CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212489Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 212489
Review 1

Drug Product Name	ONGENTYS (opicapone)
Dosage Form	Capsules
Strength	25 mg, 50 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Neurocrine Biosciences, Inc.
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Ben Zhang	Su Tran
Drug Product/Labeling	Mariappan Chelliah	Julia Pinto
Manufacturing	Qin (Stefanie) Liang	Erin Kim
Microbiology	N/A	N/A
Biopharmaceutics	Gerlie Gieser	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Woody	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submissions	Document Date	Disciplines Affected
SD-01, Original NDA	4/26/2019	All
SD-04, Response to IR	6/17/2019	Manufacturing
SD-05, Response to IR	7/3/2019	Biopharmaceutics
SD-07, Response to IR	7/19/2019	Manufacturing
SD-12, Response to IR	8/30/2019	Drug Substance, Manufacturing
SD-16, Response to IR	9/12/2019	Biopharmaceutics
SD-18, Response to IR	10/4/2019	Biopharmaceutics
SD-19, Labeling/PI	10/10/2019	Labeling
SD-21, Response to IR	11/8/2019	Biopharmaceutics, Drug Product
SD-22, Labeling/Container	11/20/2019	Labeling
SD-23, Response to IR	12/4/2019	Manufacturing
SD-24, Response to IR	12/5/2019	Biopharmaceutics
SD-25, Response to IR	12/17/2019	Biopharmaceutics, Drug Substance, Drug Product
SD-26, Labeling/Container	1/10/2020	Labeling
SD-28, Response to IR	1/14/2020	Manufacturing
SD-29, Updated LoA for DMF (b) (4)	1/15/2020	Drug Substance

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	BIAL - Portela & C[a], S.A.	Opicapone	Adequate	11/12/2019, 01/27/2020	Reviewer: Ben Zhang
	III	(b) (4)		N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	
	IV			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	

[1] Adequate information provided in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	104380	Development of opicapone.

2. CONSULTS

N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 212489 for ONGENTYS (opicapone) capsules. From a quality perspective, the application provides adequate information to ensure that the Applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Opicapone, a new molecular entity, is a peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor developed by Bial - Portela & C[a], S.A. (Bial) for adjunctive treatment of Parkinson's disease in patients treated with levodopa and carbidopa (a peripheral DOPA decarboxylase inhibitor). Similar to carbidopa, which enhances the therapeutic effect of levodopa by inhibiting peripheral conversion of levodopa to dopamine, and increasing CNS exposure to levodopa and dopamine, opicapone has no therapeutic effect on its own. Instead, it enhances the therapeutic effect of levodopa by inhibiting peripheral conversion of levodopa to 3-O-methyldopa, which also allows for increase CNS exposure to levodopa and dopamine. Opicapone is approved in the European Union, where it is marketed by Bial. The Applicant, Neurocrine Biosciences Inc. (NBI) has licensed U.S. rights to opicapone from Bial and proposes marketing opicapone as immediate release capsules in two strengths, 25 mg and 50 mg.

Proposed indication(s) including intended patient population	Adjunctive treatment of Parkinson's disease in patients treated with levodopa and carbidopa
Duration of treatment	Chronic
Maximum daily dose	50 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: **Adequate**

The bulk active pharmaceutical ingredient (API), opicapone, is a well characterized, neutral, small molecule that is manufactured by (b) (4). The Applicant provides general information about the drug substance (e.g., chemical name, structure, physical properties, etc.) and certificates of analysis for representative drug substance batches in the NDA. The Applicant indicates that the proposed commercial manufacturing process (b) (4)). Other information regarding manufacture and control of the API is cross-referenced to DMF (b) (4) which is held by Bial. The DMF was reviewed and, as amended by the Holder, is deemed adequate to support approval of the NDA.

Drug Product: **Adequate**

The proposed products are immediate release hard gelatin capsules that contain 25 mg or 50 mg opicapone and the following excipients: lactose (b) (4) pregelatinized starch, sodium starch glycolate, and magnesium stearate. (b) (4) The only differences between the registration batches and the commercial formulations are changes to capsule color.

The proposed specification includes appropriate tests for all critical quality attributes relevant to the dosage form and is deemed adequate to assure the identity, strength, quality, purity, potency, and bioavailability of opicapone capsules and ensure batch-to-batch consistency. Limits for impurities/degradants are consistent with Agency and ICH guidances and the Applicant has provided adequate justification for omission of testing for elemental impurities. Non-compendial analytical procedures are adequately described in the application and validated.

The drug product will be marketed in 30-count, 45 cc HDPE bottles. A 10-count, 45 cc bottle of the 50 mg capsules will be available as a physician sample. The Applicant requests a **60-month expiration dating period for product stored below 30°C (86°F).** Based on the extensive long-term (25°C/60% R.H.),

intermediate (30°C/65% R.H.), and accelerated (40°C/75% R.H.) stability data provided, the requested expiry and labeled storage condition are acceptable.

Manufacturing: **Adequate**

The proposed commercial manufacturing process for ONGENTYS (opicapone) capsules involves [redacted] (b) (4) Registration batches were manufactured at the proposed commercial scale.

All facilities that will be involved in commercial manufacture and testing of opicapone and ONGENTYS (opicapone) capsules are currently acceptable.

Biopharmaceutics: **Adequate**

Opicapone has low aqueous solubility across the physiological pH range, being insoluble at low pH and only slightly soluble at pH 6.8. [redacted] (b) (4) The proposed morphology test method (submitted under DMF [redacted] (b) (4)) and acceptance criteria were deemed acceptable by the Drug Substance reviewer. The Applicant has also tightened the dissolution acceptance criterion per Agency request.

Changes to the drug product formulations development included changes in [redacted] (b) (4) and capsule colorants. Changes up to the registration stability batches are supported by in-vivo data (reviewed by Office of Clinical Pharmacology). The change to capsule colors from the registration batches to the final commercial image are supported by in-vitro dissolution data.

Labeling: **Adequate**

The proposed labeling, as revised per review recommendations, is deemed adequate from a quality perspective.

Environmental: **Adequate**

The Applicant submitted a claim for categorical exclusion under 21 CFR §25.31(b). Approval of the application would increase use of opicapone. However, the expected environmental introduction concentration (EIC) is less than 1 part per billion and there are no extraordinary circumstances. **The claim for categorical exclusion is granted.**

Methods Verification:

Verification of analytical procedures submitted in the NDA by FDA laboratories was not requested during the review.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale • Equipment • Site	**L**	Compatibility with excipients evaluated during development. Drug substance is photosensitive; however, opaque capsule shells provide adequate light protection.	**Adequate**	
Physical stability, solid state		**L**	(b) (4)	**Adequate**	(b) (4)
Content uniformity		**L**		**Adequate**	
Microbial limits		**L**	Skip lot testing at release and tested on stability.	**Adequate**	
Dissolution		**M**	The proposed dissolution method can discriminate between product batches manufactured with intentional changes to composition or process parameters. In conjunction with control (b) (4) the method is adequate to ensure product quality.	**Adequate**	

E. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date: Martha R. Heimann, Ph.D. 2/12/2020

Martha 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: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ONGENTYS®	Adequate
Established name(s)	Opicapone	Adequate
Route(s) of administration	For oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 25 mg and 50 mg.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
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.	n/a	n/a

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)	n/a	n/a

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)	Capsules	Adequate
Strength(s) in metric system	25 mg, 50 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	n/a
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	25 mg: light blue opaque cap and light pink opaque body; axially printed with 'OPC' over '25' in blue ink, on both the cap and body. 50 mg: dark blue opaque cap and dark pink opaque body; axially printed with 'OPC' over '50' in white ink, on both the cap and body.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
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.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Both names are included	Adequate
Dosage form(s) and route(s) of administration	Both are described	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	n/a
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	All the excipients are listed	Adequate
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.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor.	Adequate
Chemical name, structural formula, molecular weight	All three are included	Adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	yellow powder/crystalline solid with limited aqueous solubility	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	n/a
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	n/a

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)	Capsule	Adequate
Strength(s) in metric system	25 mg, 50 mg	Adequate
Available units (e.g., bottles of 100 tablets)	25 mg: bottle of 30 capsules 50 mg: bottles of 30 (b) (4)	(b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	25 mg hard gelatin capsules, Size 1; light blue opaque cap and light pink opaque body; axially printed with 'OPC' over '25' in blue ink, on both the cap and body 50 mg hard gelatin capsules, Size 1; dark blue opaque cap and dark pink opaque body; axially printed with 'OPC' over '50' in white ink, on both the cap and body	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
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.	n/a	n/a

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.)	n/a	n/a
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."	n/a	n/a
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Do not store at a temperature above 86°F (30°C).	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: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	n/a
Include information about child-resistant packaging	CR statement is not provided.	The PI will be edited to include this statement.

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	Neurocrine Biosciences, Inc., San Diego, CA 92130	Adequate

Assessment of Prescribing Information: *Adequate*

Two items will need to be edited in section 11 of the PI: inclusion of child resistant packaging statement (b) (4). These will be completed when the PI becomes available for editing.

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

As a representative example, copy of container label for the 25 mg capsules (from eCTD seq. 0022, dated 11-20-2019) is shown below:

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Ongentys® (opicapone) capsules	adequate
Dosage strength	25 mg	adequate
Route of administration		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	n/a
Net contents (e.g. tablet count)	30 or 10 (physician sample) capsules	adequate
"Rx only" displayed on the principal display	Yes	adequate
NDC number	70370-3025-2 (25 mg; 30 count) 70370-3050-2 (50 mg; 30 count) 70370-3050-1 (50 mg; 10 count)	adequate
Lot number and expiration date	Yes	adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store below 30°C (86°F)	adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	n/a
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Bar code		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by: Neurocrine Biosciences, Inc. San Diego, CA 92130 GTIN: 00370370302524 9999999999	adequate
Medication Guide (if applicable)	n/a	n/a
No text on Ferrule and Cap overseal	n/a	n/a
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.	n/a	n/a
And others, if space is available	n/a	n/a

Assessment of Carton and Container Labeling: *Adequate*

The Applicant already revised the container labels with edits recommended by the CMC reviewer. The container labels comply with all the regulatory requirements from a product quality perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	212489
Assessment Cycle Number	1st: Original 505(b)(1) NDA
Drug Product Name/ Strength	Opicapone Capsules / 25 mg, 50 mg
Route of Administration	Oral
Applicant Name	Neurocrine Biosciences Inc.
Therapeutic Classification/ OND Division	Catechol-O-methyltransferase (COMT) inhibitor / Division of Neurology Drug Products
Proposed Indication	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "OFF" episodes Recommended dosage: 50 mg administered orally once daily at bedtime (preferably *without* food); dosage reduction to 25 mg in patients with moderate hepatic impairment

Assessment Recommendation: **Adequate**

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Dissolution	Medium	Opicapone is a low solubility drug substance, per BCS criteria. The dissolution of the drug product is not rapid in various pH media without surfactant.	Acceptable	The proposed dissolution method* and the tightened/revised dissolution acceptance criterion** for the finished drug product are acceptable.

* USP Apparatus I (basket) rotating at 100 rpm, with sinker inside the basket; 1000 mL of 0.05 M KH_2PO_4, pH 6.80, with 1% cetrimide (for Tier 1 testing), with added pancreatin (for Tier 2 testing, if needed); 37 °C ± 0.5 °C
** For batch release and stability/shelf-life testing: NLT (b) (4) (Q) at 30 min

- Adequate *in vitro* and *in vivo* bridging data were submitted to support the approval of the final proposed to-be-marketed drug product/formulation.

List of Submissions assessed:

Document(s) Assessed	Date Received
Original NDA	4/26/2019
Response to Biopharmaceutics IR (SDN-5)	7/3/2019
Response to Biopharmaceutics IR (SDN-18)	10/4/2019
Response to Biopharmaceutics IR (SDN-24)	12/5/2019
Response to Biopharmaceutics IR (SDN-25)	12/18/2019

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

The Applicant considers opicapone as a BCS-2 (low solubility, high permeability) drug substance.

Assessment:

Solubility: *Low*
Opicapone drug substance (Form A) exhibits low solubility in aqueous media across the physiologic pH range (see the pH-solubility data at room temperature in Table 4 of the Dissolution Method Development Report/DMDR). (b) (4) .

Permeability: *Indeterminate*
Per the Applicant, the API exhibited high permeability across *in vitro* cell culture systems, but is a substrate of drug efflux transporters. Note that the absolute bioavailability of the proposed drug product was not determined, although a human radiolabeled ADME study was conducted. Per the Applicant, "in the definitive ADME Study (BIA 91067-130), only trace amounts of unchanged OPC were excreted in urine and only 22.32% of the administered dose was recovered in feces as unchanged OPC". It is not clear to this Reviewer whether there are data to show that majority of the unchanged drug in the feces came from biliary secretion of the unchanged parent drug.

Dissolution: *Not Rapid (in medium without surfactant)*
The dissolution of the proposed drug product is complete and rapid in the proposed dissolution medium (pH 6.8 buffer with surfactant), (b) (4)

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

DISSOLUTION METHOD - *Adequate*

Table 12 of the Dissolution Method Development Report provides a comparison of the parameters of the dissolution methods used during clinical and pharmaceutical development of opicapone capsules. (b) (4)

The operating parameters of the *final* proposed Dissolution Method PDR-ATM-BKG-0007 (also known as Method PT-PTDTP150) are shown in the table below. To maximize discriminating power, the Applicant selected basket rotating at 100 rpm over (b) (4). A basket speed of 100 rpm was selected over (b) (4). A higher pH medium was selected (b) (4). The medium volume selected and the addition of the surfactant ensures (b) (4). A sinker is (b) (4). HPLC with UV detection at 275 nm was eventually chosen over (b) (4) for the quantification of drug in the dissolution samples, (b) (4)

In case the product fails USP Stage 3 testing using the Tier 1 dissolution medium (b) (4) Tier 2 testing is indicated. (b) (4)

Parameter	Condition/Setting
Apparatus	USP Apparatus I (basket), with sinker inside the basket[a]
Rotation Speed	100 ± 4 RPM
Media[b]	Tier 1: 0.05 M KH_2PO_4, pH 6.80± 0.05 with 1% cetrimide (cationic surfactant), 1000 ± 10 mL Tier 2: 0.05 M KH_2PO_4, pH 6.80± 0.05 with pancreatin (1750 USP units/L), 900 mL. Add 100 mL of 10% cetrimide at 10 min.
Temperature	37 °C ± 0.5 °C
Sampling volume	10 mL
Pull time	(b) (4) minutes[c]

Sampling apparatus	Syringe with stainless steel cannula
Filter	(b) (4)
Drug Quantification	HPLC with UV detection VWD (at 275 nm) or DAD

(b) (4)

The proposed dissolution method was demonstrated to be discriminating for intentional changes in formulation and process parameters, (b) (4)

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(b) (4)

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Based on the solubility of the micronized drug substance in the proposed Tier 1 dissolution medium, sink conditions are anticipated to be maintained during routine QC dissolution testing in 1000 mL of dissolution medium.

The analytical method was validated for specificity, linearity, accuracy, precision, filter compatibility, system suitability, robustness in terms of difference from nominal target [with respect to HPLC and dissolution method (Basket speed 100 RPM, Medium pH 6.80 ±, KH_2PO_4 content 6.80 g/L ±%, cetrimide content 10 g/L ± %, presence/absence of sinkers] and solution stability (at ambient temperature, standard and sample solutions for 7 and 3 days, respectively). Per the Drug Product Reviewer (Dr. Mariappan Chellia), the analytical method was deemed adequately validated for quantifying opicapone in the dissolution samples.

DISSOLUTION ACCEPTANCE CRITERION - *Tightened Dissolution Acceptance Criterion ACCEPTABLE*

For the routine QC testing of both strengths of the proposed drug product, the proposed dissolution acceptance criterion is “NLT % (Q) afte minutes”, based on the data of the clinical lots and the primary registration lots.

This Reviewer recommended tightening of the dissolution acceptance criterion to “Q = % at 30 min” for the following reasons:

1. The 25 mg and 50 mg capsules used in the Phase 3 clinical trial lots, and the primary registration/stability lots used in BE Study 119 exhibited rapid dissolution (i.e., at least % of label claim dissolved within 30 min); See Figure 13 and Figure 14 of the DMDR.
2. Setting specification time point for NLT % dissolution at 30 min rather than at min is more effective in rejecting unacceptable drug product lots such

as (b) (4)

Additionally, note that the Applicant proposed to remove the earlier dissolution acceptance criteria of "NLT (b) (4) based on the observation that drug product lots that meet the final dissolution specification of "NLT (b) (4)" would meet the dissolution specification at the earlier time point. Although opicapone is a low solubility drug substance per BCS criteria, this Reviewer considers that it is reasonable not to add an earlier dissolution specification time point for the following reasons:

3. An upper tolerance limit at an additional (earlier) dissolution specification time point to guard against faster than target drug dissolution rate of the proposed immediate release capsule is not deemed necessary because per the proposed labeling (as as confirmed by the CDER QT-IRT), opicapone capsule does not possess QT prolongation potential.
4. This Reviewer recommended that the dissolution specification time point (for when NLT (b) (4)% dissolution is achieved) be shifted to an earlier sampling time point (30 min in lieu of (b) (4) min).

Furthermore, this Reviewer determines that a single set of dissolution acceptance criterion/criteria for both strengths is appropriate, in view of the almost superimposable profiles.

Dissolution on Stability
Per the Applicant, no significant change or trends have been observed during the 60-month stability studies, and all drug product lots (bottles (b) (4)) complied with the proposed dissolution acceptance criterion, in some cases (starting at Month 24 of long term storage) after Tier 2 testing (b) (4)

Note that the proposed expiration dating period for opicapone capsules is 60 months when stored at NMT 30°C. (b) (4) .

On 12/18/2019 (SDN-25), the Applicant agreed to the FDA's recommendation to tighten the dissolution acceptance criterion for batch release and stability testing of both strengths of the Opicapone Capsules to "NLT (b) (4)% (Q) at 30 min", and revised the finished product QC specifications and other pertinent NDA documents accordingly.

B. BB.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

In Vivo Bridging of the Clinical Formulation to the Registration/Stability/Final <u>Formulation</u>

Per the Applicant (and as confirmed by the Office of Clinical Pharmacology), the results of Study BIA-91067-119 demonstrated that the opicapone micronized API capsule evaluated for efficacy/safety in the two pivotal Phase 3 clinical trials (BIA-91067-301 and -302), PK in healthy subjects in later Phase 1 studies [dosage strength equivalency (BIA-91067-121), and the repeat dose and food-effect study (BIA-91067-128)] is BE to the registration/proposed commercial formulation under fasted conditions (with respect to Cmax and AUC for the 50 mg strength, and with respect to AUC for the 5 mg and 25 mg strengths, as well as with respect to S-COMT inhibitory activity regardless of strength), despite differences between the pre-change and post-change drug products in terms of (1) the type and amounts of (b) (4) used in the formulation (b) (4) (2) the hard capsule shell colors & markings, and (3) the DP manufacturing site (BIAL → (b) (4)), and the DP production scale (b) (4). Note that at this time, there is no proposed change in the API supplier. (b) (4) a) is the manufacturer/supplier of the (b) (4) API that was/will be used to produce the clinical, registration/primary stability, and the proposed to-be-marketed drug products.

Note that the PK and pharmacodynamics of the final formulation of the 50 mg micronized capsule (when coadministered with levodopa) were also determined in Parkinson's Disease (PD) patients (NBI-OPC-1706).

The PK of the "registration" 25 mg and 50 mg micronized capsules (also manufactured using the final formulation and process) were also determined in the dosage strength equivalency study (BIA-91067-121), the repeat dose and food-effect study (BIA-91067-128).

Note that per the Applicant, the nonmicronized API and the micronized API capsules are not BE. Specifically, the drug exposures from the "nonmicronized" capsule were reported to be ~50% lower than from the "micronized" capsules (BIA-91067-120). Additionally, the results of BE Study BIA-91067-129 were unsuccessful in demonstrating equivalence between capsules manufactured by the current API supplier (b) (4) and a potential alternate "new" API supplier (b) (4).

In Vitro Bridging of the Final Formulation to the Final <u>Commercial Image</u> Product

Comparative *in vitro* dissolution profile data were provided to extend the PK bridge between the Phase 3 clinical and the registration/proposed commercial formulations to the final commercial image capsules (different in terms of the final capsule color and markings).

As shown in Figure 13 and Figure 14 of the DMDR, the change in the capsule color and markings did not impact the dissolution profiles of the final commercial image tablets relative to the Phase 3 clinical trial lots and the registration/stability lots used in the BE study using the proposed commercial dissolution method; the calculated f_2 values were all >50.

Per agreement with FDA, stability data were not provided to qualify the change in drug product packaging sites.

B. 13 BIOWAIVER REQUEST

Assessment: *NOT APPLICABLE*

Both strengths of the final proposed *formulation* were evaluated for clinical PK, and evaluated for BE (in terms of PK/PD) versus the Phase 3 clinical trial formulation.

Post-Approval Commitments

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Gerlie Gieser

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Date: 1/03/2020 08:02:05AM
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Ta-Chen Wu

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

/s/

DAHLIA A WALTERS
02/13/2020 11:42:13 AM