Division Director Summary Review

Date	January 30, 2015
From	NAM Atiqur Rahman, Ph.D. Division Director, Division of Clinical Pharmacology V Office of Clinical Pharmacology
Subject	Division Director's Memo
BLA #	125553
Applicant's Name	Sandoz, Inc.
Proposed Indication(s)	All Indications for which US-Licensed Neupogen is currently licensed
Recommendation	Clinical Pharmacology data contribute to the totality of evidence and support the approval of the product for all indications

Sandoz Inc. submitted a Biologic License Application (BLA) for EP2006 under section 351(k) of the Public Health Service Act as a biosimilar product to the US-licensed product Neupogen which is marketed by Amgen Inc. The clinical pharmacology data contribute substantially to the determination that there are **"no clinically meaningful differences"** between EP2006 and the reference product in terms of safety, purity, and potency of the product. These data contribute to the totality of evidence needed to support the approval of EP2006 as a biosimilar product to US-licensed product Neupogen.

EP2006 was approved by the EMA in 2009 and is now marketed in over 60 countries worldwide, which has resulted in a clinical exposure of more than 7.5 million patient-days (Sandoz ODAC presentation, January 7, 2015).

Granulocyte Colony Stimulating Factor (G-CSF) is a non-glycosylated, single amino acid chain, 18.8 KDa protein. Its structure is simpler than the pegylated proteins and antibodies that are marketed as therapeutic proteins. Neutrophils, the most abundant granulocytes, are depleted in patients treated with myelosuppressive therapy. The depletion of neutrophils leads to various types of infections manifested by febrile neutropenia that require intravenous antibiotic usage and hospitalization. G-CSF is a useful treatment modality for these patients because it causes hematopoietic recovery and immune response. G-CSF mediates its action by binding to the G-

CSF receptors that are present on the precursor cells in the bone marrow and initiates proliferation and differentiation of the precursor cells into mature granulocytes. The intensity and duration of severe neutropenia (neutrophil count ≤ 500/mL) correlate with the incidence and severity of infection. Duration of severe neutropenia (DSN) is an important clinical endpoint that determines efficacy of G-CSF products. Absolute neutrophil count (ANC) in blood is a measure that relates with DSN and it is considered an acceptable pharmacodynamics (PD) marker for neutropenia-related indications.

Binding of G-CSF to its receptor also causes mobilization of hematopoietic progenitor cells into the peripheral blood, which are collected by leukapheresis and transplanted into patients. The success of the mobilization of hematopoietic progenitor cells is demonstrated by the total number of Colony Forming Unit-Granulocyte, Monocyte (CFU-GM) and/or $CD34^+$ cells collected by leukapheresis for engraftment. Therefore, $CD34^+$ cell count is a PD marker for mobilization indication of G-CSF.

Sandoz developed a PK- (pharmacokinetics) and PD-based clinical program to assess the similarity of EP2006 and support the demonstration of no clinically meaningful difference in safety, purity, and potency of EP2006 compared with the US-licensed product Neupogen. The sponsor received advice from the Agency during the development of EP2006 for the US market and the program reflects evolving FDA scientific advice, which is currently reflected in the draft guidance for industry titled, "Clinical Pharmacology Data to Support Demonstration of Biosimilarity to a Reference Product" published in May 2014. Similar advice is currently being given to sponsors developing proposed biosimilar G-CSF products for marketing in the United States.

Sandoz submitted four clinical studies that evaluated single and multiple subcutaneous (SC) doses between 1 and 10 mcg/kg in healthy subjects. The objectives of these studies were to establish the PK and PD similarity of EP2006 with US-licensed Neupogen. Among these, three studies used EU-approved Neupogen. A 3-way comparison of the analytical similarity of critical quality attributes (analytical bridge) of EP2006, US-licensed Neupogen, and EU-approved Neupogen justified the relevance of the clinical PK and PD data generated using EU-approved Neupogen. Overall, the clinical studies demonstrated PK and PD similarity between EP2006 and US-licensed Neupogen based on the 90% confidence interval (CI) for the geometric mean ratio (GMR) of area under the plasma concentration and time curve (AUC) and maximum plasma concentration (C_{max}) within the pre-specified limits of 80 to 125% and the 95% CI for the GMR of area under the effect curve (AUEC) and maximum concentration of ANC and $CD34^+$ within the pre-specified 80 to 125% limits. The Advisory Committee (Oncology Drug Advisory Committee, ODAC) held on January 7, 2015 agreed with the review team's conclusion that the PK and PD study results added to the totality of the evidence to support a demonstration of biosimilarity of

EP2006 and US-licensed Neupogen and recommended that EP2006 should receive licensure as a biosimilar product for all the indications for which US-licensed Neupogen is currently licensed.

The clinical pharmacology studies of EP2006 consisting of PK similarity at single SC doses ranging from 1 to 10 mcg/kg and PD similarity at multiple SC doses ranging from 2.5 to 10 mcg/kg in healthy subjects using ANC and $CD34^+$ as PD markers is sensitive and relevant and addresses the residual uncertainties remaining after the analytical similarity assessment. The single dose and multiple dose PK and PD data were critical elements in the EP2006 program to support both the neutropenia and mobilization indications. The comparative clinical data in breast cancer patients further supported the conclusions drawn from the PK and PD studies in healthy volunteers. The PK and PD development program is consistent with the scientific expectations as articulated in the draft guidance for industry titled, "Clinical Pharmacology Data to Support Demonstration of Biosimilarity to a Reference Product." The marketing experience of EP2006 in over 60 countries and clinical experience of more than 7.5 million patient-days indicate no major safety issues. The Divisions of Clinical Pharmacology V and Pharmacometrics in the Office of Clinical Pharmacology (OCP) conclude that the clinical pharmacology data provides compelling evidence of no clinically meaningful difference in safety, purity, and potency of EP2006 and the US-licensed Neupogen and recommends that the product should be approved. Sandoz should provide a comprehensive summary of post marketing safety and immunogenicity data of EP2006 generated in countries where this product is marketed.

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02/05/2015