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

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Overview of Presentation

- Overview
  - Background
  - Definitions
  - Approval Pathway for Biosimilars – General Requirements

- Development of Biosimilars
  - FDA Guidance Documents
  - Approach to Development
  - Specific Development Concepts
Overview
Background

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.

BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product.
What is an Abbreviated Licensure Pathway for Biological Products?

- A biological product that is demonstrated to be “highly similar” to an FDA-licensed biological product (the reference product) may rely for licensure on, among other things, publicly-available information regarding FDA’s previous determination that the reference product is safe, pure and potent.

- This licensure pathway permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act (PHS Act) based on less than a full complement of product-specific preclinical and clinical data → abbreviated licensure pathway.
Definition: Biosimilarity

Biosimilar or Biosimilarity means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

- 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.
Definition: Reference Product

Reference Product means:

- the **single biological product, licensed under section 351(a) of the PHS Act**, against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.

**Note:** A biological product, in a 351(k) application, may not be evaluated against more than 1 reference product.
Definition: Interchangeability

Interchangeable or Interchangeability means:

- the biological product is [biosimilar](#) to the reference product;
- it can be expected to produce the [same clinical result](#) as the reference product [in any given patient](#); and
- for a product that is administered more than once to an individual, the risk in terms of [safety or diminished efficacy of alternating or switching](#) between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

**Note:** The interchangeable product [may be substituted](#) for the reference product without the intervention of the health care provider who prescribed the reference product.
**General Requirements**

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product;
- Utilizes the **same mechanism(s) of action** for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product;
- **Condition(s) of use** proposed in labeling have been previously approved for the reference product;
- Has the **same route of administration**, **dosage form**, and **strength** as the reference product; and
- Is manufactured, processed, packed, or held in a facility that **meets standards** designed to assure that the biological product continues to be safe, pure, and potent.
General Requirements: 351(k) Application

The PHS Act requires that a 351(k) application include, among other things, information demonstrating biosimilarity based upon data derived from:

- **Analytical studies** demonstrating that the biological product is “highly similar” to the reference product notwithstanding minor differences in clinically inactive components;

- **Animal studies** (including the assessment of toxicity); and

- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.
Standard for Licensure

- FDA shall license the biological product under section 351(k) of the PHS Act if—
  - FDA determines that the **information submitted in the application (or supplement) is sufficient to show** that the biological product—
    - (i) is **biosimilar** to the reference product; or
    - (ii) meets the standards described in 351(k)(4), and therefore is **interchangeable** with the reference product; and
  - Applicant (or other appropriate person) consents to inspection of the facility, in accordance with section 351(c).

- **Note:** BPCI Act does not require that FDA promulgate guidance or regulation before reviewing or approving a 351(k) application.
Non-US-Licensed Comparator Products

- The PHS Act defines the “reference product” for a 351(k) application as the “single biological product licensed under section 351(a) against which a biological product is evaluated.”

- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product.

- Sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.
Support for Use of Non-US-Licensed Comparator

- Type of bridging data needed would include:
  - Direct physico-chemical comparison of all 3 products (proposed biosimilar to US-licensed reference product; proposed biosimilar to non-US-licensed comparator product; US-licensed reference product to non-US-licensed comparator product)
  - Likely 3-way bridging clinical PK and/or PD study
  - All three pair-wise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity.

- A sponsor should justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.
Overview of FDA’s Approach to the Development of Biosimilars - Specific Development Concepts
FDA Biosimilars Draft Guidances

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2012)
2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2012)
4. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (2013)
5. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2014)

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
FDA Guidance

- Focus on therapeutic protein products
- Discusses general scientific principles
- Outlines a stepwise approach to generating data and the evaluation of residual uncertainty at each step
- Introduces the *totality-of-the-evidence* approach
Key Development Concepts
Goals of “Stand-alone” and Biosimilar Development are Different

- The goal of “stand-alone” development is to demonstrate that the proposed product is safe and efficacious.
- Drug development starts with preclinical research, moves to Phase 1, 2 and culminates in Phase 3 “pivotal” trials to show safety and efficacy.
- The goal is to **demonstrate biosimilarity** between the proposed product and a reference product.
- The goal is not to independently establish safety and effectiveness of the proposed product.

What does this difference mean from a development perspective?
Stepwise Evidence Development

- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
  - Evaluation of residual uncertainty at each step

- **Totality-of-the-evidence** approach in evaluating biosimilarity
  - There is no one “pivotal” study that demonstrates biosimilarity

- Apply a step-wise approach to data generation and the evaluation of residual uncertainty
  - What is the residual uncertainty?
  - What differences have been observed and how best to evaluate the potential impact?
  - What study(ies) will address the residual uncertainty?
Totality of the Evidence

- No “one size fits all” assessment

- FDA scientists will evaluate the applicant’s integration of various types of information to provide an overall assessment that a biological product is biosimilar to a US-licensed reference product.
Analytical Similarity Data - The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization** is necessary
- **Understand** the molecule and function
- Identify **critical quality attributes** and clinically active components
- **Understanding the relationship** between quality attributes and the clinical safety & efficacy profile aids ability to determine **residual uncertainty** about biosimilarity and to predict expected “clinical similarity” from the quality data.
Generating Analytical Similarity Data

- Characterize reference product quality characteristics and product variability
- Characterize proposed biosimilar product quality characteristics and product variability
  - Manufacturing process for the proposed biosimilar product should be designed to produce a product with minimal or no difference in product quality characteristics compared to the reference product
- Proposed biosimilar product must be demonstrated using analytical studies to be “highly similar” to the reference product
Summary of FDA Advice on Statistical Analysis of Analytical Similarity Data

- Statistical analysis conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product.
- Consider criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity
- Use a tiered approach for assessment
  - Equivalence testing for some high risk attributes
  - Quality ranges (mean ± X SD) for other high to low risk attributes
  - Raw/graphical comparisons for other attributes
- For advice on individual development programs submit proposal to Agency for feedback
- FDA is considering these issues further and intends to develop guidance for industry as appropriate
Observed Differences

- Identify and evaluate impact of differences observed in the analytical similarity assessment
- The potential effect of the differences on safety, purity, and potency should be addressed and supported by appropriate data
Animal Data

- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies.

- The scope and extent of animal toxicity studies will depend on publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product, and the extent of known similarities or differences between the two.

- A comparison of PK/PD in an animal model may be useful.
Clinical Studies

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products after conducting structural and functional characterization and, where relevant, animal studies.
Type of Clinical Data

- As a scientific matter, FDA expects an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and the reference product.

- As a scientific matter, at least 1 clinical study that includes a comparison of the immunogenicity of the proposed and reference product generally will be expected.

- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.
Comparative Human PK and PD Data

- Comparative human PK (and PD) data:
  - Demonstrate PK (and PD) **similarity**
  - Assess clinically meaningful differences between the proposed biosimilar and the reference product

- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences, should they exist

- Support a demonstration of biosimilarity with the assumption that **similar exposure (and pharmacodynamic response) provides similar efficacy and safety** (i.e., an exposure-response relationship exists)

- Clinical PK data generally will be expected; PD data desirable (case by case consideration)
Human PK and PD Study Considerations

- **Study Design**
  - Study population: An adequately sensitive population to detect any differences, should they exist
  - PD endpoint: Reflect the biological effect(s) of the drug, they may (or may not) be on mechanistic path of MOA or disease process
  - Route of administration: all routes vs. a single route

- **Data analysis plan**
  - Acceptance range: 80-125% (90% CI for PK and PD), scientifically justify use of other ranges
  - Choice of primary endpoints (e.g., PK—AUC, C_max; PD—AUEC)

- **Others**
  - Incidence of immunogenicity
Comparative Clinical Study Considerations

- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product.

- Consider the adequacy of population, sample size and study duration to detect differences, should they exist.

- The goal of the study is to support a demonstration of no clinically meaningful differences.
  - Typically, an equivalence design with symmetric non-inferiority and non-superiority margins would be used, but other designs may be justified depending on product-specific and program-specific considerations.
Totality of the Evidence to Demonstrate Biosimilarity

- Analytical
- Nonclinical
- Clin Pharm
- Additional Clinical Studies

Highly Similar Analytical and PK/PD Data Assumes Lower Risk of Clinical Differences
Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the US-licensed reference product is licensed based on extrapolation of clinical data intended to demonstrate biosimilarity in one condition of use.

- Sufficient scientific justification for extrapolating data is necessary.
Extrapolation Considerations

- FDA guidance outlines factors/issues that should be considered when providing scientific justification for extrapolation including, for example*:
  - The MOA(s) in each condition of use for which licensure is sought
  - The PK and bio-distribution of the product in different patient populations
  - The immunogenicity of the product in different patient populations
  - Differences in expected toxicities in each condition of use and patient population

- **Differences between conditions of use do not necessarily preclude extrapolation**

*This list is a subset of the issues outlined in the FDA guidance document*
Summary

- The content of a biosimilar development program is based on stepwise evidence development and the evaluation of residual uncertainty about biosimilarity between the proposed biosimilar product and the reference product.

- Approval of a proposed biosimilar product is based on the totality of the evidence submitted by the biosimilar sponsor.
Thank you for your attention.
Introduction to FDA Presentation

Albert Deisseroth, MD, PhD
Medical Officer Team Leader,
Division of Hematology Products, FDA
Overview of US-licensed Neupogen Approved Indications

On May 8, 2014, Sandoz submitted BLA 125553 requesting licensure of EP20006 as a biosimilar to US-licensed Neupogen. The “Interchangeability” designation was not requested by Sandoz. Sandoz requested licensure of EP2006 as a biosimilar to US-licensed Neupogen for all of the 5 indications for which US-licensed Neupogen is licensed. These indications include:

1. “Cancer Patients Receiving Myelosuppressive Chemotherapy”: to decrease the incidence of infections, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. (Approved February 20, 1991)
Overview of US-licensed Neupogen Approved Indications (Continued)

2. “Bone Marrow Transplant”: to reduce the duration of neutropenia and neutropenia-related clinical sequelae e.g. febrile neutropenia in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation (Approved June 15, 1994)

3. “Severe Chronic Neutropenia”: 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. (Approved December 19, 1994)
Overview of US-licensed Neupogen Approved Indications (Continued)

4. “Mobilization of Peripheral Blood Stem Cells”: for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. (Approved December 28, 1995)

5. “Patients with AML Receiving Chemotherapy”: for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML (Approved April 2, 1998)
On February 6, 2009, Sandoz' EP2006 was approved for marketing in the European Union (EU) under the trade name Zarzio as a biosimilar product to EU-approved Neupogen.

Marketing experience with Zarzio outside of the US includes in excess of 7.5 million days of patient exposure.
FDA Approach to Assess the Demonstration of Biosimilarity

FDA intends to consider the totality of the evidence provided by a sponsor and recommends a stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed biosimilar product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.

FDA Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, page 2, Section II
Sandoz’ Approach to Demonstrate Biosimilarity of EP2006 to US-licensed Neupogen

1. Sandoz provided extensive analytical characterization of the proposed biosimilar (EP2006) and US-licensed Neupogen (the reference product)
2. Sandoz provided data and justification for a scientific bridge between EP2006, US-licensed Neupogen, and EU-approved Neupogen
3. Sandoz provided nonclinical toxicity and PK/PD data comparing EP2006 and EU-approved Neupogen
5. Sandoz provided immunogenicity studies comparing EP2006 and US-licensed Neupogen and EU-approved Neupogen
Outline of FDA Presentation

**CMC**: Comparative analytical similarity and scientific bridge for EP2006, US-Neupogen and EU-Neupogen (Maria-Teresa Gutierrez-Lugo, PhD and Xiaoyu Dong, PhD)

**Non-clinical**: Comparative toxicity and PK/PD in rodents for EP2006 and EU-Neupogen (Chris Sheth, PhD)

**Clinical Pharmacology**: Single and multiple dose PK/PD studies in human subjects (Sarah J. Schrieber, PharmD)

**Immunogenicity**: Comparative ADA responses to EP2006, US-Neupogen and EU-Neupogen (Susan Kirshner, PhD)

**Clinical**: Clinical study in patients with breast cancer (Donna Przepiorka, MD, PhD)

**Summary**: FDA’s recommended action based on the totality of evidence provided by Sandoz
Chemistry, Manufacturing, and Controls

Maria-Teresa Gutierrez-Lugo, PhD, Reviewer
Gibbes Johnson, PhD, Acting Division Director
Steven Kozlowski, MD, Office of Biotechnology Products Director
Outline

• Background on Granulocyte Colony Stimulating Factor (GCSF) Structure and Mechanism of Action

• EP2006 (GCSF) Manufacturing

• Studies to Support Biosimilarity

• Analytical Similarity
Background on GCSF Structure and Mechanism of Action
GCSF Structure

- 175 residues, 18.8 kDa
- Non-glycosylated (*E. coli*)
- Purified to homogeneity
- Amenable to extensive analytical characterization

- Knowledge on structure-function relationship
  - Impact of chemical modification on potency
    - Methionine oxidation reduces potency
  - Critical role of the GCSF receptor

Herman, A.C. et. al. (1996). Formulation, Characterization, and Stability of Protein Drugs, 303
Tamada, T. et. al. (2006). PNAS, 103, 3135-3140
GCSF Receptor-Mediated Biological Activity

Signal transduction leads to:

- Proliferation and differentiation of neutrophil-committed progenitor cells into neutrophils
- Increase of mature neutrophils in the blood (PD marker)
- Enhanced neutrophil function

Hematopoietic stem cells are identified by the presence of the cluster differentiation protein 34 (CD 34+) marker on their surface (PD marker)

Greenbaum, AM and Link, DC (2011). Leukemia, 25, 211-217
EP2006 Manufacturing
EP2006 Drug Substance Manufacturing

• EP2006 (GCSF) is produced by recombinant technology in *E. coli* host cells

• EP2006 drug substance manufacturing process consists of various steps that purify GCSF from other *E. coli* proteins

• Process-related impurities such as residual host cell proteins (HCP) and DNA (HC DNA) and other process-related impurities specific to the EP2006 process were evaluated

• EP2006 manufacturing process is able to reduce the levels of process-related impurities to very low levels (e.g. ppm for HCP and pg/mg EP2006 protein for HC DNA)
EP2006 Drug Product Manufacturing

- EP2006 drug product is manufactured in pre-filled syringes (PFS) and has the same strengths (300 µg/0.5 ml and 480 µg/0.8 ml) as US-licensed Neupogen

- Formulation of EP2006 drug product differs from that of US-licensed Neupogen in one inactive ingredient

1 US-licensed Neupogen labeling
EP2006 Manufacturing

- Manufacturing process of EP2006 drug substance and drug product changed during clinical development

- EP2006 proposed commercial drug product (referred to as commercial product) is comparable* to the EP2006 drug product used in the clinical studies (referred as clinical product)

* A demonstration that the product quality attributes of a product before and after manufacturing changes [made by the same manufacturer] are highly similar and that no adverse impact on the safety or efficacy, including immunogenicity of the drug product occurred

1 ICH Q5E, Comparability of biotechnological/biological products subject to changes in their manufacturing process, 2004
EP2006 Manufacturing

- EP2006 drug substance and drug product processes are validated and produce product of consistent quality

- Controls for EP2006 drug substance and drug product meet regulatory expectations

- Initial assessment of the facilities where EP2006 is manufactured indicate consistency with Good Manufacturing Practices (GMP)
Studies to Support Biosimilarity
### Clinical and Non-Clinical Studies to Support Biosimilarity

#### PK/PD Similarity
- EP06-101
- EP06-102
- EP06-103
- EP06-105
- EP06-109

#### Non-clinical
- EP06-001
- EP06-002
- EP06-003
- EP06-004
- EP06-006

#### Clinical
- EP06-301
- EP06-302

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- All studies, except EP06-109 and EP06-302 used a Neupogen product that had been approved by the European Union (EU-Neupogen) as active comparator.

- A scientific bridge needs to be established to support use of EU-Neupogen as active comparator.
Analytical Similarity
Product Lots Analyzed

- 20 lots of EP2006 drug product
  - Clinical and commercial EP2006 drug product

- 6 lots of EP2006 drug substance

- 10-15 lots of US-licensed Neupogen

- 34-52 lots EU-approved Neupogen
Product Lots Analyzed

- US-licensed Neupogen and EU-approved Neupogen lots analyzed span approximately 5 and 10 years, respectively and correspond to lots across the shelf life of the products

- EP2006 lots analyzed were manufactured between June 2004 and Nov 2005 (clinical lots) and Jul-Aug 2011 (commercial lots)

- Analytical testing was conducted before expiry of the three products
Analytical Similarity Evaluations

• Analytical comparison of EP2006 and US-licensed Neupogen is used to support a demonstration that EP2006 is “highly similar” to US-licensed Neupogen

• Pair-wise comparisons of EP2006, US-licensed Neupogen and EU-approved Neupogen are used to support the analytical bridge between the three products

• Bridge is needed:
  – to justify the relevance of the data generated using EU-approved Neupogen as the comparator in some clinical and non-clinical studies intended to support a demonstration of biosimilarity to US-licensed Neupogen
### Methods Used to Evaluate Analytical Similarity

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Comparative stability studies were also conducted

Methods were validated or qualified at time of testing and demonstrated to be fit for intended use
Analytical Similarity Results
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- Assessment of analytical similarity was based on data provided by Sandoz
- Product-related species were reviewed with respect to type and levels of the species evaluated
Primary Structure

Highly similar results were obtained from:

- N-terminal Edman sequencing
- Protein molecular mass by two mass spectrometry (MS) techniques
- Peptide map with UV and MS detection


* Lot 1026606 correspond to EU-Neupogen

Lots 1025269 and 1014928 correspond to US-Neupogen

Figure excerpted from Sandoz 351(k) BLA submission
Primary Structure

Tandem MS (LC-MS/MS) analysis of digested EP2006 peptides and sequencing of the EP2006 expression construct indicate that the primary structure of EP2006 is identical to the sequence of GCSF reported in the literature ¹

Primary sequence of EP2006, US-Neupogen and EU-Neupogen is the same

---

¹ Herman, A.C. et. al. (1996). Formulation, Characterization, and Stability of Protein Drugs, 303
Biological Activity

- Activity was measured using NSF-60 cell proliferation assay
- NSF-60 cells express GCSF receptor
- Statistical analysis of bioactivity data is used to support analytical similarity
  - Statistical analysis includes bioactivity results from US-Neupogen in pre-filled syringes and vials

Biological activity is measured relative to Sandoz reference standard calibrated against an international GCSF reference standard.
Statistical Equivalence Test for Bioactivity

The biological activity of the three products is statistically equivalent (mean value)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(-8.67, -2.27)</td>
<td>(-5.47, 0.54)</td>
<td>(-6.34, 0.10)</td>
</tr>
</tbody>
</table>

Results support analytical similarity and the analytical bridge
Protein Content

Statistical Equivalence Test for Protein Content

Protein content of the three products is statistically equivalent (mean values)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(-1.87, 0.15)</td>
<td>(-2.98, -0.85)</td>
<td>(0.27, 2.09)</td>
</tr>
<tr>
<td>(-2.26)</td>
<td>(-3.23)</td>
<td>(-2.26)</td>
</tr>
<tr>
<td>2.26</td>
<td>3.23</td>
<td>2.26</td>
</tr>
</tbody>
</table>

Results indicate that the products have the same strength and also support analytical similarity and the analytical bridge.
Analytical Similarity Summary


<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary structure</td>
<td>Same amino acid sequence</td>
</tr>
<tr>
<td>Bioactivity</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Protein content</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Clarity</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Sub-visible particles</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Secondary and tertiary structure</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>High molecular weight variants/aggregates</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Oxidized species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Covalent dimers</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Partially reduced species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>fMet1 species</td>
<td>Highly Similar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence variants:</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>His→Gln</td>
<td></td>
</tr>
<tr>
<td>Asp→Glu</td>
<td></td>
</tr>
<tr>
<td>Thr→Asp</td>
<td></td>
</tr>
<tr>
<td>Succinimide species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Phosphogluconoylation</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Acetylated species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>N-terminal truncated variants</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Norleucine species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Deamidated species</td>
<td>Highly Similar</td>
</tr>
</tbody>
</table>

* For product-related species, “highly similar” means same type and levels of the species under evaluation

In addition, the three products have highly similar stability profiles
Analytical Similarity Conclusions

Analytical Similarity Conclusions

- Extent of analytical characterization of EP2006 and comparator products (US-licensed Neupogen and EU-approved Neupogen) is robust

- EP2006 clinical and commercial product is analytically “highly similar” to US-licensed Neupogen

- Analytical similarity data do not raise residual uncertainties about the similarity of EP2006 and US-licensed Neupogen. The impact of the EP2006 formulation on PK/PD will be addressed in the non-clinical and clinical studies
Thank you for your attention
EP2006
Statistical Equivalence Testing for Bioactivity and Content

Office of Biostatistics

Reviewer: Xiaoyu (Cassie) Dong, PhD
Team Leader: Meiyu Shen, PhD
Division Director: Yi Tsong, PhD
Outline

• Statistical Equivalence testing
• Testing Results of Bioactivity
• Testing Results of Content
• Conclusions

- Evaluate quality attributes consistent with the risk assessment principles the ICH Quality Guidelines Q8, Q9, Q10, and Q11.
- Consider criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity

- Use a tiered approach for assessment
  - **Equivalence testing for some high risk attributes**
  - Quality ranges (mean ± X SD) for other high to low risk attributes
  - Raw/graphical comparisons for other attributes
Statistical Equivalence Test

• For the critical quality attributes Bioactivity (%) and Content (%), analytical similarity was tested by statistical equivalence testing:
  • $-1.5\sigma_C < \text{Mean}(\text{Test}) - \text{Mean (Comparator)} < 1.5\sigma_C$;
  • Decision Rule:

\[
\begin{align*}
\text{90\% CI} & \quad \text{Statistical Equivalency} \\
(-1.5\sigma_C & \quad 1.5\sigma_C)
\end{align*}
\]
Statistical Equivalence Test

- Equivalency margin = ± 1.5\(\sigma_C\):
  - \(\sigma_C\) is the variability (SD) of the comparator depending on the specific analysis being conducted (either US-licensed Neupogen or EU-approved Neupogen);
  - \(\sigma_C\) is estimated from Sandoz’ data on comparator products;
- It is defined based on an approach to assure a sufficient power with a given number of lots when the mean values are close to each other.
Equivalence Testing Results for Bioactivity (%)

- Bioactivity (%) = % relative to the applicant’s in-house reference standard calibrated against an international G-CSF reference standard.
- 15 EP2006 lots (9 clinical lots + 6 commercial lots), 15 US-licensed Neupogen lots (10 PFS lots + 5 Vial lots), and 34 EU-approved Neupogen lots.

![Graph](image_url)

- CI = (-8.67, -2.27)
- Margin = ± 9.32

- CI = (-5.47, 0.54)
- Margin = ± 10.07

- CI = (-6.34, 0.10)
- Margin = ± 9.32
Equivalence Testing Results for Content (%)

- Content (%) = % relative to the declared content (600 mcg/mL)
- 20 EP2006 lots (13 clinical lots + 7 commercial lots), 12 US-licensed Neupogen lots, and 49 EU-approved Neupogen lots.

![Graphs showing equivalence testing results](image)

- CI = (-1.87, 0.15) Margin = ± 2.26
- CI = (-2.98, -0.85) Margin = ± 3.23
- CI = (0.27, 2.09) Margin = ± 2.26
Conclusions

- For Bioactivity (%), statistical equivalency in mean values is established among EP2006 (Clinical + Commercial), US-Neupogen (PFS + Vial), and EU-Neupogen;

- For Content (%), statistical equivalency in mean values is established among EP2006 (Clinical + Commercial), US-Neupogen, and EU-Neupogen;

- Statistical equivalency testing results support that EP2006 is analytically highly similar to US-licensed Neupogen.
Thank you for your attention
Overview

• Comparative animal studies may support the similarity of a proposed product to a reference product through an assessment of toxicity and/or PK and PD profiles.
• Animal PK and PD assessment will not negate the need for human PK and PD studies.
• The mechanism of action (MOA) by which GCSF produces its effects is the same across mammalian species and the rat is an appropriate research model for studying GCSF.
• Animal studies pivotal to the assessment of the toxicity of EP2006 and its similarity to EU-approved Neupogen
  • EP06-006: 28-day repeat dose toxicology/toxicokinetics
  • EP06-004: 12-day repeat dose pharmacodynamics
## EP06-006: Study Design

### 28-Day Repeat Dose Toxicology Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose Subcutaneous (mcg/kg/day)</th>
<th>Drug</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Main study (4-Weeks)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>Vehicle Control</td>
<td>10/sex</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>EP2006</td>
<td>10/sex</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>EU-approved Neupogen</td>
<td>10/sex</td>
</tr>
<tr>
<td>6</td>
<td>500</td>
<td>EU-approved Neupogen</td>
<td>10/sex</td>
</tr>
</tbody>
</table>
EP06-006: Exposure

- EP2006 or EU-approved Neupogen subcutaneous administration resulted in similar exposures in rats over the 28-Day study.
EP06-006: Toxicity

- Clinical signs, body weights and clinical pathology were similar between the EP2006 and EU-approved Neupogen groups.

- Increases in spleen weight (up to 2-fold) were similar in rats administered either product and were similarly reversible.

- Anatomic pathology (microscopic findings) of hyperplasia in the bone marrow, liver, lymph nodes, and spleen occurred with similar incidence, severity, and reversibility in rats administered EP2006 as compared to EU-approved Neupogen.
**EP06-004: Study Design**

12-Day Repeat Dose Pharmacodynamic Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose Subcutaneous (mcg/kg/day)</th>
<th>Drug</th>
<th>Treatment Schedule</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0, 10, 20, 80, 160</td>
<td>Vehicle Control</td>
<td>Daily on Days 1-4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP2006</td>
<td>Daily on Days 1-4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EU-approved Neupogen</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Neutropenic (50 mg/kg CPA on Day 0)</td>
<td>0, 30, 60, 100</td>
<td>CPA</td>
<td>Daily on Days 1-4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP2006</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EU-approved Neupogen</td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

All rats were male.
CPA, cyclophosphamide
EP06-004: PD (ANC) Response

- Similar biphasic increases in ANC were observed in chemotherapy-induced neutropenic rats following subcutaneous treatment with EP2006 or EU-approved Neupogen.
Conclusions

• No discipline-specific residual uncertainties have been identified.

• The animal pharmacology and toxicology studies indicate that EP2006 is similar to EU-approved Neupogen.

• The animal studies along with the scientific bridge and statistical comparison support a conclusion of biosimilarity.
Clinical Pharmacology

Reviewers
Sarah J. Schrieber, PharmD
Clinical Pharmacology Reviewer, DCP V

Anshu Marathe, PhD
Pharmacometrics Reviewer, DPM
Key Question

Does the clinical pharmacology data submitted under BLA 125553 support a determination of biosimilarity of EP2006 to US-licensed Neupogen?

PK Similarity Assessed
- EP06-109: Single dose healthy subject (HS) study for PK

PD (Absolute neutrophil count (ANC) & CD34+) Similarity Assessed
- EP06-109: Single dose, HS study for ANC
- EP06-101 & -103: Multiple dose HS studies for CD34+

Additional Supportive Clinical Studies
- PK and PD Studies: EP06-101, -103, -105
- Safety/Efficacy Study: EP06-302

Yes, the clinical pharmacology data support a determination of biosimilarity.
Overview of EP2006 PK and PD Studies

- Studies using US-licensed Neupogen as the comparator product

<table>
<thead>
<tr>
<th>Study</th>
<th>Design Features</th>
<th>Objectives</th>
<th>Dose/Route/Duration</th>
</tr>
</thead>
</table>
| **EP06-109** | Randomized, double-blind 2-way crossover in HS (N=28) | 1. ANC, PK  
2. CD34⁺, safety | 10 mcg/kg, SC  
Single dose          |
| **EP06-302** | Randomized, double-blind, active-control study in patients (N=204) | 1. Safety, efficacy  
*PK sub-study*: Parallel design, Cycle 1 PK only (n=27/arm) | 5 mcg/kg, SC  
Multiple dose |

- Studies using EU-approved Neupogen as the comparator product
  - Randomized, double-blind, 2-way crossover in healthy subjects
  - Single & multiple dose studies at various doses

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>Objectives</th>
<th>Dose/Route/Duration</th>
</tr>
</thead>
</table>
| **EP06-103**    | 1. ANC  
                  2. PK, CD34+, safety  | 2.5 & 5 mcg/kg, SC 
                                  Single and multiple (7d) dose |
| (N=28/ dose)    |                              |                                           |
| **EP06-105**    | 1. ANC  
                  2. PK, safety       | 1 mcg/kg, SC  
                                  Single dose                          |
| (N=24)          |                              |                                           |
| **EP06-101**    | 1. PK  
                  2. CD34+, ANC, safety  | 10 mcg/kg, SC  
                                  Single and multiple (7d) dose         |
| (N=32)          |                              |                                           |
EP06-109 Design

- Randomized, double-blind 2-way crossover in healthy subjects (N=28)
- Single SC 10 mcg/kg
- Washout period: 28 days
EP06-109 Primary Objectives

PK:
• AUC & $C_{\text{max}}$
  - Ratio within the 90% CI range of 80-125%

PD (ANC):
• ANC AUEC & $\text{ANC}_{\text{max}}$
  - Ratio within the 95% CI, range of 80-125%
PK and PD Study Design

- Single dose, cross-over design for PK and ANC similarity is justified
  - Short half-life (3.5 – 9h)
  - Rapid ANC response after single dose (within 24h)
  - Low incidence of immunogenicity

- Multiple dose, cross-over design for CD34+ similarity is justified
  - A robust CD34+ response is observed after 5 daily doses
Use of Healthy Subjects (HS) is Justified

- Safety in HS established at G-CSF doses up to 10 mcg/kg x 10d
- Less variability and less confounding by patient factors and treatment intervention
  - PK (AUC): CV% in HS ~20% and in patients is ~40%
  - PD (ANC): CV% in HS <25% and in patients is ~30%
- HS bone marrow is more responsive to G-CSF treatment than chemotherapy-treated patients with cancer, making HS a sensitive model for G-CSF activity assessment
- The mechanism of action (MOA) of G-CSF is fundamentally the same regardless of population
PD Marker(s) & Clinical Relevance

- PD marker(s) are sensitive and relevant
  - Relevance of PD marker(s) to the MOA
  - +/- correlates to clinical outcomes

- PK has an influence on PD response
  - Changes in dose or exposure will elicit a change in PD

- PK and PD should be evaluated with validated assays

Neutropenia: ANC is Correlated with Duration of Severe Neutropenia (DSN)

- ANC is a sensitive and relevant PD marker to detect clinically meaningful differences.

EP2006 data: Study 302 US-licensed Neupogen arm only
CD34⁺: Cell Mobilization

- CFU-GM is used as a marker for cells that promote hematopoietic recovery
  - Total number of CFU-GM and/or CD34⁺ cells collected is a significant predictor of complete hematopoietic recovery
- CD34⁺ cell counts correlates to CFU-GM cell level

- CD34⁺ cell counts are an relevant PD marker to detect clinically meaningful differences.
Doses up to 10 mcg/kg Appear Reasonable for Demonstrating PK and PD Similarity

<table>
<thead>
<tr>
<th>SC Dose (mcg/kg)</th>
<th>ANC</th>
<th>CD34+</th>
<th>PK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean ANC</td>
<td>Geometric mean CD34+</td>
<td>Geometric mean AUC0-24h</td>
</tr>
<tr>
<td></td>
<td>AUEC$_{0-120h}$ (10$^9$h/L)</td>
<td>AUEC$_{0-216h}$ (h*cells/mcL)</td>
<td>(ng*h/mL)</td>
</tr>
<tr>
<td>1</td>
<td>741</td>
<td>725</td>
<td>-</td>
</tr>
<tr>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>2815</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>2886</td>
</tr>
<tr>
<td>10</td>
<td>1524</td>
<td>1472*</td>
<td>5129</td>
</tr>
</tbody>
</table>

*U.S.-licensed Neupogen

- Increases in dose elicits changes in PD and PK in healthy subjects.

EP2006 application studies 101, 103, 105, 109
ANC & CD34+ are Clinically Relevant Markers

- PD markers are sensitive and relevant
  - Relevance of PD marker to the MOA
  - Correlates to clinical outcomes

- PK has an influence on PD response
  - Changes in dose or exposure will elicit a change in PD

- PK and PD evaluated with validated assays
## Role of EP2006 PK and PD Studies & Use of a Scientific Bridge

<table>
<thead>
<tr>
<th>Indication Categories</th>
<th>US-Neupogen PK/PD Study</th>
<th>EU-Neupogen PK/PD Supportive Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Single SC dose in HS (Study EP06-109) • Dose: 10 mcg/kg</td>
<td>Single SC dose in HS (Studies EP06-101, -105, -103) • Doses: 1, 2.5, 5, 10 mcg/kg</td>
</tr>
<tr>
<td>Mobilization</td>
<td>Multiple dose not evaluated</td>
<td>Multiple SC dose in HS (Studies EP06-103, -101) Doses: 2.5, 5, 10 mcg/kg</td>
</tr>
</tbody>
</table>

**Scientific Bridge**

- To justify the relevance of data from studies conducted with EU-Neupogen, a robust scientific bridge between US-Neupogen and EU-Neupogen was established.
PK and PD (ANC) Similarity was Met in Study EP06-109

- Met the predefined similarity limits for PK (90% CI, 80-125%) and ANC (95% CI, 80-125%)

### PK

![](image1.png)

**Statistical Analysis**

<table>
<thead>
<tr>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-last: 88 (84, 91)</td>
</tr>
<tr>
<td>Cₓ-max: 88 (84, 92)</td>
</tr>
</tbody>
</table>

### PD (ANC)

![](image2.png)

**Statistical Analysis**

<table>
<thead>
<tr>
<th>GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUEC₀-last: 103 (100, 106)</td>
</tr>
<tr>
<td>ANCₓ-max: 100 (96, 103)</td>
</tr>
</tbody>
</table>

GMR, geometric mean ratio
PD (CD34+) Similarity was Met in Multiple Dose Studies

- Multiple 2.5 – 10 mcg/kg SC doses EP2006 or EU-approved Neupogen in healthy subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mcg/kg)</th>
<th>Statistical Analysis</th>
<th>GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUEC&lt;sub&gt;0-216h&lt;/sub&gt;</td>
<td>CD34&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>EP06-103</td>
<td>2.5</td>
<td>105 (97, 113)</td>
<td>99 (84, 117)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>99 (87, 113)</td>
<td>99 (84, 117)</td>
</tr>
<tr>
<td>EP06-101</td>
<td>10</td>
<td>102 (95, 110)</td>
<td>99 (90, 110)</td>
</tr>
</tbody>
</table>

GMR, geometric mean ratio

- The results of these PD (CD34+) studies support the mobilization indication category.
Additional PK and PD Studies Support the Assessment of Similarity

- Single 1 – 10 mcg/kg SC dose EP2006 or EU-approved Neupogen in healthy subjects
- Met the predefined PK* & PD similarity limits (80-125%)

<table>
<thead>
<tr>
<th>Study</th>
<th>SC Dose (mcg/kg)</th>
<th><strong>PK GMR (90% CI)</strong></th>
<th><strong>ANC GMR (95% CI)</strong></th>
</tr>
</thead>
</table>
| EP06-105 | 1               | AUC<sub>0-24h</sub>: 91 (86, 97)  
C<sub>max</sub>: 89 (82, 96) | AUEC<sub>0-120h</sub>: 102 (97, 109)  
ANC<sub>max</sub>: 100 (94, 105) |
| EP06-103 | 2.5             | AUC<sub>0-24h</sub>: 88 (81, 85)  
C<sub>max</sub>: 87 (79*, 95) | AUEC<sub>0-24h</sub>: 102 (99, 105)  
ANC<sub>max</sub>: 104 (97, 111) |
|           | 5               | AUC<sub>0-24h</sub>: 96 (90, 102)  
C<sub>max</sub>: 96 (89, 104) | AUEC<sub>0-24h</sub>: 101 (98, 103)  
ANC<sub>max</sub>: 100 (95, 105) |
| EP06-101 | 10              | AUC<sub>0-24h</sub>: 93 (89, 98)  
C<sub>max</sub>: 89 (82, 96) | Single dose ANC not reported |

*Study 103: 2.5 mcg/kg dose Cmax fell outside the range.  
GMR, geometric mean ratio

- The results of these single dose PK and ANC studies are consistent with those of study EP06-109 conducted using US-Neupogen.
PK Sub-study in Patients (Study EP06-302)

Cycle 1 ANC profiles

- Clinical outcome will be presented by the clinical reviewer.
- Differences in PK did not translate into clinically meaningful differences in PD.
PK Sub-study in Patients (Study EP06-302)

- Depth & time of the ANC nadir in Cycle 1 were similar between groups.
  - Clinical outcomes will be presented by the clinical reviewer.
- Differences in PK did not translate into clinically meaningful differences in PD.
Clinical Pharmacology
Summary and Conclusion

• The PK and PD study results support a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen.

• The PK and PD study results add to the totality of the evidence to support a demonstration of biosimilarity of EP2006 and US-licensed Neupogen.
Acknowledgements:
Office of Clinical Pharmacology

- Nam Atiqur Rahman
- Brian Booth
- Julie M. Bullock
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- Nitin Mehrotra
- OCP Biosimilar Oversight Board Members

- Yaning Wang
- Jerry Yu
- Lian Ma
- Liang Li
- Joo-Yeon Lee
References

EP2006 Immunogenicity Data

Faruk Sheikh, PhD, Staff Fellow,
Frederick Mills, PhD, Biologist,
Susan Kirshner, PhD, Review Chief
OBP
Immunogenicity Testing for Biologics

- Treatment with therapeutic biological products can cause patients to develop anti-drug antibodies (ADAs)

- ADAs can have severe consequences including:
  - loss of activity of endogenous counterparts
  - hypersensitivity reactions including anaphylaxis
  - loss of efficacy.

- Establishing similarity in the immunogenicity profiles of the proposed biosimilar and the reference product may be an important component of the totality of the evidence supporting the demonstration of biosimilarity.
Immunogenicity of GCSF Products:

• 5 year National Marrow Donor Program publication*
  – evaluated 6,768 healthy peripheral blood stem cell (PBSC) donors exposed to GCSF and 2,726 healthy bone marrow (BM) donors not exposed to GCSF
  – there was no increased risk for developing an autoimmune disease in PBSC donors when compared to BM donors

• FDA is unaware of reports of neutralizing ADA to GCSF products.

• The literature indicates that GCSF products are low risk for ADA related severe adverse events.

EP2006 Immunogenicity and Similarity:

• One multi-dose parallel arm study in 214 patients with cancer. No patients developed ADA during the study.

• Four single and multi-dose cross-over PK and PD studies in healthy subjects. No subjects developed ADA during the study.

• One single arm multi-dose study of EP2006 in patients with cancer. No patients developed ADA during the study.
Summary:

• The results from immunogenicity studies support a demonstration of no clinically meaningful differences in immune response between EP2006 and US-licensed Neupogen.
Clinical Trial Review

Reviewers

Division of Hematology Products
Donna Przepiorka, MD, PhD
Albert Deisseroth, MD, PhD

Office of Biostatistics
Kyung Lee, PhD
Lei Nie, PhD
Presentation Outline

• Description of Study EP06-302
• Assessment of the efficacy endpoint
• Assessment of the safety endpoints
• Assessment of hypersensitivity reactions
• Conclusions
Clinical Trial Description

• **Study EP06-302**
  - Randomized, double-blinded, active-control trial
  - Patients with breast cancer undergoing 6 cycles of TAC
    • Docetaxel 75 mg/m² given day 1
    • Doxorubicin 50 mg/m² day 1
    • Cyclophosphamide 500 mg/m² day 1
  - Randomized 1:1:1:1:1 to study arms as shown in the table
    • EP2006 or US-licensed Neupogen 5 mcg/kg qD from day 2 to ANC recovery

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Neupogen</td>
<td>Neupogen</td>
<td>Neupogen</td>
<td>Neupogen</td>
<td>Neupogen</td>
<td>Neupogen</td>
</tr>
</tbody>
</table>

• **Primary Endpoint**
  - DSN in Cycle 1
Study EP06-302

• **Primary Objective**
  – To assess the efficacy of EP2006 compared to US-licensed-
    Neupogen with respect to the mean DSN in Cycle 1
  – DSN: number of consecutive days with ANC <0.5 Gi/L

• **Method**
  – ANCOVA in the per protocol population

• **Sample Size**
  – 192 subjects
  – 90% power to establish noninferiority with a 1-sided significance
    level of 2.5% and a noninferiority margin of -1 day

• **Actual Accrual**
  – 218 subjects were randomized
  – 204 subjects were in the per protocol population
  – Treatment arms were balanced for demographic characteristics
### Sandoz’s Analysis of the Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1 Mean DSN (SD)</td>
<td>1.17 days (1.11)</td>
<td>1.20 days (1.02)</td>
</tr>
<tr>
<td>DSN Difference for Neupogen minus EP2006 (one-sided 97.5% CI)*</td>
<td>0.04 days (-0.26 days)</td>
<td></td>
</tr>
</tbody>
</table>

*:ANCOVA with treatment, disease status and baseline ANC level

- Sandoz concluded that noninferiority was demonstrated.

**Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**
(February, 2012 Guidance) “Clinical studies should be designed such that they can demonstrate that the proposed product has neither decreased nor increased activity compared to the reference product.”
Efficacy Results
Primary Endpoint - FDA Analysis

- Tested using 90% confidence interval for DSN difference
- Upper and lower margins for this trial would be 1 day

**FDA’s Analysis of the Primary Endpoint**

<table>
<thead>
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<tr>
<td><strong>Cycle 1 Mean DSN (SD)</strong></td>
<td>1.17 days (1.11)</td>
<td>1.20 days (1.02)</td>
</tr>
<tr>
<td><strong>DSN Difference for Neupogen minus EP2006 (90% CI)</strong>*</td>
<td>0.04 days (-0.21, 0.28)</td>
<td></td>
</tr>
</tbody>
</table>

*:ANCOVA with treatment, disease status and baseline ANC level

- Equivalence was demonstrated
Safety Analysis
Analysis Plan

• **Safety Population** (SAF)
  – Received study drug and had a post-baseline safety assessment
  – N=214

• **Comparisons made**
  – Cycle 1 by treatment
  – Cycles 1-6 in Arm 1 vs Arm 4

• **Descriptive results only**

<table>
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</tr>
</tbody>
</table>
## Comparison of Major Safety Events

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1 by Treatment</th>
<th>Cycles 1 - 6 Arm 1 vs Arm 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>87 (81%)</td>
<td>89 (83%)</td>
</tr>
<tr>
<td>Related TEAEs</td>
<td>22 (21%)</td>
<td>21 (20%)</td>
</tr>
<tr>
<td>SAEs</td>
<td>5 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Related SAEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatal TEAEs</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Related Fatal TEAEs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## FDA Comparison of Cardinal Adverse Events

<table>
<thead>
<tr>
<th>Grouped Term</th>
<th>Cycle 1 by Treatment</th>
<th></th>
<th>Cycles 1 - 6 Arm 1 vs Arm 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal Pain⁴</td>
<td>27 (25%)</td>
<td>31 (29%)</td>
<td>21 (40%)</td>
<td>22 (42%)</td>
</tr>
<tr>
<td>Injection Site Reaction⁵</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

⁴Includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, pain, pain in extremity or spinal pain

⁵Includes injection site erythema, extravasation, haematoma, pain or pruritus


Safety Analysis
Hypersensitivity

- There were no TEAE with allergic reaction terms
- The SMQ analyses demonstrated no safety signals

### FDA Comparison of Hypersensitivity by Broad SMQ

<table>
<thead>
<tr>
<th>Broad SMQ</th>
<th>Cycle 1 by Treatment</th>
<th>Cycles 1 - 6 Arm 1 vs Arm 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic Reaction</td>
<td>8 (7%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>11 (10%)</td>
<td>8 (7%)</td>
</tr>
</tbody>
</table>
Summary


• The safety outcomes were similar for patients treated EP2006 vs US-licensed Neupogen.

• These results support the demonstration of biosimilarity of EP2006 to US-licensed Neupogen provided by the analytical comparisons and the PK/PD studies in healthy subjects.
Summary of FDA Findings

Albert Deisseroth, MD, PhD
Medical Officer Team Leader
Division of Hematology Products, FDA
Summary of FDA Findings

**CMC**: EP2006 was found to be highly similar to US-licensed Neupogen. A scientific bridge was established to justify the relevance of clinical data obtained from studies using EU-approved Neupogen to support a demonstration of biosimilarity to US-licensed Neupogen.

**Nonclinical**: EP2006 is similar to the reference product US-licensed Neupogen.

**Clinical Pharmacology**: The PK and PD study results support a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen.

**Immunogenicity**: There were no clinically meaningful differences in terms of ADA between EP2006 and US-licensed Neupogen.

**Additional Clinical Studies**: Comparison of DSN between EP2006 and US-licensed Neupogen support the conclusion that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.
Summary of FDA Findings (Continued)

Four of the 5 indications for which US-licensed Neupogen is approved relate to the effect of Neupogen on the levels of neutrophils in the peripheral blood and 1 of the 5 indications relates to the effect of Neupogen on the level of CD34 positive stem cells in the peripheral blood.

It is well documented that binding of Neupogen to the granulocyte colony-stimulating factor receptor (G-CSF R) on cells is the first step of Neupogen-mediated neutrophil differentiation and proliferation, as well as in CD34 positive stem cell mobilization.

Thus, there is scientific justification for extrapolating the clinical data submitted by Sandoz to support a determination of biosimilarity for each condition of use for which licensure is sought.

The data submitted by Sandoz demonstrate that EP2006 is highly similar to US-licensed Neupogen, and that there are no clinically meaningful differences between the two products. In addition, the totality of evidence supports that EP2006 should be granted licensure as a biosimilar product for all 5 of the indications for which US-licensed Neupogen is licensed.
Discussion Questions for AC

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

• Question 2: Does the committee agree that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen?
Voting Question for AC

• Question 1: 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?
Back-Up Slides Shown
Neutropenia: Infection risk Decreases as ANC Increases