such as tablet, capsules, and granules. The plant is located at Jhunan Science Park. All products manufactured at this site are destined for the U.S. market. The products covered during the inspection is NDA 203312, IPX066 carbidopa-levodopa extended release capsules and (b) (4) Commercial products were not covered during the inspection because of inadequate time to cover those</p>					
DO RECOMMENDATION	24-OCT-2012			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	01-NOV-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAJAZIR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 2510049 FEI: 2510049
 IMPAX LABORATORIES INC
 CASTOR AND KENSINGTON AVE
 PHILADELPHIA, PA 19124

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER

Establishment Comment: DRUG PRODUCT PACKAGING AND LABELING (on 06-JAN-2012 by T. BOUIE () 3017961649)

Profile: CAPSULES EXTENDED RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-JAN-2012				JEWELLC
SUBMITTED TO DO	10-JAN-2012	GMP Inspection			INYARDA
DO RECOMMENDATION	11-JAN-2012			ACCEPTABLE	VMATUSOV
PREVIOUS GMP EI IS DATED 10/31-11/4/11. PLEASE NOTE THAT THIS EI IS NOT YET ENDORSED, BUT IT APPEARS IT WILL BE CLASSIFIED NAI. ALTHOUGH PROFILE CLASS CTR IS NOT LISTED, SIMILAR PROFILE CLASSES (b) (4) WERE COVERED. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	17-JAN-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: FINISHED DOSAGE RELEASE TESTER
 Establishment Comment: DRUG PRODUCT MICROBIAL TESTING ONLY. (on 09-JAN-2012 by T. BOUIE () 3017961649)
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	09-JAN-2012				JEWELLC
OC RECOMMENDATION	10-JAN-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

Final Drug Product Specification (Reported in SDN 34; 1/9/2013)

P.4.1 Specifications - Hard Gelatin Capsule Shells [IPX066, Extended Release Capsule]

Table 1: Specifications for Pre-Printed Hard Gelatin Capsules

Attribute	Test Method	Acceptance Criteria or Limit
Appearance Size 2	Visual	Capsules with white opaque body and blue opaque cap. Company (IPX066) and product identifier (95) printing is legible.
Appearance Size 1	Visual	Capsules with light blue opaque body and blue opaque cap. Company (IPX066) and product identifier (145) printing is legible.
Appearance Size 0EL	Visual	Capsules with yellow opaque body and blue opaque cap. Company (IPX066) and product identifier (195) printing is legible.
Appearance Size 00	Visual	Capsules with blue opaque body and blue opaque cap. Company (IPX066) and product identifier (245) printing is legible.
Identification: Gelatin	USP monograph	(b) (4)
Disintegration	USP<701>	Disintegrates in (b) (4) minutes (b) (4)
(b) (4)		

Attribute	Test Method	Acceptance Criteria or Limit
Weight	Gravimetric	Size
		Average (n=100)
		2 (b) (4) mg/capsule
		1 (b) (4) mg/capsule
		0EL..... (b) (4) mg/capsule
00 (b) (4) mg/capsule		
Microbial Enumeration Tests and Absence of Specified Microorganisms	USP<61>, USP<62>	Total aerobic microbial count < (b) (4) CFU/g Tests for Salmonella species and E. Coli are negative.
(b) (4)		< (b) (4) ppm
		< (b) (4) ppm
		< (b) (4) ppm
		< (b) (4) ppm

Reviewer Comments: *The changes are the company identifier under appearance (IPX066) and the product identifier (number indicating strength of levodopa in mg). In the original submission the specific markings were general explanations.*

P.5.1 Specifications - [IPX066, Extended Release Capsule]

Table 1: Quality Control Specifications for IPX066 Extended Release Capsule

Test Attribute	Limit or Criteria	Procedure
Appearance		
95 mg LD Strength Capsules (23.75 mg CD)	Capsules with white (b) (4) and blue (b) (4) cap. (b) (4) Each capsule is imprinted with IPX066 on the cap and 95 on the body.	Visual
145 mg LD Strength Capsules (36.25 mg CD)	Capsules with light blue (b) (4) and blue (b) (4) cap. (b) (4) Each capsule is imprinted with IPX066 on the cap and 145 on the body.	Visual
195 mg LD Strength Capsules (48.75 mg CD)	Capsules with yellow (b) (4) and blue (b) (4) cap. (b) (4) Each capsule is imprinted with IPX066 on the cap and 195 on the body.	Visual
245 mg LD Strength Capsules (61.25 mg CD)	Capsules with blue (b) (4) and blue (b) (4) cap. (b) (4) Each capsule is imprinted with IPX066 on the cap and 245 on the body.	Visual
Identification of Carbidopa and Levodopa ¹	Retention times of Carbidopa and Levodopa correspond to standard in the Assay within (b) (4) %.	T066AS
	The UV spectra of Carbidopa and Levodopa in the sample should conform to that of standard.	T066AS
Assay	Carbidopa: 90.0 – 110.0% of the labeled amount	T066AS
	Levodopa: 90.0 – 110.0% of the labeled amount	T066AS
Uniformity of Dosage Units ¹	Carbidopa: Meets USP<905> Content Uniformity	T066AS
	Levodopa: Meets USP<905> Content Uniformity	T066AS
Degradation Products	(b) (4)	T066RS

Test Attribute	Limit or Criteria	Procedure
Dissolution for Levodopa	<p><i>Meets USP<711></i> <i>Criteria for Extended-Release Dosage Forms</i></p> <p style="text-align: right;"><u>%Dissolved</u> <u>Range</u></p> <p>Acid Stage (b) (4) (b) (4) 120 min (b) (4) % Buffer Stage (pH 7) (b) (4) (b) (4) 240 min at pH 7)..... NLT (b) (4) %</p>	T066DS
Dissolution for Carbidopa	<p><i>Meets USP<711></i> <i>Criteria for Extended-Release Dosage Forms</i></p> <p style="text-align: right;"><u>%Dissolved</u> <u>Range</u></p> <p>Acid Stage (pH 1) (b) (4) 120 min (b) (4) % Buffer Stage (pH 7) (b) (4) (b) (4) 240 min at pH 7)..... NLT (b) (4) %</p>	T066DS
(b) (4)		
Assay	Tartaric Acid: (b) (4) % average ²	T066TTA-AS
Dissolution for (b) (4)	(b) (4)	T066DS
In-process Test (b) (4)		

¹ Batch release only.

² Assay relative to target capsule content (b) (4)

(b) (4)

Reviewer Comments: For this section the specified imprint information for appearance was changed to the specific language depicted above, instead of general language provided in the original submission. This information matches the information in the drug product labeling section.

Applicant Request to Withdraw the Hayward, California Site as a Manufacturing Site

Reviewer Comments: The amendment to withdraw the Hayward, California site as a manufacturing site is acknowledged, but due to ongoing deficiencies and verification that studies to support manufacturing are continuing at this site, the overall rating of establishments in this application include consideration of findings at this site.

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

/s/

CHARLES F JEWELL
01/18/2013

RAMESH K SOOD
01/18/2013

NDA 203-312

Rytary (Carbidopa and Levodopa) Extended Release Capsules

Impax Laboratories, Inc.

**CMC Reviewer: Charles F. Jewell Jr.
Division of Neurology Products**

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APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 203-312
2. REVIEW #1
3. REVIEW DATE: 28-August-2012
4. REVIEWER: Charles F. Jewell Jr.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA Submission SDN 1 (eCTD 0000)	21-DEC-2011
Response to IR (Biopharm) SDN 7 (eCTD 0006)	30-MAR-2012
Quality Information SDN 10 (eCTD 0009)	10-APR-2012
Quality Response to IR SDN 15 (eCTD 0014) response to mid-cycle IR	25-JUL-2012
Quality Response to IR SDN 16 (eCTD 0015) Response to IR question about palatability of capsule contents when mixed with food.	27-JUL-2012
Teleconference with Applicant (Biopharm and CMC response to IR)	07-AUG-2012
Quality Responses SDN 17	10-AUG-2012
Quality Responses SDN 18 (mostly for Biopharm)	17-AUG-2012
Quality Responses SDN 20	24-AUG-2012

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Impax Laboratories, Inc.
Address: 30831 Huntwood Avenue
Hayward, CA 94544
Representative: Jeff Mulchahey, Senior Director, Regulatory
Affairs
Telephone: (510) 240-6426

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rytary
- b) Non-Proprietary Name (USAN): Carbidopa-Levodopa
- c) Code Name/# (ONDC only): IPX066
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission PriorityS

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2); Reference Listed Drug Products are: Sinemet (carbidopa-levodopa tablets) (Merck&Co) (NDA 017-555), Lodosyn (carbidopa tablets) (BMS) (NDA 017-830), Sinemet CR (carbidopa-levodopa sustained-release tablets) (Merck&Co) (NDA 019-856), and Stalevo (carbidopa, levodopa, and entacapone tablets) (Novartis) (NDA 021-485).

10. PHARMACOL. CATEGORY: Levodopa is for dopaminergic replacement therapy, carbidopa is an enzyme inhibitor to inhibit peripheral amino acid decarboxylase to improve CNS availability of levodopa and reduce some of the peripheral side effects of levodopa in the periphery.

11. DOSAGE FORM: Capsules

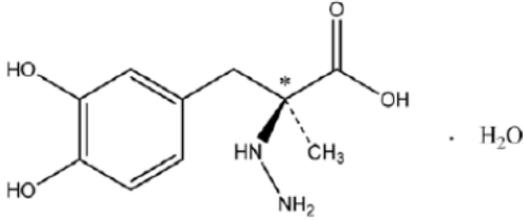
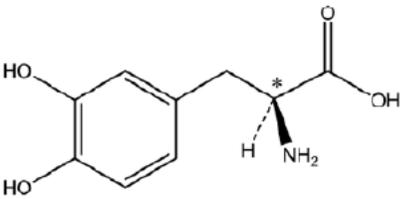
12. STRENGTH/POTENCY: 4 Different Strengths listed as mg Carbidopa/ mg Levodopa: 23.75/95; 36.25/145; 48.75/195; 61.25/245.

13. ROUTE OF ADMINISTRATION: Oral

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: X Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Two active components are Carbidopa and Levodopa:

INN: Carbidopa Other Chemical Names: <ul style="list-style-type: none"> • (-)-L-α-hydrazino-3,4-dihydroxy-α-methylhydrocinnamic acid monohydrate • Benzenepropanoic acid, α-hydrazino-3,4-dihydroxy-α-methyl-, monohydrate, (S)- • (αS)-α-Hydrazino-3,4-dihydroxy-α-methylbenzenepropanoic acid monohydrate • α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid monohydrate • α-methyl dopahydrazine • (2S)-3-(3,4-Dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate 	INN: Levodopa Other Chemical Names: <ul style="list-style-type: none"> • (-)-3-(3,4-dihydroxyphenyl)-L-alanine • 3-Hydroxy-L-tyrosine • (2S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid • L-Dihydroxyphenylalanine • (2S)-(3,4-Dihydroxyphenyl) alanine
	
$C_{10}H_{14}N_2O_4 \cdot H_2O$	$C_9H_{11}NO_4$
Relative Molecular Mass: 244.24 (monohydrate; drug substance form used in manufacture of drug product); 226.23 (anhydrous)	Relative Molecular Mass: 197.19

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Carbidopa	1	Adequate	8/10/2012	NAI review in DARRTS with comments for previously unreviewed amendments
	II		Carbidopa	1	Adequate	8/10/2012	NAI review in DARRTS with comments for previously unreviewed amendments
	II		Levodopa	1	Adequate	8/15/2012	NAI review in DARRTS with comments for previously unreviewed amendments
	II		Levodopa	3	Adequate		LOA 12/14/2010 Levodopa
	IV		(b) (4)	4	N/A		LOA 10/11/2011 (b) (4)
	IV		(b) (4)	4	N/A		LOA 12/14/2010 (b) (4)
	IV		(b) (4)	4	N/A		LOA 10/28/2011 (b) (4)
	III		(b) (4)	4	N/A		LOA 11/4/2011
	III		(b) (4)	4	N/A		LOA 10/5/2011 (b) (4)
	III		(b) (4)	4	N/A		LOA 12/20/2010
	III		(b) (4)	4	N/A		LOA 10/5/2011 (b) (4)

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		LOA 6/10/2010 (b) (4)
	III			4	N/A		LOA 8/5/2009 (b) (4)
	III			4	N/A		LOA 10/26/2011 (b) (4)
	III			4	N/A		LOA 10/13/2011 (b) (4)
	III			4	N/A		LOA 8/21/2008 (b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	IND 102,887	IPX066
	NDA 017-555	Sinemet
	NDA 017-830	Lodosyn
	NDA 019-856	Sinemet CR
	NDA 021-485	Stalevo

18. STATUS:

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	adequate	8/13/2012	Tristan S. Massie
EES	withhold; unacceptable at Hayward, CA DP manf. site; two sites pending review results	8/24/2012	
Pharm/Tox	pending; verbal adequate	8/21/2012	Luann McKinney
Biopharm	adequate	8/26/2012	Sandra Suarez-Sharp
LNC	N/A		
Methods Validation	N/A		
DMEPA	pending	8/20/2012	
EA	categorical exclusion; adequate	8/15/2012	Charles Jewell
Microbiology	N/A		

The Chemistry Review for NDA 203-312

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval from the CMC perspective, pending an overall acceptable rating in the Establishment Evaluation System (EES). The EES report is still pending for this application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Levodopa

Levodopa is the metabolic precursor to dopamine, to reduce the motor symptoms of Parkinson's disease.

Levodopa is an anhydrous compound produced for the applicant by (b) (4). Both have DMFs (# (b) (4) and # (b) (4) respectively) and the DMFs have been reviewed and are found to be adequate for other approved oral formulation drugs. Levodopa has a USP monograph and both producer supplied materials meet the limits of the USP specification.

Levodopa has high solubility according to BCS, from pH (b) (4), the solubility range is (b) (4) mg/mL to greater than (b) (4) mg/mL. Therefore the applicant proposes that the particle size of Levodopa is not a critical material attribute, but they do specify a limit for particle size of (b) (4) to control consistency across vendors, and to limit particle size to that used during development. Levodopa is not hygroscopic, it has no known polymorphs, and the materials from both vendors show consistent quality. It is a chiral amino acid with the same configuration of natural amino acids. The applicant adds tests for residual solvents and particle size, which are not included in the USP monograph. The methods are adequately validated.

Stability data supports a retest period of (b) (4) months for the (b) (4) material and (b) (4) months for the (b) (4) material. (b) (4) method of manufacture uses an (b) (4), while the (b) (4) material is manufactured in an (b) (4), no organic solvents are used.

Drug Substance: Carbidopa

Executive Summary Section

Carbidopa is an inhibitor of decarboxylases of peripheral amino acids. Its action can enhance the CNS availability of levodopa and reduce the peripheral side effects caused by too much dopamine.

Carbidopa in the form of a mono-hydrate is produced for the applicant by (b) (4). Both have DMFs (# (b) (4) respectively) and the DMFs have been reviewed and are found to be adequate for other approved oral formulation drugs. Carbidopa has a USP monograph and both producer supplied materials meet the limits of the USP specification.

Carbidopa has high solubility according to BCS, from pH (b) (4), the solubility range is (b) (4) mg/mL to greater than (b) (4) mg/mL. Therefore the applicant proposes that the particle size of Carbidopa not a critical material attribute, but they do specify a particle size in the drug substance specification of (b) (4) to assure consistency and to limit particle size to that used during development. It is non-hygroscopic. It has no known polymorphs. It is not sensitive to UV light. It is a chiral amino acid with the same configuration of natural amino acids. The applicant adds tests for residual solvents and particle size, which are not included in the USP monograph. The applicant also uses an impurities method which is validated for three additional impurities not in the USP monograph, and these three impurities are specified with appropriate limits in the carbidopa specification.

Carbidopa has one major degradant which is stability indicating and drives the total related substance level. This degradant is (b) (4). This degradant is adequately controlled in the drug substance but its growth is a critical consideration for the drug product stability.

Stability data supports a retest period of (b) (4) months for the (b) (4) material and the (b) (4) material.

Drug Product:

Rytary is a new extended release (ER) capsule formulation of carbidopa-levodopa (CD-LD). The capsules are available in four CD-LD dosage strengths (all strengths dose proportional with the fixed ratio of CD/LD being 1:4). See table below for colors:

mg CD/ mg LD	Capsule Size	Capsule Body Color	Capsule Cap Color
23.75/ 95	2	White (b) (4)	Blue (b) (4)
36.25/145	1	Light Blue (b) (4)	Blue (b) (4)
48.75/195	0EL	Yellow (b) (4)	Blue (b) (4)
61.25/245	00	Blue (b) (4)	Blue (b) (4)

Each capsule also contains tartaric acid (TA) as a functional excipient. (b) (4)

The mechanism of action of the functional excipient has not been confirmed, but it has been demonstrated that the presence of TA (b) (4), although the formulation is not particularly sensitive to the amount of TA.

(b) (4)

Executive Summary Section

(b) (4)

(b) (4)

Executive Summary Section

Table 1 Composition of IPX066 Filled Capsule

Ingredient	%w/w	IPX066 Fill Weight (mg / Capsule)			
		IPX066 23.75 CD / 95 LD mg	IPX066 36.25 CD / 145 LD mg	IPX066 48.75 CD / 195 LD mg	IPX066 61.25 CD / 245 LD mg
(b) (4)					
Total-Capsule	100.00	261.80	399.58	537.37	675.16
Hard Gelatin Capsule		White (b) (4) Body with Blue (b) (4) Cap, Size 2	Light Blue (b) (4) Body with Blue (b) (4) Cap, Size 1	Yellow (b) (4) Body with Blue (b) (4) Cap, Size 0EL	Blue (b) (4) Body with Blue (b) (4) Cap, Size 00

The enteric coating agents employed in this drug product use a mixture of (b) (4)

(b) (4) These are commonly used for this purpose and have been used in other approved drugs in similar portions, however, at maximum dose (2340 mg per day of Levodopa; translates to (b) (4) mg per day of (b) (4); (b) (4) mg per day of (b) (4); and (b) (4) mg per day of triethylcitrate), the (b) (4) polymers and triethyl citrate may exceed precedented levels compared to other approved extended release formulations. Based on studies of the toxicity of these polymers, the pharmacology/toxicology reviewer has agreed that these levels provide adequate safety. Microcrystalline cellulose and ethylcellulose are the agents used to (b) (4). Microcrystalline cellulose alone in component (b) (4), and both in component (b) (4).

The manufacturing process for the drug product is adequately described. Specifications and a control strategy are given for all components, and for all steps in the process. For all processing parameters, target values are given and used in the master batch records. The normal operating ranges around these target values are given, as well as proven acceptable ranges. Development data has been reviewed and it supports the proven acceptable ranges as described. In addition, the applicant had originally included 2 comparability protocols in the application for scale-up (b) (4)

(b) (4)

Executive Summary Section

(b) (4)

The QbD elements of risk assessment, some multi-variate studies, some DoEs and modeling driven data analysis was used in the comparison of study results and used to predict dissolution for areas of variable space not covered by experimental results. The sponsor used Monte Carlo methods to set dissolution ranges at timepoints indicated in the dissolution specification for the final drug product. These ranges were deemed higher than acceptable by the ONDQA biopharmaceutics reviewer and recommendations were made for ranges supported completely by batches of drug product used in the phase III studies. The applicant has agreed to the recommended dissolution ranges with a slight variation, that was accepted by the ONDQA biopharmaceutics reviewer.

The applicant was also directed to add (b) (4) dissolution to release, and (b) (4) assay and dissolution to stability evaluation. They have agreed to do this and the limits have been approved by the ONDQA biopharmaceutics reviewer.

The (b) (4) have been justified based on the applicant proposed dissolution ranges, but required tightening based on the biopharmaceutical reviewer tightening of dissolution specification limits. These adjustments have been captured in the application and review.

The drug product and container closure system configurations proposed for marketing are summarized in the following table from the applicant:

Table 1: Bottle Presentations for IPX066 ER Capsule

Capsule Strengths (mg)	23.75/95	36.25/145	48.75/195	61.25/245
25 Count Bottle Presentation				
Bottle size (c.c.)	30	40	50	75
(b) (4)				
(b) (4) Desiccant Packs (g)	2	2	2	2
100 Count Bottle Presentation				
Bottle size (c.c.)	120	120	200	200
(b) (4)				
(b) (4) Desiccant Packs (g)	5	5	5	5
240 Count Bottle Presentation				
Bottle size (c.c.)	200	250	400	500
(b) (4)				
(b) (4) Desiccant Packs (g)	5	5	5	5

Executive Summary Section

The 25 count bottle presentations are proposed for physician samples. This configuration scheme was adequately covered by bracketing in the registration stability studies.

For the purpose of expiration dating, the applicant originally proposed to initiate the period with the date of the (b) (4) process, as opposed to the standard practice of the initiation based on (b) (4). They proposed an expiration date of 30 months from (b) (4). It was highly recommended that they count expiration dating from the (b) (4) and they agreed. Their registration stability data coupled with statistical analysis supports (b) (4) months of stability. It is likely that as more long term storage conditions stability data becomes available, that this will increase.

B. Description of How the Drug Product is Intended to be Used

The drug product is to be used in 3 to 4 times a day dosing to control the on/off stage for Parkinson's patients. (b) (4)

For those patients unable to swallow the capsules, labeling recommends opening the capsules and putting the contents into a small amount (1 or 2 tablespoons of applesauce) and consuming this mixture immediately. This is allowed because there is a bioequivalence study showing this is valid. It should be noted that the enteric coating of the extended release (b) (4) is not designed to withstand neutral pH. Since applesauce is known to have a pH around 3.5, this labeling is allowed to stand, but the capsule contents should not be mixed with food other than applesauce, (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

- All reviewed data supports the approvability of this application from the CMC perspective, except the Establishment Evaluation System (EES) recommendation from the Office of Compliance, which is still pending, due to a pending alert at one site (manufacture of drug product in Hayward, CA) and results from inspection at two sites (manufacture of drug product in Taiwan and manufacture of Levodopa in Japan). The CMC reviewer will provide an update review prior to the PDUFA date to indicate an update of status on the pending inspections, and thus the ultimate approvability of the application from the CMC perspective.

III. Administrative**A. Reviewer's Signature**

Executive Summary Section

B. Endorsement Block

ChemistName/Date:

Charles Jewell (CMC Reviewer)/28-Aug-2012

Sandra Suarez-Sharp (ONDQA Biopharmaceutics Reviewer)/28-Aug-2012

ChemistryTeamLeaderName/Date:

Martha Heimann (CMC Lead Division of Neurology Products)/28-Aug-2012

Secondary Chemistry Reviewer/Date:

Ramesh Sood (ONDQA Division I Branch 1 Branch Chief)/28-Aug-2012

ProjectManagerName/Date:

Teshara Bouie (ONDQA)/28-Aug-2012

Tracy Peters (OND)/28-Aug-2012

C. CC Block

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immediately following this page

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/s/

CHARLES F JEWELL
08/28/2012

RAMESH K SOOD
08/28/2012

**Initial Quality Assessment
Branch I**

OND Division: Division of Neurology Product

NDA: 203-312

Applicant: Impax Laboratories, Inc.

Stamp Date: 12/21/2011

PDUFA Date: 10/21/2012

Trade Name: None assigned

Code Name: IPX066

Established Name: Carbidopa - Levodopa Extended Release Capsules

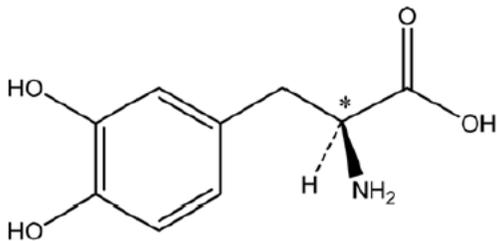
Dosage Form: Capsules

Route of Administration: Oral

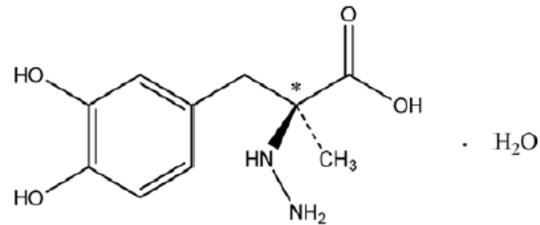
Indication: Treat Patients with (b) (4) Parkinson's Disease (b) (4), post-encephalitic parkinsonism, and (b) (4) parkinsonism (b) (4) may follow (b) (4) carbon monoxide intoxication (b) (4) or manganese intoxication.

Assessed by: Charles Jewell and Martha Heimann

ONDQA Fileability: Yes



Levodopa



Carbidopa (mono-hydrate)

Summary

This NDA is a 505 (b) (2) application that requests cross reference to previous NDA's; NDA 17-555 Sinemet® (carbidopa-levodopa) tablets, NDA 17-830 Lodosyn® (carbidopa) tablets, NDA 19-856 Sinemet® CR (carbidopa-levodopa) Sustained-Release Tablets, and NDA 21-485 Stalevo® (carbidopa, levodopa, and entacapone) Tablets.

This extended release combination product containing carbidopa and levodopa is designed to produce a rapid increase in plasma levodopa without need for supplemental immediate release carbidopa-levodopa. (b) (4)

Levodopa is the metabolic precursor to dopamine, which is effective in reducing motor symptoms associated with Parkinson's disease and similar ailments. The clinical utility of levodopa is enhanced through co-administration of carbidopa, an inhibitor of peripheral amino acid decarboxylase and this improves the central nervous system availability of levodopa and serves to reduce peripheral side effects. The 1:4 ratio of carbidopa-levodopa is used most commonly.

Current drugs lead to substantial fluctuations in plasma levodopa concentrations. (b) (4)

The applicant claims to have developed specifications for IPX066 that adequately control the drug product. They propose to qualify the Impax Hayward, CA facility and the Impax Jhunan, Taiwan site for manufacture of the drug product. (b) (4)

The drug substance used in this drug product is sourced from three different suppliers. Carbidopa is supplied by (b) (4) and (b) (4). Levodopa is supplied by (b) (4) and (b) (4). Each of these suppliers provides DMF's on the manufacture of these drug substances.

Non-clinical sections of the application rely on previous findings for carbidopa-levodopa products.

Clinical pharmacology studies are provided which:

- establish the relative bioavailability and pharmacokinetics of IPX066 compared with Sinemet, Sinemet CR, and Stalevo (Study IPX066-B08-10)
- investigate the effect of a high-fat, high-calorie meal on the PK of IPX066 capsule and evaluate the effect of sprinkling the capsule contents onto soft food such as applesauce (Study IPX066-B09-01)
- investigate the effect of 240 mL of 0%, 5%, 20%, and 40% v/v alcohol on the IPX066 capsule formulation (Study IPX066-B09-04)
- demonstrate the dose proportionality of IPX066 dosage strengths (95, 145, 195, and 245 mg; (IPX066-B08-09)
- demonstrate bioequivalence of IPX066 manufactured at Impax facilities in Hayward, USA and in Jhunan, Taiwan (Study IPX066-B10-01)

Clinical trials have also been reported in the application to support safety and efficacy. Clinical trials included a study in advanced Parkinson's disease against an immediate release carbidopa-levodopa comparator and against a carbidopa-levodopa-entacapone comparator.

Drug Substance

Levodopa

Levodopa (C₉H₁₁NO₄; MW. 197.19) has a single chiral center and is the L enantiomer with an S configurational assignment. Reference is made to (b) (4) DMF No. (b) (4) and (b) (4) DMF No. (b) (4).

Levodopa is a white to off-white, odorless, crystalline powder, melting from 276 to 278°C with decomposition at (b) (4) C. It is slightly soluble in water and freely soluble in 3 N Hydrochloric acid. (b) (4)

No other polymorphic forms are reported in the literature.

Table 4: Specification for Levodopa, USP sourced from (b) (4)

Test Attribute	Test Method	Mfr ¹	Acceptance Criteria
Appearance	Visual	(b) (4)	White to off-white crystalline powder.
Identification	A. USP<197M> B. USP<197U> C. USP monograph, Assay	(b) (4)	A. IR spectrum conforms to that of the standard B. Absorptivities at (b) (4) calculated on the (b) (4) do not differ by more than (b) (4) %. C. The retention time of the major peak in the chromatogram of the Assay preparation corresponds to the standard in the Assay test.
Specific Rotation	USP<781S>	(b) (4)	Between (b) (4) and (b) (4) (b) (4)
Residue on Ignition	USP<281>	(b) (4)	NMT (b) (4) %
Heavy Metals	USP<231> Method II	(b) (4)	NMT (b) (4) %
Related Substances	USP monograph	(b) (4)	Levodopa Related Compound A ⁴ NMT (b) (4) % L-Tyrosine NMT (b) (4) % 1-Veratrylglycine NMT (b) (4) % Individual unknown impurity ⁵ NMT (b) (4) % Total unknown impurities NMT (b) (4) % Total all impurities NMT (b) (4) %
Assay	USP monograph	(b) (4)	98.0% - 102.0% on dried basis. (b) (4)

¹ Manufacturer: (b) (4) (b) (4)

⁵ Impax limit is listed; the USP monograph limit is NMT (b) (4) %.

15 Lots of Levodopa have been used from (b) (4) in drug product and clinical studies. 10 Lots of Levodopa have been used from (b) (4). Uses have been for 10 different clinical studies, for primary registration stability and for site qualification.

(b) (4)

(b) (4)

Based on stability studies from the suppliers, a retest period of (b) (4) months is recommended by (b) (4) and (b) (4) months by (b) (4).

Carbidopa

Carbidopa ($C_{10}H_{14}N_2O_4 \cdot H_2O$; MW. 244.24; Anhydrous wt. is: 226.23) has a single chiral center and is the L enantiomer with an S configurational assignment. Reference is made to (b) (4) DMF No. (b) (4) and Teva's DMF No. (b) (4).

Carbidopa is a white to creamy-white powder, melting from 203 to 205°C with decomposition. It is slightly soluble in water and freely soluble in 3 N Hydrochloric acid.

(b) (4)
No other polymorphic forms are reported in the literature.

Table 4: Specification for Carbidopa, USP sourced from (b) (4)

Test Attribute	Test Method	Mfr ¹	Acceptance Criteria or Limit
Appearance	Visual	(b) (4)	White to creamy white powder
Identification	A) USP <197M> B) USP monograph Assay	(b) (4)	A) IR spectrum conforms to that of the standard B) The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the Assay.
Specific Rotation	USP <781S>	(b) (4)	Between (b) (4) and (b) (4) Calculated as the monohydrate
Residue on Ignition	USP <281>	(b) (4)	NMT (b) (4)%
Heavy Metals	USP <231> Method II	(b) (4)	NMT (b) (4)%
Related Substances	Method 627	(b) (4)	Methyldopa NMT (b) (4)% Carbidopa Related Compound A NMT (b) (4)%
Assay	USP monograph	(b) (4)	98.0% - 102.0%, as the monohydrate

(b) (4)

¹Not listed in USP monograph

Note that in the above specification of carbidopa, the impurities (b) (4) are not impurities listed in the USP monograph.

11 Lots of Carbidopa have been used from (b) (4) in drug product and clinical studies. 7
Lots of Levodopa have been used from (b) (4). Uses have been for 10 different
clinical studies, for primary registration stability and for site qualification.

(b) (4)

(b) (4)

Based on stability studies from the suppliers, a retest period of (b) (4) months is
recommended by each supplier.

Drug Product

IPX066 for oral administration are hard gelatin capsules containing carbidopa/levodopa (CD/LD) at a ratio of 1:4. The capsules are available in dosage strengths, 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, and 61.25 mg/245 mg, filled into the capsule sizes of 2, 1, 0EL, and 00 respectively. The capsules of different strengths share the same formulation components which are filled into capsules proportionally to achieve the capsule strength.

IPX066 is a multi-particulate formulation, designed with a (b) (4) extended drug release profile. The components characteristics are summarized below:

(b) (4)

(b) (4)

- 23.75 - 95 mg: White (b) (4) with Blue (b) (4) Cap, Size 2.
- 36.25 - 145 mg: Light Blue (b) (4) with Blue (b) (4) Cap, Size 1.
- 48.75 - 195 mg: Yellow (b) (4) with Blue (b) (4) Cap, Size 0EL.
- 61.25 - 245 mg: Blue (b) (4) with Blue (b) (4) Cap, Size 00.

The respective compositions are summarized in the following table:

Table 2: Compositions of IPX066 ER Capsules

Ingredients	Grade	Function	Composition w/w %	IPX066 ER Capsules	IPX066 ER Capsules	IPX066 ER Capsules	IPX066 ER Capsules
				23.75mg/95mg	36.25mg/145mg	48.75mg/195mg	61.25mg/245mg
Carbidopa ¹	USP	Active	9.79	25.64	39.13	52.63	66.12
Levodopa	USP	Active	36.29	95.00	145.00	195.00	245.00
Tartaric Acid	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Mannitol	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Ethylcellulose	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hypromellose (b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Starch Glycolate	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Lauryl Sulfate	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Povidone	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Talc	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Methacrylic acid Copolymer, (b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Triethyl Citrate	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Croscarmellose Sodium	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total			100.00	261.80	399.58	537.37	675.16
Hard Gelatin Capsules	N/A	Capsule	N/A	White (b) (4) Body with Blue (b) (4) Cap, Size 2	Light Blue (b) (4) Body with Blue (b) (4) Cap, Size 1	Yellow (b) (4) Body with Blue (b) (4) Cap, Size 0EL	Blue (b) (4) Body with Blue (b) (4) Cap, Size 00

¹ Carbidopa is supplied as a monohydrate, the quantity listed is equivalent to 23.75, 36.25, 48.75 and 61.25 mg carbidopa anhydrous accordingly.

The specifications of the various drug product strengths are summarized in the following table:

Table 1: Quality Control Specifications for IPX066 Extended Release Capsule

Test Attribute	Limit or Criteria	Procedure
Appearance		
95 mg LD strength capsules (23.75 mg CD)	Capsules with white (b)(4) and blue (b)(4) cap. (b)(4) Company and product identifiers are printed on each capsule.	Visual
145 mg LD strength capsules (36.25 mg CD)	Capsules with light blue (b)(4) and blue (b)(4) cap. (b)(4) Company and product identifiers are printed on each capsule.	Visual
195 mg LD strength capsules (48.75mg CD)	Capsules with yellow (b)(4) and blue (b)(4) cap. (b)(4) Company and product identifiers are printed on each capsule.	Visual
245 mg LD strength capsules (61.25 mg CD)	Capsules with blue (b)(4) and blue (b)(4) cap. (b)(4) Company and product identifiers are printed on each capsule.	Visual
Identification of Carbidopa and Levodopa ¹	A. Retention times of Carbidopa and Levodopa correspond to standard in the Assay within (b)(4)/%.	T066AS
	B. The UV spectra of Carbidopa and Levodopa in the sample should conform to that of standard.	T066AS
Assay	Carbidopa: 90.0 – 110.0% of the labeled amount	T066AS
	Levodopa: 90.0 – 110.0% of the labeled amount	T066AS
Uniformity of Dosage Units ¹	Carbidopa: Meets USP<905> Content Uniformity	T066AS
	Levodopa: Meets USP<905> Content Uniformity	T066AS

Table 1: Quality Control Specifications for IPX066 Extended Release Capsule (Continued)

Test Attribute	Limit or Criteria	Procedure
Degradation Products	(b) (4)	T066RS
Dissolution for Levodopa	Meets USP<711> criteria for Extended-Release Dosage Forms % Dissolved <u>Range</u> Acid stage (b) (4) 120 min (b) (4) % Buffer stage (pH 7) (b) (4) (b) (4) 240 min at pH 7 NLT (b) (4) %	T066DS
Dissolution for Carbidopa	Meets USP<711> criteria for Extended-Release Dosage Forms % Dissolved <u>Range</u> Acid stage (b) (4) 120 min (b) (4) % Buffer stage (pH 7) (b) (4) (b) (4) 240 min at pH 7 NLT (b) (4) %	T066DS
(b) (4)		
Assay ¹	(b) (4) % average ²	T066TTA-AS
In-process Test (b) (4)		
¹ Batch release only.		
² Assay relative to target capsule content (b) (4) (b) (4)		

The drug products are packaged in white, HDPE bottles with white, (b) (4) closures with an inside liner consisting of (b) (4). Desiccant is included in all bottles. Professional sample bottles will be packed in cartons.

(b) (4)

As a functional excipient, bioavailability studies conducted by the applicant showed that the *in vivo* effect of (b) (4) on LD bioavailability was robust. A consistent LD bioavailability was observed despite significant variations in the amount and release rate of (b) (4). Specifications and control strategy are proposed for component (b) (4) according to its role as a functional excipient and the observed robust *in vivo* effect.

(b) (4)

The IPX066 formulation used in the pivotal clinical Phase II and Phase III studies, primary registration and site qualification stability studies intended for commercial manufacture were the same except for the capsule color.

In-vitro in vivo correlation (IVIVC), (b) (4) was developed for IPX066 for both carbidopa and levodopa (IVIVC report). (b) (4)

A bioequivalence study (IPX066-B10-01) was conducted to compare capsules manufactured in Jhunan, Taiwan (Lot PB00911-120) and in Hayward, CA (Lot RB09010-80B) using the highest dosage strength CD-LD of 61.25-245 mg. They showed bioequivalence.

(b) (4)

Proven acceptable process parameter ranges for the manufacture of each intermediate are provided in tables in the manufacturing sections. Master batch records are provided for each step in the process and for each site used in the manufacturing.

The container closure system is provided as bottles of 100 and 240 counts with physician samples in 25 count bottles. The container closure systems identified for the commercial packages are 30, 40, 50, 75, 120, 200, 250, 400 and 500 cc bottle sizes of opaque white HDPE bottles with matching white (b) (4) sealed with an induction inner-seal. The HDPE is pigmented white with (b) (4)

(b) (4) fiber packs are used as desiccants. The bottle presentations are summarized in the table below:

Table 1: Bottle Presentations for IPX066 ER Capsule

Capsule Strengths (mg)	23.75/95	36.25/145	48.75/195	61.25/245
25 Count Bottle Presentation				
Bottle size (c.c.)	30	40	50	75
(b) (4) Desiccant Packs (g)	2	2	2	2
100 Count Bottle Presentation				
Bottle size (c.c.)	120	120	200	200
(b) (4) Desiccant Packs (g)	5	5	5	5
240 Count Bottle Presentation				
Bottle size (c.c.)	200	250	400	500
(b) (4) Desiccant Packs (g)	5	5	5	5

The drug product placed on stability was packaged in white HDPE bottles of various sizes with matching white (b) (4) caps, the proposed commercial container closure system. In addition, the shelf-life (bulk hold times) of the intermediate component materials and bulk finished product capsule has also been established.

It should be noted that each "Component Lot Series" represents a manufacturing campaign that produced one batch of each of the Components (b) (4). These batches of components were then used to produce multiple capsule lots of different strengths. The bulk capsules were then packaged in one or more container configurations to produce the drug product used in clinical or stability studies. Stability of materials has been studied on the bulk components, bulk capsules and packaged capsules.

An overview of the stability study test article types and sources is shown here:

Table 1: Overview of Stability Study Test Article Types and Sources

Test Article	Component Lot Series	Description	Manufacturing Site	
Drug Product	Lot 1 Lot 3 Lot 4 Lot 5	(b) (4)	Hayward, CA	
	Lot 2		Hayward, CA	
	SQ1 SQ2 SQ3		Jhunan, Taiwan	
	PK/PD Naïve Lot 0		Hayward, CA	
Bulk Capsule	Lot 0 Lot 2 Lot 3 Lot 4 Lot 5		Hayward, CA	
	SQ1 SQ2 SQ3		Jhunan, Taiwan	
Bulk Component	Lot 2 Lot 3 Lot 4 Lot 5		Hayward, CA	
	SQ1 SQ2 SQ3		Jhunan, Taiwan	
			(b) (4)	

The applicant proposes that the shelf life period of the drug product be defined as beginning at (b) (4). The drug product shelf life would be determined by a combination of data (b) (4)

(b) (4) The stability studies of the components and capsules have shown that the primary stability-indicating attribute that defines bulk or packaged shelf-life is the level of the (b) (4) related degradant (b) (4).

Prior to (b) (4), all (b) (4) components will be tested and released at bulk batch materials, with defined maximum bulk hold times and conditions (6 months at room temperature). The bulk hold time of each component has been established through bulk holding studies using stability-indicating chemical (assay, impurities, (b) (4)) and functional (dissolution) tests.

Based on data reported, the applicant proposes a shelf life of 30 months for drug product when stored at controlled room temperature, defined as 25°C (77°F) with excursions

permitted to 15-30°C (59-86°F). The expiry dating of the packaged drug product will be 30 months from the (b) (4).

Critical Issues for Review

Drug Substance

All drug substance info is contained in four DMFs: # (b) (4) ((b) (4) - Carbidopa, USP), # (b) (4) ((b) (4) - Levodopa, USP), # (b) (4) ((b) (4) - Levodopa), # (b) (4) ((b) (4) - Carbidopa). All of these have been previously reviewed (b) (4), but this should be verified so that it is certain the DMF's review status is up-to-date.

Are any additional manufacturing sites involved in the drug substance manufacture (determined on review of the DMFs), if so this should be updated in EES as soon as possible.

Drug Product

The applicant proposes proven acceptable ranges for process parameters used in component manufacturing, are these supported by the development data, which were generated under a quality by design paradigm, including multivariate design of experiments? Does the applicant plan to "adjust" targeted parameters described in master batch records within the proven acceptable ranges? If so these ranges could be considered a design space.

The applicant reports that they have demonstrated that (b) (4) levels are stable with time in the drug product. Is this acceptable, or should it be assayed for on stability?

Do stability studies bracket strength, container configurations in an adequate way?

The applicant proposes an *in-vitro in vivo* correlation (IVIVC) to support a biowaiver request for minor changes in IPX066 manufacturing parameters. The IVIVC was developed for IPX066 for both carbidopa and levodopa (b) (4) .. Suitability of the IVIVC model is deferred to the Biopharmaceutics reviewer. The applicant should be asked to confirm that future changes based on the IVIVC correlation will be reported to the Agency via the appropriate submission route.

Are both manufacturing sites qualified based on the established bioequivalence data? Has the applicant submitted a biowaiver request for the lower capsule strengths; and is the request acceptable to the Biopharmaceutics review team?

(b) (4)
The applicant should be asked to verify that these are the only proposed changes to be supported by the protocols.

The applicant proposes that the shelf life period of the drug product be defined as beginning at (b) (4). This is not consistent with current policy. The firm should

be asked to acknowledge that shelf life of the drug product is based on the [REDACTED] (b) (4)

Additional Issues

Administrative: A claim for categorical exclusion for environmental assessment is included in Module 1.12.14 of the application.

Establishment Evaluation: An updated list of manufacturing sites and contract testing facilities was provided on 1/19/2012 through EES, double checked by M. Heimann and C. Jewell for completeness in the context of the application. **Currently in EES, there is an OAI alert for the Impax drug product manufacturing site in Hayward, CA.**

Comments for the 74-day letter

None have been identified yet.

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. This application is essentially a follow-up combination product, attempting to provide a better formulation of the drug product in order to provide more stable plasma levels of levodopa than existing products. The nature of the extended release drug product put emphasis on the need for biopharmaceutical reviewer in conjunction with the CMC reviewer. There are QbD elements in the formulation development and in the establishment of proven acceptable ranges for drug product intermediates.

Charles Jewell, Ph.D. (CMC Reviewer) 1/11/2012

Martha Heimann, Ph.D. (CMC Lead) 1/11/2012

Ramesh Sood, Ph.D. (Branch Chief) 1/11/2012

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 203-312 **Supplement Number and Type:** Original Application **Established/Proper Name:** Carbidopa-Levodopa

Applicant: Impax Laboratories, Inc. **Letter Date:** 12/21/2011 **Stamp Date:** 12/21/2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	Y		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Y		
3.	Are all the pages in the CMC section legible?	Y		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Y		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Y		with form FDA 356h
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	NA		Not applicable here

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Y		DMF numbers listed on form, other manufacturing information listed on continuation sheets.
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Y		DMF numbers listed on form, other manufacturing information listed on continuation sheets.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Y		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>		N	<p>Declaration of readiness for inspection is not described for Microbial Testing, Raw material testing, particle size testing and container testing. The rest of the manufacturing sites are marked ready for testing.</p>

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	Y		<p>Request for waiver under 1.12 Other correspondence.</p>

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	Y		refers to four DMFs, two each for each drug substance component.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	Y		refers to DMFs
14.	Does the section contain information regarding the characterization of the DS?	Y		
15.	Does the section contain controls for the DS?	Y		
16.	Has stability data and analysis been provided for the drug substance?	Y		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		N	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		N	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Y		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	Y		
21.	Is there a batch production record and a proposed master batch record?		N	There are executed batch records but no proposed master batch record.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Y		Investigational formulation is the same as proposed commercial except for capsule color.
23.	Have any biowaivers been requested?	Y		(b) (4) 
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Y		
25.	Does the section contain controls of the final drug product?	Y		
26.	Has stability data and analysis been provided to support the requested expiration date?	Y		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	Y		Risk analysis, simulation and DOEs were used in the development of the optimized formulation.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		N	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	Y		Summary of this data is in Regional Information

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	Y		Discussion in 3.2.P.2.5 demonstrates that the packaged drug product is not a microbial growth-promoting media.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	Y		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Carbidopa	12/12/2010	Carbidopa (b) (4)
	II		Carbidopa	12/14/2010	Carbidopa
	II		Levodopa	11/7/2011	Levodopa
	II		Levodopa	12/14/2010	Levodopa
			(b) (4)	10/11/2011	(b) (4)
	IV			12/14/2010	
	IV			10/28/2011	
	III			11/4/2011	
	III			10/5/2011	
	III			12/20/2010	
	III			10/5/2011	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

(b) (4)	III	(b) (4)	6/10/2010	(b) (4)
	III		8/5/2009	
	III		10/26/2011	
			10/13/2011	
	III		8/21/2008	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	Y		
33.	Have the immediate container and carton labels been provided?	Y		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	Y		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		None	Describe filing issues here or on additional sheets
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		None	Describe potential review issues here or on additional sheets

{See appended electronic signature page}

Name of
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of
Branch Chief
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

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

/s/

CHARLES F JEWELL
01/24/2012

MARTHA R HEIMANN
01/24/2012

RAMESH K SOOD
01/24/2012