U.S. FOOD & DRUG ADMINISTRATION

December 19, 2017
BLA APPROVAL

Our STN: BL 125610/0

Spark Therapeutics, Inc.
Attention: Jim Wang, MBA, PhD
3737 Market Street, Suite 1300
Philadelphia, PA 19104

Dear Dr. Wang:

Please refer to your Biologics License Application (BLA) for voretigene neparvovec-rzyl dated April 26, 2017, and received May 16, 2017, submitted under section 351(a) of the Public Health Service Act (PHS Act).

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2056 to Spark Therapeutics, Inc., Philadephia, PA, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product voretigene neparvovec-rzyl, which is indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT 00516477, NCT 01208389, and NCT 00999609.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture voretigene neparvovec-rzyl drug substance at Spark Therapeutics, Inc., 3737 Market Street, Philadelphia, PA 19104, USA. The final drug product and diluent will be manufactured, filled, and labeled at (b) (4) . Final packaging and package labeling will be performed at (b) (4) .

You may label your product with the proprietary name LUXTURNA and market it in single-use plastic vials containing 0.5 mL extractable volume at a concentration of 5 x 10^{12} vector genomes/mL.

DATING PERIOD

The dating period for voretigene neparvovec-rzyl and for diluent shall be 18 months from the date of manufacture when stored at ≤-65 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4) . The expiration date for the packaged product, voretigene neparvovec-rzyl plus diluent, shall be dependent on the shortest expiration date of any component. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance, drug product, and diluent under 21 CFR 601.12.

FDA LOT RELEASE

You are required to submit lot release protocols for future lots of voretigene neparvovec-rzyl 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, at the following address:

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 voretigene neparvovec-rzyl, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 60, dated December 12, 2017, and the draft carton and container labeling submitted under amendment 57, dated December 7, 2017.

Please provide your final content of labeling including the carton and container labels in Structured Product Labeling (SPL) format. All final labeling should be submitted as Product Correspondence to this BLA 125610 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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.

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.
WO71-G112
Silver Spring, MD 20993-0002

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) and you must 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 http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse Event reporting System website

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.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 125610. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "**Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher**."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

- the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
- the estimated demand in the U.S. for the product, and
- the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf

(see Section 908 of FDASIA on pages 1094-1098 which amends the FDCA by adding Section 529). Formal guidance about this program will be published in the future.

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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in amendment 56, dated December 7, 2017, and in amendment 63, dated December 15, 2017 as outlined below:

#1 Spark Therapeutics, Inc. commits to provide the shipping validation study protocol for shipment of the drug product from the distributor to a clinical site (or to Spark Therapeutics, Inc.) by January 31, 2018. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by June 30, 2018.

Final Report Submission: June 30, 2018

#2 Spark Therapeutics, Inc. commits to complete the verification studies for the following assays:

a. (b) (4)

b. (b) (4) tests for particulate matter for the drug product and diluent, performed by (b) (4).

A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by March 31, 2018.

Final Report Submission: March 31, 2018.

#3 Spark Therapeutics, Inc. commits to perform an analysis of the lot release test results obtained from all drug substance (DS) and drugproduct (DP) lots manufactured in the first (b) (4) following approval, and evaluate if the acceptance criteria for LUXTURNA lot release tests (including (b) (4)) continue to provide adequate quality control for DS and DP based on the new data obtained from those tests. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by March 31, 2020.

Final Report Submission: March 31, 2020.

#4 Spark Therapeutics, Inc. commits to conduct stability studies on the HEK293 Master Cell Bank (MCB) used for drug substance manufacture. (b) (4) , "Postmarketing Commitment - Final Study Report" by March 31, 2018.

Final Report Submission: March 31, 2018.

#5 Spark Therapeutics, Inc. commits to qualify the (b) (4) . A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by March 31, 2018.

Final Report Submission: March 31, 2018

#6. Spark Therapeutics, Inc. commits to revise procedures for visual inspection to incorporate statistically sound sampling plans (e.g., AQL) following the 100% inspection. The sampling plan will include appropriate acceptance criteria for critical and major defects. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by June 30, 2018 to include the procedure and the results of the revised visual inspection process for the next product lot manufactured.

Final Report Submission: June 30, 2018

#7. Spark Therapeutics, Inc. commits to perform (b) (4) as cleaning verification. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by September 30, 2018 to include the revised procedure for

performing cleaning verification and the results of testing for the next lot manufactured.

Final Report Submisssion: September 30, 2018

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA 125610. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

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 Manager for this application.

Sincerely yours,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research