

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217186Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	217186
Applicant Name	Impax Laboratories
Drug Product Name	Crexont (carbidopa and levodopa)
Dosage Form	Extended-release capsule
Proposed Strength(s)	35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, 87.5 mg/350 mg
Route of Administration	Oral
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Drug Product Description	Capsules have white to off-white granules and beads and capsule strengths are compositionally proportional. 35 mg/140 mg: White opaque body imprinted with "140" in black ink and yellow opaque cap imprinted with "IPX203" in white ink. 52.5 mg/210 mg: White opaque body imprinted with "210" in black ink and green opaque cap imprinted with "IPX203" in white ink. 70 mg/280 mg: White opaque body imprinted with "280" in black ink and purple opaque cap imprinted with "IPX203" in white ink. 87.5 mg/350 mg: White opaque body imprinted with "350" in black ink and medium orange opaque cap imprinted with "IPX203" in white ink.
Co-packaged product information	N/A
Device information	N/A
Storage Temperature/ Conditions	20°C to 25°C

Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	N/A	N/A
	<i>Drug Product/ Labeling</i>	Grace Chiou	Martha Heimann/ Julia Pinto
	<i>Manufacturing</i>	Prashanth Manda	Chengjiu Hu
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Erica Keafer	
	<i>ATL</i>	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months when stored at 20°C to 25°C.

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This is the second integrated quality review for NDA 217186 for Crexont (carbidopa and levodopa) extended-release capsules). OPQ recommended approval of the application during the original review cycle. However, a Complete Response letter was issued due to safety concerns. In the resubmission, the applicant proposed to reduce the recommended maximum daily slightly, (b) (4)

. The revised maximum dose can be achieved with a combination of lower strengths without changes to the previously proposed strengths. Based on our evaluation of the available information, the application remains adequate to support APPROVAL. The overall manufacturing inspection

recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate	– Adequate first cycle. No new information.
Drug Product	-	Adequate	
Quality Labeling	-	Adequate	
Manufacturing	-	Adequate	– Adequate first cycle. No new information.
Biopharmaceutics	-	Adequate	– Adequate first cycle. No new information.
Microbiology	-	N/A	

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.

Application Technical Lead: Martha R. Heimann, Ph.D.
Date: 7/22/2024



Martha
Heimann

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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

NDA Number	217186
Assessment Cycle Number	2
Drug Product Name	Carbidopa and levodopa extended-release capsules

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Choose an item.	0017
Patient Information	N/A	See original review
Instruction for Use (IFU)	N/A	See original review
Container Labels	Adequate	See original review
Carton Labeling	N/A	See original review

There were no updates provided in eCTD 0017 with regards to container and carton labels. The labeling is adequate pending minor revisions as described below.

Brief Description of Outstanding Issues: NA

Submissions being reviewed:

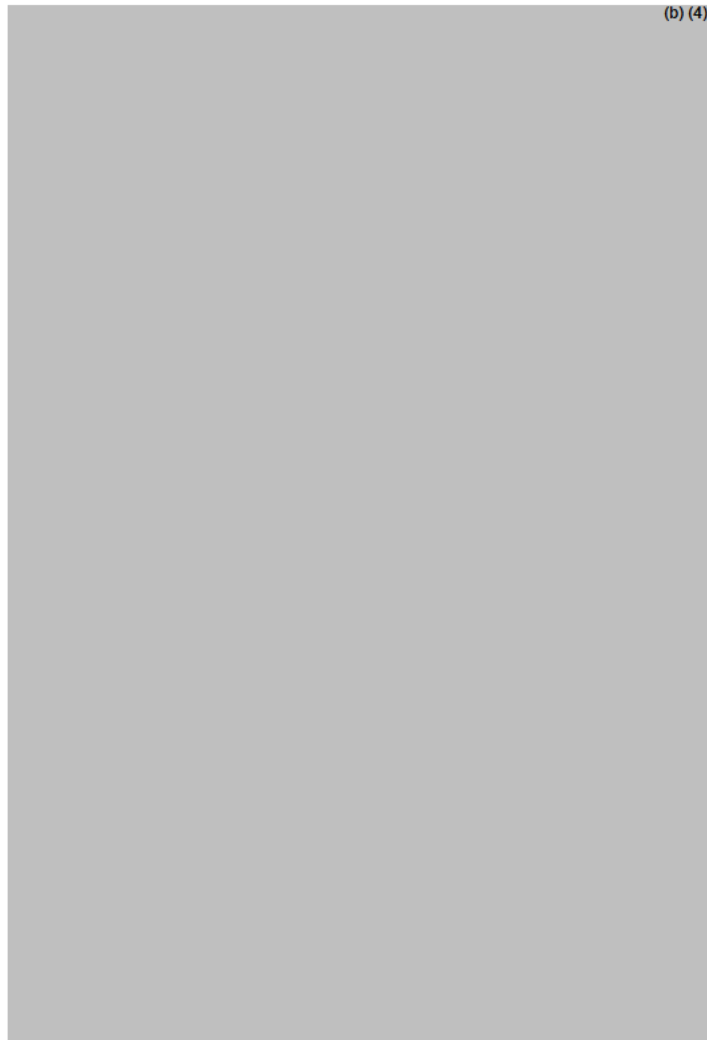
Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
Package insert (SD 0017)	February 07, 2024	Package insert

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

¹ [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION



Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	Adequate
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	

² Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	Adequate
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient- use). Other package terms include pharmacy bulk package and imaging bulk package. ⁸	N/A	

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

⁴ Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

⁶ Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

⁷ Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

⁸ Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

(b) (4)



⁹ See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format](#) (January 2023); Labeling Review Tool (March 2022, page 25)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
dilution, compatible diluents and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures."</i> ^x with x numerical citation to "OSHA Hazardous Drugs."	N/A	

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

(b) (4)

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Adequate
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active	Adequate	

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.3 Section 11 (DESCRIPTION)¹⁴

(b) (4)



¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	Inadequate: Revise inactive ingredients to be in alphabetical order; remove (b) (4) as this is extraneous.
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	Replace "(b) (4)" with "pellet" or "granule" (choose one) throughout as it is not in-line with the "Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format" guidance.
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	Move second paragraph to where inactive ingredients are listed. The inactive ingredients should be delineated between the immediate release granules and the extended-release pellets.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Adequate	
If alcohol is present, must provide the amount of alcohol in	N/A	

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].		
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	Adequate
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: Adequate

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

Adequate, pending revision.

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”***

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Inadequate: Revise units to include capsules (i.e., "Bottles of 120

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	capsules") and recommend formatting as table
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Inadequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i> ²¹	N/A	
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Adequate	

Assessment: *Adequate*

Adequate, pending revision.

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)



1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Adequate

Assessment: *Adequate*

Adequate, pending revision.

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

2. OUTSTANDING ISSUES AND RECOMMENDATIONS

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these issues in this section.

Primary Labeling Assessor Name and Date: Grace Chiou, Ph.D.

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)



Grace
Chiou

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Julia
Pinto

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NDA Executive Summary

1. Application/Product Information

NDA Number	217186
Applicant Name	Impax Laboratories
Drug Product Name	Crexont (carbidopa and levodopa)
Dosage Form	Extended-release capsule
Proposed Strength(s)	35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, 87.5 mg/350 mg
Route of Administration	Oral
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Drug Product Description	Capsules have white to off-white granules and beads and capsule strengths are compositionally proportional. 35 mg/140 mg: White opaque body imprinted with "140" in black ink and yellow opaque cap imprinted with "IPX203" in white ink. 52.5 mg/210 mg: White opaque body imprinted with "210" in black ink and green opaque cap imprinted with "IPX203" in white ink. 70 mg/280 mg: White opaque body imprinted with "280" in black ink and purple opaque cap imprinted with "IPX203" in white ink. 87.5 mg/350 mg: White opaque body imprinted with "350" in black ink and medium orange opaque cap imprinted with "IPX203" in white ink.
Co-packaged product information	N/A
Device information	N/A
Storage Temperature/ Conditions	20°C to 25°C

Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Jeffrey Medwid	Gaetan Ladouceur
	<i>Drug Product/ Labeling</i>	Grace Chiou	Martha Heimann
	<i>Manufacturing</i>	Prashanth Manda	Chengjiu Hu
	<i>Biopharmaceutics</i>	Jia Leo	Ta-Chen Wu
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Erica Keafer	
	<i>ATL</i>	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months when stored at 20°C to 25°C

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends **APPROVAL** of NDA 217186 for Crexont (carbidopa and levodopa) extended-release capsules). Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	- Adequate
Drug Product	- Adequate
Quality Labeling	- Adequate
Manufacturing	- Adequate
Biopharmaceutics	- Adequate
Microbiology	- N/A

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.



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Heimann

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing

Information: The labeling is acceptable with the exception of the minor revisions in red. The review is of carton and container closures submitted in eCTD 0012 and PI submitted in eCTD 0001.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	CREXONT™ (carbidopa and levodopa) extended-release capsules, for oral use	Adequate
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Extended-Release Capsules: Carbidopa and Levodopa 35 mg / 140 mg, 52.5 mg / 210 mg, 70 mg / 280 mg, 87.5 mg / 350 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	Adequate
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA
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1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	Inadequate Remove promotional language highlighted in yellow.
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.

(b) (4)

Inadequate
Revise to ensure excipients are in alphabetical order (specifically "amino methacrylate copolymer").

For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/therapeutic class	See above	Adequate

Chemical name, structural formula, molecular weight	(b) (4)	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	See above	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed		

by Drug Company X,” “structurally unique molecular entity”		
--	--	--

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4)	Adequate
Strength(s) in metric system		
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4)	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		

Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging		

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4)	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4)	Adequate
Dosage strength		
Route of administration		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g. tablet count)	(b) (4)	Adequate
"Rx only" displayed on the principal display		
NDC number		Adequate
Lot number and expiration date		Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.		Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	(b) (4)	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4)	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal		
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available		

Assessment of Carton and Container Labeling: Adequate

This application is recommended for approval per labeling/labels perspective once the following changes (in red) have been made to the label.

ITEMS FOR ADDITIONAL ASSESSMENT

This application is recommended for approval per labeling/labels perspective once the following changes (in red) have been made to the label.

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes (in red) have been made to the label.



Grace
Chiou

Digitally signed by Grace Chiou

Date: 5/02/2023 03:22:44PM

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Martha
Heimann

Digitally signed by Martha Heimann

Date: 5/02/2023 03:27:18PM

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CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

NDA Number	NDA-217186-ORIG-1
Assessment Cycle Number	01
Drug Product Name/ Strength	IPX203 (Carbidopa and Levodopa) Extended-Release Capsules, 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg
Route of Administration	Oral
Applicant Name	Impax Laboratories, LLC
Therapeutic Classification/OND Division	Neurologic Disorders /DN1
RLD/RS Number	NDA 017555 Sinemet® (carbidopa and levodopa) tablet
Proposed Indication	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.
Primary Reviewer	Jia Leo, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: Adequate

Assessment Summary:

The Applicant is seeking approval of IPX203 (Carbidopa and Levodopa) Extended-Release Capsules, 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg via 505(b)(2) pathway. The listed drug is Sinemet® (carbidopa and levodopa) Tablets 10 mg/100 mg, 25 mg/250 mg, and 25 mg/100 mg under NDA 017555. The key Biopharmaceutics review findings with respect to the proposed dissolution method and acceptance criteria, in vitro alcohol dose-dumping potential, Extended-Release (ER) claim, and formulation bridging are summarized below.

Dissolution Method:

Carbidopa

The drug substance, carbidopa, is highly soluble, per BCS criteria. As carbidopa is only present in the IR granule, the Applicant was recommended to adopt the standard dissolution method and acceptance criterion in 2018 FDA Guidance for Industry "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" (2018 FDA Dissolution Guidance) in the information request dated 2/7/2023. In response, the Applicant revised the dissolution method for carbidopa to "**0.1N HCl, 500 mL, USP Apparatus I, 50 rpm**", which is slightly different from the stand basket method in 2018 FDA Dissolution Guidance in the agitation speed, where the agitation speed is 100

rpm. As the proposed dissolution method for carbidopa used a lower agitation speed, the dissolution method for Carbidopa is acceptable.

Levodopa

The initially proposed dissolution method (2-stage) for levodopa was deemed inadequate due to concerns (b) (4) and deficiencies in medium volume selection, agitation speed selection, and discriminating ability. In response to the information request dated 2/7/2023, the Applicant provided the explanation for (b) (4) release of levodopa in pH < 6 environment, which is deemed acceptable, and revised dissolution method to “**Acid stage: 0.1N HCl for 2 hr, Buffer stage: pH 6.8 phosphate buffer, 500 mL, USP Apparatus I, 50 rpm**”. The selection of the dissolution parameters is acceptable. The Applicant also provided data to support the discriminating ability of the proposed dissolution method for levodopa. The data showed the revised dissolution method is able to reject variant batches (b) (4)

(b) (4). The variant batches (b) (4) can be rejected by the newly proposed dissolution acceptance criteria for levodopa. Overall, the revised dissolution method for levodopa is acceptable.

Dissolution Acceptance Criteria:

The initially proposed dissolution acceptance criterion of “**Q = (b) (4) in 30 min**” for **carbidopa** is deemed acceptable.

The initially proposed dissolution acceptance criteria of “Acid Stage: 30 min NMT (b) (4), 120 min (b) (4) and Buffer Stage: 180 min (b) (4), 300 min NLT (b) (4) for levodopa is deemed permissive. The Applicant was recommended to propose a new set of dissolution acceptance criteria for levodopa in the information request dated 2/7/2023. In response, the Applicant revised the dissolution acceptance criteria for **levodopa** to “**Acid Stage: 30 min NMT (b) (4), 120 min (b) (4) and Buffer Stage: 180 min (b) (4), 300 min NLT (b) (4)**”. The revised dissolution acceptance criteria for levodopa are acceptable.

In Vitro Alcohol Dose Dumping:

The in vitro alcohol dose dumping was investigated in 0.1N HCl up to 2 hours with 0%, 5%, 20%, 40% ethanol for the lowest (CD/LD 35 mg/140 mg) and the highest (CD/LD 87.5 mg/350 mg) strengths. The data showed increased levodopa release with 40% (v/v) ethanol for the lowest strength after 30 min and for the highest strength after 75 min. The data suggest alcohol dose dumping potential for levodopa with 40% (v/v) ethanol. The proposed labeling language is shown below.

(b) (4)

Extended-Release Claim:

The Applicant conducted a multiple dose study comparing IPX203 (the proposed CD-LD ER capsule) and CD-LD IR table (Sinemet) in study IPX203-B16-01 and evaluated the food effect on the pharmacokinetics (PK) of IPX203 in study IPX203-B16-04. The PK profile of levodopa from the proposed ER capsule (IPX203) when given at a lesser dosing frequency exhibited an extended/flatter plasma concentration-time profile (with wider range of Tmax values), longer duration above the designated plasma concentration, and smaller degree of fluctuation. The results of food effect study suggest the proposed drug product is devoid of significant food effects and food-induced dose-dumping potential. The provided data meet the requirements per 21 CFR 320.25(f) to support the extended-release claim.

Formulation bridging:

The proposed commercial formulation and the formulation used in pivotal clinical studies are the same as the final formulation. No in vivo bridging study is needed.

Recommendation:

From a Biopharmaceutics perspective, NDA 217186 for IPX203 (Carbidopa and Levodopa) Extended-Release Capsules, 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg is ADEQUATE.

FDA-approved dissolution method and acceptance criteria:

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
I (Basket)	50	<u>Carbidopa:</u> 0.1N HCl <u>Levodopa:</u> Acid stage: 0.1N HCl for 120 min Buffer stage: pH 6.8 phosphate buffer 37 °C ± 0.5°C	500	<u>Carbidopa:</u> Q = (b) (4) in 30 min <u>Levodopa:</u> Acid Stage: 30 min NMT (b) (4) 120 min (b) (4) Buffer Stage: 180 min (b) (4) 300 min NLT (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	8/31/2022
Sequence 008 / Response to Biopharmaceutics Information Request	3/21/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment:

No BCS designation was requested. No permeability data for the drug substances were provided. Based on the provided aqueous solubility data, the drug substances (carbidopa and levodopa) are highly soluble per BCS criteria and exhibit pH-dependent solubility.

Solubility:

Table 1. Aqueous solubility of carbidopa across pH 1.0 – 7.4

Table 2. Solubility Study Results for Carbidopa								
Medium	(b) (4)	Final pH After Testing	Solubility (mg/mL)	Average Drug Solubility (mg/mL)	Volume Required to Dissolve Highest Dose Strength (mL) ¹	Solubility Category as per BCS ²	Average mL/g	Solubility Category by USP Classification ³
SGF w/o Enzyme, pH 1.2	(b) (4)			11.367	7.70	Highly Soluble	88	Sparingly Soluble
Sodium Acetate Buffer, pH 4.5				1.764	49.60	Highly Soluble	567	Slightly Soluble
Potassium Phosphate Buffer, pH 6.8				1.676	52.20	Highly Soluble	597	Slightly Soluble
Potassium Phosphate Buffer, pH 7.4				2.150	40.70	Highly Soluble	465	Slightly Soluble
DI Water				1.325	66.02	Highly Soluble	755	Slightly Soluble
1. The highest dose strength for Carbidopa is 87.5 mg.								
2. A drug substance is considered to be highly soluble when the highest dose strength is completely soluble in 250 mL of aqueous medium.								
3.Sparingly Soluble when parts of solvent needed is between 30 to 100; Slightly Soluble when parts of solvent needed is between 100 to 1000 as per USP.								
Lab Book/Page # AR-BR-176-19/95-96								

Figure 1. Carbidopa pH solubility profile

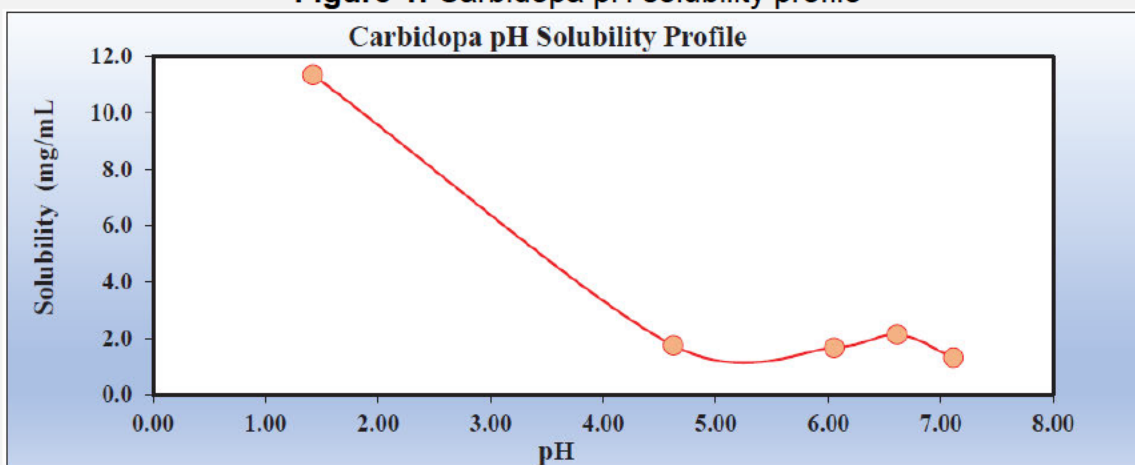
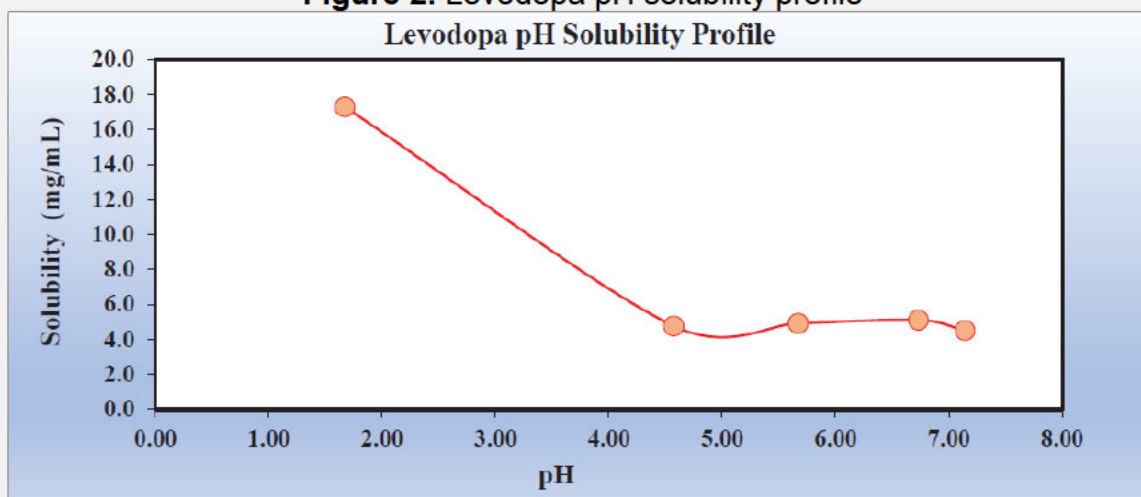


Table 2. Aqueous solubility of levodopa across pH 1.0 – 7.4

Table 3. Solubility Study Results for Levodopa								
Medium	(b) (4)	Final pH After Testing	Solubility (mg/mL)	Average Drug Solubility (mg/mL)	Volume Required to Dissolve Highest Dose Strength (mL) ¹	Solubility Category as per BCS ²	Average mL/g	Solubility Category by USP Classification ³
SGF w/o Enzyme, pH 1.2	(b) (4)			17.295	20.24	Highly Soluble	58	Sparingly Soluble
Sodium Acetate Buffer, pH 4.5				4.779	73.24	Highly Soluble	209	Slightly Soluble
Potassium Phosphate Buffer, pH 6.8				4.926	71.06	Highly Soluble	203	Slightly Soluble
Potassium Phosphate Buffer, pH 7.4				5.117	68.40	Highly Soluble	195	Slightly Soluble
DI Water				4.514	77.53	Highly Soluble	222	Slightly Soluble
1. The highest dose strength for Levodopa is 350 mg.								
2. A drug substance is considered to be highly soluble when the highest dose strength is completely soluble in 250 mL of aqueous medium.								
3. Sparingly Soluble when parts of solvent needed is between 30 to 100; Slightly Soluble when parts of solvent needed is between 100 to 1000 as per USP.								
Lab Book/Page # AR-BR-176-19/95-96								

Figure 2. Levodopa pH solubility profile**Permeability:**

No permeability data for the drug substances were provided.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: {Adequate}

1. Dissolution Method**Table 3. Originally proposed dissolution method**

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)
I (Basket)	(b) (4)	<u>Carbidopa:</u> (b) (4) <u>Levodopa:</u> Acid stage: (b) (4) for 120 min Buffer stage: pH 6.8 phosphate buffer 37 °C ± 0.5°C	35 mg/140 mg strength: 500 mL All other strengths: (b) (4)

Table 4. Revised dissolution method in response to IR dated 2/7/2023

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)
I (Basket)	50	<u>Carbidopa:</u> 0.1N HCl <u>Levodopa:</u> Acid stage: 0.1N HCl for 120 min	500

		Buffer stage: pH 6.8 phosphate buffer 37 °C ± 0.5°C	
--	--	--	--

1) Dissolution method development

(b) (4)



(b) (4) The selection of dissolution parameters for levodopa is acceptable.

2) Discriminating power of the dissolution method for levodopa

In the original dissolution method development report, the Applicant used (b) (4) for evaluating the discriminating ability of the dissolution method for levodopa. As there are also deficiencies in the dissolution parameter selection, the Applicant was requested to re-evaluate the discriminating ability of the updated dissolution method using the proposed commercial formulation/product.

In response, the Applicant evaluated the discriminating ability of the revised dissolution method for levodopa against (b) (4)

Table 6. Variables used in evaluation of the discriminating ability of the dissolution method

(b) (4)

The data showed that the new dissolution method is able to reject variant batches (b) (4) (b) (4) (Table 7 and 8). The

dissolution profile of levodopa for variant batches (b) (4) is similar to that of the target batch, but the proposed dissolution acceptance criteria for levodopa could reject the variant batches with (b) (4) (Table 9 and 10).

Table 7. Dissolution profile of levodopa for the variant batch and the target batch with different (b) (4) levels

N = 12		USP Apparatus I (Baskets), 50 RPM, 500 mL			
		0.1N HCl for 2 hours Followed by pH 6.8 Phosphate Buffer			
Time (Min)	Proposed Finished Product Specifications	(b) (4)		Target (b) (4)	
		RD1793-12		BJ03220	
		Mean % Dissolution	%RSD	Mean % Dissolution	%RSD
15	-	24	7.5	28	1.9
30	NMT (b) (4)	27	3.8	31	1.7
120	(b) (4)	32	3.5	49	3.3
180	(b) (4)	61	2.4	77	2.1
240	-	80	2.7	93	1.5
300	NLT (b) (4)	93	2.4	101	1.2
F2 (50-100)		47			
LNB #		AR-BR-359-20/185		AR-BR-361-20/111	

Table 8. Dissolution profile of levodopa for the variant batch and the target batch with different (b) (4) levels

N = 12		USP Apparatus I (Baskets), 50 RPM, 500 mL			
		0.1N HCl for 2 hours Followed by pH 6.8 Phosphate Buffer			
Time (Min)	Proposed Finished Product Specification	(b) (4)		Target (b) (4)	
		RD1793-11		BJ03220	
		Mean % Dissolution	%RSD	Mean % Dissolution	%RSD
15	-	36	6.7	28	1.9
30	NMT (b) (4)	49	7.4	31	1.7
120	(b) (4)	65	6.9	49	3.3
180	(b) (4)	105	2.5	77	2.1
240	-	109	1.9	93	1.5
300	NLT (b) (4)	110	1.8	101	1.2
F2		38			
LNB #		AR-BR-008-23/123		AR-BR-361-20/111	

Table 9. Dissolution profile of levodopa for the variant batch and the target batch with different (b) (4) levels

N = 12		USP Apparatus I (Baskets), 50 RPM, 500 mL			
		0.1N HCl for 2 hours Followed by pH 6.8 Phosphate Buffer			
Time (Min)	Proposed Finished Product Specifications	(b) (4)		Target (b) (4)	
		RD1793-07		BJ03220	
		Mean % Dissolution	%RSD	Mean % Dissolution	%RSD
15	-	31	4.2	28	1.9
30	NMT (b) (4)	38	2.4	31	1.7
120	(b) (4)	61	2.3	49	3.3
180	(b) (4)	86	1.5	77	2.1
240	-	97	1.1	93	1.5
300	NLT (b) (4)	103	0.8	101	1.2
F2		57			
LNB #		AR-BR-004-23/98		AR-BR-361-20/111	

Table 10. Dissolution profile of levodopa for the variant batch and the target batch with different (b) (4)

N = 12		USP Apparatus I (Baskets), 50 RPM, 500 mL			
		0.1N HCl for 2 hours Followed by pH 6.8 Phosphate Buffer			
Time (Min)	Proposed Finished Product Specification	(b) (4)		Target (b) (4)	
		RD1793-15		BJ03220	
		Mean % Dissolution	%RSD	Mean % Dissolution	%RSD
15	-	25	13.8	28	1.9
30	NMT (b) (4)	30	8.3	31	1.7
120	(b) (4)	36	4.5	49	3.3
180	(b) (4)	68	3.0	77	2.1
240	-	85	1.7	93	1.5
300	NLT (b) (4)	95	2	101	1.2
F2		55			
LNB #		AR-BR-184-22/162, 164		AR-BR-361-20/111	

Reviewer's comment:

The provided data have demonstrated the discriminating ability of the dissolution method for levodopa.

2. Dissolution Data and Acceptance Criterion

In the original submission, Biopharmaceutics deemed the dissolution acceptance criteria (**Table 11**) for levodopa permissive. As the dissolution method also has deficiency, the Applicant was requested to propose new dissolution acceptance criteria for levodopa based on the new dissolution profile data generated using the updated dissolution method in the IR dated 2/7/2023.

In response, the Applicant provided new dissolution data using the updated dissolution method for all bio-batches, registration batches, and stability batches (**Table 13**) and proposed new dissolution acceptance criteria for levodopa (**Table 12**). Based on the provided data, the revised dissolution acceptance criteria are acceptable.

Table 11. Originally proposed dissolution acceptance criteria

API	Dissolution Acceptance Criteria
Carbidopa	Q = (b) (4) in 30 min
Levodopa	Acid Stage: 30 min NMT (b) (4) 120 min (b) (4) Buffer Stage: 180 min (b) (4) 300 min NLT (b) (4)

Table 12. Revised dissolution acceptance criteria in response to IR dated 2/7/2023

API	Dissolution Acceptance Criteria
Carbidopa	Q = (b) (4) in 30 min
Levodopa	Acid Stage: 30 min NMT (b) (4) 120 min (b) (4) Buffer Stage: 180 min (b) (4) 300 min NLT (b) (4)

Table 13. summary of the dissolution profile data of all bio-batches, registration batches, and stability batches using the updated dissolution method for levodopa

Strength	(%) Levodopa Dissolved														
	Lot #	Acid Stage (0.1N HCl)										Buffer Stage (pH 6.8 Phosphate Buffer)			
		5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min	120 min	180 min	240 min	300 min	360 min	420 min
35 mg/140 mg	BA11319-21s														
	BA11319-180s														
	BA21219-21s														
	BA21219-180s														
	BJ03220-21s														
	BJ03220-180s														
	BG13920-180s														
	BL17019-180s														
	BH01019-100s														
	BF05520-100s														
51.5 mg/210 mg	BA11419-21s														
	BA11419-180s														
	BA21319-21s														
	BA21319-180s														
	BJ03420-21s														
	BJ03420-180s														
	BG04520-180s														
70 mg/280 mg	BA11219-21s														
	BA11219-180s														
	BA21419-21s														
	BA21419-180s														
	BJ03520-21s														
	BJ03520-180s														
	BG04620-180s														
87.5 mg/350 mg	BA08819-21s														
	BA08819-180s														
	BA21519-21s														
	BA21519-180s														
	BJ03320-21s														
	BJ03320-180s														
	BG04720-180s														
Overall Mean	14	23	26	28	31	34	37	43	48	75	90	99	102	102	
Overall Mean-10%	4	13	16	18	21	24	27	33	38	65	80	89	92	92	
Overall Mean+10%	24	33	36	38	41	44	47	53	58	85	100	109	112	112	
Existing Limits					(b) (4)					(b) (4)					
Proposed Limits															

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol-Induced Dose Dumping*

Assessment: Adequate

The Applicant evaluated the in-vitro alcohol dose dumping potential by testing the lowest (CD/LD 35 mg/140 mg) and the highest (CD/LD 87.5 mg/350 mg) strengths with sampling up to 2 hours in 0.1N HCl medium containing 0%, 5%, 20%, and 40% (v/v) ethanol using the updated dissolution method.

CD/LD 35 mg/140 mg

As shown in **Figure 10 and 11**, for the lowest strength, no in vitro dose dumping was observed for carbidopa. For levodopa, no in vitro dose dumping was observed at 5% and 20% (v/v) ethanol levels. Increased release of levodopa was observed with 40% (v/v) ethanol at 30 min and after. At 120 min, mean levodopa release was 87% with 40% (v/v) ethanol compared to mean release of 49% levodopa with 0% (v/v) ethanol.

Figure 10. Dissolution profile of **carbidopa** in 0.1N HCl containing 0%, 5%, 20% and 40% (v/v) ethanol

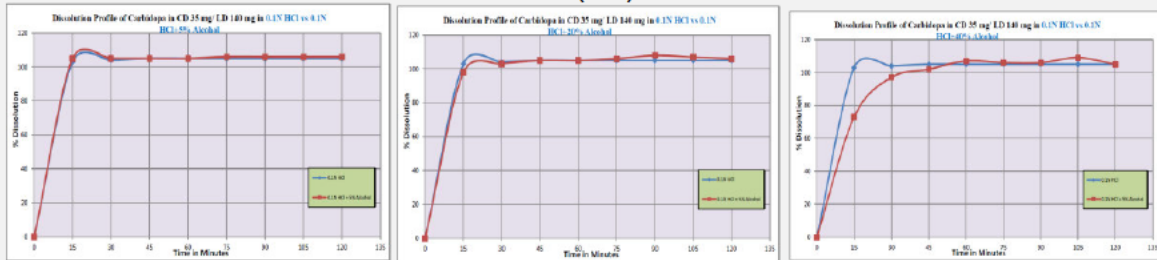
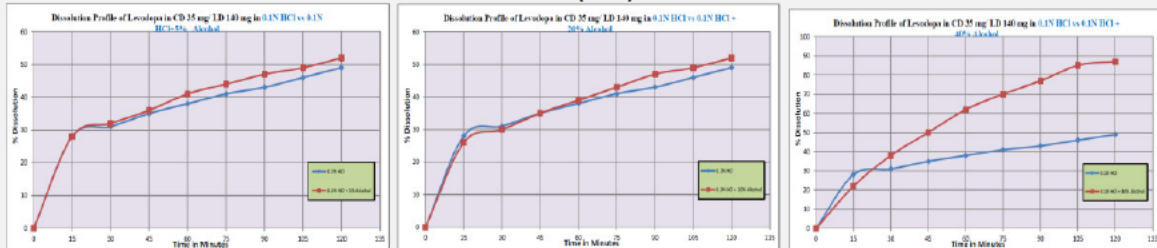


Figure 11. Dissolution profile of **levodopa** in 0.1N HCl containing 0%, 5%, 20% and 40% (v/v) ethanol



CD/LD 87.5 mg/350 mg

As shown in **Figure 12 and 13**, for the lowest strength, no in vitro dose dumping was observed for carbidopa. In fact, at 40% (v/v) ethanol level, the release of carbidopa was decreased. For levodopa, no in vitro dose dumping was observed at 5% and 20% (v/v) ethanol levels. Increased release of levodopa was observed with 40% (v/v) ethanol after 75 min. At 120 min, mean levodopa release was 58% with 40% (v/v) ethanol compared to mean release of 48% levodopa with 0% (v/v) ethanol.

Figure 12. Dissolution profile of **carbidopa** in 0.1N HCl containing 0%, 5%, 20% and 40% (v/v) ethanol

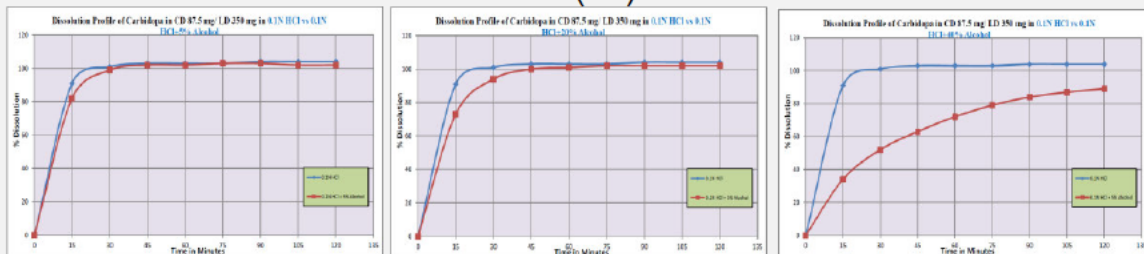
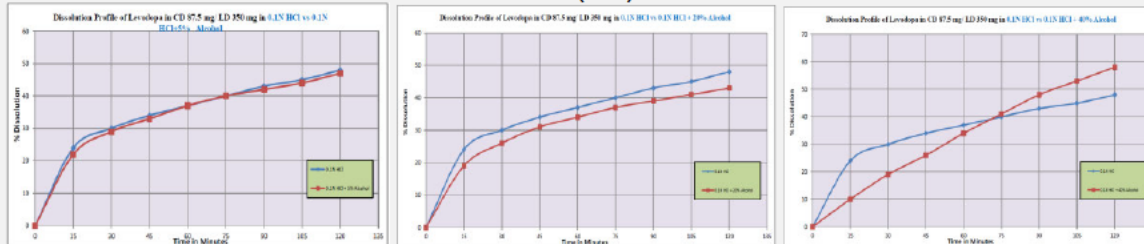


Figure 13. Dissolution profile of **levodopa** in 0.1N HCl containing 0%, 5%, 20% and 40% (v/v) ethanol



Based on the results of the in vitro alcohol dose dumping study, the Applicant proposed below labeling language:

(b) (4)

Reviewer's Assessment:

The data showed increased levodopa release with 40% (v/v) ethanol for the lowest strength after 30 min and for the highest strength after 75 min. The data suggest alcohol dose dumping potential for levodopa with 40% (v/v) ethanol.

B.11 EXTENDED RELEASE DOSAGE FORMS – *Extended Release Claim*

Assessment: *Adequate*

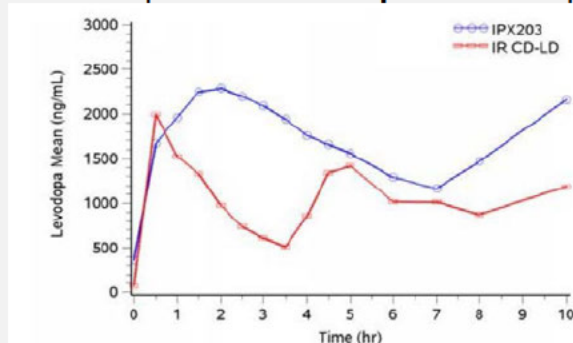
The Applicant conducted a multiple dose study in patients with advanced Parkinson's Disease (PD) comparing IPX203 (the proposed CD-LD ER capsule) and CD-LD IR table (Sinemet) in study IPX203-B16-01 and evaluated the food effect on the pharmacokinetics (PK) of IPX203 in study IPX203-B16-04.

As shown in results of the multiple dose study IPX203-B16-01 (**Figure 14** and **Table 14 - 16**), the PK profile of levodopa from the proposed ER capsule (IPX203) when given at a lesser dosing frequency exhibited an extended/flatter plasma concentration-time profile (with wider range of Tmax values), longer duration above the designated plasma concentration, and smaller degree of fluctuation. The PK profile of levodopa exhibits extended-release characteristics.

The results of food effect study (**Figure 15** and **Table 17**) showed similar Cmax, delayed median Tmax, and slightly increased AUC of levodopa under fed condition. When IPX203-B16-01 was sprinkled on apple sauce (representing soft food), the PK parameters of levodopa are similar to that under fasted condition, other than the median Tmax is shorter. The results suggest that the proposed drug product is devoid of significant food effects and food-induced dose-dumping potential.

The provided data meet the requirements per 21 CFR 320.25(f) to support the extended-release claim.

Figure 14. Mean PK profile of levodopa after multiple doses (day 15)



Source: Study IPX203-B16-01 Clinical Study Report, Figure 8
 Abbreviation: IR CD-LD = immediate-release carbidopa-levodopa
 Note: On Day 15, the median times to redose were 4.0 hours for IR CD-LD and 7.0 hours for IPX203.

Table 14. Mean PK parameters for levodopa after multiple doses (day 15)

Parameter	IPX203	IR CD-LD
<i>All Dose Levels (N=27)</i>	<i>All Doses</i>	<i>All Doses</i>
C_{max} (ng/mL)	2768 ± 1259	2357 ± 1179
T_{max} (h)	1.5 (0.5–6.0)	0.5 (0.5–2.0)
AUC_{tau} (ng*h/mL)	11214 ± 4887	3879 ± 1744

Table 15. Levodopa duration above defined plasma concentrations after multiple doses (day 15)

Parameter	IPX203	IR CD-LD
<i>All Doses (N=27)</i>		
Duration > 50% C_{max} (h)	6.2 ± 1.9	3.9 ± 2.2
Duration > 430 ng/mL (h)	9.0 ± 1.3	7.4 ± 2.0

Table 16. Levodopa accumulation, fluctuation, and time invariance parameters after multiple doses (day 15)

Treatment	Mean ± SD (N=27)		
	Accumulation Ratio	Fluctuation Index	Time Invariance
IPX203	1.0 ± 0.3	1.7 ± 0.5	0.87 ± 0.3
IR CD-LD	1.1 ± 0.2 ^a	2.7 ± 1.0	0.93 ± 0.2 ^a

Source: Study IPX203-B16-01 Clinical Study Report, Table 22

Abbreviations: IR CD-LD = immediate-release carbidopa-levodopa; max = maximum; min = minimum; SD = standard deviation

Note: Accumulation ratio was calculated as the ratio of AUC_{tau} on Day 15 to AUC_{tau} on Day 1, where tau (dosing interval) on Day 1 was assigned the same value as tau on Day 15.

Fluctuation index was calculated as $(C_{max} - C_{min})/C_{avg}$ over the 10-h assessment period.

Time-invariance was calculated as the ratio of AUC_{tau} on Day 15 to AUC_{∞} on Day 1.

^a N = 26

Figure 15. Mean PK profile of **levodopa** under fed (treatment A), sprinkled (treatment B), and fasted (treatment C) conditions

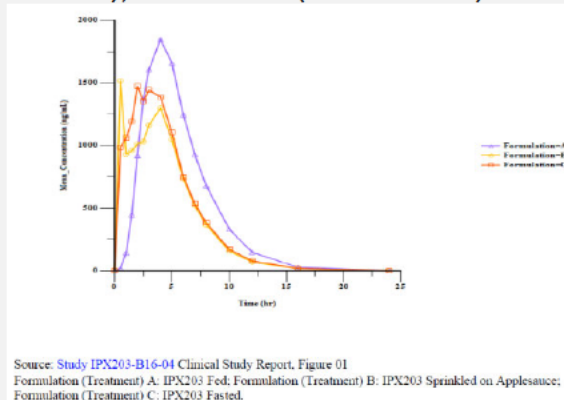


Table 17. PK parameters for **levodopa** under fed (treatment A), sprinkled (treatment B), and fasted (treatment C) conditions

Pharmacokinetic Parameters (Units)	Arithmetic Mean $\pm$ SD (N = 27)		
	IPX203 Fed	IPX203 Sprinkled on Applesauce	IPX203 Fasted
C_{max} (ng/mL)	2185.564 $\pm$ 472.7236	1634.170 $\pm$ 409.3129	1826.947 $\pm$ 385.3425
T_{max} (h) ^a	4.000 (2.00-5.00)	0.500 (0.50-5.00)	2.000 (0.50-5.00)
AUC_{0-t} (ng $\cdot$ h/mL)	10552.789 $\pm$ 1425.5710	8330.925 $\pm$ 1965.0426	9124.960 $\pm$ 2149.7628
$AUC_{0-\infty}$ (ng $\cdot$ h/mL)	10611.158 $\pm$ 1433.6441	8371.116 $\pm$ 1969.8153	9161.364 $\pm$ 2153.0025
$t_{1/2}$ (h)	1.786 $\pm$ 0.3135	2.024 $\pm$ 0.3079	1.988 $\pm$ 0.3000
K_{el} (1/h)	0.397 $\pm$ 0.0559	0.350 $\pm$ 0.0517	0.356 $\pm$ 0.0515
$AUC_{\%Extrap_obs}$ (%)	0.548 $\pm$ 0.3488	0.493 $\pm$ 0.3266	0.409 $\pm$ 0.2109

Source: Study IPX203-B16-04 Clinical Study Report, Table 22

Abbreviations: AUC_{0-t} = area under the plasma concentration-time curve from time 0 h to the last measurable concentration at time t; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 h extrapolated to infinity; C_{max} = maximum observed plasma concentration; K_{el} = apparent elimination rate constant; max = maximum; min = minimum; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration.

^a. T_{max} , median (min-max)

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The IPX203 (Carbidopa and Levodopa) Extended-Release Capsules formulation used in the clinical Phase II and Phase III and registration stability studies is also the intended commercial formulation with the exception of (b) (4) as per the proposed market trade dress (Table 18).

Since the final formulation (Table 19) was used in pivotal clinical studies (Phase III IPX203-B16-02 and IPX203-B16-03) and is the proposed commercial formulation, no additional in vivo bridging is needed.

Table 18. Hard gelatin capsules used in IPX203 (carbidopa and levodopa) extended-release capsule

Purpose	IPX203 (Carbidopa and Levodopa) Extended-Release Capsules																	
	45 mg/180 mg			67.5 mg/270 mg			35 mg /140 mg			52.5 mg /210 mg			70 mg /280 mg			87.5 mg /350 mg		
	Size	Body	Cap	Size	Body	Cap	Size	Body	Cap	Size	Body	Cap	Size	Body	Cap	Size	Body	Cap
Phase II Clinical Study IPX203-B16-01	1EL	(b) (4)					N/A											
Phase III Clinical Study	N/A						(b) (4)											
Registration Stability Study (manufactured in Amneal)	N/A																	
Registration Stability Study (manufactured in Amneal)	N/A																	
Site Qualification Stability Study(manufactured in Bora-Amneal)	N/A																	
Commercial Manufacture	N/A						2	White	Yellow	1EL	White	Green	0EL	White	Purple	00	White	Medium Orange

*Size 2 is selected for CD/LD- 35 mg /140 mg for registration batches and proposed commercial batch as per trade dress.

Table 19. Final formulation of IPX203 (carbidopa and levodopa) extended-release capsule

Ingredients	Function	Composition
		%w/w (b) (4)
Carbidopa ¹	Active	(b) (4)
Levodopa	Active	
Microcrystalline Cellulose	(b) (4)	
Croscarmellose Sodium		
Magnesium Stearate		
Mannitol		
Sodium Lauryl Sulfate		
Povidone		
Cellulose Acetate		
Copovidone		
Amino Methacrylate, Copolymer (b) (4)		
Methacrylic Acid and Methyl Methacrylate Copolymer (b) (4)		
Triethyl Citrate		
Talc		
(b) (4)		
(b) (4)		
(b) (4)		
Total	-	100.00

¹ Carbidopa is supplied as a monohydrate; the quantities shown, (b) (4) mg and (b) (4) mg, are equivalent to 45 mg and 67.5 mg carbidopa anhydrous, respectively. (b) (4)

Appendix

Biopharmaceutics IRs and Applicant's responses

IR #1 dated 2/7/2023 and Response received 3/21/2023

(b) (4)

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The Applicant's response:

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Reviewer's assessment:

The response to deficiencies is discussed in the review body.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.



Jia
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/s/

MARTHA R HEIMANN
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