Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
January 7, 2015

Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland

Topic: The committee met to discuss biologics license application (BLA) 125553 for EP2006, a proposed biosimilar to Amgen Inc.'s NEUPOGEN (filgrastim), submitted by Sandoz, Inc. The proposed indications (uses) for this product are: (1) 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; (2) for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia; (3) 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 marrow transplantation; (4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and (5) for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

These summary minutes for the January 7, 2015, meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on March 2, 2015.

I certify that I attended the November 6, 2014, meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Caleb D. Briggs, PharmD
Designated Federal Officer, ODAC

/S/
Deborah K. Armstrong, MD
Chairperson, ODAC
The following is the final report of the Oncologic Drugs Advisory Committee (ODAC) meeting held on January 7, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Office of Hematology and Oncology Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm394134.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on January 7, 2015 from 8:00 a.m. until 4:00 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA, and the Sponsor, Sandoz, Inc. The meeting was called to order by Deborah Armstrong, MD, (Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 300 people in attendance. There were 18 Open Public Hearing speakers.

**Issue:** The committee met to discuss biologics license application (BLA) 125553 for EP2006, a proposed biosimilar to Amgen Inc.’s NEUPOGEN (filgrastim), submitted by Sandoz, Inc. The proposed indications (uses) for this product are: (1) 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; (2) for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia; (3) 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 marrow transplantation; (4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and (5) for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

**Attendance:**

**ODAC Members Present (Voting):** Deborah K. Armstrong, MD (Chairperson); Bernard F. Cole, PhD; Tito Fojo, MD, PhD; James Liebmann, MD; Bruce J. Roth, MD; Jane Zones, PhD (Consumer Representative)

**ODAC Members Present (Non-Voting):** Howard Fingert, MD (Industry Representative)

**ODAC Members Not Present (Voting):** Harold J. Burstein, MD, PhD; Aman Buzdar, MD, FACP; Louis F. Diehl, MD; Michael Menefee, MD
Temporary Members (Voting): William Bensinger, MD; Randy Hillard, MD (Patient Representative); Ginna G. Laport, MD; Donald Mager, PharmD, PhD; Antonio Moreira, PhD; Kathleen Neville, MD, MS; David F. Stroncek, MD; Scott Waldman, MD, PhD

FDA Participants (Non-Voting): Leah Christl, PhD; John Jenkins, MD; Edvardas Kaminkas, MD; Steven Kozlowski, MD; Richard Pazdur, MD

Designated Federal Officer (Non-Voting): Caleb Briggs, PharmD

Open Public Hearing Speakers: Larry McNeely (National Coalition on Health Care); Gordon Johnston (Generic Pharmaceutical Association); Dr. Richard Markus (Amgen, Inc.); Mary Jo Carden, RPh, JD (Academy of Managed Care Pharmacy); John Klimek, RPh (National Council for Prescription Drug Programs, Inc.); Thair Phillips (RetireSafe); Diane Dorman (National Organization for Rate Disorders); Dr. Sarfaraz Niazi (Therapeutic Proteins International); Kathleen Arnsen (Lupus and Allied Diseases Association, Inc.); Jim Roach, MD, FACP, FCCP (Momemta Pharmaceuticals, Inc.); Stephen Marmaras (Gloval Healthy Living Foundation); Andrew Spiegel, Esq. (Global Colon Cancer Association); Amye Leong, MBA; Jonah Houts (Express Scripts); Robert Yapundich, MD (Alliance for Patient Access); Lawrence La Motte (Immune Deficiency Foundation); Dr. Sumant Ramachandra (Hospira, Inc.); Donna Cryder, JD.

The agenda proceeded as follows:

Call to Order and Introduction of Committee

Deborah Armstrong, MD
Chairperson, ODAC

Conflict of Interest Statement

Caleb Briggs, PharmD
Designated Federal Officer, ODAC

Opening Remarks

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research (CDER), FDA

FDA Presentation

Overview of the Regulatory Pathway and FDA’s Guidance for the Development and Approval of Biosimilar Products in the US

Leah Christl, PhD
Associate Director for Therapeutic Biologics Office of New Drugs (OND) Therapeutic Biologics and Biosimilars Team (TBBT) OND, CDER, FDA

Clarifying Questions to the Presenter
**APPLICANT PRESENTATIONS**

<table>
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<th>Topic</th>
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| Introduction                                                          | **Mark McCamish, MD, PhD**  
Global Head of Development  
Sandoz Biopharmaceuticals                                            |
| Analytical Demonstration of Biosimilarity                             | **Hansjoerg Toll, PhD**  
Head Analytical Characterization  
Sandoz Biopharmaceuticals                                              |
| Biosimilar Clinical Development Program                               | **Sigrid Balser, PhD**  
PK/PD Expert and Global Head Biostatistics  
Sandoz Biopharmaceuticals                                             |
| A Clinical Perspective on Biosimilarity                               | **Louis Weiner, MD**  
Professor and Director of Lombardi Comprehensive Cancer Center  
Georgetown University                                                 |
| Totality of Evidence and Concluding Remarks                           | **Mark McCamish, MD, PhD**                                                |
| Clarifying Questions to the Presenters                                |                                                                           |

**FDA PRESENTATIONS**

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<th>Topic</th>
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| Introduction to FDA Presentation                                       | **Albert Deisseroth, MD, PhD**  
Medical Officer Team Leader  
Division of Hematology Products (DHP)  
Office of Hematology and Oncology Products (OHOP), OND, CDER, FDA  |
| Chemistry, Manufacturing, and Controls                                | **Maria-Teresa Gutierrez-Lugo, PhD**  
Chemistry Reviewer  
Office of Biotechnology Products (OBP)  
Office of Pharmaceutical Quality (OPQ)  
CDER, FDA                                                              |
| EP2006 Statistical Equivalence Testing for Bioactivity and Content     | **Xiaoyu (Cassie) Dong, PhD**  
CMC Biostatistics Reviewer  
Division of Biometrics VI (DB VI)  
Office of Biostatistics (OB)  
Office of Translational Sciences (OTS), CDER, FDA                      |
**FDA PRESENTATIONS (CONT.)**

**Pharmacology and Toxicology**  
Chris Sheth, PhD  
Pharmacology/Toxicology Reviewer  
Division of Hematology Oncology Toxicology (DHOT), OHOP, OND, CDER, FDA

**Clinical Pharmacology**  
Sarah J. Schrieber, PharmD  
Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology V (DCP V)  
Office of Clinical Pharmacology (OCP)  
OTS, CDER, FDA

**EP2006 Immunogenicity Data**  
Susan Kirshner, PhD  
Review Chief  
Office of Biotechnology Products (OBP)  
Office of Pharmaceutical Quality (OPQ)  
CDER, FDA

**Clinical Trial Review**  
Donna Przepiorka, MD, PhD  
Clinical Reviewer  
DHP, OHOP, OND, CDER, FDA

**Summary of FDA Findings**  
Albert Deisseroth, MD, PhD

**Clarifying Questions to the Presenters**

**Open Public Hearing**

**Questions to the Committee and Committee Discussion**

**ADJOURNMENT**

**Questions to the Committee:**

1. **DISCUSSION:** Does the committee agree that EP2006 is highly similar to the reference product, US-licensed Neupogen, notwithstanding minor differences in clinically inactive components?

   **Committee Discussion:** The committee members agreed that EP2006 was highly similar to US-licensed Neupogen, based on the package of information provided in the application. The Chairperson asserted that the applicant had satisfied the required components to demonstrate similarity, and that robust safety and efficacy data from extensive use outside of the United States provides further comfort with this conclusion. One member noted specifically that EP2006 was identical in terms of amino acid composition but was
formulated differently, which would lead to certain differences in chemical properties but that these chemical differences would be minor in terms of clinical activity.

2. **DISCUSSION:** Does the committee agree that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen?

**Committee Discussion:** Overall, the committee agreed that there were no clinically meaningful differences between EP2006 and US-licensed Neupogen, and that any apparent differences in the products are unlikely to have a significant clinical impact. One committee member noted a discrepancy in the data presented by FDA and Sandoz on rate to recovery of absolute neutrophil counts, raising some uncertainty over which data set was accurate. Because of this discrepancy, the committee member noted, it was unclear whether there was a group of patients in one group who did not recover their baseline absolute neutrophil count at the specified time as compared to the other group. This member of the committee again noted that robust data from usage in Europe encourages comfort with the data. One member noted that these small differences could have clinical implications in the pediatric setting where doses are personalized. Another committee member noted that the difference seen was probably due to a small set of outliers and would perhaps not been seen if a trial had been done with a larger sample size. Members agreed that this issue may be resolved by clarifying which set of data was accurate, and that this likely did not amount to a clinically meaningful difference in most situations. Additionally, one member noted that there is no difference in the common and expected adverse effects, but there is not much data on rare adverse effects, which could be impactful for use that includes healthy patients.

3. **VOTE:** 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?

**Vote Result:** Yes: 14 No: 0 Abstain: 0

**Committee Discussion:** The committee unanimously agreed 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. One member particularly noted the strong evidence shown by the sponsor for biosimilarity that included numerous studies, the structure/function and clinical performance of EP2006. This member stated that the data demonstrated equivalence in duration of severe neutropenia with a small difference in pharmacokinetic parameters. The committee commended the FDA and sponsor for quality of their materials and presentations.

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:00 p.m.