Our STN: BL 125739/0 **BLA APPROVAL**

Ferring Pharmaceuticals Inc. November 30, 2022
Attention: Karen Kuphal, Ph.D.
2660 Patton Road
Roseville, MN 55113

Dear Dr. Kuphal:

Please refer to your Biologics License Application (BLA) received November 30, 2021, submitted under section 351(a) of the Public Health Service Act (PHS Act) for fecal microbiota, live-jslm.

LICENSING

We have approved your BLA for fecal microbiota, live-jslm effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, fecal microbiota, live-jslm under your existing Department of Health and Human Services U.S. License No. 2112. fecal microbiota, live-jslm is indicated 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 review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT02299570; NCT02589847; NCT03931941; NCT03244644; NCT01925417.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture fecal microbiota, live-jslm at Rebiotix Inc. at 2660 Patton Road, Roseville, MN, 55113-1136. You may label your product with the proprietary name REBYOTA and market it in a 250 mL ethylene vinyl acetate bag containing 150 mL dose of fecal microbiota suspension.

DATING PERIOD

The dating period for fecal microbiota, live-jslm shall be 36 months from the date of manufacture when stored at -80°C. The date of manufacture shall be defined as the date of initiation of drug substance manufacturing when the donor human stool is combined with the polyethylene glycol 3350/saline solution. The expiration date for the packaged product, fecal microbiota suspension plus administration set, shall be dependent on the shortest expiration date of any component.

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of fecal microbiota, live-jslm to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations :

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of fecal microbiota, live-jslm, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert submitted under amendment 60, dated November 29, 2022 and the draft carton and container labels submitted under amendment 60, dated November 29, 2022. This is a reminder that as of September 24, 2014, device constituents of combination products may be subject to certain provisions of the final Unique Device Identifier (UDI) rule. These provisions include the requirement to provide a UDI on the device constituent label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, please identify each device identifier implemented for the subject device constituent, and the device identifiers that have been discontinued for the subject device constituent as a labeling change in an annual

report consistent with 21 CFR 601.12(f)(3). For more information on these requirements, please see the UDI website at http://www.fda.gov/udi.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert, submitted on November 29, 2022. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on November 29, 2022, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125739 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
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You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). In addition to the reporting requirements in 21 CFR 600.80, you must provide expanded adverse experience reporting to include all reports of serious adverse events as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). The expanded reporting is required for 3 years following the date of product licensure. You must also submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm458559.pdf and FDA's Adverse Event reporting System website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

For information on the postmarketing safety reporting requirements for combination products as described in 21 CFR 4, Subpart B, and the dates by which combination product applicants must comply with these requirements, please refer to the Postmarketing Safety Reporting for Combination Products webpage available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to

learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Managers for this application.

Sincerely,

David C. Kaslow, MD
Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research