CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125553Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	125553
Applicant Name	Sandoz Pharmaceuticals, Inc.
Date of Submission	05/08/14
BsUFA Goal Date	03/08/15
Proprietary Name / **Non-proprietary Name**	ZARXIO / filgrastim-sndz/EP2006
Dosage Forms / Strength	Pre-filled syringe containing 300 mcg/0.5 mL Pre-filled syringe containing 480 mcg/0.5 mL
Proposed Indication(s)	• 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 • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia • 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 • Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis • 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
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Donna Przepiorka, M.D., Ph.D./Albert Deisseroth, M.D., Ph.D.
Statistical Review	Kyung Yul Lee, Ph.D./Lei Nie, Ph.D./Thomas Gwise, Ph.D./ Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Christopher Sheth, Ph.D./Haw-Jyh Chiu, Ph.D./John Leighton, Ph.D.
CMC Review/OBP Review	Maria-Teresa Gutierrez-Lugo, Ph.D./ Faruk Sheikh, Ph.D./ Frederick Mills, Ph.D. /Susan Kirshner, Ph.D./Jibril Abdus-Samad, Pharm.D./ Gibbes Johnson, Ph.D./ Xiaoyu Dong, Ph.D./Meiyu Shen, Ph.D./Yi Tsong, Ph.D.
Microbiology Review	N/A Bo Chi, Ph.D./Steve Fong, Ph.D./Patricia Hughes, Ph.D./
Clinical Pharmacology Review	Sara Schreiber,Pharm.D./Anshu Marathe, Ph.D./Vikram P Sinha, Ph.D./Nam Atiqur Rahman, Ph.D.
OPDP/DDMAC	Adam George, Pharm.D./Nathan Caulk, MS BSN, RN/Barbara Fuller BSN,RN/ LaShawn Griffiths, BSN, RN
OSI	Anthony Orencia, M.D./ Janice Pohlman, M.D., M.P.H./Susan Thompson, M.D./Michael F. Skelly, Ph.D./Sam Haidar, Ph.D.
CDTL Reviews	Albert Deisseroth, M.D., Ph.D.
OSE/DMEPA	Neil Vora/Yelena Maslov/Kellie Taylor
CDRH	Ryan McGowan/Nicholas W. Werner/Alan Stevens/Richard C. Chapman/Rakhi Dalal, Ph.D./Francisco Vicenty

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Sandoz submitted a biologics license application (BLA) under Section 351(k) of the Public Health Service Act (PHS Act) for EP 2006, a proposed biosimilar to US-licensed Neupogen (filgrastim). Amgen's BLA # 103353 for Neupogen was initially licensed by FDA on February 20, 1991, and US-licensed Neupogen is the reference product for Sandoz' 351(k) BLA. Sandoz is seeking licensure of filgrastim-sndz (referred to as EP2006 during development) for the same indications as approved for US-licensed Neupogen. The product is proposed to be available for use as a pre-filled syringe (PFS).

Sandoz has marketed Zarzio (EP2006) in Europe since 2009.

The BsUFA goal date is March 8, 2015.

2. Background

The following text is from the January 7, 2015 Oncologic Drugs Advisory Committee Briefing Document:

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the"reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data…

Section 351(k) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences.

The level of residual uncertainty after the comparative analytical characterization drives both the type and amount of data needed to resolve remaining questions about whether the proposed product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and whether there

are "no clinically meaningful differences" between the proposed product and the reference product in terms of safety, purity, and potency. The results of nonclinical and/or clinical studies to resolve remaining questions should further reduce residual uncertainty and support a demonstration of biosimilarity. For example, additional data may resolve certain questions (e.g., a structural difference with unknown impact may show no difference(s) when evaluated in appropriate functional assays) or may identify other differences (e.g., pharmacokinetic (PK) differences) that would raise concerns as well as residual uncertainty such that additional studies/data would be necessary. In both examples, while the differences may raise questions about whether the proposed biosimilar product is highly similar to the reference product, or whether there may be clinically meaningful differences between the products, identified differences should not be considered in isolation and do not necessarily preclude continued development to support a demonstration of biosimilarity. However, the applicant would need to evaluate the observed differences and explain why the differences between the proposed biosimilar product and the reference product should not preclude FDA from finding the proposed product meets the standard for biosimilarity.

The 'totality of the evidence' submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the US-licensed reference product. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

3. CMC/Device

No issues exist that would preclude approval. The following text is taken from the Office of Biotechnology Executive Summary:

Approval of Zarxio as a biosimilar is supported by analytical similarity studies. A total of 20 lots of Zarxio DP, 6 lots of EP2006 drug substance (DS), and 10-15 lots of US-licensed Neupogen were evaluated using the methods listed …. The results from these studies demonstrated that Zarxio is highly similar to US-licensed Neupogen notwithstanding minor differences in clinically inactive components. The analytical similarity studies did not raise residual uncertainties about the demonstration of highly similar between Zarxio and US-licensed Neupogen. …

The non-clinical and clinical program for Zarxio, including five PK/PD studies used a non US-licensed product (i.e. EU-approved Neupogen) as active comparator. Pair-wise analytical comparisons of Zarxio (up to 20 lots), US-licensed Neupogen (up to 10-15 lots) and EU-approved Neupogen (34-52 lots) supported a scientific bridge based on the relatively simple structure of the protein, lack of post-translation modifications, and the robustness of the pair-wise analytical characterization.

From the Statistical Review and Evaluation of the Functional and Structural Assessment:

Based on the Agency's assessment, the results from statistical equivalency testing of Bioactivity (%) and Content (%) support the demonstration that EP2006 drug product is highly similar to US-licensed Neupogen. The results of similarity between US-licensed and EU-approved Neupogen provide relevant information for bridging.

From the immunogenicity review:

There are no clinically meaningful differences between EP2006 and the US- licensed Neupogen® with respect to anti-drug antibody responses resulting from administration of these products.

The Sponsor validated 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) 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 these studies was appropriate to assess immunogenicity. Additionally, the Sponsor submitted immunogenicity results from five clinical studies that used EP2006 and EU-approved Neupogen®. None of the samples were identified as positive for the presence of anti-drug antibodies to EP2006 or Neupogen® indicating that there is no clinically significant difference between US-licensed Neupogen and EP2006 with respect to anti-drug-antibody responses.

From the Microbiology reviews of drug substance and drug product:
The drug substance part of this BLA is recommended for approval from quality microbiology perspective with the following post-market commitments:
Establish bioburden and endotoxin action limits (b) (4) *after data from more than 20 batches are available.*

Conduct studies to support the worst-case hold times (b) (4) (b) (4) *at scale from microbiology perspective.*

The 351(k) BLA is recommended for approval from a product quality microbiology perspective. One PMC is listed at the end of the Review.

The recommended PMC is:

To re-adjust the [redacted] bioburden limit of [redacted] based on process capability from 20 batches of product.

In total six PMCs are proposed based on the product reviews and CDRH reviews.

The dating period for the drug substance is [redacted] from the date of manufactured when stored at [redacted]

4. Nonclinical Pharmacology/Toxicology

No issues exist that would preclude approval. From the Non-Clinical Pharmacology/Toxicology primary review:

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. According to the approved Neupogen labeling, endogenous G-CSF is a lineage specific colony-stimulating factor which is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and 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). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production of hematopoietic cell types other than the neutrophil lineage.

As part of Sandoz's global development strategy for EP2006, EP2006 was compared head-to-head with EU-approved Neupogen as the comparator product in five animal studies assessing the pharmacodynamics (PD), toxicity, toxicokinetics (TK) and local tolerance of the product. A graphical representation of the development program is presented in Figure 1. The nonclinical development of EP2006 involved selecting dose levels and use of the subcutaneous (SC) route of administration to maximize the sensitivity to detect potential differences between EP2006 and EU-approved Neupogen. Analytical bridging studies (see CMC review) comparing EP2006, EU-approved Neupogen, and US-licensed Neupogen established that all three products are similar at the physiochemical level. From the perspective of nonclinical pharmacology and toxicology, there are no residual uncertainties regarding the similarity of EP2006 to the reference product.

5. Clinical Pharmacology/Biopharmaceutics

No issues exist that would preclude approval. From the primary review:

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.

The Applicant submitted four pharmacokinetic (PK) and pharmacodynamic studies in healthy volunteers and three of the studies included EU-approved Neupogen. In order to be able to utilize the comparative data, the Applicant needed to provide data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product. As noted in the product reviews and clinical pharmacology reviews, the Applicant was successful in establishing a scientific bridge thus allowing the Agency to consider the data generated from studies where the comparator was EU-approved Neupogen as a part of the totality of the evidence demonstrating biosimilarity.

The following text is from the primary review regarding the Agency analyses:

The 90% CI for AUC and Cmax after a single dose were within the pre-defined limits of 80-125%. The 95% CI for AUEC and ANCmax for ANC after 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 (7 daily 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.

There are no outstanding clinical pharmacology issues which would preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No issues exist that would preclude approval. The clinical and statistical review teams reviewed the submitted clinical pharmacology studies and the clinical study.

The following summary is from the primary clinical review:

None of the studies submitted was designed prospectively to assess equivalence of EP2006 and US-licensed Neupogen for a clinical efficacy or safety endpoint in an intended population.

Study EP06-302 was a randomized, double-blind comparison of EP2006 and US-licensed Neupogen for prevention of severe neutropenia in patients with breast cancer being treated with up to 6 cycles of combination chemotherapy using docetaxel, doxorubicin, and cyclophosphamide (TAC). Chemotherapy was

administered on day 1 of each 21-day cycle, and EP2006 or US-licensed Neupogen 5 µg/kd/day sc was given from day 2 until neutrophil recovery. There were 218 subjects randomized equally into one of four groups to receive EP2006 for all cycles, US-licensed Neupogen for all cycles, EP2006 then US-licensed Neupogen in alternate cycles, or US-licensed Neupogen then EP2006 in alternate cycles. Baseline demographics and disease characteristics were adequately balanced between arms.

The primary endpoint was duration of severe neutropenia (DSN) in Cycle 1. Although Study EP06-302 was designed as a noninferiority trial, FDA conducted a post hoc 2-sided analysis to ensure there were no clinically meaningful differences between EP2006 and US-licensed Neupogen with regard to the primary endpoint. The between-group analysis of the primary endpoint of Cycle 1 DSN included 101 subjects treated with EP2006 and 103 subjects treated with US-licensed Neupogen. The DSN difference (control-experimental) was 0.04 days with a 90% confidence interval (CI) of -0.21 to 0.28 days. It was estimated that the results represented no more than a 3% increase or decrease in the incidence of febrile neutropenia, and this was considered clinically insignificant.

Key secondary endpoints, including febrile neutropenia, days of fever, absolute neutrophil count (ANC) nadir, and time to ANC recovery in Cycle 1 and across all cycles, were to be reported descriptively. The between-group comparisons and within-subject comparisons of the key secondary endpoints showed similar results for EP2006 and US-licensed Neupogen.

Study EP06-302 was conducted in a patient population addressed by only one of the five indications approved for US-licensed Neupogen. The applicant proposed to use extrapolation based on the mechanism of action along with a demonstration of biosimilarity to obtain the other four indications for which US-licensed Neupogen is currently licensed.

The safety outcomes were assessed for similarity in all seven clinical studies. The Product Quality Reviewer indicated that the data submitted by the applicant provided an adequate scientific bridge to justify the relevance of the clinical studies that used EU-approved Neupogen as a comparator to support a demonstration of biosimilarity in this application.

Safety outcomes were assessed in Study EP06-302 in 53 subjects with breast cancer 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 incidence of the cardinal adverse events musculoskeletal pain (25% vs 29%) and injection site reaction (2% vs 1%) were similar between subjects treated with EP2006 or US-licensed Neupogen in Cycle 1. Results were comparable across Cycles 1-6, and there was no excess discordance for either of these cardinal adverse events in a within-subject comparison.

Common treatment emergent adverse events (TEAE) at the Preferred Term level as well as related TEAE were similar in incidence when compared between subjects treated with EP2006 or US-licensed Neupogen in Cycle 1 or across Cycles 1-6, and when compared within subjects who alternated treatments. 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 standardized MedDRA query (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.

Among the 204 healthy volunteers in the 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 System Organ Class (SOC) Musculoskeletal and connective tissue disorders were similar for both treatment periods.

In summary, the analysis of Study EP06-302 showed no clinically meaningful differences between EP2006 and US-licensed Neupogen with respect to DSN in cycle 1, and safety outcomes were similar for patients treated with either EP2006 or US-licensed Neupogen. These results would support the demonstration of biosimilarity based on the analytical comparisons and the assessment of pharmacokinetic and pharmacodynamic parameters in healthy subjects. The use of extrapolation to support all five currently-approved indications based on mechanism of action is reasonable in conjunction with a finding of biosimilarity for this product.

From the statistical team review:

To support a demonstration of biosimilarity, a stepwise approach was used following the FDA's scientific recommendation. The stepwise approach starts with structural and functional characterization of both the proposed biosimilar product and the reference product. Results of nonclinical and/or clinical studies follow to assess remaining questions with regards to potential residual uncertainty about biosimilarity.

This review is to evaluate the results of the clinical study, EP06-302 (PIONEER) which was a randomized, double-blind, parallel-group, multi-center study of EP2006 and Neupogen® in histologically proven breast cancer patients. 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 Cytoxan® [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 Neupogen for Cycles, 2, 4, and 6; Group 3 Neupogen cycles 1, 3, and 5 and EP2006 for Cycles 2, 4, and 6; Group 4 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 Neupogen® (US-licensed) 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 × 109/L), during Cycle 1 of the neoadjuvant or adjuvant TAC regimen in breast cancer patients. 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 and 103 patients in the Neupogen group). 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 evaluate the claim that the products are similar 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.

We conclude that there was no clinically meaningful difference between the EP2006 group and the 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 Neupogen, respectively. The 90% CI of the mean difference is (-0.21, 0.28). The analysis showed that EP2006 is equivalent to Neupogen in terms of efficacy as measured by the mean difference of DSN between EP2006 and Neupogen being less than 1 day for both the upper and lower bounds of the 90% CI.

Our conclusion is consistent with the advisory committee's recommendation. The advisory committee meeting for oncology drug products was held on January 7, 2015 for this application. The advisory committee voted unanimously (14-0) that EP2006 should receive licensure as a biosimilar product for each of the five indications for which US-licensed Neupogen is currently approved.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstrations of efficacy for both indications. I also concur with Dr. Deisseroth's CDTL review, which provides certain additional explanation of review issues.

8. Safety

See Clinical section above. The primary reviewer did not identify any new safety signals for EP2006 that had not been previously identified for US-licensed Neupogen. Similar frequencies of adverse events were observed for both products in the clinical trial.

9. Advisory Committee Meeting

This product was discussed at an Oncologic Drugs Advisory Committee meeting on January 7, 2015. The Committee voted 14 (yes) to 0 (no) that the EP2006 should receive licensure as a biosimilar product for each of the five indications for which US-licensed Neupogen is approved.

10. Pediatrics

The applicant submitted that the pediatric assessment for all proposed indications is complete based on its proposal to extrapolate pediatric data and information from the reference product (Neupogen) to EP2006 based on a proposed demonstration of biosimilarity, and the pediatric review committee concurred. However, the safety mechanism on the prefilled syringe obscures the ability of the healthcare provider or caregiver to directly administer doses of the product less than 0.3 mL; therefore, it was determined that the pediatric assessment was inadequate to support direct administration for pediatric patients requiring less than 0.3 mL. A deferral was discussed with the pediatric review committee and considered appropriate; therefore, there will be a PMR for the sponsor to develop a presentation that can be used to directly administer doses less than 0.3 mL. A statement will also be placed in the labeling regarding this issue.

11. Other Relevant Regulatory Issues

Office of Scientific Investigation (OSI)
The following text is from the summary review prepared by OSI:
The preliminary regulatory classification of Dr. Cseh and Sandoz Pharmaceuticals is No Action Indicated (NAI). The study data collected from these clinical sites appear reliable in support of the requested indication.

Additionally from the Bioequivalence Establishment Inspection Report Review, the team concluded:
The results from the pharmacokinetic and pharmacodynamics portions of studies EP06-101, EP06-103, EP06-109, and EP06-301 are acceptable for Agency review.

There are no unresolved relevant regulatory issues. No residual uncertainty exists which would preclude approval.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  Approval for Sandoz' ZARXIO, filgrastim-sndz (referred to as EP2006 during development), is based on the totality of the evidence presented in BLA 125553. Sandoz presented sufficient analytical (structural and functional) similarity data to support a conclusion that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. Sandoz presented sufficient animal study data to support the demonstration of biosimilarity between EP2006 and the reference product. Sandoz also presented sufficient human PK and pharmacodynamic (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data to demonstrate that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Due to the fact that EP2006 was initially approved in the EU and the application contained comparisons to EU-approved Neupogen, Sandoz had to provide an adequate scientific bridge between all three products (EP2006, EU-approved Neupogen and US-licensed Neupogen). Thus, Sandoz performed a three way, pair-wise analytical comparison of US-licensed Neupogen, EU-approved Neupogen, and EP2006 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. The scientific bridge established between EP2006, US-licensed Neupogen, and EU-approved Neupogen, justified the relevance of these comparative data with EU-approved Neupogen to support a demonstration of biosimilarity to US-licensed Neupogen. No residual uncertainty exists which would preclude licensing of this product.

  It must be noted that Sandoz requested a determination of biosimilarity, and not interchangeability, and therefore the Agency did not evaluate whether the proposed product could satisfy the additional standard for interchangeability under the BCPI. Therefore, ZARXIO has not been determined to be interchangeable.

- Risk Benefit Assessment
  Based on the Agency's review of the rigorous analytical and clinical data package submitted in BLA 125553, Sandoz' ZARXIO has a favorable risk-benefit profile, as does the currently marketed US-licensed Neupogen. As discussed above, the two products are biosimilar, which means ZARXIO is highly similar to US-licensed Neupogen notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between ZARXIO and US-licensed Neupogen in terms of safety, purity, and potency of the product. Although routine

pharmacovigilance will be conducted as for all other marketed products, the Agency does not anticipate any efficacy or new safety issues.

- Recommendation for Post marketing Risk Management Activities (PMR) – We have asked the applicant to do the following:
  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.

- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)
  We have asked the applicant for the following six PMCs (draft not final language):
  1) To enhance the control strategy (b) (4).
  2) 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.
  3) To re-adjust the (b) (4) bioburden limit of (b) (4) for the (b) (4) based on process capability from 10 batches of product.
  4) Establish bioburden and endotoxin action limits (b) (4) (b) (4) after data from more than 10 batches are available and provide the limits in an Annual Report.
  5) Conduct studies to support the worst-case hold times (b) (4) (b) (4) (b) (4) at scale from a microbiology perspective.
  6) To update the stability program for ZARXIO (filgrastim-sndz) pre-filled syringe drug product to include syringe force measurements, glide force and functional testing of the needle safety device.

     For final versions of the PMRs and PMC see the approval letter.

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/s/

JESSICA L BOEHMER
03/05/2015

ANN T FARRELL
03/06/2015