

CBER CMC BLA Review Memorandum

BLA STN 125739

RBX2660 (Fecal Microbiota, Live-jslm); REBYOTA

Paul Carlson, PhD., Biologist, CBER/OVRR/DBPAP/LMPCI

1. **BLA#:** STN 125739

2. **APPLICANT NAME AND LICENSE NUMBER** – Ferring Pharmaceuticals Inc;
License # 2112

3. **PRODUCT NAME/PRODUCT TYPE**

REBYOTA; RBX2660 (Fecal Microbiota, Live-jslm)

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Dosage form: Suspension
- b. Strength/Potency: 1×10^8 – 5×10^{10} CFU/mL
- c. Route of administration: Rectal
- d. Indication(s): For the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI

5. **MAJOR MILESTONES**

Filing meeting – 13 January 2022
Mid-Cycle Meeting – 31 May 2022
Late-Cycle Meeting – 30 August 2022
Advisory Committee Meeting – 22 September 2022
PDUFA action date – 30 November 2022

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Paul Carlson, OVRP/DBPAP/LMPCI	Drug substance (DS) and drug product (DP) manufacture, (3.2.S and 3.2.P) and associated files in 3.2.R (regional information)

7. **INTER-CENTER CONSULTS REQUESTED**

NA

8. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
05/03/2021	STN 125739/0	Part 1/3 of rolling submission
07/01/2021	STN 125739/00.1	Part 2/3 of rolling submission
07/06/2021	STN 125739/0.2	Response to IR#1 – donor screening

10/06/2021	STN 125739/0.3	Incorporation of changes to donor screening requested in IR#1
11/30/2021	STN 125739/0.4	Part 3/3 of rolling submission
12/06/2021	STN 125739/0.5	Proprietary naming information
03/07/2022	STN 125739/0.12	Draft labeling information
05/25/2022	STN 125739/0.20	Product naming information
06/15/2022	STN 125739/0.22	Response to IR#13
07/01/2022	STN 125739/0.26	Updated 4°C stability data
07/15/2022	STN 125739/0.27	Response to IR – potency assay validation
07/28/2022	STN 125739/0.30	Updated validation protocol for precision of potency assay
08/03/2022	STN 125739/0.31	Responses to IR#19
08/22/2022	STN 125739/0.34	Responses to IR#20, updated validation protocol for potency assay
08/26/2022	STN 125739/0.35	Validation report – precision validation for potency assay
09/30/2022	STN125739/0.40	Addition of screening questions to assess monkeypox exposure
10/06/2022	STN 125739/0.42	Response to IR#26, updated control of materials section and extractables information
10/19/2022	STN 125739/0.45	Response to IR#29 – updated documents to adjust product potency throughout, submission of master batch record and extractables study for tubing

10/28/2022	STN 125739/0.47	Response to IR#30 – combination product/device question
10/29/2022	STN 125739/0.48	Response to IR#31 – monkeypox and hepatitis B donor screening
11/02/2022	STN 125739/0.50	Response to IR#34 – acknowledgment of regulatory status of the administration tube set

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	Ferring uses EVA bags manufactured by (b) (4) from (b) (4) for Drug Substance container	yes	Reviewed as part of container closure information, however the applicant provided specific information for review on the final manufactured EVA bags used in the container closure. Those data were used for final review of the container closure rather than the cross-referenced file.

10. REVIEWER SUMMARY AND RECOMMENDATION
A. EXECUTIVE SUMMARY

Ferring submitted a BLA (STN 125739/0) for licensure of Fecal Microbiota, Live – jsIm (REBYOTA). Ferring submitted this BLA as a rolling BLA in three sections dated May 3, 2021, July 7, 2021, and November 30, 2021. REBYOTA is an opaque fecal microbiota suspension for rectal administration. REBYOTA is indicated to for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

The source material for REBYOTA is donor human stool. Ferring qualifies donors through extensive screening by questionnaire and physical examination for health concerns and potential risk factors. Donor screening also includes blood and stool testing for a wide array of potentially transmissible viral, bacterial, and parasitic pathogens of concern. Ferring collects donor stools, administers the donor questionnaire, and performs physical examinations of donors at their manufacturing facility in Roseville, MN. Ferring ships donor stool and blood samples for donor testing to (b) (4) in (b) (4). Ferring only releases final drug product from quarantine after receipt of acceptable donor screening results.

Ferring manufactures the drug product (DP) at their Roseville, MN facility using a (b) (4) manufacturing process. Ferring initiates the manufacturing process (b) (4) after collection of a stool donation from a single donor by combining the donor stool with a cryoprotectant excipient solution of PEG3350 and 0.9% saline to form the drug substance (DS). The final DP contains no more than 5.97g of PEG3350 in saline per dose. Ferring then fills a 250 mL ethylene vinyl acetate (EVA) bag with 150 mL of the DS (fecal microbiota suspension) to produce the final DP. Ferring then affixes a temporary label to each bag and stores them at -80°C under quarantine while awaiting final stool and blood pathogen test results. Once negative testing results are received for a lot of product, Ferring removes the product from the quarantine freezer, removes the temporary label, adds the final label and packages product in the final carton, and then stores it in a separate -80°C freezer until it is shipped. Ferring supplies the DP with an administration tube set consisting of a rectal tube, spike port adaptor, and clamp. Ferring packages and labels the final DP and the administration tubing set separately then ships both to a distributor. The distributor performs the final packaging steps then ships the product to end users. The distributor packages the DP on dry ice and packages the administration tubing set at ambient temperature, then ships both together in a dual temperature shipper.

Ferring stores REBYOTA at -80°C and they have requested a 36-month shelf life for the product. The dating period for the final drug product begins on the Date of Manufacture (DOM), which Ferring defines as the date the donor human stool and the PEG/saline solution are mixed together. Ferring submitted data from stability studies to support this shelf-life request. Data from these studies demonstrated product stability out to 36 months when stored at -80°C. In the product labeling, Ferring instructs end users to store in an ultracold freezer, -60°C to -90°C (-76°F to -130°F). Alternatively, they instruct users to thaw REBYOTA under refrigerated (2-8°C) conditions for 24 hours and indicate that subsequent storage for up to four days at 2-8°C prior to administration is allowable.

I identified the following deficiencies in Ferring's donor testing methods, validation of the potency assay, and refrigerated storage stability studies.

1. I requested that Ferring submit additional information on the specific blood and stool test methods for donor screening. Ferring provided the requested information, which included verification data demonstrating that FDA-cleared

and/or approved assays were performing to manufacturer's standards, and relevant qualification data for routine clinical laboratory tests being performed on stool samples.

2. In their initial submissions, Ferring did not adequately demonstrate precision of their potency assay. They made changes to their precision criteria during their validation study and did not include enough operators to fully assess whether the observed variability could be attributed to operator error or inherent variability of the assay. I requested that Ferring repeat their validation study for precision to address these deficiencies. Ferring repeated their validation for precision and submitted the data for review.
3. I requested that Ferring perform additional stability studies since the stability data they provided did not support their proposed label instructions for thawing the product under refrigerated conditions for 24 hours and then allowing an additional (b) (4) days of storage under refrigerated conditions prior to use. Ferring provided the requested stability data. In addition, based on all available stability data and their experience during clinical studies, they reduced the time allowed in refrigerated storage to four days after thawing.

Ferring addressed the above deficiencies and all other deficiencies I identified during my review. The CMC product information and data in this BLA support manufacturing consistency and product quality. I recommend approval of this BLA.

B. RECOMMENDATION

I. APPROVAL

Based on the CMC information and data provided in this application, I recommend approval of this BLA. We determined that CBER review of lot release protocols prior to Ferring distributing REBYOTA drug product lots is not required to assure the safety and potency of this product. Therefore, the mode of release on the CBER lot testing plan for this product will be "Alternative to Lot Release, Exempt".

II. COMPLETE RESPONSE (CR)

NA

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Paul E. Carlson, PhD, Biologist, DBPAP/LMPCI	Concur	
Earle S. Stibitz, PhD, Chief, DBPAP/LMPCI	Concur	

Jay E. Slater, MD, Director, DBPAP	Concur	
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Review of CTD
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Module 3

3.2.S DRUG SUBSTANCE¹

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

The Drug Substance (DS) is a mixture of human stool with polyethylene glycol 3350 and 0.9% sodium chloride prior to filling into the final container. The DS is filled into the final container (enema bag) to make the final Drug Product (DP) as part of a (b) (4) manufacturing process. The DS is an opaque suspension of stool in excipient solution.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

1. Rebiotix Inc
 - a. Address:
2660 Patton Road
Roseville, MN 55113
 - b. Registrations:
FEI: 3012047188
DUNS: 047695166
 - c. Responsibilities:
Collection, inspection, storage, and release of donor human stool.
Collection of donor blood and SARS-CoV-2 samples for pathogen testing.
Manufacture of drug substance.

 2. (b) (4)
 - b. Registrations:
FEI: (b) (4)
CLIA Number: (b) (4)
 - c. Responsibilities
Pathogen testing of donor human stool, donor blood, and donor SARS-CoV-2 nasopharyngeal swabs.
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3. (b) (4)

b. Registrations:

FEI: (b) (4)

DUNS: (b) (4)

c. Responsibilities:

Testing of (b) (4) excipients.

3.2.S.2.2 Description of Manufacturing Process

The DS manufacturing process consists of ^{(b) (4)} steps: (b) (4)

□ **Manufacturing process steps**

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

□ **Batch Numbering, (b) (4) and Scale Definition**

The applicant uses a batch/lot numbering scheme for this product that includes (b) (4)

[Redacted]

represent the dose number from a given DP lot.

Ferring illustrated this numbering scheme in the BLA (figure 1, section 3.2.S.2.2), summarized below.

Ferring DP lot number example:

DP lot number: (b) (4)

[Redacted]

□ **Storage and Shipping**

(b) (4)

Ferring did not indicate what they considered to be the date of manufacturing for their product, that would be used when setting the expiration dates for each lot. To address this, I sent the following additional comments to the applicant in IR#32 on 25 October 2022:

You propose a dating period for your drug product of 24 months when stored at –60 to -90°C. The dating period for a product must begin on the date of manufacture, as specified in 21 CFR 610.50. Please specify the date of manufacture for your drug product.

Ferring responded to this IR in STN125739/0.47 on 28 October 2022. In this response they indicated that the date of manufacturing is considered to be the time that the DHS and PEG/saline solution are mixed together. They also clarified that they are requesting an expiry of 36 months for product stored in the -80C. These responses are acceptable and the DOM information is reflected in my executive summary above.

3.2.S.2.3 Control of Materials

Ingredients

1. Human Donor Stool (DHS)
2. Excipients
 - a. polyethylene glycol 3350, (b) (4)
 - b. 0.9% sodium chloride irrigation, (b) (4).
3. Single use systems

(b) (4)

- b. Stool collection kit – Stool collection containers are used for collection of stool from donors. The kit includes a collection vessel with lid and a scaffold to be placed on the toilet for ease of stool collection. (b) (4)

Ferring indicated in their BLA that the source of polyethylene glycol 3350, 0.9% sodium chloride, (b) (4), and stool collection kits will change. They must provide

information on all changes made to the manufacturing process, including changing the source of individual components. Therefore, we sent an IR to the applicant to clarify when they intend to make these changes.

IR comment (IR#20) sent to Ferring on 8 August 2022:

In your control of materials document (Section 3.2.S.2.3), you indicate plans to change the source of polyethylene glycol 3350, 0.9% sodium chloride, (b) (4), and stool collection kits. Please clarify the current suppliers of each of the items and whether these have changed since the manufacture of the DP lots used in your Phase 3 trial. Please note that any changes to the manufacturing process, including changes to the source of excipients and single use systems must be reported and sufficient information must be provided to ensure that these changes will not have an impact on product quality.

Ferring submitted amendment 34 (125739/0.34) in response to our comments in IR#20 on 22 August 2022. Ferring updated this section in the dossier to remove the statement about changing suppliers. They clarified that the suppliers of these items have not changed since before manufacture of phase 3 clinical material. They indicated that they have historically used (b) (4) suppliers for 0.9% sodium chloride irrigation, (b) (4). (b) (4) are supplied by (b) (4). Stool collection containers are supplied by (b) (4). The (b) (4) supplies the PEG3350. These responses are acceptable, and the applicant has addressed all CMC concerns related to this section.

□ **Control of Raw Materials NOT of Biological Origin**

The product contains two raw materials that are not of biological origin, the excipients polyethylene glycol 3350 and (b) (4) 0.9% sodium chloride irrigation, (b) (4). Ferring uses these two materials to produce the excipient solution that is added to donor human stool to generate a liquid suspension. The final concentration of PEG 3350 ((b) (4)) in the cryoprotectant buffer is (b) (4) PEG per (b) (4) saline. Ferring qualifies all raw materials by verifying the manufacturer's Certificates of Analysis.

□ **Control of Raw Materials of Biological Origin**

The raw material that the applicant uses to manufacture this product is donated human stool. Ferring tests every stool donation for the presence of pathogens prior to release of the product from quarantine. The donor stool testing methods used are outlined below in the "Control of Starting Materials" section. The stool tests are performed on donor stool prior to enrollment and on all stool donations provided for manufacture of product.

□ **Control of Starting (i.e., Source) Material(s)**

The source material for this product is human stool. The applicant describes their stool donor qualification and eligibility requirements in their donor qualification program, which includes an initial health screening of individuals, screening by

questionnaire for behavioral risk factors, pathogen testing of blood and stool, and ongoing monitoring as outlined below:

1. Initial screening – At this visit the potential donor signs an informed consent form, fills out a qualification questionnaire, and a SARS-CoV-2 sample collection questionnaire. As of September 2021, Ferring requires donors to show proof of vaccination against SARS-CoV-2, including all currently recommended doses for the vaccine received. Potential donors also provide samples for blood testing for pathogens, stool pathogen testing, and SARS-CoV-2 testing using a nasopharyngeal swab for sample collection.
 - Donor informed consent – I defer to the clinical team for comment on the donor informed consent form.
 - Donor qualification questionnaire – I defer to the clinical team for comment on the donor questionnaire.
 - COVID questionnaire – I defer to the clinical team for comment on the donor COVID questionnaire.
 - Initial testing of blood for pathogens by antibody/antigen tests – Ferring sends the initial blood sample from the prospective donor to a CLIA-certified laboratory ((b) (4) ; information above) for testing. Table 1 from Section 3.2.3.S.2.3, Control of Materials, lists the pathogens tested, the test method used, and the acceptance criteria required for an individual to qualify as a stool donor. All blood pathogen tests are FDA cleared. These include:
 - Treponema Antibodies – (b) (4) *Treponema pallidum*
 - (b) (4) – (b) (4) assay
 - Hepatitis B Surface Antigen – (b) (4) , HBsAg assay
 - Hepatitis C Antibody – (b) (4) , Anti-HCV assay
 - Human Immunodeficiency Virus (HIV) (b) (4) assay.

- The acceptance criterion for each of these tests is non-reactive. For (b) (4) reactive results are acceptable in immunized individuals. Rebioitx originally had the acceptance criterion for Hepatitis B antigen testing set at “nonreactive or immunized” also, however this is not acceptable because the vaccination status of an individual should not impact this test. I sent an IR to Ferring (IR#31 on 21 October 2022) indicating the need to adjust the

- Initial SARS-CoV-2 Testing and Screening – Ferring performs an initial test for SARS-CoV-2 on each donor using a sample collected via nasopharyngeal swab by a health care professional. The current test method they perform is the (b) (4) SARS-CoV-2 Assay ((b) (4)). This method is a nucleic acid amplification test for detection of SARS-CoV-2 RNA that has received FDA emergency use authorization. Donors who test positive are excluded from the donor stool program for at least (b) (4) weeks.

- Pathogen testing of donor human stool – Ferring collects stool from donors as described above. Each stool donation is tested for a panel of pathogens as indicated in the table below from Section 3.2.S.2.3.1.1.5 of the BLA. (b) (4) performs all of the tests listed above using FDA cleared (510k) or approved (PMA) test methods or other validated test methods where appropriate, including tests for pathogens of concern for fecal transmission as well as multidrug resistant organisms (MDROs) that could be carried by donors. The majority of the tests are performed using the (b) (4), for which Ferring has provided the clinical laboratory’s protocol and qualification information demonstrating that the assay performs as specified by (b) (4). Ferring also provided the laboratory protocols and qualification information for the (b) (4).
 (b) (4). Ferring provided SOPs for the (b) (4) but did not provide verification or qualification information for these methods.

Ferring sends stool samples to (b) (4) for testing using the (b) (4) test method, a (b) (4) assay, for the organisms listed below. The acceptance criteria for all (b) (4) tests is “negative”.

- (b) (4) species
- (b) (4)
- Enteropathogenic *E. coli* (EPEC)
- Shiga Toxin producing *E. coli* (STEC)
- (b) (4)
- (b) (4) species
- (b) (4) species
- (b) (4)
- (b) (4) species
- (b) (4)

- (b) (4)
- (b) (4)

(b) (4) performs additional tests for Ferring to detect the organisms listed below. The test methods and acceptance criteria are listed for each organism.

(b) (4)

[Redacted text block]

Methicillin-resistant *Staphylococcus aureus* (MRSA)

- Method – (b) (4)
- Acceptance Criterion – No MRSA isolated.

Vancomycin Resistant *Enterococci* (VRE)

- Method – (b) (4)
- Acceptance Criterion – No VRE isolated

Extended-spectrum β -lactamase (ESBL) producing organisms

- Method – (b) (4)
- Acceptance Criterion – No ESBL-producing organisms isolated

Carbapenem-resistant organisms (CRE)

- Method – (b) (4)
- Acceptance Criterion – No carbapenem non-susceptible organisms isolated

(b) (4)

[Redacted text block]



Qualified Donor – Ferring detailed requirements for qualified donors in Section 3.2.S.2.3. To be considered a qualified donor, an individual must have completed the informed consent form and must meet the acceptance criteria of the Donor Qualification Questionnaire, donor blood testing for pathogens of concern, the SARS-CoV-2 Sample collection questionnaire, SARS-CoV-2 testing, SARS-CoV-2 vaccination, and stool pathogen testing as outlined above. Ferring will terminate from the program any donors who fail to meet any of these criteria. Terminated donors may subsequently re-enter the donor program unless they were terminated for a reason that makes them permanently ineligible for the program. Previously terminated donors must repeat the full donor qualification process to re-enter the program. The time that must elapse until qualification can occur depends upon the specific screening question or pathogen test that led to disqualification.

Ferring quarantines all DP lots and only releases DP lots from quarantine after confirming that donors passed all book-ended blood tests during the donation period and that the donated stool used for the manufacture of the DP lots passed all stool testing.

Overall Reviewer’s Assessment of Section 3.2.S.2.3:

The information Ferring provided was generally acceptable. However, I identified some deficiencies in this section related to implementation of donor screening assays. I sent IRs to Ferring requesting additional information on the assays. The IRs are listed below followed by summaries of their responses and my review of their responses.

IR comment (IR#1) sent to Ferring on 17 June 2021:

1. *You indicate that you are using FDA cleared/approved test methods performed in a CLIA certified laboratory for the majority of your donor screening assays. However, you have not provided information about the performance of these tests in your BLA submission. To provide assurance that the assays are performing as specified, please submit the following information from your clinical testing partner, (b) (4), to your BLA:*
 - a. *510(k) or PMA clearance numbers and associated product information for all FDA cleared or approved assays being used for donor screening.*

b. *Laboratory verification data demonstrating assay performance based on manufacturer's specifications for the following FDA cleared or approved devices:*

- i. (b) (4)
- ii. (b) (4)
- iii. (b) (4)
- iv. (b) (4)
- v. (b) (4)
- vi. (b) (4)
- vii. (b) (4)

c. *Laboratory SOPs along with verification data demonstrating assay performance based on manufacturer's specifications for the FDA cleared (b) (4) methods for detection of (b) (4), Vancomycin resistant Enterococcus (VRE), Methicillin-resistant Staphylococcus aureus (MRSA), Extended-spectrum B-lactamase producing (ESBL) Enterobacteriaceae, Carbapenem-resistant Enterobacteriaceae (CRE).*

d. *Laboratory SOPs along with available qualification data demonstrating assay performance for the indicated purpose for each laboratory developed test method, including (b) (4)*

e. *Laboratory SOPs along with verification data demonstrating assay performance based on manufacturer's guidelines for the (b) (4)*

2. The (b) (4) provides data on pathogens that you are not using for decisions about donor suitability, either because you are using other tests to detect these pathogens, or because you have not included these pathogens in your donor screening plan. Please include this information in your donor screening plans or justify the exclusion of these data by addressing the following:

a. Please exclude donors who test positive by the (b) (4)

b. The (b) (4) also includes (b) (4)

, which you have not included in your donor screening plans. Please add exclusion of donors based on a positive test result for these pathogens or provide justification for why these specific pathogens are not included in your donor screening plan.

3. *We acknowledge your plans to use the (b) (4) SARS-CoV-2 Assay currently available under Emergency Use Authorization to screen donors for SARS-CoV-2 as part of your donor screening program. While this test is acceptable at this time, we expect you to update your donor screening plan once FDA cleared/approved COVID-19 diagnostic test(s) are available. Please acknowledge and confirm.*
4. *We note that it will take over (b) (4) days to obtain results from the (b) (4) test. Please clarify the timing of your donor testing for (b) (4) with respect to product quarantine and release.*

Ferring submitted an amendment (STN 125739/0.2) on 06 July 2021, responding to the IRs. They provided acceptable SOPs and verification or qualification data for the majority of the tests being performed. However, they only provided SOPs with no verification or qualification data for the (b) (4) donor screening tests. Ferring incorporated the additional pathogens that are included in the (b) (4), but were not included in the original exclusion list. They submitted these changes in STN 125739/0.03 on 06 October 2021.

I sent additional IRs (IR#13) on 18 May 2022 requesting more information on some of the donor screening tests being used.

We have the following comments/requests regarding your donor screening/testing protocols:

- a. *You state that you are using the (b) (4) SARS-CoV-2 Assay ((b) (4)) to test donor nasopharyngeal (NP) swabs for SARS-CoV-2. This assay is currently only authorized for emergency use under EUA. Once available, we request that you perform your donor NP swab SARS-CoV-2 screening using a SARS-CoV-2 test that is cleared by FDA. Please acknowledge.*
- b. *You provided SOPs for the (b) (4) test, (b) (4) donor screening tests. Please provide qualification data for these tests, including controls used to ensure test performance and training requirements for technicians.*
- c. *Please describe how “inconclusive” donor screening/testing results are handled.*
- d. *Please provide detailed plans for monitoring the need to update your donor screening program and how these changes will be implemented post licensure. Please include document 8038 “Donor Program Trending and Surveillance”, which is referenced in your donor program overview (Doc # 7347), in your response.*

Ferring submitted an amendment (STN 125739/0.22) responding to these IR comments on 15 June 2022. Their responses regarding COVID-19 testing and handling of inconclusive donor screening results are acceptable. Ferring provided additional information on the donor screening tests, training, and controls as requested in the IR comments, but they did not provide the identity of the controls being used for both the (b) (4) test and the (b) (4) test. As information on the controls is required to assess these tests, I sent IR #20 on 8 August 2022 requesting this information. Ferring also indicated that (b) (4), is exempt from QC “per the associated laboratory standard.” In the IR, I asked Ferring to clarify why this specific (b) (4) is exempt. Also, regarding the monitoring plan assessing the need for additions to the donor screening protocol post-licensure, Ferring submitted a plan for monitoring but did not indicate how they will implement these changes or communicate them to us. Therefore, I asked Ferring to provide additional information in the IR.

I sent the following additional comments to the applicant in IR#20 on 8 August 2022:

1. *We acknowledge the additional donor screening assay information you provided in amendment 22 on June 15, 2022. Please address the following remaining questions regarding your donor screening protocols:*
 - a. *Please indicate the positive and negative control organisms being used for both the (b) (4) tests.*
 - b. *You state that (b) (4) used for the (b) (4) test is exempt from QC per the associated laboratory standard. Please provide the associated laboratory standard and explain why this specific (b) (4) type is exempt from QC.*
2. *Regarding your plans for ongoing monitoring and modification of donor screening protocols, we acknowledge that you have provided information on how you plan to monitor for emerging pathogens of concern. However, you have not described how you will implement these changes in your program. Please provide a summary of how you will implement any necessary changes into your donor screening program including notification of FDA of these changes, recall of units that might be affected, back screening of lots already manufactured if necessary, and incorporation of new testing requirements into your overall program.*

Ferring submitted an amendment (STN 125739/0.34) responding to comments in IR#20 on 22 August 2022. They stated that the positive control for the (b) (4) assay is a known (b) (4) positive human specimen and that this assay has no negative control. For the (b) (4), the controls are purchased (b) (4)

(b) (4) as a positive control and one that contains no organisms, which serves as the negative control. They also explained that the (b) (4) is exempt from additional QC because it is a purchased commercially prepared (b) (4). The clinical microbiology lab ((b) (4)) performs a visual inspection of incoming (b) (4) at the time of receipt to ensure that the (b) (4) are not damaged or contaminated and stores and handles the (b) (4) in accordance with the manufacturer's requirements.

Regarding plans for ongoing monitoring and changes to the donor screening program, Ferring outlined the steps they plan to take if they identify a trend or an on-going threat. They indicate that they plan to implement any changes to donor testing and screening plans via their change and control document request programs. The change control procedure includes regulatory review of the change and determination of type of submission that will be required. They further indicate that the timing of implementation will be dependent on the type of notification required, which will be determined by their Quality Event procedures. For any situation that has the potential to affect product quality for both manufactured and marketed products, Ferring follows their Quality Event procedures. In the event of a significant Quality Event, the issue is referred to the Quality Review Board Escalation Process. This board will then evaluate the quality event and determine the best course of action. The Quality Review Board includes representatives from Regulatory, Quality, Clinical, Technical Operations departments, and other subject matter experts as needed, and is responsible for reviewing and evaluating product quality issues. I reviewed the Quality Event procedures and SOPs that Ferring submitted in response to the above IR and agree with their proposed plans for monitoring and changing their donor screening program. Their responses are acceptable.

The clinical team sent one additional IR to Ferring on 13 September 2022 (IR #25) regarding the ongoing Monkeypox outbreak and potential risk for transmission via the drug product. We requested that Ferring include additional questions in their donor screening questionnaire to assess risk factors for exposure to monkeypox virus to mitigate the risk of transmission. Ferring responded to this IR in STN 125739/0.40 on 30 September 2022. Ferring indicated that they would allow donor reinstatement (b) (4) weeks after a positive monkeypox case or exposure. This is not acceptable, individuals with a positive case or exposure must be excluded from donating indefinitely.

To address the remaining issue with monkeypox screening and one additional issue with hepatitis B screening that was identified, I sent the following additional comments to the applicant in IR#31 on 21 October 2022:

- 1. Since the longevity of shedding of monkeypox virus in stool is unknown, and there is currently no validated test to allow for confirmation of clearance of monkeypox virus from the stool, it is necessary to exclude stool donors with suspected or confirmed monkeypox infection or exposure indefinitely from future stool donation at this time. Please revise all documents corresponding to the Donor Questionnaire (e.g., Donation Questionnaire Review, Donor Qualification*

Questionnaire Review, and SOP 7318 Donor Qualification Status and Donor Donating Status) accordingly.

2. We note that you are testing donors for Hepatitis B using an antigen test, but you have the acceptance criterion listed as “Nonreactive or immunized.” Since this test is detecting the presence of antigen and not antibody, a positive result would be indicative of infection even in an individual who was vaccinated. Please change this acceptance criterion to “Nonreactive.”

Ferring responded to IR#31 in STN125739/0.48 on 28 October 2022. In this response, they made the requested changes. Anyone with a positive case of monkeypox or a known exposure is not excluded from donation indefinitely. They also adjusted the acceptance criterion for Hepatitis B to “nonreactive” as requested. These changes are acceptable and I have no further concerns regarding the donor screening/testing program for this product.

3.2.S.2.4 Controls of Critical Steps and Intermediates

As described previously, Ferring uses a (b) (4) manufacturing process for this product. Stool is processed by mixing with excipient solution, (b) (4), and moved directly into DP manufacturing. There are no storage steps or specification/release tests performed on the DS prior to moving into DP manufacturing. Ferring identified the (b) (4) as the (b) (4) with a critical process parameter for DS manufacturing. The parameters for this step include (b) (4).

Overall Reviewer’s Assessment of Section 3.2.S.2.4:

The information Ferring submitted in this section is acceptable.

3.2.S.2.5 Process Validation and/or Evaluation

Ferring combined the process validation sections for both DS and DP Section 3.2.P.3.5 as the manufacturing process is continuous.

Overall Reviewer’s Assessment of Section 3.2.S.2.5:

Since there are no additional manufacturing steps between manufacture of the DS and filling into enema bags to make the final DP, combining these sections in the dossier is acceptable. Ferring submitted all documents related to process validation in Section 3.2.P.3.5. Please see my review for that section for details about their process validation.

3.2.S.2.6 Manufacturing Process Development

As above, the applicant has combined the manufacturing process development sections for both DS and DP due to the nature of the manufacturing process for this product.

Overall Reviewer’s Assessment of Section 3.2.S.2.6:

As above, since there are no additional manufacturing steps between manufacture of the DS and filling into enema bags to make the final DP, combining these sections in the dossier is acceptable. Ferring submitted all documents related to process development in section 3.2.P.2. Please see my review for that section for details about their manufacturing process development.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

The DS for this product consists of human fecal material from screened and cleared donors in a suspension of PEG 3350 and saline. This section is not applicable to this product.

3.2.S.3.2 Impurities

The DS for this product consists of donor stool in a PEG3350 /saline solution. The applicant screens stool donors extensively to mitigate the risk of the presence of pathogenic organisms in the donor source material. Ferring provided the manufacturer’s information on the PEG material being used, which states that it contains (b) (4)

[Redacted]

. Ferring had (b) (4) qualification batches of PEG 3350 tested for (b) (4) and the results are provided in Table 1 of this section. Specifically, no (b) (4) were detected.

Overall Reviewer’s Assessment of Sections 3.2.S.3.1 and 3.2.S.3.2

I have reviewed the information in this section and have not identified any deficiencies.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures

3.2.S.4.4 Batch Analyses

3.2.S.5 Reference Standards or Materials

Overall Reviewer’s Assessment of Sections 3.2.S.4.1 – 3.2.S.5:

As detailed previously in this memo, Ferring uses a (b) (4) manufacturing process for this product and there are (b) (4) steps from DS to DP. The DS is manufactured (b) (4) filled into enema bags and is final DP at that time. Therefore, Ferring does not have separate specifications, analytical

methods, or batch analyses for the DS, and they do not use reference standards or materials. Ferring did not submit data for these DS sections. I agree with their approach due to the (b) (4) manufacturing process and I have not identified any deficiencies in these sections.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data

(b) (4)

Ferring has not performed stability studies on the DS because there are no storage or hold steps for the DS. They performed all stability testing on the final DP.

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

Ferring is not proposing any stability studies on the DS for the reasons outlined above.

Overall Reviewer's Assessment of Section 3.2.S.7:

Ferring performed a stability study on donated human stool stored at (b) (4) to demonstrate stability of (b) (4) during the collection and short-term storage of DHS. They have not tested the stability of the DS for this product. However, since they do not store or hold the DS due to the (b) (4) nature of the manufacturing process for this product their approach is acceptable. Ferring performed additional stability studies on the DP, which are reviewed below.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The DP is a single dose of microbial suspension (150-170 mL - manufactured from donor human stool (DHS) in a 250 mL ethylene vinyl acetate (EVA) enema bag provided with tube set for rectal administration. The suspension consists of human fecal material resuspended in a PEG 3350/0.9% saline solution for cryoprotection, (b) (4), and packaged into the final container closure system (enema bag). The tubing for administration is packaged separately. The final drug product composition is (b) (4) DHS (active ingredient) and between (b) (4) of a (b) (4) PEG3350/0.9% saline solution. Based on the allowed variance in saline and PEG3350 content of the buffer, the maximum possible PEG3350 concentration in the buffer is (b) (4) and, therefore the maximum amount of PEG3350 per dose of DP is 5.97g.

3.2.P.2 Pharmaceutical Development

The pharmaceutical development document includes sections outlining the components, formulation, and critical quality attributes of the DP. Additionally, Ferring provided information on the development of the manufacturing process and assessment

of suitability of materials for the container closure system, including biological compatibility as well as chemical and physical assessments.

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The DS consists of donor human stool (DHS), which contains live microbial species, which are the active ingredient in the DP. The DS also contains PEG3350 and 0.9% sodium chloride irrigation. Donor stool is provided by donors who qualify for the donor program through routine testing using the screening protocols described above. Both the donors and all donated stools must pass all required donor screening tests prior to release of DP manufactured from each donation.

3.2.P.2.1.2 Excipients

The excipients in the DP include PEG3350 (b) (4) and 0.9% saline. All starting materials are (b) (4) grade and Ferring provided representative certificates of analysis in their submission. The purpose of PEG3350 is as a cryoprotectant to (b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The commercial product formulation has not changed between clinical and commercial formulations. Ferring reported that the only difference between clinical and commercial product is the change (b) (4)

3.2.P.2.2.2 Overages

Not applicable.

3.2.P.2.2.3 Physicochemical and Biological Properties

As previously stated, manufacture of this product is a (b) (4) process. Therefore, the composition and properties of the DS and DP are identical. To make the final DP, Ferring fills DS into the enema bags, which are then co-packaged with enema tubing to make the final DP. The final filled DP will have a target potency of $1.0 \times 10^8 - 5 \times 10^{10}$ CFU/mL on (b) (4), including (b) (4)

During process development, Ferring measured (b) (4) of the DP, but decided to discontinue this measurement, as they did not observe any differences between lots. Since we agree that this is not a critical quality attribute, the removal of this measurement is acceptable.

3.2.P.2.3 Manufacturing Process Development

Ferring chose parameters during clinical development with the goal of maximizing the total viable microorganisms in the final product. Therefore, process development studies primarily assessed the impact of storage and hold times and temperatures. From these studies, they determined that a (b) (4) initial hold time at (b) (4) did not impact the overall viability of the product. Ferring provided relevant stability data supporting this conclusion, which I reviewed in section 3.2.S.7.1 above.

Ferring did not significantly change their manufacturing process during product development. They listed the minor changes that they implemented during Phase 3 in Table 11 of section 3.2.P.2.3.2.1.

3.2.P.2.4 Container Closure System

The final container closure system for the product is a sterile 250 mL ethyl vinyl acetate (EVA) bag (purchased from (b) (4)), which was originally designed for use with blood or plasma. The DS is added to the EVA bag through the fill port, and subsequently sealed. The filled EVA bag is the final DP. Ferring then packages the EVA bag in an overwrap and labels it. The final packaged product includes the final product (RBX2660; filled EVA bag), the administration tube set, and instructions for use.

Ferring assessed multiple aspects of the container during product development prior to finalizing the container closure system for their final DP formulation. They assessed

(b) (4)

filled EVA bags with

(b) (4)

(b) (4)

Ferring submitted information on safety testing performed by the manufacturer of the EVA bags, including biocompatibility, chemical characterization testing, and physical property testing per (b) (4) protocols. These data were provided to Ferring by the EVA bag manufacturer, (b) (4), Item number (b) (4). (b) (4) performed a compliance review of the EVA bag on 01 June 2015 (b) (4) Product Compliance Report, (b) (4), 250 mL EVA Bag, Revision A). Ferring summarized the results of this information in both section 3.2.P.2.4.3 and document QR-519 (EVA Bag Biocompatibility Testing and Chemical Characterization). The data provided in these reports are summarized below. Ferring uses the EVA bag as supplied by (b) (4) without any modifications.

- Biocompatibility – Ferring submitted biocompatibility testing data for the EVA bags. The biocompatibility testing was performed for the bag manufacturer (b) (4) by (b) (4) per (b) (4) protocols. There were no signs of toxicity, irritation, inflammation, or cytotoxicity in tests performed, other than in the (b) (4), which showed slight irritation. (b) (4) also provided Ferring with an assessment of the EVA (b) (4) that is used to manufacture the EVA bags. The EVA (b) (4) that is used to manufacture the EVA bags passed Bacterial Endotoxin testing in accordance with (b) (4)
- Extractables – (b) (4) performed extractable studies on the sterile EVA bags for the EVA bag manufacturer (b) (4)

Ferring also includes an independently packaged administration tube set ((b) (4) Rectal Tube; (b) (4)) with the final DP. Ferring switched to this tube set after the manufacturer of their previous tube set discontinued

their product (b) (4). The rectal tube set is a single use, non-sterile assembly for delivery of DP from the EVA bag into the patient's rectum. One end of the tube set has a rounded end with one opening in the side wall of the tubing, which is inserted into the rectum. The other end contains a capped spike for puncturing the DP bag at the spike port. A clamp is included to allow/block flow of DP through the tubing.

Ferring assessed the administration tube set as a surface device with intact skin/mucosal membrane contact with a limited contact duration of less than or equal to 24-hours in accordance with FDA Guidance for Industry and Food and Drug Administration Staff, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation of testing within a risk management process" and ISO standard 10993-1:2018 (Biological Evaluation of Medical Devices). The applicant states that they expect DP administration to be completed within 5-10 minutes and that the maximum expected patient exposure to the rectal tubing is approximately 20 minutes. Ferring performed biocompatibility and chemical characterization testing (summarized in QR-344 Rev 001), to confirm that the (b) (4) Rectal Tube is a suitable replacement for component (b) (4).

- Biocompatibility (QR-564) – (b) (4) performed biocompatibility studies on the administration tubing set. Extracts from the tubing sets were tested for cytotoxicity, irritation, and sensitization via (b) (4) methods. No cytotoxic effects, dermal irritation, or sensitization responses were observed.
- Extractables (QR-568) – (b) (4) performed simulated extractable testing on (b) (4) Rectal tube set and compared to the (b) (4) tube set that was previously used with the DP. The spike port cap and clamp were excluded from testing as these components do not have patient/product contact. (b) (4) performed the extraction studies using the excipient/cryopreservative solution used in DS manufacturing as described above (PEG/saline). Extractions were performed at (b) (4). Extracts were assessed by analysis of volatile, semi-volatile, and non-volatile extractables utilizing (b) (4) and evaluated for the following compounds of concern:

(b) (4)



These specific compounds were chosen based on evaluation of the previous tubing (b) (4), which was discontinued by the supplier. Ferring did not provide the previous extractables study or the risk assessment associated with the change. Therefore, I sent them comments (IR#26) on 23 September 2022 to request this information. I provided the text of the IRs and my review of their response below.

Results – none of the compounds of concern were identified in extracts from either tube set at (b) (4).

- Leachables – Ferring did not provide leachable studies for either the EVA bag or the administration tubing. They need to either provide these studies or a justification for excluding them from the BLA. I sent a comment (IR#26) to Ferring on 23 September 2022 to request this information. I provided the text of the IRs and my review of their response below.

3.2.P.2.5 Microbiological Attributes

The product is non-sterile and consists of an uncharacterized microbial community. The applicant mitigates the risk of pathogen contamination in the product through the extensive donor screening/testing process outlined above, as well as control of facility, equipment, and changeover protocols between manufacturing runs/donors.

3.2.P.2.6 Compatibility

Compatibility of the EVA bag and the administration tubing is discussed above in the container closure section (3.2.P.2.4) of the pharmaceutical development document. Additionally, Ferring assessed compatibility of the DP with the final container closure as part of the overall stability studies, which I reviewed below in section 3.2.P.8.

Overall Reviewer’s Assessment of Section 3.2.P.2:

The extractables studies provided by Ferring for the EVA bags are acceptable, however they did not provide leachable studies or a justification for the lack of these studies. Although Ferring provided a simulated extractables study for the new (b) (4) Rectal tube set and discussed a previous study performed on the old (b) (4) tube set and a risk assessment performed for the change in tubing, these documents were not submitted to the BLA. Additionally, as with the EVA bags, Ferring has not performed leachables studies on the tubing and must either perform these studies or provide justification for their absence. I communicated these deficiencies to Ferring in IR#26 sent on 23 September 2022. The IRs are listed below followed by summaries of their responses and my review of their responses.

IR comment (IR#26) sent to Ferring on 23 September 2022:

- We note that you have not performed leachable studies on your EVA bag or the administration tubing set. Please submit a risk assessment and justification for the lack of leachable studies for both the EVA bag and (b) (4) administration tubing set.
- You did not provide a risk assessment of the original (b) (4) tube set in your BLA submission for our review. As noted in QR-568 Rev000 ((b) (4) Chemical Characterization Report), reduced chemical characterization testing was conducted as part of the protocol because you consider the (b) (4) Rectal Tube sets to be equivalent. Please submit the (b) (4) report QR-344 Rev 000 to the BLA along with a justification for why the (b) (4) risk assessment applies to the new (b) (4) tube set.

Ferring submitted an amendment (STN 125739/0.45) responding to the IRs on 19 October 2022 containing the requested file, QR-344 Rev 000. This file contains the original biocompatibility and extractables testing that (b) (4) performed for Ferring on the original (b) (4) rectal tubes. In this study, (b) (4) assessed extractable from the tube set in using (b) (4)

(b) (4) All identified compounds are listed in the appendices in file QR-344 Rev 000.

(b) (4) next performed a risk assessment based on the compounds that were identified in this extractables study according to (b) (4) guidelines. All of the chemical identified in the extractables study were assessed as part of this risk assessment. (b) (4) established a margin of safety for all of the chemicals based on tolerable intake levels for each and the amount of chemical that was extracted. For the purpose of this study, they assumed (b) (4) of the extracted chemical would be delivered. Based on this risk assessment, the majority of the extracted compounds were considered to be present at levels below those of concern. The following compounds (also listed above) were identified as potential compounds of concern that were identified in the extractables studies using (b) (4) (margin of safety less than (b) (4)).

(b) (4)

(b) (4)



As such, Ferring used this list of compounds to perform targeted extractables studies using the placebo formulation (PEG/saline) as the media for extraction. They performed these studies both on the old (b) (4) and new (b) (4) tube sets and did not detect the presence of any of these compounds (as discussed above in 3.2.P.2.4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

1. Rebiotix Inc
 - a. Address:
2660 Patton Road
Roseville, MN 55113
 - b. Registrations:
FEI: 3012047188
DUNS: 047695166
 - c. Responsibilities:
Manufacture, packaging, quality control testing (release and stability), quality release, and storage of DP.

3.2.P.3.2 Batch Formula

Ferring defines one batch of DP as an EVA bag filled with 150-170 mL of DS. Each batch is one dose of product. The final composition of the DP per dose is (b) (4) donor stool in a solution of PEG3350 (b) (4) and 0.9% saline. One lot of product can yield multiple batches depending on the size of the original stool donation(s).

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

The information provided for manufacturers and batch formula is acceptable. No additional information is required.

3.2.P.3.3 Description of Manufacturing Process

Filling – Ferring manufactures the DP by (b) (4) DS into the final container. Prior to (b) (4), they take samples for final release testing, which includes (b) (4) from the batch into the primary container closure (EVA bag) through the fill port and replace the fill tube cap. They then seal the fill tube

Packaging of administration tube sets – Ferring packages and ships the administration tube sets separately from DP bags. These tubes are stored at room temperature and should not be frozen.

Shipping – Ferring describes using a distributor for shipping of their product. They did not include sufficient information about these plans or provide a detailed description of their current shipping procedures in the original BLA submission.

- The applicant has provided this information in response to IRs sent on 18 May 2022 (IR#13). I have reviewed the applicant's response to these IRs and found them acceptable. I have reviewed the responses in detail below.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

The manufacturing information provided is acceptable. However, Ferring did not specify the maximum allowable time out of the freezer for their labeling process. Additionally, they did not provide adequate details about some of the shipping procedures. They need to clarify whether they plan to change their shipping procedures at the time of initial licensure and, if so, who that distributor will be and how the samples will be handled by that entity. They also need to clarify the DP and the administration tubing are packaged and shipped together. I sent Ferring IR comments on 18 May 2022 requesting clarification about their plans. The IRs are listed below followed by summaries of their responses and my review of their responses.

IR comments (IR#13) sent to Ferring on 18 May 2022

- *Please provide the following information related to your product manufacturing/labeling protocol in section 3.2.P.3.3 of your BLA:*
 - *In section 3.2.P.3.3.1.3, step ^(b)₍₄₎, please specify the maximum allowable time each bag can remain out of the freezer for the labeling process.*
 - *In section 3.2.P.3.3.1.5, you state that drug product and administration tube sets may be shipped to the distributor. Please provide additional details including information about potential distributors and how samples will be stored and handled by the distributor. If you have not identified a distributor to date, please indicate when you anticipate implementing this plan.*
 - *Please clarify whether the administration tubing and drug product are shipped together or if these can be ordered and shipped separately.*
 - *Please provide a picture(s) of the final packaging for both drug product and the accompanying administration tube set.*

Ferring submitted an amendment (STN 125739/0.22) responding to the IR comments on 15 June 2022.

Ferring stated that the maximum allowable time out of the freezer for labeling is (b) (4). They also provided the requested information about their shipping procedures and clarified that they will be shipping DP and tube set to (b) (4) for distribution to the end users. They (b) (4)

(b) (4) then ships the DP to end users using the same shipping methods developed by Ferring. Ferring provided a picture of the final packaging for both the DP and the administration tubing as requested in their shipping validation study, which includes details about the shipper and shipping methods as well as distributor activities. This information is in document QR-480 (Labeling, Secondary packaging, and Shipping PPQ protocols and reports (Section 3.2.R. image on page 66), which I review in in section 3.2.P.3.5 below.

The information provided on the questions of labeling, packaging, and shipping of both DP and the accompanying administration tubing set are acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Ferring states that they do not have any critical steps, intermediates, or controls in the manufacture of this DP.

Overall Reviewer's Assessment of Section 3.2.P.3.4:

The manufacturing process for DP involves filling EVA bags with DS. However, I do not agree that there are no critical steps or intermediates in the manufacturing process. The process of product quarantine while awaiting the results of donor testing is critical to the safety of the product and should be described in this section of the BLA submission. I sent Ferring an IR comment (IR#26) on 23 September 2022 to address this issue.

IR comment (IR#26) sent to Ferring on 23 September 2022:

We note that you have not provided information in section 3.2.P.3.4 "Controls of Critical Steps and Intermediates." We consider your product quarantine/release protocol to be a critical control step in the manufacture of your final DP. Please submit a description of your DP quarantine process and your procedures for quality release of lots to this section of the BLA. In your description please also include hyperlinks to all relevant documents in your BLA pertaining to quarantine and release of your DP.

Ferring submitted an amendment (STN125739/0.42) responding to this IR on 06 October 2022. In this amendment, Ferring outlines their quarantine and release program, including storage in designated "quarantine" freezer while awaiting the

of final donor testing results. They also provide information and links to corresponding documentation regarding the release process, which includes confirmation of all donor testing and release testing results. This response is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

Ferring used multiple product batches generated from individual donors for their PPQ (Process Performance Qualification) study. To evaluate allowable hold times, they staggered the hold times for the donated stool prior to initiation of the manufacturing process from (b) (4) as specified in their protocols. PPQ Batches (b) (4) were multi-dose batches. PPQ batches (b) (4) were (b) (4) prior to manufacturing to assess the effect of (b) (4) times of donor stool. Ferring (b) (4) these donations and manufactured them into (b) (4) separate doses as indicated below. All PPQ batches were stored at (b) (4) for the times indicated below.

- Lots tested

(b) (4)



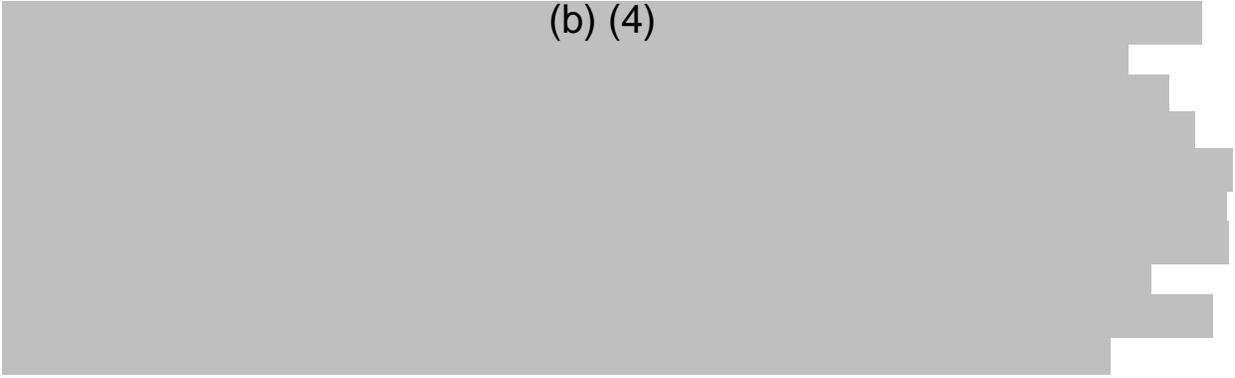
Ferring included (b) (4) sampling points in the study. For the (b) (4), they took samples from DS lots (b) (4) to the final container closure. (b) (4). For the (b) (4), they added DS to the final enema bag to generate DP, which they stored at -80°C for subsequent testing. Frozen storage is part of their manufacturing and storage plan for this product and therefore relevant to the process assessment. For the multidose batches, Ferring obtained (b) (4) sample sets; (b) (4)

The following variable parameters were assessed in the PPQ study (QR-527):

- (b) (4)
-
-
-

Results of the PPQ study (QR-527):

(b) (4)



Ferring also provided the Validation Report (QR-480) for the validation study they performed of their shipping procedures. They performed these studies (b) (4)



The initial shipping validation study (QR-480 Rev 000) failed due to (b) (4)



Overall Reviewer’s Assessment of Section 3.2.P.3.5:

I find the validation information that Ferring provided on both the manufacturing and shipping processes is acceptable. I have no outstanding issues related to these items. However, please refer to the DMPQ reviewer’s memo for review and assessment of shipping validation.

3.2.P.4 Control of Excipients

There are no additional excipients used in the manufacturing of DP.

Overall Reviewer’s Assessment of Section 3.2.P.4:

The manufacture of DP for this BLA does not include the use of any excipients, so this section is not applicable to this file.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Manufacturing of this product is a (b) (4) process from DS to DP. The DS is filled into EVA bags to generate final DP. Samples for release testing are taken from the (b) (4) prior to (b) (4).

The DP release specifications include:

1. Appearance – Ferring performed appearance testing by visual inspection of the final product. The acceptance criteria reflect the qualitative description of the physical state in accordance with (b) (4). They have not changed the appearance test through the clinical development phase. Ferring does not perform appearance testing on stability lots.
2. Bacteroides Species Growth – Ferring performs this test by (b) (4) DP (b) (4) *Bacteroides* (b) (4), with a requirement that at least (b) (4) *Bacteroides spp.* are detected after (b) (4) of product. Ferring asserts that *Bacteroides* are a component of a healthy microbiome, and depleted levels of *Bacteroides* have been associated with *Clostridioides difficile* infection in some individuals. They have not changed this acceptance criterion since clinical development.
3. Potency – Ferring determines the potency of the DP by (b) (4). They proposed an acceptance criterion for this assay of (b) (4) - 5.0×10^{10} CFU/mL. This proposed range differs from the acceptance criterion used for lots used in clinical trials and the PPQ lots, which was 1.0×10^8 - 5.0×10^{10} CFU/mL. Ferring justifies this change, indicating that the

new criterion is based on the viability results for clinical batches, statistical evaluation of batch data from long-term frozen storage conditions and refrigerated conditions. This change is not acceptable. Because they did not use DP with a potency below 1×10^8 CFU/mL at release in their clinical studies, we do not have efficacy data supporting the use of the DP in this range. We sent IRs to Ferring regarding these concerns (IR#13 sent 18 May 2022), which are outlined in detail at the end of this section. After these discussions, Ferring agreed to restore the acceptance criterion to the original range of $1.0 \times 10^8 - 5.0 \times 10^{10}$ CFU/mL as this is the range that was tested in their phase 3 clinical trial.

4. Diversity – Ferring asserts that microbial diversity is an important component of FMT based products. As a surrogate marker for overall diversity, they assess DP for the presence of (b) (4). Each product batch must have a minimum of (b) (4) present for release. This acceptance criterion has not changed since clinical development.

Overall Reviewer’s Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

The DP release specification listed in the BLA documentation (section 3.2.P.5.1, table 1) is not acceptable. Ferring has lowered the bottom end of the allowable range of potency to a level not tested in their clinical trials.

IR comment for Ferring (sent in IR#13) sent on 18 May 2022:

We do not agree with your currently proposed acceptance criterion range for potency release specifications for final DP. In section 3.2.P.5.1, table 1, we note that you have lowered your release specification to match the potency specification. We refer you to our responses to your preBLA meeting request dated 06 October 2020, where we requested that you change the stability specification to match the release specification. The minimum potency allowed for product release during your clinical trials was 1.0×10^8 CFU/mL. Therefore, you do not have data indicating that product released at a lower level, (b) (4) CFU/mL, is effective in the treatment of recurrent CDI. Your stability data indicate some loss over time, particularly for samples stored short term at refrigerated conditions. Release of product at this lowered concentration could lead to shipment and use of product that is no longer considered potent based on clinical experience. Please adjust the potency release specification for final DP back to $1.0 \times 10^8 - 5.0 \times 10^{10}$ CFU/mL, the range indicated in your preBLA package and supported by the specifications of product released and used in your clinical trials. Additionally, please provide an analysis on the efficacy of product at different points within your potency range to ensure that the final specification for potency reflects a range where product has been observed to be effective in preventing CDI recurrence.

Ferring submitted an amendment (STN 125739/0.22) responding to the IR on 15 June 2022. They indicated in their response that there was confusion over the potency acceptance criterion, in part due to previous comments from CBER. The final potency acceptance criterion for product release is 1×10^8 - 5×10^{10} CFU/mL and for product stability is (b) (4) - 5×10^{10} CFU/mL. The different acceptance criteria ranges for release and product stability is supported by data from lots used in the phase 3 clinical trial. These criteria are acceptable; however, the applicant needs to ensure the dossier contains the appropriate acceptance criteria for release and stability.

Additional IR comment sent to Ferring in IR#20 on 8 August 2022:
We agree with the justification and data you provided to support setting different acceptance criteria for potency for product release (1×10^8 and 5×10^{10} CFU/mL) and stability (b) (4) and 5×10^{10} CFU/mL). Please ensure that you correct all references to these two values throughout the BLA documentation for consistency. Note that these release criteria may need to be adjusted based on the results of your ongoing assay validation.

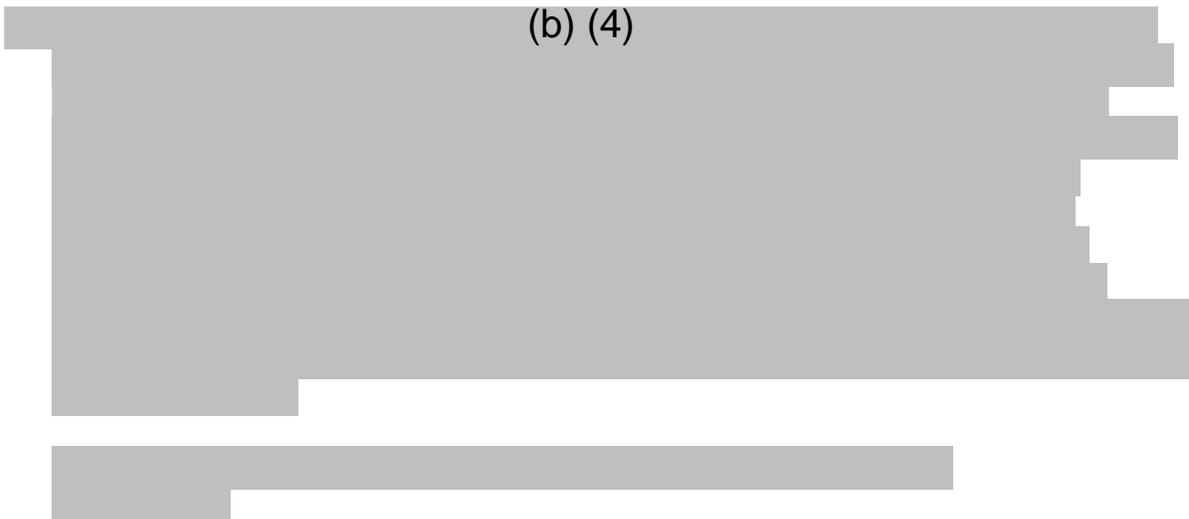
Ferring submitted an amendment (STN 125739/0.34) responding to the IR comment in IR#20 on 22 August 2022. They acknowledged this IR and revised modules 3.2.P.2, 3.2.P.5.1, 3.2.P.5.4, and 3.2.P.5.6 to reflect the correct acceptance criteria for potency for product release and stability.

Ferring has addressed all CMC related concerns related to their release specifications.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Analytical Procedures

(b) (4)



8 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.5.4 Batch Analyses

Ferring provided a list of all product batches used in their clinical studies and included the batch number, manufacture date, and release specification results. They also provided a list of batches that failed to meet specifications and the reasons for these failures. In total, 27 batches (out of (b) (4) total batches manufactured) failed to meet specifications, mainly due to low potency numbers and a lack of *Bacteroides* growth.

3.2.P.5.5 Characterization of Impurities

Ferring performed characterization of potential impurities in the product at earlier stages in product manufacturing, primarily through donor screening for potential pathogens. They also provided additional studies assessing residual solvents in the product excipients in the DS manufacturing section I reviewed above.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

The information provided in these sections is acceptable. While Ferring provided batch information for many DP batches, they did not indicate the total number of batches manufactured to support their phase 3 clinical trial.

IR comment (IR#13) sent to Ferring on 18 May 2022:

We acknowledge receipt of batch report information for all DP lots manufactured during the clinical trials provided in section 3.2.P.5.4. In addition to the tables provided (Tables 1.9, section 3.2.P.5.4), please indicate the number of batches you have manufactured to date. While you have already included those lots that failed release testing, please also include those lots that were destroyed due to donor positivity or other donor testing issues. Please indicate what percentage of overall donations resulted in generation of final released product lots during your phase 3 clinical trial.

Ferring submitted their response to this IR on 15 June 2022 in an amendment (STN 125739/0.22). In this amendment, they indicated that they manufactured a total of (b) (4) batches of DP as of 29 April 2022 and specified that (b) (4) % of the total stool donations they received during their phase 3 clinical trial period (6 June 2016 through 8 June 2019) resulted in generation of final released DP.

During this time, they collected a total of (b) (4) stool donations and manufactured (b) (4) lots of DP. Of those DP lots, they released (b) (4) lots for use in the phase 3 trial. Ferring provided a document (Appendix 3:drug-product-lots-manufactured-ir-13.pdf) that lists all (b) (4) batches and the reason for failure of (b) (4) lots. The applicant has addressed our questions in this response. The information provided is acceptable.

3.2.P.6 Reference Standards or Materials

No reference standards have been created for use in the analysis of the DP.

3.2.P.7 Container Closure System

The final container closure system for the product is a sterile ethyl vinyl acetate (EVA) bag, which was custom designed by (b) (4) for Ferring. Ferring uses the EVA bag as supplied by the manufacturer (b) (4) without any modifications. The applicant wraps the filled EVA bag in an overwrap and labels it for delivery as the final DP. Ferring also provides an independently packaged administration tube set, (b) (4) Rectal Tube (b) (4) along with the DP. This tubing is designed for rectal administration of fluids. The end of the tubing that is inserted into the rectum is rounded with one opening in the sidewall of the tubing. The other end of the tubing contains a capped spike for puncturing the DP bag at the spike port. A clamp is included to allow/block flow of DP through the tubing. The final packaged product shipped includes the final product (RBX2660; filled EVA bag), the administration tube set, and instructions for use.

Ferring submitted biocompatibility and extractables data on the EVA bags, which was provided to them by the manufacturer of the bags (QR-519 “EVA Bag Biocompatibility Testing and Chemical Characterization”). Additionally, the applicant performed biocompatibility (QR-564) and extractables (QR- 568) studies on the rectal tube set that they provide with the product. I have reviewed these studies in the pharmaceutical development section above (3.2.P.3.5).

Overall Reviewer’s Assessment of Section 3.2.P.7:

The container closure system for this product is acceptable. The applicant has demonstrated that the bags withstand freezing and maintain product viability.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Ferring provided data from stability studies they conducted to support frozen storage (-60°C to -90°C) of the final drug product for the 36-month expiration date. They also provided stability data to support thawing of the product under refrigerated conditions (2°C to 8°C) for 24 hours followed by storage of the thawed product for an additional 4 days under refrigerated conditions (2°C to 8°C) prior to use. The lots used in the stability studies and the storage conditions and timepoints for the stability studies are provided in Table 1 from section 3.2.P.8.1.1 and are described in more detail below.

Long-term Stability – Frozen Conditions (-60°C to -90°C)

Ferring tested long-term frozen storage stability on (b) (4) batches of DP ((b) (4)) as well as on (b) (4) PPQ batches ((b) (4)). They performed DP stability studies on product stored in both DP EVA bag (b) (4) , while the PPQ samples were stored in (b) (4) . These were tested 0, 3, 6, 9, 12, 18, 24, and 36 months. They provided data demonstrating DP frozen lot stability through the 36 months. Similarly, PPQ lots remained within specifications for the full (b) (4) time course assessed.

Short-term Stability – Refrigerated Conditions (2°C to 8°C)

Ferring performed a short-term stability study under refrigerated conditions using batches of product that were previously stored under frozen conditions. They initially tested (b) (4) batches ((b) (4)). Each was assessed at 0, 24, and (b) (4) hours of storage in refrigerated conditions (2°C to 8°C). All (b) (4) lots were manufactured from stool donated by a (b) (4) . These lots continued to meet all release specifications at each time point tested. They performed a second stability study under refrigerated conditions, this time measuring product stability at 0, 72, and (b) (4) hours in refrigerated storage. The (b) (4) lots ((b) (4)) tested in this study were derived from (b) (4) independent donors. One of these lots, (b) (4) , exhibited significant loss in viability at 72 and (b) (4) hours, although the final numbers were still within the current specifications for product release.

Long-term Stability – Refrigerated Conditions (2°C to 8°C)

Ferring performed an additional study looking at longer term refrigerated storage in (b) (4) product lots manufactured from stool from (b) (4) individual donors. For this study, Ferring tested lots for potency at 0, 96, (b) (4) , and (b) (4) hours of storage in refrigerated conditions (2°C to 8°C). As before, all lots remained within release specifications throughout this time course, though some viability loss was evident in these lots. Ferring has proposed labeling that allows for product to be thawed/stored under refrigerated conditions for up to (b) (4) days ((b) (4) hours). The provided data indicate that all product tested remained within specification during this time frame, however there was significant loss of viability reported, up to (b) (4) -fold reduction in viable counts for some lots. There is the potential for lots initially at lower potency to fall out of specification during this storage period. I did not consider this data to be supportive of the hold times Ferring proposed and requested that they perform additional stability studies to support this 4°C hold prior to product administration in an IR (IR#13) sent on 18 May 2022. Ferring submitted additional data in an amendment (STN125739/0.26) on 01 July 2022 to support these hold times. These IRs and responses are reviewed in detail at the end of this section. In conclusion, Ferring provided stability data supporting a 24-hour thaw at 2-8°C followed by storage for up to an additional four days at 2-8°C.

Ferring indicated that they performed a stability study looking at product potency during (b) (4) storage for (b) (4) . They performed this study on (b) (4) lots of product ((b) (4)). The results from this

study indicate

(b) (4)

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Ferring plans to continue testing stability of the validation batches through the expiration period (24 months) in accordance with their post-approval stability protocol discussed above. Ferring submitted a plan to store DP at -60°C to -90°C in the primary container closure intended for commercial use (250 mL EVA bag) (b) (4) for QC testing. The applicant will use product in EVA bags for stability testing at 0, 12, and 24 months (b) (4).

These plans are unacceptable as all stability studies must be performed in the final container closure for the product, in this case, the EVA bags. I reported these concerns to Ferring in an IR. In response, they revised their stability plans to only include samples in the EVA bags. The IR and response are reviewed below.

Ferring stated that they will determine the number of batches to be put on stability testing annually as determined by ICH guidelines and the number of donors in the program. To achieve this, they plan to enter (b) (4) batches per year or batches from (b) (4) % of all donors, whichever is greater. During the first year of production, the applicant indicates that they expect to have (b) (4) active donors and, therefore, would put (b) (4) batches into the stability program. I asked Ferring to provide additional information and justification for the plans for the number of lots to go on long term stability. Based on their response, I agreed with their proposal to place (b) (4) lots per year on stability, (b) (4) per (b) (4), selected (b) (4). They will select different donors for the stability lots each (b) (4). The IR and applicant's response are reviewed below.

Overall Reviewer's Assessment of Section 3.2.P.8:

Ferring provided stability data to support storage of the final DP at -80°C with an expiry of 36 months. However, I identified deficiencies in their stability data and plans to support short-term storage under refrigerated conditions. Specifically, the stability data did not support short term storage at 4°C storage as significant variability was observed in overall stability during this storage condition. Additional stability studies were required to support this storage condition. Ferring also proposed to allow (b) (4) thawing of product prior to use and provided stability data for long term (b) (4) storage, but they did

not provide data for the proposed use and (b) (4) thawing was not allowed in the clinical trial. Therefore, based on the current data, I requested that Ferring remove reference to (b) (4) thawing and submit additional data to support this proposal after BLA approval. For their post-marketing stability plan, Ferring proposed to store some stability samples in (b) (4) but the (b) (4) were not representative of drug product storage in enema bags. Therefore, I asked them to remove (b) (4) storage of samples from their stability plan. Finally, Ferring only proposed placing (b) (4) DP lots per (b) (4) in their (b) (4) stability plan. Given the inherent variability of this product, (b) (4) DP lots were not sufficient, so I asked them to revise their stability plan. I issued IR comments regarding these deficiencies. The IRs are detailed below.

IR comments (IR#13) sent on 18 May 2022:

Regarding your proposed storage and thawing conditions provided in your instructions for use (provided in section 1.14.1.3) and suspension bag carton label (provided in section 1.14.1.1), we do not agree with your plan to allow thawing at (b) (4), since this was not done as part of your phase 3 clinical trial protocol. Additionally, we do not agree that the data you have provided in section 3.2.P.8.1.3 tables 6-11 and section 3.2.P.8.3.2 tables 12-13 support stability of your product under refrigerated conditions for (b) (4) days after thawing are adequate. We have the following comments regarding these items:

- a. *Based on the data provided in section 3.2.P.8.1.3 (tables 6-11) and section 3.2.P.8.3.2 (tables 12-13), we recommend not allowing any refrigerated storage post thaw prior to use of product. We note significant loss of viability in multiple lots of product when stored under refrigerated conditions. Since the lots tested were at a relatively high overall concentration initially (i.e., (b) (4)), some of these remained within specification despite losing (b) (4)-fold total viable counts. Based on these data, the potential exists for lots starting at lower initial concentrations to fall out of specification during this storage period. Please either remove the allowable refrigerated storage conditions post thaw from -80C or provide the following information to support storage under these conditions:*
 - i. *The maximum time allowed for refrigerated storage in your phase 3 clinical trial.*
 - ii. *An additional stability study assessing product viability when stored for shorter time periods (i.e., immediately after 24 hour thawing and at shorter intervals post thaw) to determine whether refrigerated storage for shorter times could be acceptable.*
- b. *Since (b) (4) thawing and storage was not performed as part of your phase 3 clinical trial, adding this method of thawing sample prior to use will require defining specific allowable hold times and protocols and performing a study assessing product stability during this process. The*

stability data provided in Section 3.2.P.8.1.4 are not sufficient to support this change. We note that your (b) (4) storage stability study (Section 3.2.P.8.1.4) was performed with samples stored in (b) (4). This is not acceptable. Additionally, the only timepoint tested in the study was (b) (4), while your proposed instructions for use only allow storage at (b) (4) "until thawed." Given the temperature of storage and the time lapse between allowable use and the stability time points tested, we are concerned that initial viability loss is masked by subsequent growth of some bacterial strains in the product. Please revise your instructions for use to specify thawing and storage only at refrigerated conditions.

- c. If you wish to pursue a (b) (4) method of thawing, you may submit a Prior Approval Supplement (PAS) after approval of your BLA. In support of your PAS, you will need to design and perform a stability study assessing (b) (4) storage with DP in the final container closure system and at the intended storage conditions to determine a maximum allowable hold time at (b) (4) for thawing prior to administration. This hold time would need to be included in your instructions for use and product label. The study should be designed to not only detect loss of potency of the product, but to also detect any bacterial growth that may occur at this temperature during the hold time. We recommend that you submit your study plans for our review and comment prior to initiating the study.

We have the following comments regarding your proposed post-marketing stability plan (Section 3.2.P.8.2):

- a. We do not agree with your plan to store some samples in (b) (4). CFR 211.166 (a)(4), states that stability testing should include "Testing of the drug product in the same container closure system as that in which the drug product is marketed." Please adjust your stability plans to include only samples stored in final container closure system (EVA bags).
- b. Regarding the number of lots to be put into the stability program annually, please propose a percentage of the total lots manufactured, not of the total number of donors enrolled at a given time. In your justification, include a statistical analysis demonstrating how the proposed numbers will provide representative data across all of the anticipated lots annually. Additionally, please indicate how the lots to be placed into the stability program will be chosen.

Ferring submitted an amendment (STN 125739/0.22) responding to these IR comments on 15 June 2022. Regarding the request for additional information on the (b) (4) thawing of product, the applicant has indicated that they plan to remove (b) (4) thawing from all packaging material and instruction and will indicate that only thawing at 4°C is acceptable for their product. This change is acceptable and eliminates the need for additional stability studies performed at (b) (4).

Regarding the 2-8°C stability study that I requested, Ferring performed this study, and submitted data from the study in an amendment (STN 125739/.026), submitted 01 July 2022. In the amendment, Ferring provided data demonstrating stability of product at 2-8°C including after a 24-hour thaw period and then at 30, 48, 54, 72, 78, 96, (b) (4) hours of total time at 2-8°C (including the initial 24 hours). They performed this testing on a total of (b) (4) batches of product. All batches met specifications for potency within the acceptance criteria ((b) (4) – 5x10¹⁰ CFU/mL) through the (b) (4)-hour time point. Ferring also indicated in this amendment that the maximum hold time for lots tested in their clinical trial was 4 days. For this reason, they have set the maximum hold time to 4 days (including the initial thaw period). This hold time is supported by the stability data they have provided and is acceptable. Ferring needs to submit these data to the proper location in the BLA (it is currently submitted at a response to IR only) and they also need to update all documentation to include this new maximum hold time, which they have committed to do as part of the labeling discussions.

The following comment was sent to the applicant as part of IR#20 on 8 August 2022:

We acknowledge the additional stability data you provided to support product storage at 4°C for up to four days post 24-hour thaw. Please update your BLA accordingly. The stability study and all data provided in your responses in amendment 26 should be added to section 3.2.P.8, and all documentation should be updated to reflect the change in storage recommendations.

Ferring responded to this IR on 22 August 2022 in an amendment (STN 125739/0.34). They submitted a revised Module 3.2.P.8.1 to include this updated stability data and to reflect the revised product storage information. In addition, they proposed updating the product labeling accordingly during labeling negotiations. These changes are acceptable.

Regarding their routine annual stability (post-licensure) studies, Ferring agreed to perform these studies on DP packaged in the final container closure system (enema bags) and they eliminated the use of product stored in (b) (4) from their stability plans. This change is acceptable. They also proposed putting (b) (4) of DP on stability per (b) (4) ((b) (4) per year). These lots will be (b) (4) chosen from lots with sufficient material for all stability timepoints planned. The DP stability lots will be stored at -80°C. The lots will be removed from -80°C storage then thawed at 2-8 C for 24 hours prior to performing stability testing. The lots will be tested after 0, 3, 6, 9, 12, 18, 24, and 36 months for potency, the presence of *Bacterioides* species, and diversity. This plan is acceptable, and we have no further comments on their annual stability protocol post-licensure.

The applicant has addressed all CMC concerns regarding their stability data and plans.

3.2.R Regional Information (USA)

□ Executed Batch Records

Ferring has provided three executed batch records, however they have not provided a blank master batch record document. We have requested that they submit this document in IR#29 sent on 12 October 2022. Ferring submitted the requested document in STN 125739/0.45 on 19 October 2022.

□ Combination Products

Ferring supplies the REBYOTA final drug product in an EVA bag. The enema bag is custom made for Ferring by (b) (4) and does not have an associated regulatory status. As the enema bag is pre-filled with the drug product, CBER classified this product as a CP3 combination product. Ferring provided a CoA from the supplier which states that the supplier complies with the device GMP regulations at 21 CFR part 820. Ferring has also provided additional information in response to the IRs indicated below (IR#31 sent on 21 October 2022) demonstrating that they do comply with the necessary device GMP regulations.

In addition to the filled final DP, Ferring provides a rectal administration set that is composed of tubing, capped spike, and clamp. Ferring purchases the tubing etc. from a supplier ((b) (4) Rectal Tube; (b) (4)). The tubing set is put together and packaged as a unit for Ferring by the supplier. Since this is a custom tubing set, we do not consider it to be 510(k) exempt and it does not have an associated regulatory status. Ferring has also provided additional information in response to the IRs indicated below (IR#31 sent on 21 October 2022) demonstrating that they do comply with the necessary device GMP regulations. Andrea Gray, Ph.D. (CBER/ORO/DROP/RPB) provided assistance in review of the device constituents (EVA bag and rectal tubing set) for this product.

I sent the following comments to the applicant in IR#31 on 21 October 2022:

1. *You indicate that (b) (4) manufactures the EVA bags that you fill with final drug product. The Certificate of Analyses that you provided for the EVA bags indicate that (b) (4) is FDA registered but do not specify the regulatory status for the bags. Please provide the regulatory status (e.g., 510(k) clearance number) for the bag.*
2. *Please provide information on the regulatory status of the tubing used in the enema kit. Specifically, please indicate the device classification of the tubing (i.e., Class I or Class II) and provide a citation to the appropriate regulation or a 510(k) clearance number.*
3. *Your product is biologic-device combination product. Please note that CGMP requirements that apply to each constituent part apply to the combination product they constitute. Please provide a complete summary of how you have satisfied the applicable CGMP requirements of the device constituent parts. For more information regarding application of CGMP requirements to combination*

products, please refer to the 2017 FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products
(<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>).

Ferring responded to these IRs in an amendment (STN 125739/0.47) on 28 October 2022. In their response, Ferring explained (b) (4) custom manufactures the EVA bag and the rectal tubing administration set utilizing off the shelf components. Therefore, neither the bag nor the administration set have an associated regulatory status. In their response to IR #3, Ferring proposed that the EVA bag and the tubing set resembled an enema kit as defined in the device regulations at 21 CFR 876.5210 but acknowledged the bag and tubing are not intended to evacuate the bowels as specified in the regulation. Ferring indicated that enema kits are Class 1 devices are 510(k) exempt and exempt from the device GMP regulations. Ferring further indicated that the intended use of the EVA bag is not different from the intended use of other legally marketed similar devices and thus also considers the bag a Class 1 device. Ferring agreed that as the EVA bag contains the final drug product, the product is a combination product under 21 CFR Part 4.4, and the GMP regulations for drugs (21 CFR part 211) and devices (21 CFR part 820) both apply.

Ferring explained that their Quality Management System (QMS) is structured to align with FDA's CGMP's for drugs (21 CFR parts 210 and 211) and biologics (21 CFR parts 600, 601, 610). Additionally, Ferring has incorporated specific provisions of the device CGMP's into the QMS including Management Responsibility (820.20), Design Control (820.30), Purchasing Controls (820.50) and Corrective and Preventative Actions (820.100). Ferring uses the drug CGMP-based streamlined approach in their QMS. The complete CGMP operating system is outlined in their Quality Manual (SOP 4000) and in specific procedures.

Ferring controlled the design of the EVA bag throughout the Pharmaceutical Development process (Section 3.2.P.2) as the primary container/closure. Refer to the Pharmaceutical Development and Container/Closure sections of this memo for details on all studies performed to support design and use of the EVA bag. Ferring also established design controls for the rectal tubing set. Design control elements for the rectal tube administration set included the elements required under the regulations: design plan, design input, design output, design verification, design validation, design review, design transfer, design change and a design history file. Ferring delegated design, production, and development activities for the rectal tubing set to their contract manufacturer, (b) (4). Ferring and (b) (4) both maintain design elements to comprise a complete design history file. Ferring submitted their SOP 7328 with Design Control elements. Ferring provided development aspects of the EVA bag in a Pharmaceutical Development report. Ferring explained that the design control elements applicable to the EVA bag in conjunction with the tubing set include the design plan, design input, design output, and design verification. Design and production activities for the bag are

maintained by (b) (4). Ferring has a written agreement with (b) (4) including management of design changes and the device history file.

I sent one additional IR to Ferring to clarify our position on the regulatory status of the administration tube set (IR#34 sent on 1 November 2022).

In our teleconference on October 25, 2022, we stated that it appeared reasonable to conclude that the administration set (tubing with pinch clamp and spike) of your delivery system is within the limits of GMP-exemption stated in 21 CFR 876.5210 Enema Kits. However, based on further internal discussion with the Center for Devices and Radiological Health (CDRH), we determined that both the bag and tubing set exceed the limits of GMP-exemption stated in 21 CFR 876.5210 Enema Kits. While the tubing set is used for instillation of the bag contents into the rectum as described in the regulation, the intended use is not “to promote evacuation of the contents of the lower colon”, and the different questions of safety and effectiveness include biologic/device compatibility (as with the bag). Therefore, we consider GMPs to be required for both the bag and the tubing set. Based on the October 25, 2022 teleconference discussion and your response dated October 28, 2022 to Comment 4 of our Information Request dated October 21, 2022, it appears your quality management system already addresses the relevant device GMPs, and that you apply them to both the bag and tubing. Please acknowledge our determination of the regulatory classification of the tubing set stated above.

Ferring acknowledged this position in an amendment (STN 125739/0.50) submitted on 03 November 2022. No additional deficiencies were identified. The information Ferring provided on the device constituents of the combination product is acceptable.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

In section 1.12.14, Ferring claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR part 25.31 (c). Ferring states that is appropriate as the active moiety for this product is fecal microbiota from human donor stool. Since stool is naturally occurring in the environment, the product does not significantly alter the concentration or distribution of the active moiety in the environment. I agree with this assessment.

B. Reference Product Designation Request

Rebiotix has requested product exclusivity for REBYOTA on 30 November 2021. They assert that the product is a first-in-class product with no similar product previously licensed by FDA. I agree that this product should receive exclusivity as requested and

have completed the T846.02: Reference Product Exclusivity Period Determination Review.

C. Labeling Review

Full Prescribing Information (PI):

I identified the following deficiencies in the draft Prescribing Information (PI) (submitted in STN 125739/0.12 on 07 March 2022) that Ferring submitted:

- a. Ferring refers to their product as a “microbiota suspension.” For clarity regarding the source material for the product, Ferring needs to change this to “fecal microbiota suspension” throughout the document.
- b. Dosage Forms and Strengths: Ferring has listed the strength of the product as (b) (4) colony forming units (CFU).” This is not an accurate representation of the strength of the product, which has an upper and lower limit for potential potency on release. The applicant must change this to read “ $1 \times 10^8 - 5 \times 10^{10}$ colony forming units (CFU) / mL.
- c. Description (11): The information that Ferring included this section is insufficient. We have updated this section to include the following information (per CFR 210.57: Proprietary name, Nonproprietary name, Type of dosage form, route of administration, ingredient information and source material.
- d. How supplied/storage and handling: The strength of the product is indicated incorrectly in this section as in the Dosage forms and Strength section. This should be updated here as well. They have not provided an additional NDC number for the administrative tubing set. The storage section needs to be updated. Ferring performed additional stability studies after the original submission, which have changed their recommendations for storage post thawing from (b) (4) days at 2°C to 8°C (36°F to 46°F) to 4 days under this condition. The applicant also must remove references to (b) (4) thawing as they have not used this method in their clinical trials and have not provided any data supporting this method of thawing the product.

Carton and Container Label:

I have reviewed the product information in the current versions of the Carton labels and found it to be incorrect. I have identified similar issues to those indicated in my review of the prescribing information above. Ferring will need to update the dose strength, the product name, and the storage and use instructions. Additionally, Ferring should indicate that the two cartons (drug product and administration tubing) must be provided together.

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Clostridioides difficile diagnostic tools were used to identify subjects for enrollment and also to identify study failures (i.e. recurrence of *C. difficile* infection). With input from the agency during phase 2 and 3 clinical trials, Ferring adopted a two-step diagnostic algorithm to reduce false positive test results. The applicant's algorithm consisted of and Enzyme Immunoassay (EIA) targeting a *C. difficile* specific antigen (GDH) and the *C. difficile* toxin. Any individual testing positive for both antigens was considered a positive infection, while those with negative results for both antigens are considered to be *C. difficile* negative. Those exhibiting discordant results (i.e. GDH⁺, toxin⁻, or GDH⁻, toxin⁺) were also tested for toxin by PCR. Ferring called samples that were PCR positive for toxin following discordant EIA results as positive for *C. difficile* infection/recurrence. This diagnostic algorithm is consistent with current clinical recommendations for *C. difficile* clinical diagnostics. No validation of methods was required for these studies as both EIA and PCR tests for *C. difficile* are FDA cleared diagnostic assays that are commercially available, and testing was performed by accredited clinical microbiology laboratories.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

The assays used in this study are FDA cleared, commercially available diagnostics being used for their intended purpose. Additional validation is not required.