DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125553

BLA APPROVAL

Sandoz Inc.
Attention: John M. Pakulski, RPh
Head, US Biopharmaceutical Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) dated May 8, 2014, received May 8, 2014, submitted under section 351(k) of the Public Health Service Act for Zarxio (filgrastim-sndz).

We acknowledge receipt of your amendments dated May 23; June 5, 12, 16, 18, and 24 (2); July 1 and 24; August 22; September 4, 19, and 30; October 10, 14, 21, 28 and 31; November 12; December 2, 5, and 19, 2014; January 22 and 30 (2); and February 6, 11, and 24; and March 4 and 5, 2015.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2003 to Sandoz Inc., Princeton, NJ, under the provisions of section 351(k) of the Public Health Service 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 Zarxio (filgrastim-sndz). Zarxio is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML); to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT); to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture filgrastim-sndz drug substance at Sandoz GmbH in Kundl, Austria. The final formulated drug product will be manufactured, filled, labeled, and packaged at GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany. You may label your product with the proprietary name, Zarxio, and market it in 300 mcg/0.5mL in single-use prefilled syringes and 480 mcg/0.8 mL in single-use prefilled syringes.

DATING PERIOD

The dating period for Zarxio shall be 24 months from the date of manufacture when stored at 5 ± 3°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4) The stability protocol in your license application is considered approved for the purposes of extending the expiration dating period of Zarxio drug product as specified in 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Zarxio to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. 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.

Any changes in the manufacturing, testing, packaging, or labeling of Zarxio, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "*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.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on March 5, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "*Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).*" Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 125553**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring your assessment for pediatric patients who weigh less than 36 kg for this application because this product is ready for approval for use in adults and your assessment in this population has not yet been completed.

Your deferred assessment required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a postmarketing requirement. The status of this postmarketing requirement must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(C) of the FDCA. This requirement is listed below.

PMR 2883-1 To develop a presentation that can be used to directly and accurately administer filgrastim-sndz to pediatric patients who weigh less than 36 kg requiring doses that are less than 0.3 mL (180 mcg), and conduct any necessary human factors studies to evaluate the ability of caregivers to measure the appropriate doses.

Preliminary Protocol Submission:	07/06/15
Final Protocol Submission:	09/06/15
Study Completion:	06/06/16
Final Report Submission:	09/06/16

Submit the protocols to your IND 109197, with a cross-reference letter to this BLA.

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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

We remind you of your postmarketing commitments:

PMC 2883-2 To enhance the control strategy of [redacted] (b) (4) by development, validation, and implementation of an analytical method to assess [redacted] (b) (4) concentration for release or in-process testing of Zarxio drug product.

The timetable you submitted on March 4, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission:	05/2016
Implementation of analytical test for release to assess [redacted] (b) (4) concentration in the drug product:	05/2020

Specifications will be set latest after testing of 20 commercial batches
The final study report(s) will be reported according to 21CFR 601.12

PMC 2883-3 To confirm the stability of Zarxio (filgrastim-sndz) drug product in 5% glucose at concentrations ranging from 5 mcg/ml to 15 mcg/ml of Zarxio (filgrastim-sndz), in the presence of 2 mg/ml human serum albumin, in glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Testing will include potency and sub-visible particles.

The timetable you submitted on March 4, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2016

The final study report(s) will be reported according to 21CFR 601.12

PMC 2883-4 To re-adjust [redacted] (b) (4) bioburden limit of [redacted] (b) (4) for the [redacted] (b) (4) drug substance based on process capability from 10 batches of product.

The timetable you submitted on March 4, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 08/2017
Final Report Submission: 05/2018 Annual Report

PMC2883-5 Establish bioburden and endotoxin action limits for [redacted] (b) (4) after data from more than 10[1)] batches are available and provide the limits in an Annual Report.

The timetable you submitted on March 4, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 03/2017
Final Report Submission: 08/2017

[1)] In case that less than 10 batches are manufactured by the date set for study completion, a preliminary action limit for bioburden and endotoxin will be set and re-assessed as soon as required number of batches is available.

PMC 2883-6 Conduct studies to support the worst-case hold times [redacted] (b) (4) at scale from a microbiology perspective. Provide study results in an Annual Report.

The timetable you submitted on March 4, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 12/2015
Final Report Submission: 05/2016 Annual Report

PMC 2883-7 To update the stability program for Zarxio (filgrastim-sndz) pre-filled syringe drug product to include the syringe force measurements glide force and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.

The timetable you submitted on March 4, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2016 Annual Report

For functional testing on the devices constituent parts of the combination product:

Implementation of analytical test for stability and inclusion of functional tests in the postapproval stability commitment (with test frequency t0 and thereafter once a year until end of shelf life) on one commercial batch per strength:

- Syringe freedom of movement inside the needle safety device;
- Removability of the flag label
- Activation of the needle safety device

For break loose and glide force on the pre-filled syringes
(combination product): 05/2016 Annual Report

- Implementation of analytical test for stability and inclusion of test in the post-approval stability commitment (with test frequency t0 and thereafter once a year until end of shelf life) 05/2020

- Shelf life specification will be set and specification included in the post-approval stability commitment after testing of sufficient commercial batches (i.e. 10 batches each per 300 mcg/0.5mL and 480 mcg/0.8mL

The updated annual stability protocol including testing and acceptance criteria (specifications) will be reported according to 21 CFR 601.12

Submit clinical protocols to your IND 109197 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans

since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with

processing, testing, packing, 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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
03/06/2015