

Application Type	Original BLA
STN	125739/0
CBER Received Date	30-Nov-2021
PDUFA Goal Date	30-Nov-2022
Division / Office	OVRR
Committee Chair	Qun Wang
Project Managers	Margaret Dayhoff-Brannigan, Girish Ramachandran, Debra Vause
Priority Review	No
Reviewer Name	Ho-Hsiang Wu
Review Completion Date / Stamped Date	
Supervisory Concurrence	Jennifer L. Kirk Team Lead, Vaccine and Related Products Team, DNCE, DB
	Chunrong Cheng Acting Branch Chief, Device and Non-Clinical Evaluation Branch, DB
	John Scott Division Director, Division of Biostatistics, OBPV
Applicant	Ferring Pharmaceuticals, Inc.
Established Name	Fecal Microbiota, Live
(Proposed) Trade Name	REBYOTA
Pharmacologic Class	Live Biotherapeutic

Formulation(s), including Adjuvants, etc	Single-dose 150 mL microbiota suspension of (b) (4) colony forming units (CFU) of diverse spore-forming and non-spore-forming bacteria, including Bacteroides solution containing Polyethylene Glycol in Saline.
Dosage Form(s) and Route(s) of Administration	Suspension; Rectal administration.
Dosing Regimen	Administration from 24 to 72 hours after the last dose of antibiotics.
Indication(s) and Intended Population(s)	To reduce the recurrence of Clostridioides difficile infection (CDI) in adults following antibiotic treatment for recurrent Clostridioides difficile infection.

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BLA	biologics licensing application
CDI	<i>Clostridioides</i> difficile infection
CMC	chemistry and manufacturing controls
IR	Information Request
CFU	Colony-forming unit
TM8014	Test method # 8014
QR644	Validation Study Report # 644

## 1. EXECUTIVE SUMMARY

In this original BLA, Ferring Pharmaceuticals, Inc. seeks licensure for their live microbiota suspension intended to reduce the recurrence of *Clostridioides* difficile infection (CDI) in adults following antibiotic treatment for recurrent CDI. At the request of the product reviewer, Paul Carlson, on 25 July 2022, I reviewed the responses to information request (IR) #16 sent on 8 July 2022 and IR #20 sent on 8 August 2022. In these responses, Ferring Pharmaceuticals proposed a validity criterion for the (b) (4)-replicate variability, changed the statistical method for assessing precision in a second supplementary validation study, and provided the results of a second supplementary validation study that assessed precision at the low and high end of the specification on 26 Aug 2022.

The proposed validity criterion was based on historical data and appears reasonable. The original change in statistical method was not acceptable; however, Ferring Pharmaceuticals revised the statistical methods based on CBER's comments and these revisions were acceptable. The second supplementary validation results met the pre-defined acceptance criteria for both the low and high end of the specification. While Ferring Pharmaceuticals responses and second supplementary validation results were acceptable, because I only reviewed a small part of the submission, I defer to the product reviewer for an overall recommendation related to the potency assay.

## 2. REGULATORY BACKGROUND

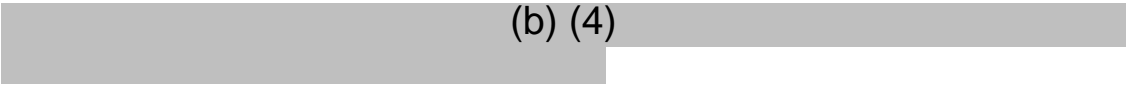

### 2.1 Pre- and Post-submission Regulatory Activity Related to the Review

In this original BLA, Ferring Pharmaceuticals seeks licensure for their live microbiota suspension intended to reduce the recurrence of CDI in adults following antibiotic treatment for recurrent CDI. This statistical review focuses on the validation of the viable bacteria count (colony forming units; CFU) potency assay (referred to as TM8014) for drug product release testing and stability monitoring and was performed because of a 25 July 2022 request from the product reviewer, Paul Carlson.

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### 3. SUBMISSION QUALITY

The submission was adequately organized for conducting a complete CMC statistical review without unreasonable difficulty.

### 4. SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES

#### 4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review.

### 5. SOURCES OF INFORMATION CONSIDERED IN THE REVIEW

#### 5.1 Review Strategy

This review focuses on the responses to IRs #16 and #20 and the second supplementary validation study report, per the product reviewer's request.


#### 5.2 BLA/IND Documents That Serve as the Basis for the Review

The documents referenced in this review are:

1. 25 July 2022 email communication in response to IR #16:  
Questions\_Following\_Part\_1\_BLA-STN1257390-0-IR16.pdf
2. BLA 125739/0.27 (seq. #0028):  
Section 3.2.R: viable-bacterial-count-and-diversity-method-doc-8014-rev-02.pdf
3. BLA 125739/0.30 (seq. #0031):  
Section 3.2.R: qp-644-rev-000-validation-protocol-for-tm-8014.pdf
4. BLA 125739/0.34 (seq. #0036):  
Section 1.11.1: response-to-ir-dated-08-aug-2022.pdf
5. BLA 125739/0.35 (seq. #0037):  
Section 3.2.R: qr-644-rev-001-validation-report-for-tm-8014.pdf

## 6. DISCUSSION OF PROTOCOLS, ANALYSES, AND STUDY REPORTS

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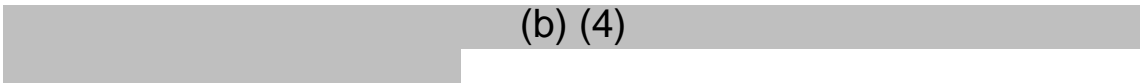
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***Reviewer's Comment:** All results met the pre-defined acceptance criteria. I found no statistical issues.*

## 8. CONCLUSIONS

### 8.1 Statistical Issues and Collective Evidence

Ferring Pharmaceuticals proposed a validity criterion for the %CV between (b) (4) - replicates of not more than (b) (4) % based on historical data. In their second supplementary validation study protocol, Ferring Pharmaceuticals revised their statistical methods for assessing precision to correctly calculate the repeatability and intermediate precision %CV and to use a less complicated statistical method that is more appropriate for their study design. In the second supplementary validation study, the acceptance criteria for repeatability and intermediate precision were met for the low and high lots.

### 8.2 Conclusions and Recommendations

Ferring Pharmaceuticals' proposed validity criterion for the (b) (4) replicates and their changes to the statistical methods for assessing precision in the second supplementary validity study were acceptable. The secondary supplementary validity also met all of the pre-specified acceptance criteria. However, because I only reviewed a small portion of the submission in this memo, I defer to the product reviewer for an overall recommendation related to the potency assay.