

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203952Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

JULY 31, 2013

NDA: 203952

Drug Product Name

Proprietary: TRADE NAME

Non-proprietary: Levodopa-Carbidopa Intestinal Gel

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
May 28, 2013	May 28, 2013	June 06, 2013	June 06, 2013

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor

Name: AbbVie Inc.

Address: 1 North Waukegan Road,
North Chicago, IL 60064

Representative: Matthew Kuntz, PharmD, MBA, Director, RA

Telephone: 847-938-0009

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Resubmission, Original NDA
 2. **SUBMISSION PROVIDES FOR:** Levodopa-Carbidopa Intestinal Gel
 3. **MANUFACTURING SITE:** [REDACTED] (b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Intestinal gel, Levodopa 20 mg/mL and Carbidopa 5 mg/mL in a cassette reservoir delivered through PEG-J tube.
 5. **METHOD(S) OF STERILIZATION:** Non-sterile drug product.
 6. **PHARMACOLOGICAL CATEGORY:** Long-term treatment of motor fluctuations in patients with advanced [REDACTED] (b) (4) Parkinson's disease.
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF [REDACTED] (b) (4)
- C. **REMARKS:** This is an electronic resubmission of an Original NDA for a non-sterile drug product LCIG - Levodopa-Carbidopa Intestinal Gel. Although Section 3.2.P.2.4 provided adequate information regarding the container closure system [Enteral Medication Cassette Reservoir], the applicant referred to DMF [REDACTED] (b) (4) for specific information. However, there was no microbiological data to review.

filename: N203952R1

Executive Summary**I. Recommendations**

- A. **Recommendation on Approvability** - Recommend Approval.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is a non-sterile drug product which involves (b) (4)
- B. **Brief Description of Microbiology Deficiencies** - None
- C. **Assessment of Risk Due to Microbiology Deficiencies** – N/A
- D. **Contains Potential Precedent Decision(s)** - Yes No

. Administrative

- A. **Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPS/CDER
- B. **Endorsement Block** _____
John W. Metcalfe, Ph.D., Sr. Review Microbiologist, OPS/CDER
- C. **CC Block**
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)

S DRUG SUBSTANCE – N/A

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –
The drug product, Levodopa-Carbidopa Intestinal Gel (LCIG) is a non-sterile intestinal gel, packaged in a Medication Cassette Reservoir for delivery through a PEG-J tube (Percutaneous Endoscopic Gastrostomy with Jejunal extension), from an infusion pump (CADD-Legacy® 1400 portable infusion pump).
- Drug product composition – The drug product composition is provided in Table 1(copied from Table 1, Section 3.2.P.1).

Table 1. Composition of Levodopa-Carbidopa Intestinal Gel

Component	Quality Standard	Function	Amount per mL
Levodopa	USP	Drug Substance	20.0 mg
Carbidopa monohydrate	USP	(b) (4)	5.0 mg
Carmellose sodium ⁽¹⁾	USP	(b) (4)	(b) (4)
Purified Water	USP	(b) (4)	(b) (4)

- Description of container closure system – The container closure system consists of a (b) (4) bag in a Cassette Reservoir as shown in Table 2 (copied from Table 1, Section 3.2.P.1). The (b) (4) bag is the one which comes in direct contact with the drug product. There is also an external administration system consisting of Naso-Jejunal (NJ) Tubing, Percutaneous Endoscopic Gastrostomy (PEG) Tubing, Jejunal (J) Tubing and an Infusion Pump which does not come in product contact until enteral administration at the patient bedside.

Table 2. Container Closure System for Levodopa-Carbidopa Intestinal Gel

Description	Container Materials
Medication Cassette Reservoir	(b) (4) bag in a (b) (4) cassette
Secondary Container	Corrugate Box (containing 7 Medication Cassettes)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity –
The (b) (4) bag containing the drug product sits in the cassette and the unit is purchased from (b) (4). Besides visual inspection for damage and seal quality, the bag is certified for integrity based on bubble test and burst strength. (b) (4)
Only bags certified for integrity were released by the manufacturer. This information could not be verified in the application or in the referenced DMF (b) (4).
- Preservative Effectiveness – N/A
- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

ADEQUATE

REVIEWER COMMENT – Applicant's method for verification of container closure integrity of the (b) (4) bag meets the regulatory expectations for this non-sterile drug product.

P.3 Manufacture

P.3.1 Manufacturer: Manufacturing, packaging and testing will be performed at (b) (4) Establishment Registration Number: (b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

Figure1. Process Flow Diagram**Microbiological Attributes of the Non-Sterile Drug Product:**

The sponsor states that while there is no requirement for an enterally administered drug product to be sterile, the risk for microbial growth in an aqueous gel suspension was considered. Adequate quality controls were in place to minimize bioburden in raw materials and during the manufacture of the drug product. The sponsor claims that experience from the large number of batches from development through those prepared according to the commercial, validated manufacturing process has shown very low levels of bacteria or fungi, but in all cases passing USP limits; and in no cases *Escherichia coli*, *Salmonella* or *Staphylococcus aureus* were isolated. Because the majority of the drug product shelf life involves storage in frozen and refrigerated states this reduces the risk of microbial growth during storage. As a result, preservation was not considered necessary. Results (see Review Section P.5.2) from the drug product Batch Analyses which were then placed on Stability confirmed the lack of microbial growth.

Microbial Limits testing: Per USP 35 Microbial Limits testing of LCIG is performed on each batch at release, and at stability time points. The results (Review Section P.5.2) meet acceptance criteria of \leq (b)(4) cfu/g total aerobic microbial count (TAMC) and \leq (b)(4) cfu/g total yeasts and molds

(TYMC) as performed per USP <61>/Ph. Eur. 2.6.12. These also meet the acceptance criteria for *Escherichia coli* testing, performed per USP <62>/Ph. Eur. 2.6.13.

ADEQUATE

REVIEWER COMMENT – See comment, Review Section P.5.2.

P.3.5 Process Validation and/or Evaluation

In order to validate the manufacturing process, three process validation batches 10C14G10, 10C15G11 and 10C16G12 were manufactured and the results are summarized in Review Section P.5.2.

ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations for validating the (b) (4) manufacturing process for the non-sterile drug product.

P.5 Control of Drug Product

P.5.1 Specifications – Drug Product Specifications were provided in Table 13, Section 2.3.P.5.1. Specification for product quality microbiology is discussed in the Review Section P.5.2 below.

P.5.2 Analytical Procedures

- Endotoxin – N/A
- Sterility – N/A
- Microbial Limits – The non-sterile drug product is intended for single use for continuous infusion into the jejunum. The single use (b) (4) µg product is stored at -20°C for 24 months and a maximum of (b) (4) weeks at refrigeration (5°C). Once thawed, the product must be used within (b) (4) hours.

Justification of Microbiological Quality Limits Specification for Levodopa-Carbidopa Intestinal Gel:

The following microbiological quality limit tests and associated acceptance criteria were applied to the drug product specifications:

- Total aerobic microbial count: USP <61> at NMT (b) (4) cfu/g
- Absence of objectionable bacteria *Escherichia coli*: USP <62>, Absent/g
- Total combined yeasts and molds count: USP <61> at NMT (b) (4) cfu/g

Microbiological Quality Limits testing was performed on process validation or primary stability lots and the results are summarized in Table 3 (copied from Table 1, Section 3.2.P.5.6). No growth was observed for any of the monitored organisms at -20°C and at 5°C, nor at the supportive conditions of 25°C/60%RH or 30°C/75%RH at initial stability testing.

Although, the tests for the absence of objectionable bacteria *Salmonella* and bile-tolerant gram-negative bacteria counts were performed during the development of the product as well as on stability lots, the sponsor feels that the inclusion of these microbiological tests from the shelf life specification may no longer be necessary. This justification is based on the frozen state of the drug product during its shelf life and the data generated from lot release and stability time points showing the absence of these organisms.

Table 3. Summary – Microbial Limits Testing for LCIG.

Lot Number	Total Aerobic Microbial Count (cfu/g)	Absence of E. coli, and Salmonella (cfu/g)	Total Combined Yeasts and Molds Count (cfu/g)	Bile-Tolerant Gram-Negative Bacteria Count (cfu/g)
10C14G10	(b) (4)			
10C15G11				
10C16G12				

ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of microbial limits test.

P.7 Container Closure System – See Review Section P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

For three primary stability lots placed on long term storage, microbiological data at initial point is provided in Review Section P.5.2.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The sponsor commits to continuing the stability testing program such that at least one production batch (if manufactured) of LCIG will be placed on stability each year at the long-term storage condition at -20°C (Table 24, Section 2.3.P.8) and tested for microbiological quality at initial, 6, 12 and 24 months and at subsequent storage at 5°C (Table 25, Section 2.3.P.8) and tested for microbiological quality at initial, 5, 10 and 15 weeks.

P.8.3 Stability Data – See Review Section P.8.1.

ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations with regard to the design of the stability testing program to support the drug product’s microbiological quality throughout its shelf life.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)
MODULE 1**

A. PACKAGE INSERT

From microbiology product quality standpoint, there are no labeling issues with this non-sterile drug product. Labeling meetings have been scheduled for any labeling issues that may arrive from CDRH or DMEPA.

ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology as was provided in the product labeling.

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND
COMMENTS: None.**

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

/s/

VINAYAK B PAWAR
08/01/2013

JOHN W METCALFE
08/01/2013
I concur.