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RESEARCH**

APPLICATION NUMBER:
125553Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL (Cross Discipline Team Leader) Review

Date	February 26, 2015
From	Albert Deisseroth, MD, PhD
Subject	CDTL Review
BLA Number	125553
Applicant	Sandoz
Date of Submission	May 8, 2014
BSUFA Goal Date	March 8, 2015
Proprietary Name	Zarxio
Dosage Regimen	300 mcg/0.5 mL PFS, 480 mcg/0.8 mL PFS
Approved Indications	Patients with cancer receiving myelosuppressive chemotherapy; Patients with AML receiving induction or consolidation chemotherapy; Patients with cancer receiving bone marrow transplant; Patients undergoing peripheral blood progenitor cell collection; Patients with severe chronic neutropenia.
Recommendation:	Approval of EP2006 as a biosimilar to US-licensed Neupogen for all 5 indications for which US-licensed Neupogen is currently licensed

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Donna Przepiorka, MD, PhD
Clinical Pharmacology	Sarah Schrieber, PhD, Anshu Marathe, PhD, and NAM Atiqur Rahman, PhD
Biostatistics	Kyung Lee, PhD, and Lei Nie, PhD
Pharmacology/Toxicology	Christopher M Sheth, PhD, Haw-Jyh Chiu, PhD, and John Leighton, PhD
Immunogenicity	Farouk Sheikh, PhD, Frederick Mills, PhD, and Susan Kirshner, PhD
CMC Statistics	Xiaoyu Dong, PhD, Meiyu Shen, PhD, and Yi Tsong, PhD
OC/OMPQ/DGMPA/BMAB	Bo Chi, PhD, Steve Fong, PhD, and Patricia Hughes, PhD
Chemistry Manufacturing and Controls	Maria-Teresa Gutierrez-Lugo, PhD, Gibbes Johnson, PhD, and Steven Kozlowski, MD
Project Manager	Jessica Boehmer

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1. EXECUTIVE SUMMARY: (This section was derived in part from the review of Dr. Donna Przepiorka).

On May 8, 2014, Sandoz submitted BLA 125553 requesting licensure of EP2006 as a proposed biosimilar to US-licensed Neupogen under Section 351(k) of the Public Health Service Act. The proposed proprietary name is Zarxio. Filgrastim is an N-methionyl analog of granulocyte colony-stimulating factor (G-CSF) which is a hematopoietic growth factor that induces proliferation and differentiation of neutrophil committed progenitor cells into neutrophils. Filgrastim also induces the release of neutrophils as well as CD34+ hematopoietic progenitor cells from the marrow into the peripheral blood. Filgrastim is made up of 175 amino acids and is without glycosylation so that from a molecular perspective, this product is a relatively simple protein.

In this application, Sandoz requested that EP2006 be licensed as a biosimilar to US-licensed Neupogen for all of the five currently approved indications for US-licensed Neupogen. These include: decreasing the incidence of infections in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs; reducing the duration of neutropenia in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation; reducing the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with AML.

EP2006 was approved in 2009 under the trade name Zarzio for marketing in the European Union as a biosimilar product to EU-approved Neupogen. Marketing experience with Zarzio outside of the USA includes in excess of 7.5 million days of patient exposure. I recommend approval based on my review of the various disciplinary reviews, as summarized below. I also provided certain clarifications, as necessary and appropriate.

Summary of BLA 125553:

CMC: The foundation of biosimilar applications is the structural and functional characterization of the proposed product and the reference product, which informs whether the proposed biosimilar product is “highly similar” to the reference product from an analytic perspective. Sandoz’s extensive analyses of the physical and functional properties of EP2006 and US-licensed Neupogen demonstrated that EP2006 is “highly similar” to US-licensed Neupogen within the meaning of the BPCI Act. In addition, Sandoz carried out a three way, pair-wise analytical comparison of US-licensed Neupogen, EU-approved Neupogen, and EP2006 to establish a scientific bridge to justify the relevance of comparative data obtained using EU-approved Neupogen to support a demonstration of biosimilarity of EP2006 to US-licensed

Neupogen. Sandoz established this scientific bridge by meeting pre-specified acceptance criteria for analytical similarity across all three pairwise comparisons.

Non-clinical Studies: Sandoz's nonclinical studies comparing the toxicity, pharmacokinetic, and pharmacodynamic properties of EP2006 and EU-approved Neupogen were sufficient to demonstrate that EP2006 was similar to EU-approved Neupogen. The scientific bridge established between EP2006, US-licensed Neupogen, and EU-approved Neupogen, justifies the relevance of these comparative data with EU-approved Neupogen to a demonstration of biosimilarity to US-licensed Neupogen. Based on the comparative animal study data and the scientific bridge, these animal study data support a demonstration of biosimilarity between EP2006 and US-licensed Neupogen.

Clinical Pharmacology Studies: Two studies in which the pharmacokinetics and pharmacodynamics of EP2006 were compared in normal human subjects to US-licensed Neupogen, as well as 4 studies in which the pharmacokinetics and pharmacodynamics of EP2006 were compared to EU-approved Neupogen at doses ranging from 1, 2.5, 5 and 10 mcg/kg in normal human subjects, supported a demonstration that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen. The scientific bridge established between EP2006, US-licensed Neupogen, and EU-approved Neupogen, justifies the relevance of comparative data with EU-approved Neupogen to a demonstration of biosimilarity to US-licensed Neupogen.

Immunogenicity and Safety: Sandoz submitted immunogenicity and safety studies which had been carried out in normal human subjects. These studies supported a conclusion that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.

Additional Efficacy, Safety and Immunogenicity Studies: Finally, Sandoz presented safety, efficacy and immunogenicity data from a study that randomized patients with breast cancer receiving TAC chemotherapy between EP2006 and US-licensed Neupogen. These studies supported a demonstration that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.

***Reviewer Comment:** The study in patients with breast cancer was conducted as part of the clinical development program to support the approval of Zarzio in the EU in 2009. A study in patients with breast cancer would not be necessary to support development of EP2006 as a proposed biosimilar to US-licensed Neupogen.*

Regulatory Recommendation: Review of BLA 125553 supports a determination that EP2006 is biosimilar to US-licensed Neupogen: EP2006 is highly similar to US-licensed Neupogen notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between EP2006 and US-licensed Neupogen in terms of safety, purity, and potency. This CDTL reviewer recommends that EP2006 be licensed as a biosimilar product to US-licensed Neupogen, for all five of the indications for which US-licensed Neupogen is currently licensed. The recommendation is based on the totality of the evidence presented by Sandoz including the demonstration that EP2006 utilizes the same mechanism of action as US-licensed Neupogen for each of these indications.

2. BACKGROUND: (This section was derived in part from the review of Dr. Donna Przepiorka).

EP2006 acts on hematopoietic cells by binding to specific cell surface receptors. Signaling through the receptor affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation, including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC):

3.A. CMC: (This section was excerpted from the review of Dr. Maria-Teresa Gutierrez-Lugo). Assessment of analytical similarity between EP2006 and US-licensed Neupogen and establishment of a scientific bridge between EP2006, US-licensed Neupogen and EU-approved Neupogen were based on analytical comparison between EP2006, US-licensed Neupogen and EU-approved Neupogen using data provided by Sandoz for the following quality attributes: primary structure, bioactivity, protein content, receptor binding, clarity, sub-visible particles, secondary and tertiary structure, high molecular weight variants/aggregates, oxidized species, covalent dimers, partially reduced species, fMet1 species, sequence variants, succinimide species, phosphoglucunoylation, acetylated species, N-terminal truncated variants, norleucine species, and deamidated species. The conclusion of the CMC review team was that EP2006 is analytically highly similar to US-licensed Neupogen.

These data were also used to establish a robust scientific bridge between EP2006, US-licensed Neupogen and EU-approved Neupogen, to justify the relevance of comparative data obtained using EU-approved Neupogen to support a demonstration of biosimilarity to US-licensed Neupogen. For details, please see the CMC review.

Regulatory Recommendation of the CMC Review Team: Approval with postmarketing commitments, including one post marketing commitment relating to product stability.

3.B. OC/OMPQ/DGMPA/BMAB: (This section was excerpted from the review of Dr. Chi Bo). The BMAB team evaluated during inspection the manufacturing process of EP2006 drug substance from a microbiology perspective. For details, please see the review of Dr. Chi Bo.

Regulatory Recommendation of BMAB Review Team: The drug substance part of this BLA is recommended for approval from a quality microbiology perspective with the following post-market commitments:

- A. Establish bioburden and endotoxin action limits [REDACTED] (b) (4) after data from more than 20 batches are available.
- B. Conduct studies to support the worst-case hold times [REDACTED] (b) (4) [REDACTED] (b) (4) at scale from microbiology perspective.

4. PHARMACOLOGY/TOXICOLOGY: (This section was based on the review of Dr. Christopher M. Sheth).

The nonclinical data submitted to the BLA support the biosimilarity of EP2006 to US-licensed Neupogen. The nonclinical data demonstrate the similarity (i.e., similar PD characteristics and similar safety) of EP2006 and EU-approved Neupogen, and the scientific bridge between EP2006, US-licensed Neupogen, and EU-approved Neupogen justifies relevance of these comparative data with EU-approved Neupogen to a demonstration of biosimilarity to US-licensed Neupogen. The PD study (EP06-004) examined the hematological response in normal and neutropenic rats for 12 days following administration of either EP2006 or Neupogen. In normal rats, EP2006 and EU-approved Neupogen produced similar relatively sustained dose-related increases in ANC from Days 2 to 5. Both EP2006 and EU-approved Neupogen produced similar biphasic increases in ANC in neutropenic rats with two peak responses occurring on Days 2 and 5 with lower values on Days 3 and 4. Local tolerance study (EP06-003) was conducted to assess for potential erythema, edema, hematomas, pain reactions, gross pathology, and histopathology in rabbits administered undiluted EP2006 or EU-approved Neupogen via the SC, intravenous (IV), perivascular (PV), intraarterial (IA) and intramuscular (IM) routes. No definitive drug related changes occurred in the local tolerance study.

The 14-day TK study (EP06-002) showed that the toxicokinetics of EP2006 and EU-approved Neupogen at dose levels between 20 and 500 µg/kg are relatively similar in rats following single (on Day 0) and repeated (on Day 13) subcutaneous dosing. Two 28-day toxicity/TK studies (EP06-001 and EP06-006) with 6-week recovery periods were conducted in rats. Both studies were essentially identical in design, however the EP06-006 study was the most informative (pivotal) as it was conducted with the formulation of EP2006 (to be marketed in the US) containing L-glutamic acid as the buffering agent.

The EP06-001 study is supportive as it was conducted with EP2006 formulated in acetic acid which is the same buffer system used in the EU-approved Neupogen comparator. No drug-related deaths occurred in either 28-day study. Dose- and time-related increases in white blood cells, notably neutrophils, were observed in males and females treated with ≥ 20 µg/kg EP2006 or EU-approved Neupogen on Days 3, 14 and 28.

Other noteworthy findings were similar between EP2006 and EU-approved Neupogen in both studies and included: swollen joints and paralysis and/or some hind leg dysfunction at 500 µg/kg; dose-related increases in alkaline phosphatase up to 9-fold greater than controls; dose-related increases in spleen weights; hyperplasia of myeloid cells, increased hematopoietic cells in bone marrow and spleen, myeloid hyperplasia in the liver (EP06-006) and riddled compacta or

myelofibrosis in the femur bone (EP06-001). Exposures to rhG-CSF were similar in animals receiving equivalent dose levels of EP2006 or EU-approved Neupogen during the 28-day studies.

On the basis of these results, the review team concluded that EP2006 was similar to EU-approved Neupogen, and the scientific bridge between EP2006, US-licensed Neupogen, and EU-approved Neupogen justifies relevance of these comparative data with EU-approved Neupogen to a demonstration of biosimilarity to US-licensed Neupogen. For details, please see the review of the Pharmacology/Toxicology reviewer.

Regulatory Recommendation of the Pharmacology/Toxicology Reviewer: Recommend approval.

5. CLINICAL PHARMACOLOGY: (This section was excerpted from the review of Dr. Sarah Schrieber).

This Biologic License Application (BLA) for EP2006, a recombinant human granulocyte stimulating factor (G-CSF) has been submitted under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for EP2006 as a proposed biosimilar to US-licensed Neupogen licensed under BLA 103353 by Amgen Inc., and is seeking licensure for all the indications for which US-licensed Neupogen is currently approved. EP2006 drug product was developed as a liquid for injection, filled in a pre-filled syringe in the strengths of 300 mcg/0.5 mL and 480 mcg/0.8 mL.

The applicant submitted four pharmacokinetic (PK) and pharmacodynamic (PD) studies that evaluated subcutaneous (SC) doses of 1-10 mcg/kg in healthy subjects to evaluate the PK and PD similarity of EP2006 with US-licensed Neupogen. In addition to PK, these studies evaluated absolute neutrophil counts (ANC) and CD34+ cell counts as relevant and sensitive PD markers for the similarity assessment. Among these, three studies utilized EU-approved Neupogen. As such, adequate data and information was needed to scientifically justify the relevance of these comparative data to an assessment of biosimilarity to the US-licensed reference product.

Sandoz utilized pairwise comparisons of EP2006, US-licensed Neupogen, and EU-approved Neupogen, which met the pre-specified criteria for analytical similarity and established a scientific bridge, to justify the relevance of the PK/PD data generated using EU-approved Neupogen (refer to CMC review). Given the relatively simple structure of G-CSF, other product-specific considerations, the robustness of analytical data provided as described in the CMC section, availability of robust and sensitive analytical assays, and the breadth of clinical data submitted, a 3-way analytical bridge was considered acceptable for this program to provide an adequate scientific bridge between US-licensed Neupogen and EU-approved Neupogen. The 90% CI for AUC and Cmax after a single dose were within the pre-defined limits of 80-125%. Similarly, the 95% CI for AUEC and ANCmax for ANC after a single dose were within the pre-defined limits of 80-125%. The 95% CI for AUEC and CD34max for CD34+ cell counts after multiple doses were within the limits of 80-125%.

Overall, the PK and PD studies support a demonstration of PK and PD similarity between EP2006 and US-licensed Neupogen. The PK and PD studies results add to the totality of the evidence to support a demonstration of biosimilarity of EP2006 and US-licensed Neupogen. For details, please see the Clinical Pharmacology review.

Regulatory Recommendation: The Office of Clinical Pharmacology has determined that the PK and PD results support a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen and recommends approval of EP2006.

6. EFFICACY (This section is excerpted from the reviews of Dr. Kyung Lee.)

This review evaluates the results of the clinical study, EP06-302 (PIONEER) which was a randomized, double-blind, parallel-group, multi-center study of EP2006 and US-licensed Neupogen in histologically proven patients with breast cancer. Patients eligible for neoadjuvant or adjuvant treatment were treated with myelosuppressive TAC chemotherapy (Taxotere [docetaxel 75 mg/m²] in combination with Adriamycin [doxorubicin 50 mg/m²] and Cytosan [cyclophosphamide 500 mg/m²]), all given IV on day 1 of each of six 21-day cycles).

A total of 192 patients were planned to be assigned into four arms (48/group) randomly; Group 1: EP2006 for Cycle 1 through 6; Group 2: EP2006 for Cycles 1, 3, and 5 and US-licensed Neupogen for Cycles, 2, 4, and 6; Group 3: US-licensed Neupogen cycles 1, 3, and 5 and EP2006 for Cycles 2, 4, and 6; Group 4: US-licensed Neupogen for Cycles 1 through 6 (See Table 2). The pre-specified primary objective of this study was to demonstrate non-inferiority of EP2006 versus US-licensed Neupogen with respect to the mean duration of severe neutropenia (DSN), which was defined as the number of consecutive days with grade 4 neutropenia (absolute neutrophil count [ANC] less than $0.5 \times 10^9/L$), during Cycle 1 of the neoadjuvant or adjuvant TAC regimen in patients with breast cancer.

The primary endpoint was the duration of severe neutropenia (DSN) in days in cycle 1 and analysis conducted in the per-protocol population (PP) (101 patients in the EP2006 group in Cycle 1 and 103 patients in the US-licensed Neupogen group in Cycle 1). The analysis of DSN for the EP2006 group and the US-licensed Neupogen group was restricted to Cycle 1, and did not consider subsequent cycles.

In the presentation of the daily mean ANC in Cycle 1 (see Figure 1 on page 18 of the review of Dr. Kyung Lee), the number of subjects still being monitored on each day is based on the subjects still being monitored irrespective of whether there was an ANC value for that patient on that day, whereas in Figure 2 on page 19 of Dr. Kyung Lee's review which depicts the sponsor's representation of the mean ANC on each day of Cycle 1, if a subject's ANC value is missing, then this subject is not counted in the sample size on that day in the sponsor's graph.

The randomization stratification factor was kind of therapy (adjuvant therapy vs. neoadjuvant therapy). The primary analysis was analysis of covariance with covariates treatment status (adjuvant vs neoadjuvant) and baseline absolute neutrophil count, based on the per-protocol

population (the subgroup of subjects who received treatment and had no major protocol violations).

The data provided in the submission could be used to provide a supportive evaluation of the similarity of the products by considering the width of the confidence interval for the difference in mean DSN. If the difference is sufficiently small (± 1 day) with a narrow confidence interval, one might conclude that the difference is not clinically meaningful. This conclusion is supported by a discussion in the Clinical Pharmacology review of Dr. Sarah Schrieber on page 8, paragraph 2, lines 1-3, as well as another discussion on page 15 (see reviewer's comment) in the Statistics review of Dr. Kyung Lee. We conclude that there was no clinically meaningful difference between the EP2006 group and the US-licensed Neupogen group with respect to the efficacy endpoint results. The mean DSN in Cycle 1 was 1.17 days and 1.20 days for EP2006 and US-licensed Neupogen, respectively. The 90% CI of the mean difference is (-0.21, 0.28). The analysis showed that EP2006 is equivalent to US-licensed Neupogen in terms of efficacy as measured by the mean difference of DSN between EP2006 and US-licensed Neupogen being less than 1 day for both the upper and lower bounds of the 90% CI. For details, please see the review of Dr. Kyung Lee.

Regulatory Recommendation: On the basis of the efficacy results, the recommendation is for approval.

7. SAFETY: (This section is excerpted from the review of Dr. Donna Przepioraka).

A detailed analysis of safety outcomes was conducted using data from Study EP06-302, a randomized study comparing EP2006 to US-licensed Neupogen for prevention of chemotherapy-induced neutropenia in patients with breast cancer. The patient population included 53 subjects randomized to treatment with EP2006, 52 subjects to treatment with US-licensed Neupogen, and 109 subjects to treatment with both study agents in an alternating fashion. The study agents regimen was consistent with the proposed dose-schedule for chemotherapy-induced neutropenia. The majority of the subjects (89%) received all six planned cycles of therapy. The study population was monitored for deaths, serious adverse events, adverse events of interest, common adverse events, immunogenicity and common laboratory tests. Follow-up was through 4 weeks after the last dose of study drug.

Analysis of the safety data for Study EP06-302 showed:

- There were no related fatal TEAE or related SAEs reported.
- The incidence of the cardinal adverse events musculoskeletal pain and injection site reaction were similar between subjects treated with EP2006 or US-licensed Neupogen in Cycle 1 and across Cycles 1-6 (which considered only arms 1 and 4). There was no excess discordance for either of these cardinal adverse events in a within-subject comparison.

- The incidence of related TEAE was also similar between EP2006 and US-licensed Neupogen. There were too few grade ≥ 3 TEAE or grade ≥ 3 laboratory abnormalities for a meaningful comparison.
- There were no related TEAE with allergic reaction event terms specifically. The broad SMQ analysis showed a similar incidence of nonspecific signs and symptoms of hypersensitivity events for both study agents when compared in Cycle 1 and across Cycles 1-6, which only considered the non-switching arms 1 and 4.

There were 204 healthy subjects in six studies comparing EP2006 and either US-licensed Neupogen or EU-approved Neupogen in a cross-over fashion using various single- or multiple-dose schedules. The incidences of any TEAE or any TEAE in the SOC Musculoskeletal and connective tissue disorders were similar for both treatment periods in these studies.

In summary, safety outcomes were similar for patients or healthy volunteers treated with either EP2006 or US-licensed Neupogen. For details, please see the review of Dr. Donna Przepiorka.

Regulatory Recommendation: Based on this analysis of safety, approval is recommended.

8. IMMUNOGENICITY: (This section was derived in part on the review of Dr. Farouk Sheikh).

The Sponsor validated their anti-drug antibody binding assay using a Radio Immuno Precipitation (RIP) method and determined a screening assay cut-point and a confirmatory cut-point using serum samples from healthy subjects (study EP06-109 and study) as well as from breast cancer patients (EP06-302). Using these validated assays, the Sponsor evaluated the immunogenicity in study subjects who received EP2006 and US-licensed Neupogen. The design of the clinical studies where samples were obtained was appropriate for an adequate assessment of immunogenicity. Additionally, the Sponsor submitted immunogenicity results from five clinical studies that used EP2006 and EU-approved Neupogen.

The Sponsor's ADA screening assay found 2 of 1583 samples (0.001%) from study EP06-302 in patients with cancer were ADA-positive whereas 3 of 81 samples (3.7%) from study EP06-109 in healthy volunteers screened ADA-positive. FDA recommends a 5% false positive detection incidence for ADA screening assays as a method to minimize false negative results. The discrepancy in these results indicated that the screening assay did not perform consistently.

Therefore, the Agency advised the sponsor in a teleconference on December 3, 2014 to re-establish the cut-point using the pre-dose and pre-chemotherapy samples obtained from study EP06-302 and reanalyze the samples. Following determination of a new cut-point, the sponsor reanalyzed 1583 samples from study EP06-302. This analysis indicated that 13% of these samples screened ADA positive. These putatively positive samples were further evaluated in the

confirmatory assay and no samples were confirmed to be positive. The CDTL agrees with this analysis and its conclusion.

In summary, none of the samples were identified as positive for the presence of anti-drug antibodies to EP2006 or filgrastim, which is supportive that there is no clinically meaningful difference between US-licensed Neupogen and EP2006 with respect to anti-drug-antibody responses.

The Immunogenicity Review Team concluded on the basis of its review that the results from the immunogenicity studies support a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen. The CDTL agrees with this conclusion. For details, please see the Immunogenicity Review.

Regulatory Recommendation: Approval.

9. ADVISORY COMMITTEE MEETING: Following presentations by both the sponsor and the FDA, the Advisory Committee was asked to vote on the following question: “Does the committee agree that based on the totality of the evidence, EP2006 should receive licensure as a biosimilar product for each of the 5 indications for which US-licensed Neupogen is currently licensed?” The Advisory Committee voted unanimously for approval of EP2006 as a biosimilar product for each of the 5 indications for which US-licensed Neupogen is currently licensed.

10. PEDIATRICS: As currently presented, Zarxio prefilled syringe with BD Ultrasafe™ Passive Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg), which impacts children who weigh less than 36 kg. The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of Zarxio less than 0.3 mL (180 mcg) for direct administration to patients. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors.

Thus, the pediatric assessment was inadequate to support dosing and administration for pediatric patients requiring less than 0.3 mL (for pediatric patients weighing less than 36 kg). A deferral was discussed with PeRC and considered appropriate.

Thus, a Post Marketing Requirement (PMR) is being issued (see PMR #1 in Section 11 below), the goal of which is the development of a presentation that allows direct administration of the product of doses less than 0.3 mL to pediatric patients, and to evaluate whether that the doses can be measured accurately using this presentation.

11. DRAFT POST MARKETING COMMITMENTS AND REQUIREMENTS: (for final language, see approval letter).

PMR - 1 PMR Description of study:	To develop a presentation that can be used to directly and accurately administer Zarxio 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.
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PMR Schedule Milestones:	Preliminary Protocol Submission:	03/06/2015
	Final Protocol Submission:	06/06/2015
	Study Completion:	03/06/2016
	Final Report Submission:	06/06/2016

PMC - 2 PMC Description of study:	To enhance the control strategy (b) (4) by development, validation, and implementation of an analytical method to assess (b) (4) concentration for release or in-process testing of Zarxio drug product
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PMC Schedule Milestone:	Final Report Submission:	MM/YYYY
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PMC - 3 PMC Description of study:	To confirm the stability of Zarxio drug product in 5% glucose at concentrations ranging from 5 mcg/ml to 15 mcg/ml of Zarxio, 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.
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PMC Schedule Milestone:	Final Report Submission:	MM/YYYY
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PMC - 4 PMC Description of study:	To re-adjust the (b) (4) bioburden limit of (b) (4) for the (b) (4) drug substance based on process capability from 20 batches of product.
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PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 5 PMC Description of study:	Establish bioburden and endotoxin action limits (b) (4) after data from more than 20 batches are available and provide the limits in an Annual Report.
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PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
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	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 6 PMC Description of study:	Conduct studies to support the worst-case hold times [REDACTED] ^{(b) (4)} [REDACTED] at scale from a microbiology perspective. Provide study results in an Annual Report.	
PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 7 PMC Description of study:	To update the stability program for Zarxio pre-filled syringe drug product to include the syringe force measurements glide force and injection 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.	
PMC Schedule Milestone:	Final Report Submission:	MM/YYYY

12. LABELING: Labeling is currently under negotiation between the FDA and the Applicant.

13. REGULATORY RECOMMENDATION: This CDTL reviewer recommends approval of EP2006 as a biosimilar to US-licensed Neupogen for all 5 indications for which US-licensed Neupogen is currently licensed. Review of BLA 125553 supports a determination that EP2006 is biosimilar to US-licensed Neupogen: EP2006 is highly similar to US-licensed Neupogen notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between EP2006 and US-licensed Neupogen in terms of safety, purity, and potency of the product.

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/s/

ALBERT B DEISSEROTH
02/26/2015