

**CBER DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125739/0**

**RBX2660 (Fecal Microbiota, Live – jsIm); REBYOTA**

**Miriam Ngundi, Reviewer, MRB1/DMPQ**

1. **BLA#:** STN 125739/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Ferring Pharmaceuticals, Inc. License #: 2112. The BLA was originally submitted by Rebiotix, Inc.; however, Ferring Pharmaceuticals, Inc. took ownership of the product on September 23, 2022. Due to the applicant ownership change in the BLA cycle, the review memo will note Rebiotix or Ferring.

3. **PRODUCT NAME/PRODUCT TYPE**

REBYOTA; RBX2660 (Fecal Microbiota, Live – jsIm)

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

a. **Pharmacological category:** Fecal Microbiota Transplantation

b. **Dose form:** Suspension

c. **Strength/Potency:** (b) (4) CFU per 150 mL

d. **Route of administration:** Rectal

e. **Indication(s):** Reduce the recurrence of *Clostridioides difficile* (*C. difficile*) infection in adults following antibiotic treatment for recurrent *C. difficile* infection.

5. **MAJOR MILESTONES**

Filing meeting: January 13, 2022

Facility inspection: May 02-06, 2022

PDUFA action date: November 30, 2022

6. **DMPQ CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Miriam Ngundi, CSO OCBQ/DMPQ/MRBI	Drug substance (DS), drug product (DP), and facilities (3.2.S, 3.2.P, and 3.2.A.1)

7. **INTER-CENTER CONSULTS REQUESTED**

None

8. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
05/03/2021	STN 125739/0	Pre-submission to rolling submission – part 1 of 3
07/01/2021	STN 125739/0.1	Pre-submission to rolling submission – part 2 of 3
10/06/2021	STN 125739/0.3	Response to Information Request #1
11/30/2021	STN 125739/0.4	Pre-submission to rolling submission – part 3 of 3
01/25/2022	STN 125739/0.11	Response to Information Request #5
03/07/2022	STN 125739/0.12	Response to Information Request #6
04/21/2022	STN 125739/0.15	Response to Records Request
05/16/2022	STN 125739/0.18	Response to Information Request #10
11/07/2022	STN 125739/0.54	Response to Information Request #37

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB-MF (b) (4)	(b) (4)	Rebiotix, Inc. uses bags provided by (b) (4) that have been fabricated from (b) (4).	Yes	(b) (4) provides toxicology reports in their MF, evaluation deferred to Office of Vaccines Research and Review (OVR). No review required by DMPQ

## 10. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

Rebiotix, Inc. (hereafter referred to as Rebiotix or the sponsor) submitted a three-portion rolling Biologics License Application (BLA) for REBYOTA under STN125739/0 on May 3, 2021, July 1, 2021, and November 30, 2021. During the review of the BLA, Rebiotix transferred the ownership of the product to Ferring Pharmaceuticals Inc. (referred to as Ferring) on September 23, 2022. REBYOTA is a fecal microbiota transplantation (FMT) frozen suspension consisting of donor human stool (the drug substance, DS) and an excipient solution made of Polyethylene Glycol 3350 (PEG) and 0.9% sodium chloride (saline). The DS formulated with PEG/Saline solution is filled into the final container, a 250 mL ethylene vinyl acetate (EVA) bag closure with a spike port and a fill port, to make the drug product (DP). The DP is supplied with an administration tube set (unattached to the EVA bag) consisting of a rectal tube, a clamp, and a spike port adapter positioned at one end of the rectal tube. REBYOTA is proposed to be marketed as a prescription product to reduce the recurrence of *C. difficile* infection (CDI) in adults following antibiotic treatment for recurrent CDI.

Manufacture of REBYOTA consists of the following process steps:

- Collection of donor human stool (DHS)
- Testing of DHS
- Formulation and mixing of DHS with PEG/saline solution
- Transfer of DS into EVA bag
- Sealing container closure and visual inspection of DP EVA bag

The following facilities support the manufacture of REBYOTA:

- Rebiotix, Inc. (collection of DHS, donor blood and nasopharyngeal swabs samples, and manufacture of drug substance and drug product)

- (b) (4) (testing of donor stool and blood for pathogens, and nasopharyngeal swabs for SARS-CoV-2)
- (b) (4) (testing of (b) (4) excipients)

All manufacturing sites are new establishments to the application. DMPQ requested records for review of the manufacturing site, according to FD&C 704(a)(4), in advance of a pre-license inspection (PLI). Items identified to be of concern during the manufacturing site's record review were followed up during the on-site PLI (see Compliance Management System (CMS) Work # 453728 and also in CBER Connect - uploaded November 03, 2022). DMPQ performed the PLI on May 02-06, 2022, which resulted in a No Action Indicated. All manufacturing steps to produce REBYOTA have been validated and the overall control strategy appears acceptable to assure consistent manufacture of quality product.

## **B. RECOMMENDATION**

### **I. APPROVAL**

Based on information provided in this application, we recommend the approval of REBYOTA which is manufactured at Rebiotix, Inc. Roseville, MN.

### **II. COMPLETE RESPONSE (CR)**

N/A

### **III. SIGNATURE BLOCK**

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Miriam Ngundi, CSO, DMPQ/MRB1	Concur	
Kathleen Jones, Biologist, DMPQ/MRB1	Concur	
CDR Donald Ertel, Branch Chief, DMPQ/MRB3	Concur	
Lori Peters, Branch Chief, DMPQ/MRB1	Concur	
Carolyn Renshaw, Director, DMPQ	Concur	

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### **3.2.S Drug Substance**

#### **3.2.S.2 Manufacture**

##### **3.2.S.2.1 Manufacturer(s)**

The manufacturers that support the production of REBYOTA and the associated responsibilities are as follows.

- Rebiotix, Inc., 2660 Patton Road, Roseville, MN, USA. FEI # 3012047188
  - Collection, inspection, storage, and release of donor human stool.
  - Collection of donor blood and nasopharyngeal swabs samples for pathogen testing.
  - Manufacture of DS
  - Manufacture, package, quality control testing (release and stability), quality release, and storage of DP
- (b) (4)
  - Pathogen testing of donor human stool, blood, and nasopharyngeal swabs (for SARS-CoV-2).
- (b) (4)
  - Testing of (b) (4) excipients

##### **3.2.S.2.2 Description of Manufacturing Process**

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

### **3.2.P DRUG PRODUCT**

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

The DP is provided as a single dose of microbiota suspension (150 mL to 170 mL) at a strength of (b) (4) CFU/150 mL, consisting of (b) (4) DHS suspended in PEG/saline solution in a 250 mL EVA bag (container closure). The opaque suspension is administered rectally. The DP is supplied with an unattached administration tube set consisting of a rectal tube, a clamp, and a spike port adapter positioned at one end of the rectal tube.



### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)

The manufacturers for the DP are the same as those listed under Section 3.2.S.2.1 for the DS.

#### 3.2.P.3.3 Description of Manufacturing Process

The process flow for DP manufacture includes the following five steps:

1. Sampling of (b) (4) and filling of DP into EVA bags
2. Container closure (fill tube) sealing and visual inspection
3. Storage
4. Labeling and secondary packaging
5. Shipping to distributor

The start of DP manufacture is (b) (4) with the end of DS manufacture. Inside a biological safety cabinet (BSC), (b) (4) representative samples of the (b) (4) in a (b) (4) are (b) (4) for quality testing and retain purposes. (b) (4) of a multidose batch is sampled. For each dose of DP, 150.0 – 170.0 (b) (4) of the DS is (b) (4) filled into the EVA bag (primary container closure) through a port using a (b) (4) and the fill tube cap is replaced to close the bag. An average of (b) (4) doses are manufactured per batch (single DHS donation, lot).

Filled bags are removed from the BSC, and (b) (4) seal is applied between the bag and tube cap using a (b) (4) sealer. The DP is visually inspected for appearance, with acceptance criteria of “opaque suspension”, and the DP bag for seal integrity and leaks.

A temporary label is placed on the DP bag and the DP is stored at 2°C to 8°C for up to 24 hours followed by long-term storage at -60°C to -90°C in a -80°C freezer. Following disposition, the DP is permanently labeled and placed in a secondary packaging.

During labeling, the DP is removed from the freezer (b) (4) at a time and processed at (b) (4) conditions. A label carrier is inserted through the “hang” hole in the flange of the DP bag and the container label is affixed to the label carrier. The temporary label is removed and the labels (container label and DP global trade item number (GTIN)) are visually inspected.

The labeled DP is placed in a shroud (an opaque bag encasing the DP bag with a clear area for visual inspection of the DP and visibility of the DP bag label), and the shroud opening is sealed using a (b) (4) sealer. After inspection of the seal, the packaged DP is inserted into the pullout tray and the tray is placed inside the outer carton which is pre-labelled with the DP GTIN label. The packaged DP is placed in the freezer until shipping to distributor in (b) (4) using a cold shipper.

Neither reprocessing nor reworking is considered part of the routine commercial manufacturing of drug product.

***Reviewer's comment:*** The sponsor provided a clear stepwise description of the DP manufacturing process. Manufacturing process flow diagrams were included in Section 3.2.R, Manufacturing PPQ Protocol and Report QR-527. The information provided appears acceptable.

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

Reviewer's comment: Manufacture of REBYOTA does not have intermediates or specified critical steps.

### 3.2.P.3.5 Process Validation and/or Evaluation

Approximately (b) (4) REBYOTA batches have been manufactured between (b) (4) [REDACTED]. During that timeframe a total of 27 batches were rejected due to failure to meet one or more of the critical quality attributes acceptance criteria for bacteroides species growth, viable bacteria count, or diversity. Based on these failed batches, Rebiotix calculated a (b) (4)% failure rate of the commercial manufacturing process under current controls. Batches rejected due to positive pathogen test results were excluded from this data since failure to meet these acceptance criteria is not reflective of the manufacturing process or indicative of potential manufacturing process failures batches.

The (b) (4) batches used in clinical studies were manufactured between (b) (4). Rebiotix states that there was no manufacturing performed from March 12, 2020 to February 2021 due to the SARS-CoV-2 pandemic.

Rebiotix combined the process performance qualification (PPQ) for DS and DP, because the evaluation criteria for DS is applied to the DP and executed a (b) (4) process verification. The sponsor states that the donor program activities and DHS collection are considered out of scope of REBYOTA process validation. REBYOTA manufacturing process is completely (b) (4) and there is no depyrogenation, sterilization, lyophilization and aseptic processing performed.

The PPQ study used a total of (b) (4) DP batches manufactured using DHS from (b) (4) unique donor batches (Batch #s (b) (4) ) manufactured on (b) (4) . (b) (4) manufactured from each of Donor (b) (4), while (b) (4) batches were manufactured from each of Donors (b) (4). The following PPQ manufacturing parameters were assessed:

(b) (4)

(b) (4)

Rebiotix evaluated the process capabilities to produce product that consistently meets quality attributes by assessing the following DP attributes, tested for the commercial DP manufacturing qualification which must meet the DP specifications as indicated:

- Visual appearance: opaque suspension
- Viable bacterial count: (b) (4) to  $5.0 \times 10^{10}$  CFU/mL
- Diversity: (b) (4)
- *Bacteroides Species* growth: growth observed (b) (4)

Rebiotix states that there were no observed deviations to the test protocol, the protocol's execution, or failure of any test result to meet the protocol acceptance criteria.

The data from these assessments were evaluated using process capability indices – process width (Pp), process centering (Pk), and confidence interval (CI) on the mean – to determine if the process meets the acceptable quality limit (AQL) target for each quantitative attribute (viability and diversity) established based on the associated severity determined by risk assessment.

Rebiotix proposes a continuous process verification (CPV) plan to confirm the long-term performance of the manufacturing process. Based on the results of the PPQ study, the sponsor concluded that additional batches are required to confirm the long-term process performance for the diversity attribute. The CPV will apply the nominal manufacturing parameters and use the same assessment as in the PPQ study.

*Reviewer's comment: Rebiotix did not report failure in the equipment or facility related process. The information provided for the process validation under DMPQ purview appears acceptable to support consistent manufacture of REBYOTA. DMPQ defers the assessment of the critical quality attributes for DS and DP during the PPQ study, as well as the proposed CPV for long-term process performance for the diversity attribute to OVR.*

*REBYOTA is not a sterile product, therefore there is no documentation for qualification of the aseptic processing, sterilization of materials and sterilization of product, which is acceptable.*

### **Labeling and secondary packaging process performance**

Rebiotix executed a labeling and secondary packaging process performance qualification using (b) (4) batches, across (b) (4) days and (b) (4) primary operators within (b) (4) packaging campaigns. The sponsor used failure modes and effects analysis (FMEA) and determined the risk associated with finished DP attributes, (b) (4), to be low. The (b) (4) attributes were assessed using the (b) (4) instead of the DP. The qualification batches were packaged and labeled per the instructions in the approved manufacturing batch record and quality inspected per standard operating procedure. All testing results met the following acceptance criteria:

(b) (4)

[Redacted text block]

**Process Performance Qualification of Drug Product Shipment**

(b) (4)




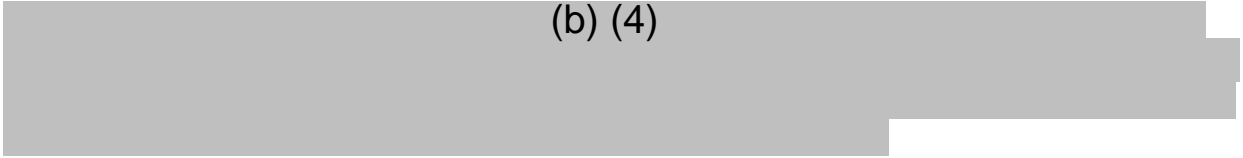
[Redacted text block]

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(b) (4)



### **3.2.P.4 Control of Excipients**

Reviewer's comment: DMPQ defers the evaluation to OVRR reviewer.

### **3.2.P.5 Control of Drug Product**

Each batch is assessed with the following tests:

- *Bacteroides* species growth
- Viable bacterial count
- Diversity
- Appearance

Reviewer's comment: DMPQ defers the assessment of the DP specifications to OVRR.

**3.2.P.7 Container Closure System**

The primary container closure for REBYOTA is a single-use 250 mL EVA bag received by Rebiotix when sterile. The bag has two ports; a fill port and a spike port for dispensing the contents of the bag. The DP bag is encased in an opaque bag (i.e., shroud) designed not to be removed, even during product administration. The shroud has a clear area for visual inspection of the DP and to provide visibility of the container label which is attached to the DP bag via a label carrier. The DP bag and shroud are housed in a pullout tray which is packed into an outer carton.

The bag is manufactured and supplied by (b) (4), a subsidiary of (b) (4). The bag is made up of a (b) (4)-layer (b) (4) film consisting of EVA (fluid contact surface), (b) (4) (exterior surface).

Incoming inspection of the DP bag includes visually inspecting to ensure (b) (4). The Certificate of Compliance from the bag manufacturer includes the following sterility related specifications:

- Monitoring of (b) (4) :
  - (b) (4)
  - (b) (4)
  - (b) (4)
- Batch testing:
  - Visual inspection: 100% inspection and pass (b) (4) specification
  - Product conformity: Drawing compliance and batch record reviewed
  - (b) (4) : (b) (4) certificate from approved contractor is enclosed

Rebiotix considers the administration tube set (ATS, also referred to as rectal tube set or tube set) as part of the container closure system since it is provided with the DP. The ATS is a single-use, non-sterile assembly used for puncturing the DP bag and delivering the DP into the patient's rectum. The ATS is contained in a peelable bag and packed in a separated carton from the DP. The EVA bag and ATS constitute the device part of the DP, therefore making REBYOTA a combination product.

Incoming inspection by the sponsor include visual inspection of a sample of tube sets to ensure the (b) (4). The certificate of compliance includes a statement that the (b) (4) raw materials conform to (b) (4) and (b) (4), and specifies the following batch testing:

- Visual inspection, 100% inspection and pass (b) (4) specification
- Product conformity, technical drawing compliance and batch record review

Rebiotix executed a study to determine the integrity of the sterile EVA bag which is the primary container of the DP. The study assessed bags filled with (b) (4) and stored in different configurations ( (b) (4) ) at -80°C for (b) (4) .

(b) (4)

*The information provided appears acceptable. Assessment of the endotoxin test and all other aspects of EVA bag and ATS suitability including the biocompatibility test are under the purview of OVR.*

### **3.2.P.8 Stability**

The stability of REBYOTA is assessed by the following tests:

- Visual appearance
- *Bacteroides* species growth
- Viable bacterial count
- Phenotypic diversity

*Reviewer's comment:* DMPQ defers the review of the DP stability information to OVR.

### 3.2.A APPENDICES

#### 3.2.A.1 Facilities and Equipment

##### 3.2.A.1.2 Manufacturing Facility

The Rebiotix facility is located at 2660 Patton Road, Roseville MN and is approximately (b) (4) ft<sup>2</sup> in size and includes general office, research and development, quality control laboratory, donor collection, manufacturing, and packaging, receiving, and shipping areas, and warehouse and storage areas. All the areas used for manufacturing activities are within the (b) (4) floor of the building.

Rebiotix provided the diagrams for the following:

- Incoming/outgoing materials flow
- Donated source material flow
- Manufacturing process flow
- Packaged product flow
- Waste flow
- Personnel flow
- Differential pressure

There are (b) (4) pass-throughs in the manufacturing facility:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Processes that occur in the manufacturing suite (Room (b) (4)) include:

- Preparation of PEG/saline solution
- Formulation of DS
- (b) (4)
- Sampling and filling
- Sealing and inspection

The manufacturing suite contains (b) (4) work areas ( (b) (4) ) and concurrent manufacturing may occur in the work areas. The work areas are demarcated by (b) (4), creating a physical barrier between (b) (4). Each work area has dedicated processing equipment, work surfaces, and operators. Entry into the manufacturing suite is through the anteroom (room (b) (4)), with a gowning area where operators don personal protective equipment (PPE) prior to entering the manufacturing suite.

Rebiotix identifies the following areas as controlled non-classified (CNC):

- Manufacturing suite (controlled area) – Room (b) (4)
- DHS receiving and inspection room (protected area) – Room (b) (4)
- Anteroom (protected area) – Room (b) (4)



- Quality control (QC) laboratory (protected area) – Room (b) (4):
- Sampling – Room (b) (4) (protected area)

The biological safety cabinets (BSCs) in rooms (b) (4) are the only ISO classified zones (ISO (b) (4)).

Other general areas within the building associated with the manufacture of REBYOTA are designated as CNC, and include:

- Donor restrooms (Rooms (b) (4) )
- Material receiving (Room (b) (4)), material storage (Room (b) (4))
- Warehouse with controlled room temperature (Room (b) (4))
- Warehouse-ambient (Room (b) (4))
- Packaging and shipping (Room (b) (4))
- Warehouse docks.

### Utilities and Computerized Systems

There are no utilities used for critical operations in the Rebiotix facility. General utilities such as potable water, power, and conditioned air, as well as computer systems were assessed as part of facility qualification as documented in validation report (QR-512 Rev 005). Rebiotix indicated that computer systems are applicable to environmental monitoring system only, which is used for temperature, relative humidity, and differential pressures.

### Qualification of HVAC System for Manufacturing Suite (Room (b) (4))

(b) (4)

(b) (4)

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

Rebiotix reported that none of the deviations had impact on the qualification.

***Reviewer's comment:** The flow diagrams as provided in the submission appear acceptable to support segregation controls during the manufacture of REBYOTA. The qualification of the facility assessed the general utilities including the HVAC used to support the manufacture of REBYOTA. All the requirements for each facility attribute were met. The deviations occurring during the facility qualification appear to have been resolved with no impact to the qualification. The information provided appears acceptable.*

### 3.2.A.1.3 Manufacturing Equipment

No equipment used in the manufacture of DS and DP is product-contact. Rebiotix provided a table, in Facility Validation Report, QR-512 Rev 005, indicating the location of the following equipment:

- (b) (4) system (Room (b) (4))
- (b) (4) (Room (b) (4))
- (b) (4) (Room (b) (4))
- (b) (4) (Rooms (b) (4))
- Environmental monitoring system (server room)
- Freezers (Room (b) (4))
- HVAC systems (rooftop)
- Incubators (Room (b) (4))
- (b) (4) (Room (b) (4))
- Refrigerators (Rooms (b) (4))
- Sealers (Rooms (b) (4))
- Ultra-low freezers (Rooms (b) (4))

***Reviewer's comment:** Rebiotix did not provide the IQ/OQ/PQ for the manufacturing equipment. An IR was issued for summaries of the IQ/OQ/PQ protocols and final reports for the following equipment used in the manufacture and storage (warehouse/packing and shipping) of REBYOTA: BSC Class (b) (4) Type (b) (4), refrigerators, freezers, ultra-low freezers, (b) (4). The information that Rebiotix provided in the response, summarized below, appears acceptable to support the IQ/OQ/PQ of the main non-product-contact equipment. The specified acceptance criteria appear acceptable to assess the equipment functionality and the study results met the criteria. The information provided appears acceptable.*

In response to IR request #10 (amendment 125739/0.18), Rebiotix provide an overview of the IQ/OQ/PQ strategy and acceptance criteria for each type of equipment (BSCs,

(b) (4), refrigerators and ultralow freezers) utilized in the manufacture and storage of REBYOTA. The sponsor states that Rebiotix does not utilize (b) (4) freezers (i.e. (b) (4)) in the manufacture or storage of REBYOTA. Each of the (b) (4) equipment types has multiple pieces of equipment. Therefore, the sponsor provided representative protocols, raw data and final reports for each type of equipment. Rebiotix also provided the summary reports of the IQ, OQ and PQ for each specific equipment.

The functional requirements assessed during the IQ/OQ for BSCs are based on the (b) (4)

The results for IQ and OQ for all (b) (4) BSCs met the acceptance criteria. Regular certification of the BSCs is conducted (b) (4).

The OQ acceptance criteria for the (b) (4) include (b) (4) used during the manufacture of REBYOTA. The results for IQ and OQ for the (b) (4) met the acceptance criteria.

The OQ/PQ acceptance criteria for the refrigerators include (b) (4)

The results for IQ, OQ and PQ for the (b) (4) refrigerators met the acceptance criteria.

The OQ/PQ acceptance criteria for the ultralow freezers ( (b) (4) ) include (b) (4)

The results for IQ, OQ and PQ for the (b) (4) ultralow freezers met the acceptance criteria.

### **Product Contact Materials**

Rebiotix provided a list of product-contact materials and their handling procedures (Table 3 of Document Q-3.2.A.1 Facilities and Equipment-17867). All the materials are single-use and are received sterile, except for the collection container and (b) (4) which are non-sterile. The sponsor provided material handling and risk mitigation for the two non-sterile materials which are also received in bulk. Using process FMEA, the

tolerable risk identified based on the requirement that containers are clean and free from visual foreign material was mitigated by the supplier qualification including certificate of conformance and incoming inspections. Additionally, all risks related to contaminants in the collection container and collection process were mitigated by donor human stool pathogen testing and were classified as negligible risks. (b) (4) are used to (b) (4) PEG for the preparation of PEG/saline solution. Risk mitigation of contamination due to use of non-sterile (b) (4) was by (b) (4) of the PEG/saline solution using a (b) (4) system into a (b) (4) container.

#### 3.2.A.1.4. Manufacturing Equipment Cleaning

Equipment used in the manufacture of DS and DP is not product-contact, therefore, Rebiotix/Ferring did not provide the validation of equipment cleaning. Specific equipment used in the manufacturing process (BSCs, (b) (4) ) is cleaned (b) (4) the manufacture of each lot as part of the contamination control strategy. Other equipment, such as refrigerators and freezers, as well as the manufacturing areas are cleaned at regular intervals.

The pre-/post-process cleaning procedures for manufacturing equipment, all of which have no contact with the product is exterior surface clean using (b) (4) disinfectant (b) (4) .

BSCs are cleaned with the following (b) (4) disinfectants:

(b) (4)

All materials are (b) (4) with (b) (4) outside of the BCS prior to placing them in the BSC.

(b) (4)

(b) (4)

There were no deviations during the study.

*Reviewer's comment: The qualification of clean hold-time of (b) (4) for the BSCs appears acceptable. The results of the study met the acceptance criteria which are based on (b) (4). (b) (4) tests were performed during the IQ/OQ of the BSCs. No further evaluation of the (b) (4) studies is necessary due to the non-sterile nature of the product. The information provided appears acceptable.*

### 3.2.A.1.5 Cleaning of Manufacturing Areas

Rebiotix provided the cleaning process and minimum cleaning intervals for the manufacturing areas, refrigerators and freezers. The following list indicates the cleaning process:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

*Reviewer's comment:* Rebiotix's processes to mitigate cross-contamination and mix-up appears acceptable. The use of labelled single-use DS/DP materials and process of a (b) (4) and cleaning process appear acceptable to minimize cross-contamination. The information provided appears acceptable.

### 3.2.A.1.7 Environmental Monitoring Program

Rebiotix executed Study QR-469 to qualify the environmental monitoring (EM) program, at static and dynamic conditions, in the manufacturing suite and supporting areas. All manufacturing areas, with the exception of the BSCs, are designated as CNC. Rebiotix classified BSCs as ISO (b) (4) for particulates at static and dynamic conditions, and as Grade (b) (4) (static) and Grade (b) (4) (dynamic) for viable air and surface.

The EM study assessed

(b) (4)



One page has been determined to be not releasable: (b)(4)

(b) (4)

Rebiotix plans to apply the conditions and limits of the completed EM studies towards the routine EM program. The sponsor states that the alert and action limits will be reassessed based on the results of the EM Phase 3 study for the purpose of tightening the limits.



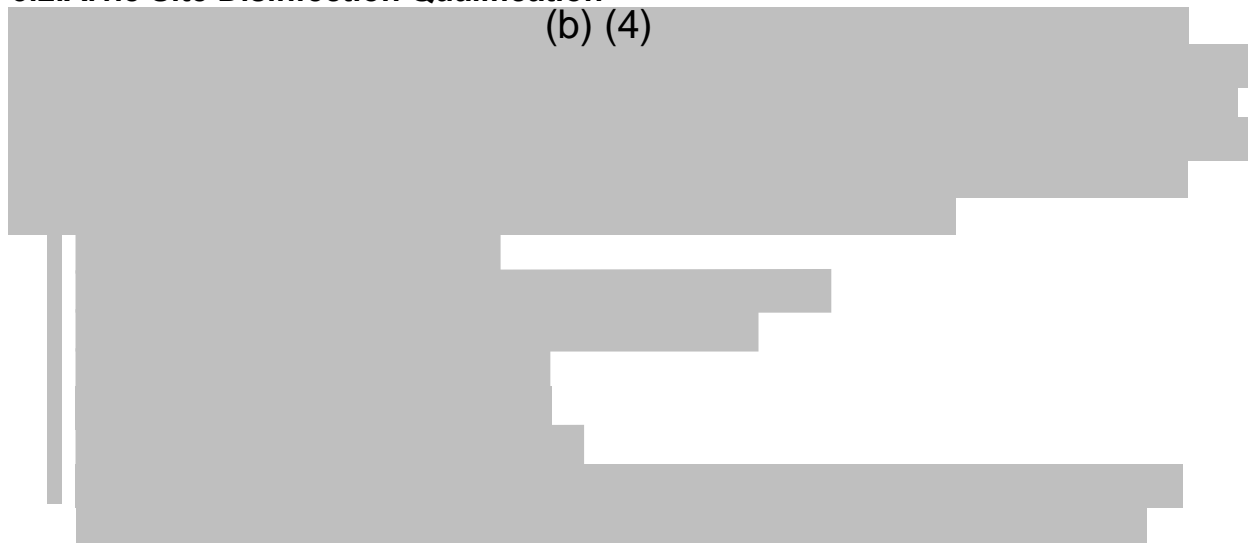
In response to IR request #10 for the justification for the sampling locations (amendment 125739/0.18), Rebiotix explained sampling locations were based on the

(b) (4) and the capabilities of the room/BSC design, taking into consideration the activities/operations within each individual space and the risk associated with product quality. The number of particulate sample locations within each space were determined based on the room area (m<sup>2</sup>) in accordance with (b) (4). The viable air sample locations were selected to coincide with the non-viable particulate sampling locations. Viable surface sample sites within the BSCs were selected based on the proximity to open product handling during manufacturing and industry standard practice for monitoring of BSCs. Sampling frequency for routine EM was based on risk assessment of the individual space. Rebiotix states that there is no difference between sample locations and sampling frequency of static, dynamic, and routine monitoring.

*Reviewer's comment: The results of the static and dynamic EM studies appear acceptable to demonstrate that the environment in the manufacturing areas is in a state of control based on (b) (4) limits for the designated areas. The sampling locations appear to be adequately distributed in the individual space and include the pass-throughs. Rebiotix provided the area for each room and the number of sample locations. The numbers appear to correspond to those provided in Table A.1 of (b) (4). Although the rooms are designated as CNC, Rebiotix monitors them at ISO (b) (4) in operation. All the study results met the acceptance criteria. The information provided appears acceptable.*

### 3.2.A.1.8 Site Disinfection Qualification

(b) (4)



One page has been determined to be not releasable: (b)(4)

(b) (4)

*Reviewer's assessment: The disinfectant efficacy study results met the (b) (4) criteria recommended in (b) (4). The results of the study appear acceptable to support the use of the disinfectants at the manufacturing facility. The information provided appears acceptable.*

### **3.2.A.1.9 Shared Space with Development and Approved Products**

The donor restrooms and DHS receiving and inspection room are dedicated to the collection, receiving, and inspection of DHS. The manufacturing suite is dedicated to the manufacture of REBYOTA. Material receiving, material storage/warehousing, secondary packaging, and shipping activities for REBYOTA may be performed in space shared with other investigational or commercial product.

### **3.2.R Regional Information (USA)**

#### **Combination Products**

The administration tube set (also referred to as rectal tube set or tube set) used to puncture the EVA bag and rectally administer REBYOTA to the patient is commercially available, marketed for rectal administration of liquids. Ferring/Rebiotix has contracted (b) (4) to manufacture the rectal tube set. Based on 21CFR876.5210, the enema kit is classified as Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to § 876.9. The device is exempt from the current good manufacturing practice requirements of the quality system regulation in part 820 of this chapter, with the exception of § 820.180 of this chapter, with respect to general requirements concerning records, and § 820.198 of this chapter, with respect to complaint files.

*Reviewer's comment:* *DMPQ defers to OVRR for the assessment of the enema kit and administration tube set as device component of the DP.*

**Comparability Protocols**

Rebiotix provided a comparability protocol (CP) to address potential changes to the components of the (b) (4). The CP evaluated the biocompatibility and chemical characterization of product- and patient-contact components.

*Reviewer's comment:* *DMPQ defers the review of the CP to OVRR.*