

Overview of the Regulatory Framework and FDA's Guidance the Development and Approval of Biosimilar Products in the US

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Overview of Presentation

- Overview
 - Background
 - Terminology
 - Approval Pathway for Biosimilars – General Requirements
- Development of Biosimilars
 - Approach to Development
 - Specific Development Concepts

Overview of the BPCI Act

Background



- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was 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.
 - 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**.

What is Meant by Abbreviated Licensure Pathway?

- The abbreviated licensure pathway does not mean that a lower approval standard is applied to biosimilar or interchangeable products than to originator biological products.
- The ability to rely on FDA's previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly drug development program. This is what is meant by an **abbreviated** licensure pathway.
- The **data package** required for approval of a biosimilar or interchangeable product is quite extensive; biosimilar applicants submit data from analytical, nonclinical, and clinical studies to support a demonstration of biosimilarity with the reference product.
- Once a biosimilar or interchangeable has been approved by FDA, patients and health care providers will be able to rely upon the safety and effectiveness of an FDA-approved biosimilar or interchangeable product just as they would for the reference product that the biosimilar was compared to.

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.

Reference Product

Reference Product:

- 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.
- An application submitted under section 351(a) of the PHS Act is a “stand-alone” application that contains all information and data necessary to demonstrate that the proposed product is safe, pure and potent.
- In contrast, an application submitted under section 351(k) needs to demonstrate that the proposed product is biosimilar to the reference product. For licensure, a proposed biosimilar relies on (among other things) comparative data with the reference product, as well as publicly-available information regarding FDA’s previous determination that the reference product is safe, pure and potent.

Interchangeability



Interchangeable or Interchangeability:

- 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.

An 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 Data Elements : 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.

Use of 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 physicochemical 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

FDA Guidance



1. **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (final, 2015)**
2. **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (final, 2015)**
3. **Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (final, 2015)**
4. **Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (final, 2015)**
5. **Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (final, 2016)**
6. **Nonproprietary Naming of Biological Products (final, 2017)**
7. Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (draft, 2014)
8. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (draft, 2015)
9. Labeling for Biosimilar Products (draft, 2016)
10. Considerations in Demonstrating Interchangeability With a Reference Product (draft, 2017)

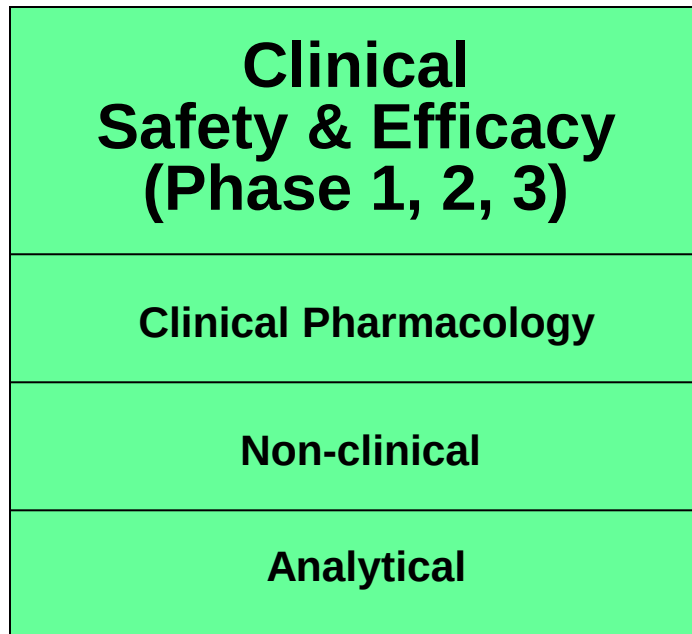
Key Development Concepts



Key Concept #1: Goals of “Stand-alone” and Biosimilar Development are Different

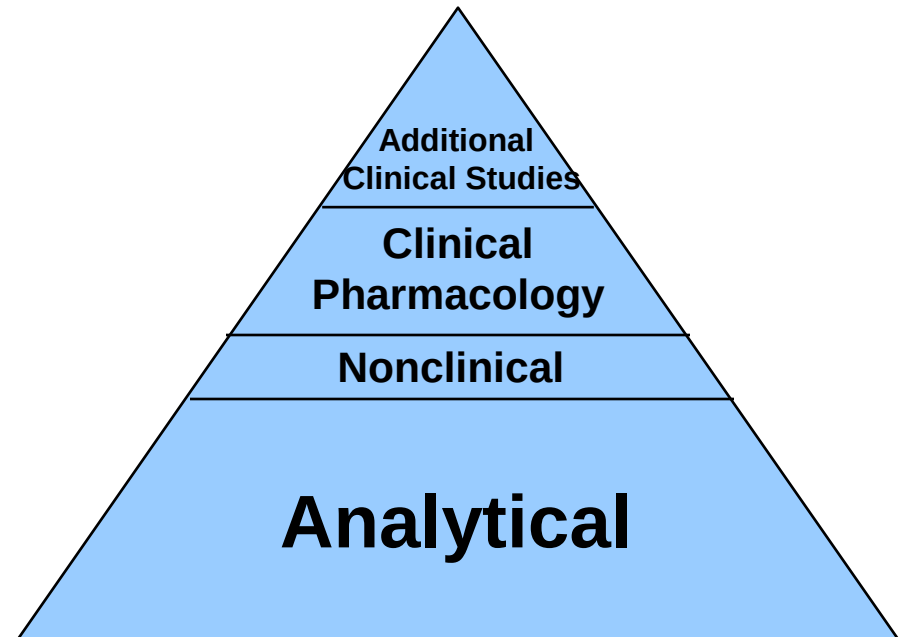
“Stand-alone” Development Program, 351(a)

Goal: To establish safety and efficacy of a new product



“Abbreviated” Development Program, 351(k)

Goal: To demonstrate biosimilarity (or interchangeability) to a reference product

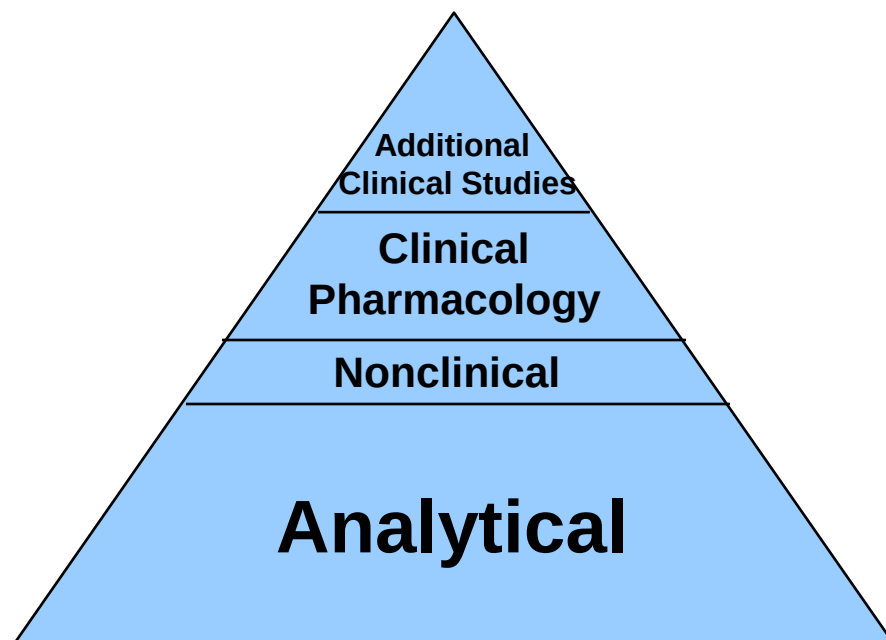


What does this difference mean from a development perspective?

Key Concept #2: 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 of data generation
- *Totality-of-the-evidence* approach in evaluating biosimilarity
- There is no one “pivotal” study that demonstrates biosimilarity



No “one size fits all” assessment



- Apply a step-wise approach to data generation and the evaluation of residual uncertainty*

Analytical Studies



Animal Studies



Clinical PK/PD Studies



Clinical Immunogenicity Assessment



Additional Clinical Studies

- What differences have been observed and what is the potential impact?
- What is the residual uncertainty and what study(ies) will address the residual uncertainty?

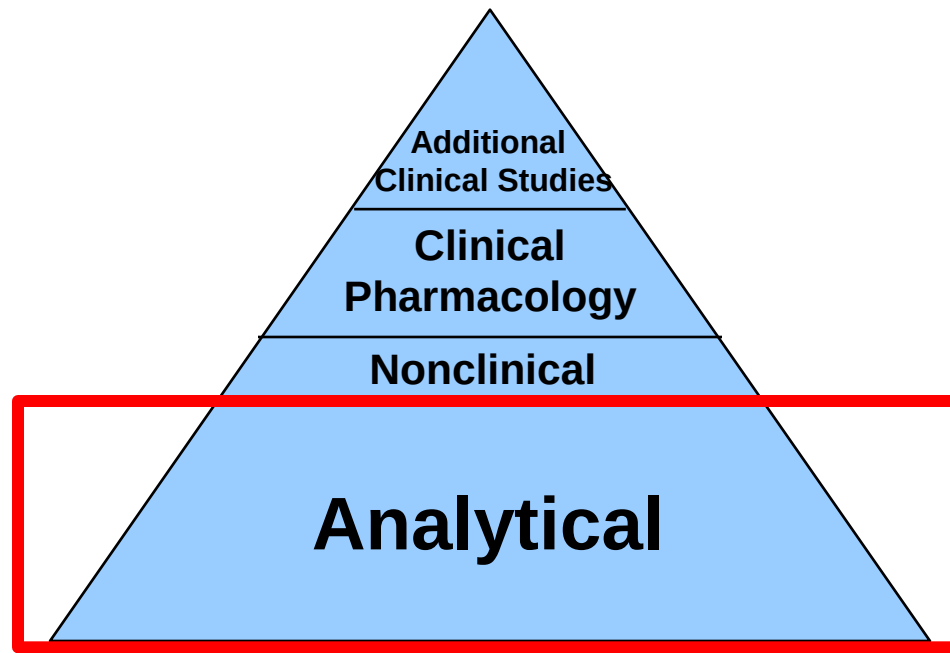
* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application.

Key Concept #3:

Analytical Similarity Data -

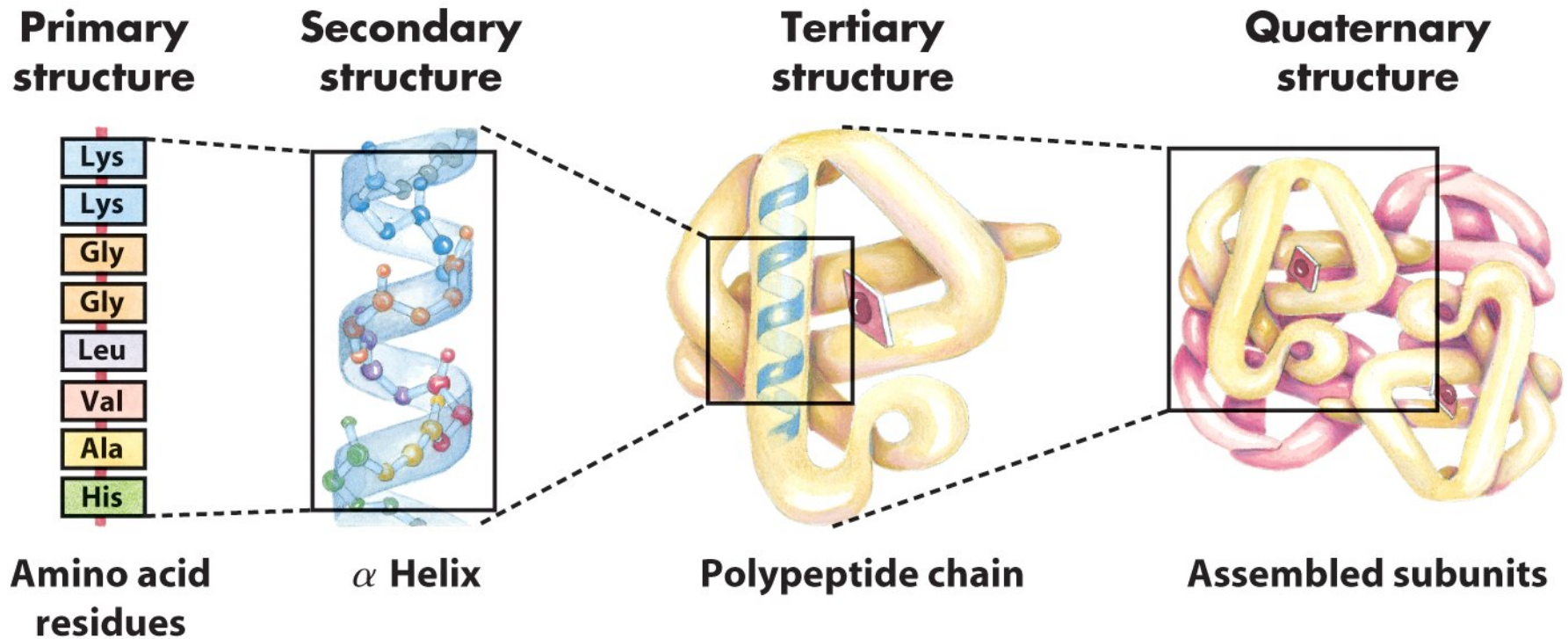
The Foundation of a Biosimilar Development Program

- Extensive structural and functional characterization



"Abbreviated" Development Program, 351(k) BLA

Hierarchy of protein structure



- Protein Heterogeneity
- Lot-to-lot variability
- All need to be evaluated as part of analytical similarity studies

Assessing Analytical Similarity

- Comprehensive structural and functional analyses
- Comparative assessment of attributes including:
 - Amino acid sequence and modifications
 - Folding
 - Subunit interactions
 - Heterogeneity (size, aggregates, charge, hydrophobicity)
 - Glycosylation
 - Bioactivity
 - Impurities
- If a molecule is known to have multiple biological activities, where feasible, each should be demonstrated to be highly similar between the proposed biosimilar product and the reference product
- **Understand** the molecule and function and identify **critical quality attributes**

Generating Analytical Similarity Data



- Characterize reference 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
- Identify and evaluate the potential impact of differences observed and what study(ies) will address the residual uncertainty
- **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.

Statistical Analysis of Analytical Similarity Data



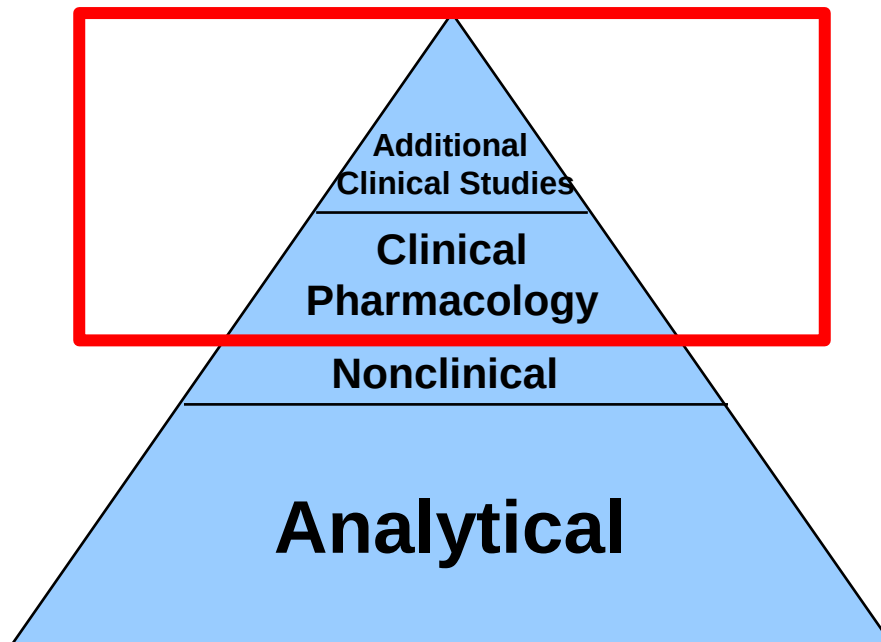
- Statistical analyses of the analytical similarity data are conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product
- Quality attributes are ranking based on criticality with regard to their potential impact on activity, PK/PD, safety, immunogenicity, and other factors
- Data are then analyzed by various testing methodologies

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 studies, including 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

Key Concept # 4: Role of 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.



“Abbreviated” Development Program, 351(k) BLA

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



- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences between products, should they exist
- PK
 - Demonstrate PK similarity in an adequately sensitive population to detect any differences, should they exist
- PD
 - Similar PD using PD measure(s) that reflects the mechanism of action (MOA) or reflects the biological effect(s) of the drug
- **PK and PD similarity** data supports a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response, if applicable) will provide **similar efficacy and safety** (i.e., an exposure-response relationship exists)

Comparative Clinical Study

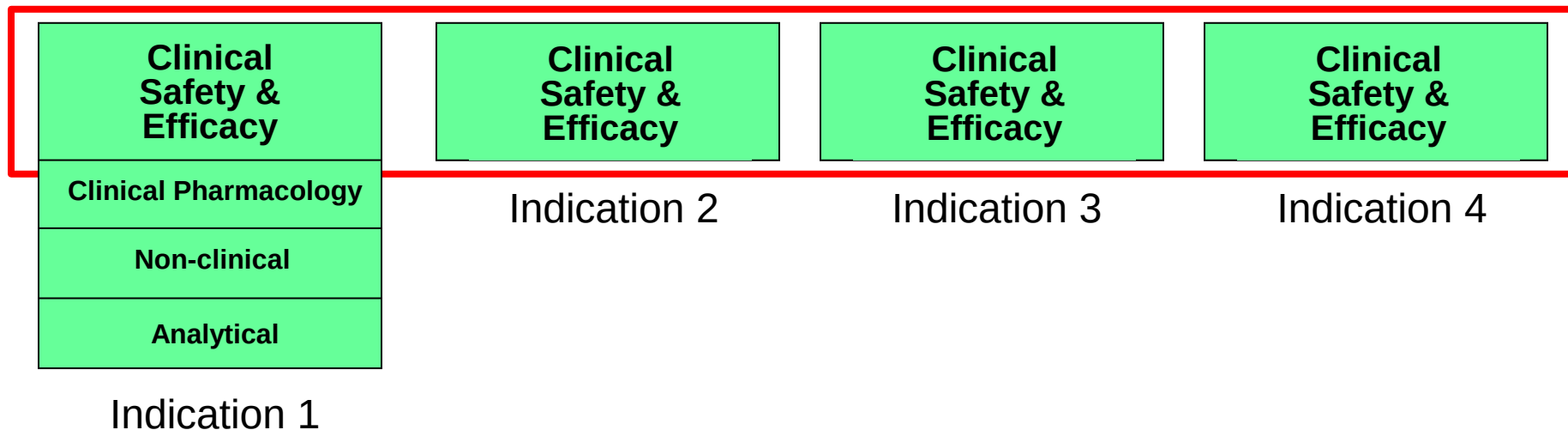
- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product.
- Population, endpoint, sample size and study duration should be adequately sensitive to detect differences, should they exist.
- Typically, an equivalence design would be used, but other designs may be justified depending on product-specific and program-specific considerations.
- Assessment of safety and immunogenicity

Key Concept # 5: Extrapolation

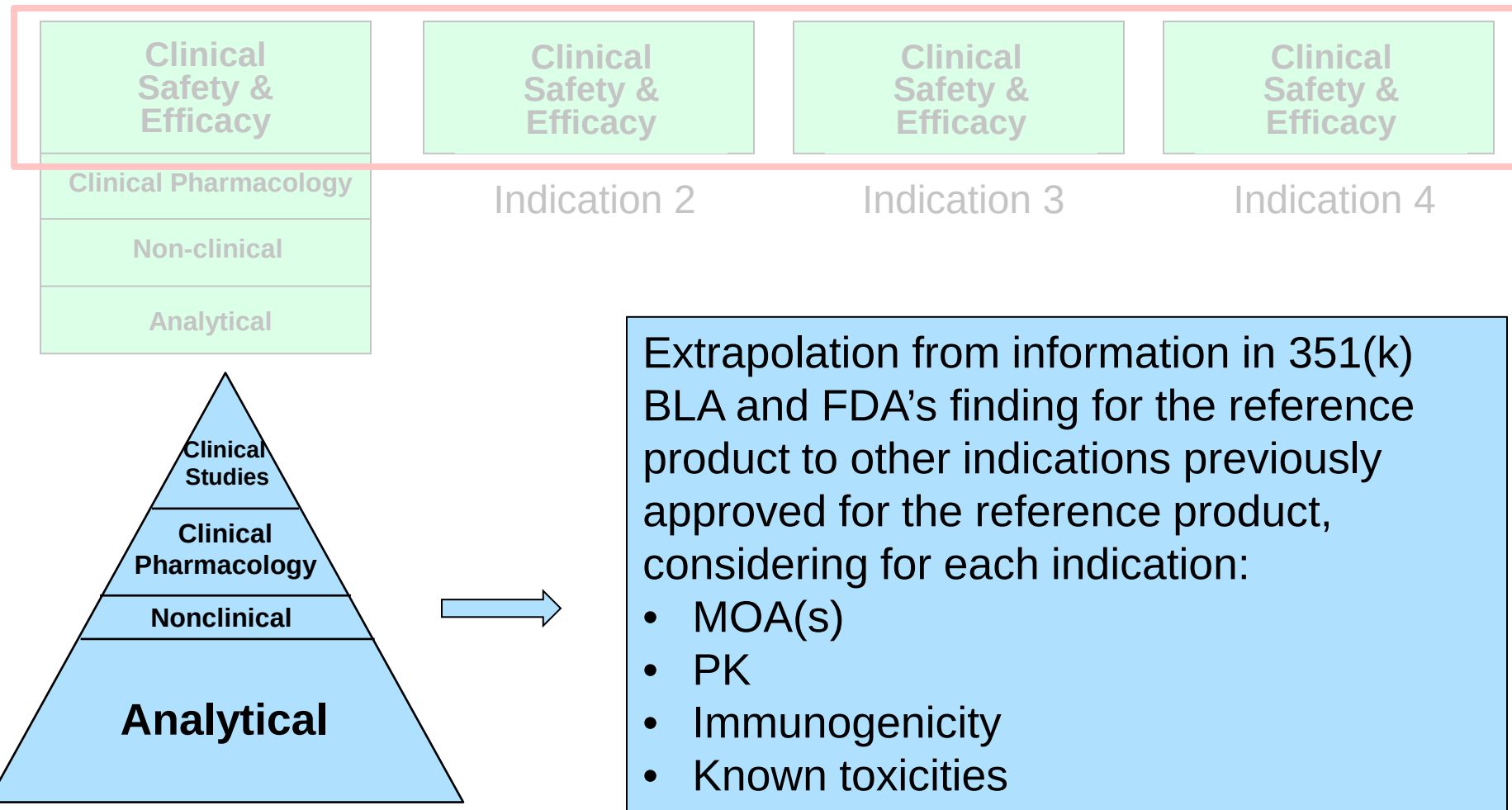


- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- Differences between conditions of use (e.g., indications) do not necessarily preclude extrapolation
- FDA guidance outlines factors to consider, including:
 - MoA in each condition of use
 - PK and biodistribution in different patient populations
 - Immunogenicity in different patient populations
 - Differences in expected toxicities in each condition of use and patient population

Extrapolation Considerations: “Stand-alone” Drug Development



Extrapolation Considerations: “Stand-alone” vs. Biosimilar Development



Biosimilar extrapolation is based on all available data in the 351(k) BLA and FDA's finding for the reference product, not from the indication(s) studied for biosimilar to other non-studied indications

Summary



- Development of a biosimilar product is different from “stand-alone” product development
 - Development goal is not to re-establish safety and effectiveness but to demonstrate the biosimilar product is highly similar to the reference product, and that there are no clinically meaningful differences
- Analytical comparisons are the foundation for determining whether the products are highly similar
- Clinical PK (and/or PD) is generally considered the most sensitive endpoint for detecting differences between products; an assessment of immunogenicity is needed and comparative clinical data are collected if questions remain
- Approval of a proposed biosimilar product is based on the **integration of various information and the totality of the evidence submitted** by the biosimilar sponsor to provide an overall assessment that the proposed product is biosimilar to the reference product.
- The FDA’s high standard for approval of biosimilar and interchangeable products means that patients and health care professionals **can be confident of the safety and effectiveness of a biosimilar or interchangeable product**, just as they would for the reference product.

Thank you for your attention.

Questions?

FDA Overview

BLA 125545

**“Epoetin Hospira”, a proposed biosimilar to
US-licensed Epogen/Procrit**

R. Angelo de Claro, MD

Medical Officer Team Leader

Division of Hematology Products

U.S. Food and Drug Administration

May 25, 2017



Proposed Indications

Same as US-licensed Epogen/Procrit:

US-Epogen/Procrit Indications	Year of FDA Approval
1. For the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion	1989
2. For the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL	1991
3. For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy	1993
4. To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery	1996

Key Topics to Consider

Topic 1: highly similar notwithstanding minor differences in clinically inactive components based on evidence from analytical studies

- Use of multiple orthogonal physicochemical and functional methods
 - Primary-, secondary-, and tertiary structure
 - Post-translational modification
 - Biological activity
 - Stability profiles

Key Topics to Consider

Topic 2: no clinically meaningful differences in terms of safety, purity, and potency

- Comparative clinical studies in healthy subjects and patients with chronic kidney disease
 - Pharmacokinetics/Pharmacodynamics
 - Efficacy
 - Safety
 - Immunogenicity

“Epoetin Hospira” Clinical Studies

Study ID	Design	Route	Number	Subjects	Dose	Schedule	Primary Endpoint
EPOE-12-02	Cross-over	Subcutaneous	81	Healthy subjects	100 U/kg	Single dose	PK and PD similarity (reticulocyte count)
EPOE-14-01	Parallel	Subcutaneous	129	Healthy subjects	100 U/kg	3 times / week for 4 weeks	PD similarity (Hb)
EPOE-10-13	Parallel	Subcutaneous	246	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose
EPOE-10-01	Parallel	Intravenous	612	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose

CKD: chronic kidney disease

HD: hemodialysis

PK: pharmacokinetics

PD: pharmacodynamics

Hb: hemoglobin

Key Topics to Consider

Topic 3: adequate scientific justification to support licensure for all of the proposed indications

- Scientific justification
 - Mechanism of action
 - Similarity
 - Product quality attributes
 - Pharmacokinetics/pharmacodynamics
 - Immunogenicity
 - Efficacy and safety

Key Topics to Consider

Topic 4: totality of evidence supports licensure of “Epoetin Hospira” as a biosimilar product to US-licensed Epogen/Procrit for the indications for which US-licensed Epogen/Procrit is currently licensed and for which the Applicant is seeking licensure (voting question)

“Epoetin Hospira”, a proposed biosimilar to US-licensed Epogen/Procrit BLA 125545

FDA Presentation

Oncologic Drugs Advisory Committee

May 25, 2017



FDA Presentation Outline

- | | |
|--|--|
| A. Chemistry, Manufacturing, and Controls (CMC) and CMC Statistics | Frances Namuswe, PhD
Chao Wang, PhD |
| B. Pharmacology/Toxicology | Natalie Simpson, PhD |
| C. Clinical Immunogenicity | Steven Bowen, PhD |
| D. Clinical Pharmacology | Vicky Hsu, PhD |
| E. Clinical Efficacy | Lola Luo, PhD |
| F. Clinical Safety | Lori Ehrlich, MD, PhD |
| G. Overall Summary | Lori Ehrlich, MD, PhD |

Chemistry, Manufacturing, and Controls (CMC)

Frances Namuswe, PhD

CMC Reviewer, Office of Biotechnology Products
U.S. Food and Drug Administration

Chao Wang, PhD

CMC Statistical Reviewer, Office of Biostatistics
U.S. Food and Drug Administration

Erythropoietin (EPO)

Mechanism of Action (MOA)

- Endogenous EPO is produced in the kidney and stimulates production of red blood cells (RBCs).
- EPO binds to the EPO receptor on erythroid precursor cells.
- Receptor binding initiates signal transduction that leads to survival, proliferation and differentiation of erythroid progenitor cells into RBCs.
- Reticulocyte count and hemoglobin levels are pharmacodynamics markers.
- MOA is the same for endogenous and recombinant EPO.

Erythropoietin (EPO) Structure

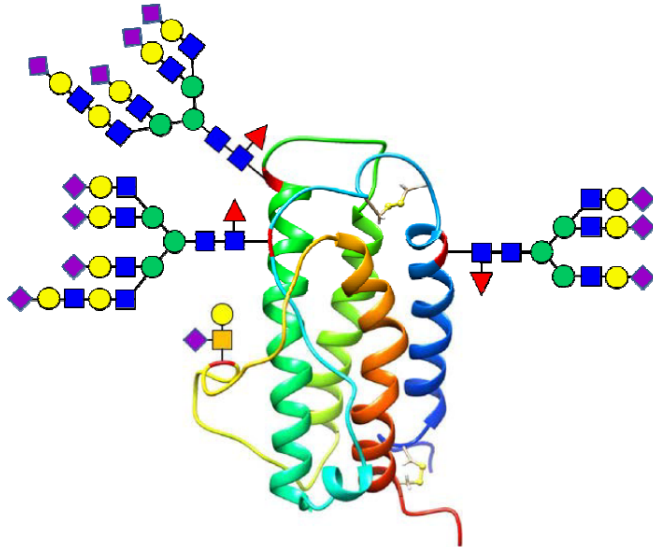


Figure excerpted from Applicant's 351 (k) BLA submission

- Glycosylation impacts the half life of circulating EPO

- Glycosylation = ~40% of EPO molecular weight

Examples of EPO Glycan Heterogeneity

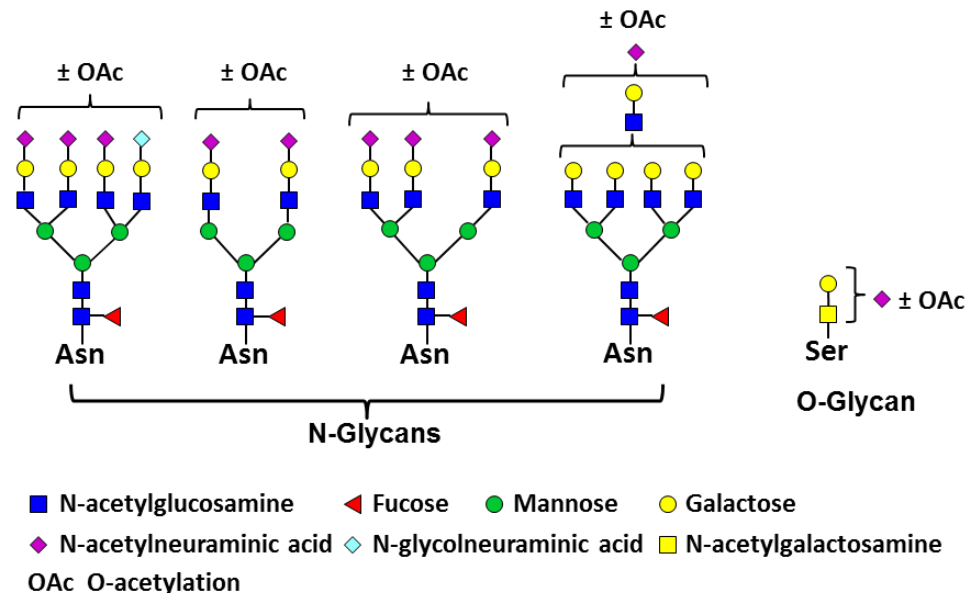


Figure drawn by FDA reviewer based on Consortium for Functional Glycomics glycan nomenclature

Studies Reviewed

Analytical Similarity

- Physicochemical characterization
- Functional activity

Animal Studies

- 70882
- 60486

Pharmacokinetic/ Pharmacodynamic Similarity

- EPOE-12-02
- EPOE-14-01*

Additional Clinical Studies

- EPOE-10-13*
- EPOE-10-01*

* Studies reviewed to support clinical immunogenicity assessment

All studies used US-licensed Epogen/Procrit as comparator

Quality Attributes Evaluated



Primary structure

- Amino acid sequence
- Disulfide bonds
- Sites of post-translational modification
- Free thiols
- Molecular weight

Higher order structure

- Secondary structure
- Tertiary structure
- Whole protein Molecular weight

Biological activity

- In vivo activity
- Specific in vivo activity
- In vitro activity
- Specific in vitro activity,
- Receptor binding

Glycosylation

- N-glycan site occupancy
- N-glycan antennarity
- Lactosamine repeats
- N- and O-acetylation
- N-glycan fucosylation
- Sialic acid (total, distribution, types)
- O-site occupancy and O-glycan profile
- Monosaccharide comp.
- α -Gal-1,3-Gal
- Isoform distribution

Drug product attributes

- Epo content
- Sub-visible particles
- Container volume
- Total activity per vial

Product related species

- Oxidation (Met, Trp)
- Deamidation (Asn, Glu)
- Asp isomerization
- Trisulfide species
- Disulfide scrambling
- Dimers and high-molecular weight species (HMWS)
- Inactive protein variants

Stability

- Degradation profiles under accelerated and Stress conditions

- Multiple orthogonal methods were used for most attributes
- Removal of human serum albumin (HSA) in US-Epogen/Procrit needed for several methods

Product Lots Used and Data Analysis

Product	Number of lots
“Epoetin Hospira” drug product	35
“Epoetin Hospira” drug substance	9
US-Epogen/Procrit	54

Attribute Assessment	Statistical tools
Tier 1	Equivalence testing
Tier 2	Quality ranges
Tier 3	Graphical comparison

- Lots used in clinical studies and proposed commercial process were included in analytical similarity assessment
- Applicant’s comparative analysis was supported by statistical analysis.
- FDA’s analysis also included independent statistical analysis

Analytical Similarity Summary

Quality Attribute	Supports a Demonstration of Highly Similar
Primary structure	Yes-same amino acid sequence
Secondary & Tertiary structure	Yes
Overall Glycosylation	Yes (#)
Protein content	Yes
In vivo activity	Yes
In vitro activity	Yes
Receptor binding	Yes

Quality Attribute	Supports a Demonstration of Highly Similar
Dimers & High Molecular Weight Species	Yes
Oxidized species	Yes
Deamidated species	Yes
Asp isomerization	Yes
Disulfide scrambling	Yes
Trisulfide species	Yes (#)
Sub-visible particles	Yes
Stability profiles	Yes

Differences in the levels of some glycosylation species and Cys29-Cys33 trisulfide species did not preclude a demonstration that “Epoetin Hospira” is highly similar to US-Epogen/Procrit

Glycosylation Profile

- Same glycosylation sites, occupancy & species
- Minor differences in amounts of some species observed

HILIC-UPLC-FLD Chromatograms of Native N-glycans

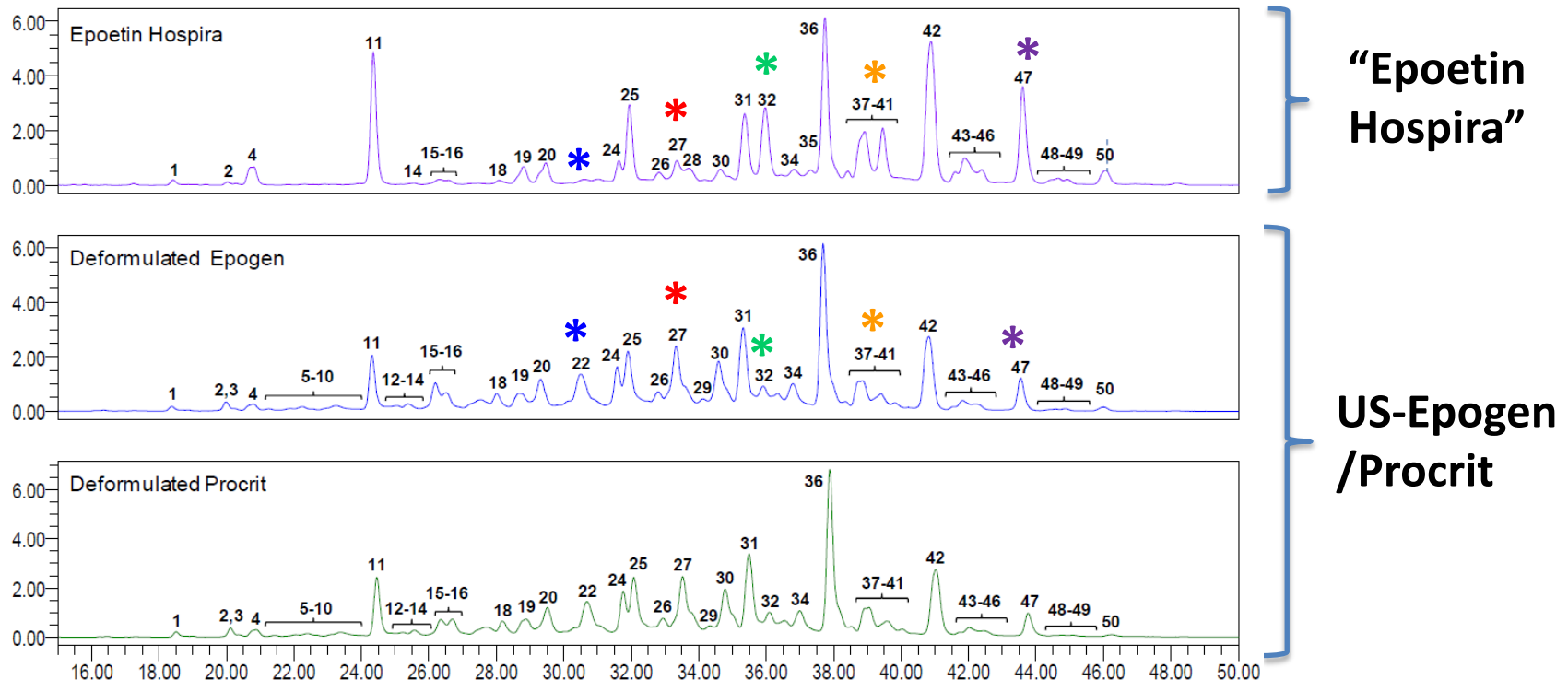


Figure excerpted from Applicant's 351(k) BLA submission

Addressing Glycosylation Differences



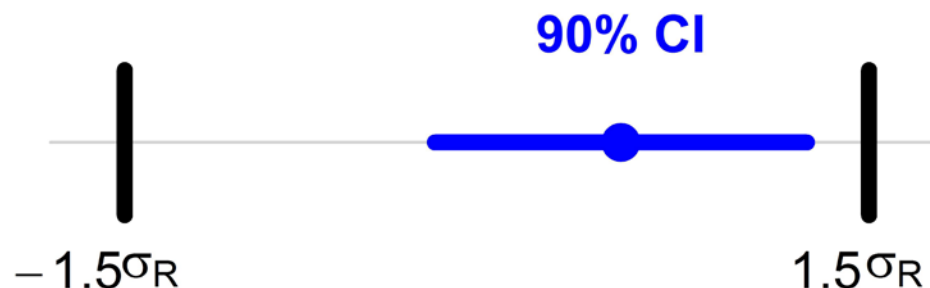
- EPO glycosylation is important for in vivo biological activity
- Potential impact of glycosylation differences on biological activity primarily evaluated using a sensitive mouse-based assay
- Assessment of biological activity and receptor binding using in vitro cell-based and receptor binding assays provided additional data
- Differences in glycosylation did not result in an observable net effect on biological activity or the intrinsic properties of the molecule
- In vivo biological activity and in vitro specific activity of “Epoetin Hospira” and US-licensed Epogen/Procrit were assessed by Tier 1 equivalence testing

Statistical Equivalence Test

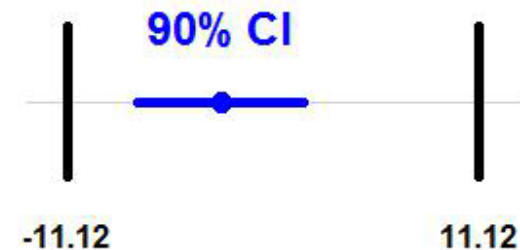
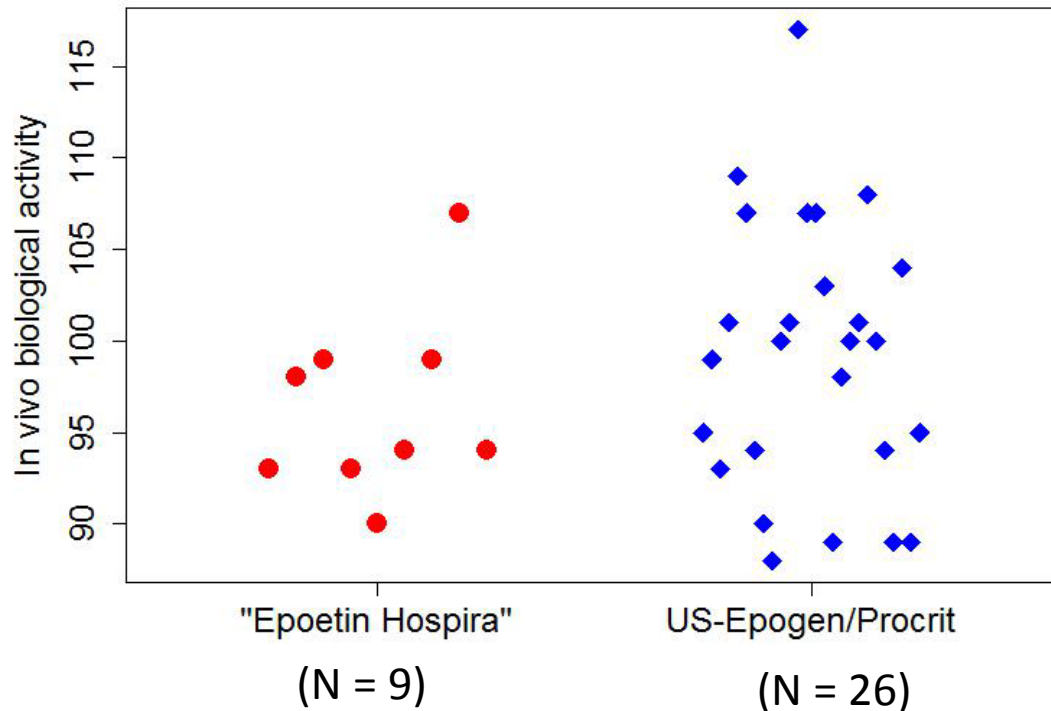
- **MeanDif** = Mean(Test) – Mean (Reference)
- σ_R : standard deviation of reference product
- The hypotheses:

Null	MeanDif $\leq -1.5\sigma_R$ or MeanDif $\geq 1.5\sigma_R$
Alternative	$-1.5\sigma_R < \text{MeanDif} < 1.5\sigma_R$

- Test and reference pass the equivalence test if

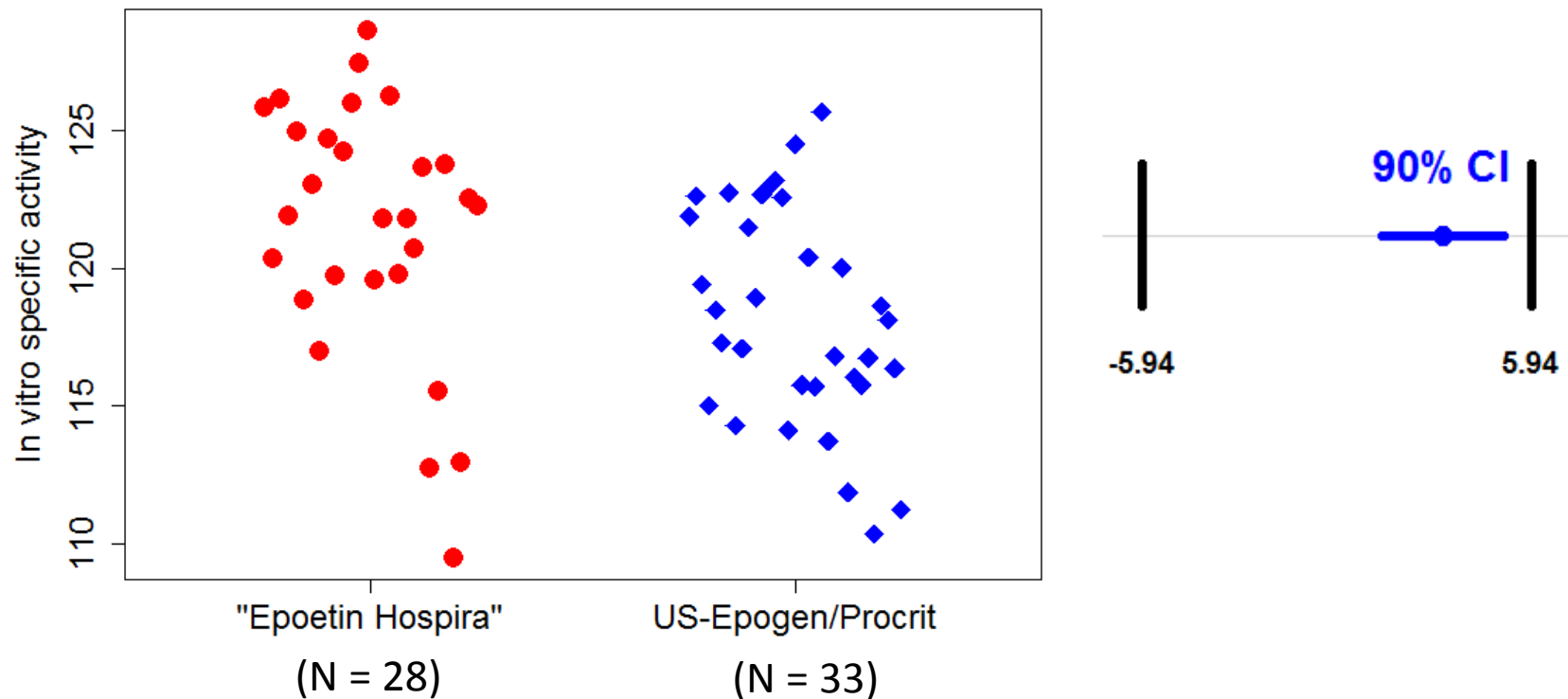


In Vivo Biological Activity by a Normocythemmic Mouse Model



Mean difference	90% CI for mean difference	Equivalence margin	Pass equivalence test?
-2.82	(-7.29, 1.65)	(-11.12, 11.12)	Yes

In Vitro Specific Activity by a Cell-Based Assay



Mean difference	90% CI for mean difference	Equivalence margin	Pass equivalence test?
3.23	(1.36,5.1)	(-5.94, 5.94)	Yes

Addressing Cys29-Cys33 Trisulfide Differences



- “Epoetin Hospira” contains 4.5% more Cys29-Cys33 trisulfide than US-Epogen/Procrit
- Species form by insertion of an extra sulfur atom into the Cys29-Cys33 EPO disulfide bond
- This difference is not expected to have clinical impact:
 - >10% Cys29-Cys33 trisulfide content did not result in differences in either in vivo or in vitro specific activity in an earlier version of “Epoetin Hospira”
 - Literature indicates that trisulfide species can convert to disulfide species in vivo

CMC Conclusions

The totality of the analytical similarity data supports a conclusion that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit notwithstanding minor differences in clinically inactive components.

Pharmacology/Toxicology

Natalie Simpson, PhD

Pharmacology/Toxicology Reviewer

Division of Hematology Oncology Toxicology

U.S. Food and Drug Administration

Overview

- Comparative animal studies may support the similarity of a proposed product to a reference product.
 - *FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*
- Animal studies will be discussed for completeness. However, these studies were not designed to support a demonstration of biosimilarity.
- Comparative animal studies submitted for “Epoetin Hospira” and US-Epogen/Procrit:
 - Study 70882: 13-week subcutaneous (SC) repeat dose toxicology/pharmacokinetic (PK) in rats
 - Study 60486: 13-week intravenous (IV) repeat dose toxicology/PK in dogs
- The rat and dog are appropriate species based on the mechanism of action of EPO; however, immunogenicity is associated with long-term repeat SC dosing of human EPO in rats.

Conclusions from Animal Studies

Study Title	Test Article	Doses (IU/kg 3x/week)	Endpoints		
			PD	PK	Toxicity**
<u>Study 70882</u> : “Epoetin Hospira”: A 13-Week Subcutaneous Repeat Dose Comparative Toxicity Study Followed by a 4-Week Recovery Period in Sprague-Dawley Rats	“Epoetin Hospira” US-Epogen/Procrit	150, 450, 1500/900 150, 450, 1500/900	↓ PD activity with US-Epogen	↓ Exposure, ↑ ADA with US-Epogen	No difference between arms
<u>Study 60486</u> : “Epoetin Hospira”: A 13-Week Intravenous Repeat Dose Comparative Toxicity Study Followed by a 4-Week Recovery Period in Beagle Dogs	“Epoetin Hospira” US-Epogen/Procrit	150, 450, 1500/900 150, 450, 1500/900	↑ PD activity for both test articles	↓ Exposure with “Epoetin Hospira”*	No difference between arms

PD: pharmacodynamics; PK: toxicokinetics; ADA: anti-drug antibodies

* = within the range of individual animal variability

** = examples of toxicities include multi-organ inflammation, hemorrhage, and necrosis

Pharmacology/Toxicology Summary

- In stepwise evidence development, the differences observed from the perspective of Pharmacology/Toxicology would be addressed by subsequent clinical studies.
- Immunogenicity in animals is not predictive of immunogenicity in humans.
- In general, there were no major differences in the toxicity profile between “Epoetin Hospira” and US-Epogen/Procrit.

Clinical Immunogenicity

Steven Bowen, PhD

Immunogenicity Reviewer
Office of Biotechnology Products
U.S. Food and Drug Administration

Immunogenicity risk of Erythropoiesis-Stimulating Agents (ESA)

- Therapeutic proteins have the potential to induce anti-drug antibodies (ADA) that can impact the safety and efficacy of the drug.
- Erythropoietin is a non-redundant critical growth factor.
- Precedent from other ESAs showed that changes to critical product attributes and impurities can lead to the development of neutralizing antibodies (NABs) and onset of pure red cell aplasia (PRCA) in patients.
- Is “Epoetin Hospira” similar to US-Epogen/Procrit with respect to immunogenicity, particularly NABs, supporting a demonstration of no clinically meaningful differences?

Clinical Immunogenicity Data

Study ID	Design	Route	Number	Subjects	Dose	Schedule	Primary Endpoint
EPOE-12-02	Cross-over	Subcutaneous	81	Healthy subjects	100 U/kg	Single dose	PK and PD similarity (reticulocyte count)
EPOE-14-01	Parallel	Subcutaneous	129	Healthy subjects	100 U/kg	3 times / week for 4 weeks	PD similarity (Hb)
EPOE-10-13	Parallel	Subcutaneous	246	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose
EPOE-10-01	Parallel	Intravenous	612	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose

CKD: chronic kidney disease
 PK: pharmacokinetics
 PD: pharmacodynamics
 Hb: hemoglobin
 HD: hemodialysis

Serum samples were tested for ADA using a strategy consistent with FDA Draft Guidance for Industry: *Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products* (April 2016)

Clinical Incidence of ADA for “Epoetin Hospira” and US-Epogen

EPOE-10-01 (CKD; intravenous)

	N	Baseline ADA	Treatment-Induced ADA	NAbs
“Epoetin Hospira”	301	0.7%	0.4%	0.0%
US-Epogen	304	1.1%	0.4%	0.0%

EPOE-10-13 (CKD; subcutaneous)

	N	Baseline ADA	Treatment-Induced ADA	NAbs
“Epoetin Hospira” (Titration)	80	1.4%	0.0%	0.0%
US-Epogen (Titration)	86	1.3%	0.0%	0.0%
“Epoetin Hospira” (Maintenance)	122	0.9%	1.0%	0.0%
US-Epogen (Maintenance)	122	1.0%	0.9%	0.0%

EPOE-14-01 (Healthy subjects; SC)

	N	Baseline ADA	Treatment-Induced ADA	NAbs
“Epoetin Hospira”	66	4.5%	3.0%	0.0%
US-Epogen	63	3.2%	3.2%	0.0%

Immunogenicity Conclusions



- Immunogenicity of “Epoetin Hospira” and US-Epogen was compared in 3 multiple-dose, parallel-arm studies in 849 patients with CKD (EPOE-10-01 and EPOE-10-13) and 129 healthy subjects (EPOE-14-01).
- ADA (anti-drug antibodies) in serum samples were tested using adequately validated assays.
- Similar rates of binding ADA were observed between the “Epoetin Hospira” and US-Epogen treatment groups in patients with CKD and healthy subjects.
- No neutralizing antibodies were observed in subjects treated with “Epoetin Hospira” or US-Epogen.
- These data show no increase in immunogenicity risk and support a conclusion that there are no clinically meaningful differences between "Epoetin Hospira" and US-Epogen.

Clinical Pharmacology

Vicky Hsu, PhD

Clinical Pharmacology Reviewer
Office of Clinical Pharmacology
U.S. Food and Drug Administration

Clinical Pharmacology Overview

- The goal of the clinical pharmacology program is to evaluate PK and PD similarity
 - **Single-dose** pharmacokinetic (PK) and pharmacodynamic (PD) (reticulocyte count) similarity between “Epoetin Hospira” and US-licensed Epogen
 - **Multiple-dose** PD (hemoglobin level) similarity between “Epoetin Hospira” and US-licensed Epogen
- Review Question
 - Do the clinical pharmacology data submitted in this BLA support a demonstration of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen?

Clinical Pharmacology Studies

Study ID	Design	Route	Number	Subjects	Dose	Schedule	Primary Endpoint
EPOE-12-02	Cross-over	Subcutaneous	81	Healthy subjects	100 U/kg	Single dose	PK and PD similarity (reticulocyte count)
EPOE-14-01	Parallel	Subcutaneous	129	Healthy subjects	100 U/kg	3 times / week for 4 weeks	PD similarity (Hb)
EPOE-10-13	Parallel	Subcutaneous	246	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose
EPOE-10-01	Parallel	Intravenous	612	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose

CKD: chronic kidney disease

PK: pharmacokinetics

PD: pharmacodynamics

Hb: hemoglobin

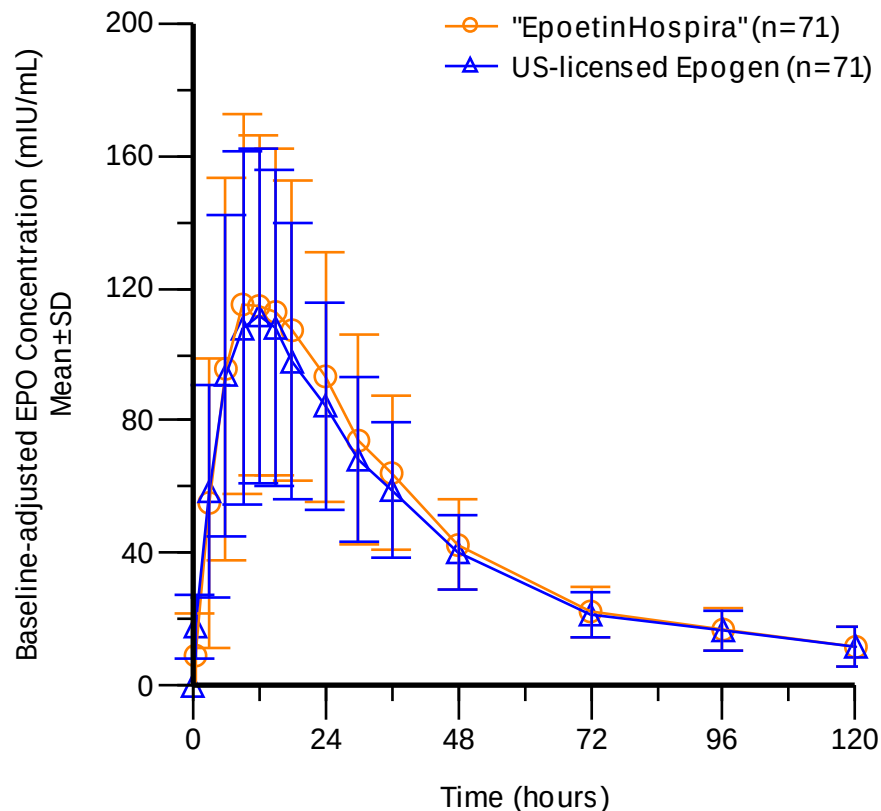
HD: hemodialysis

Single-Dose: EPOE-12-02 (SC)

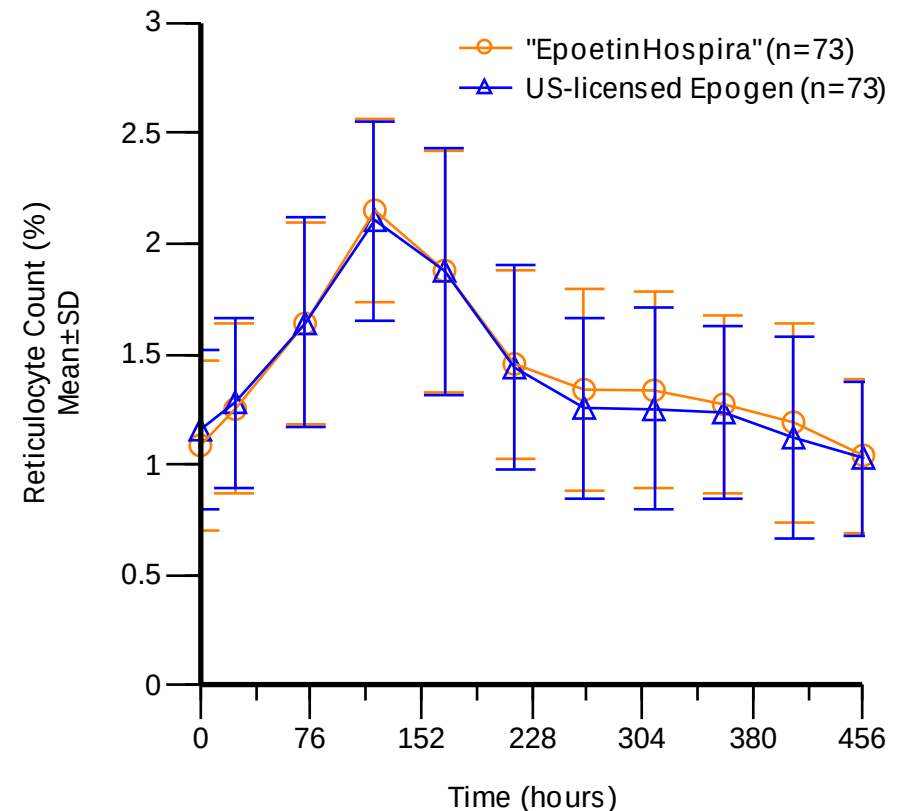
PK and PD Profile Results



PK: post-100 U/kg over 5 days

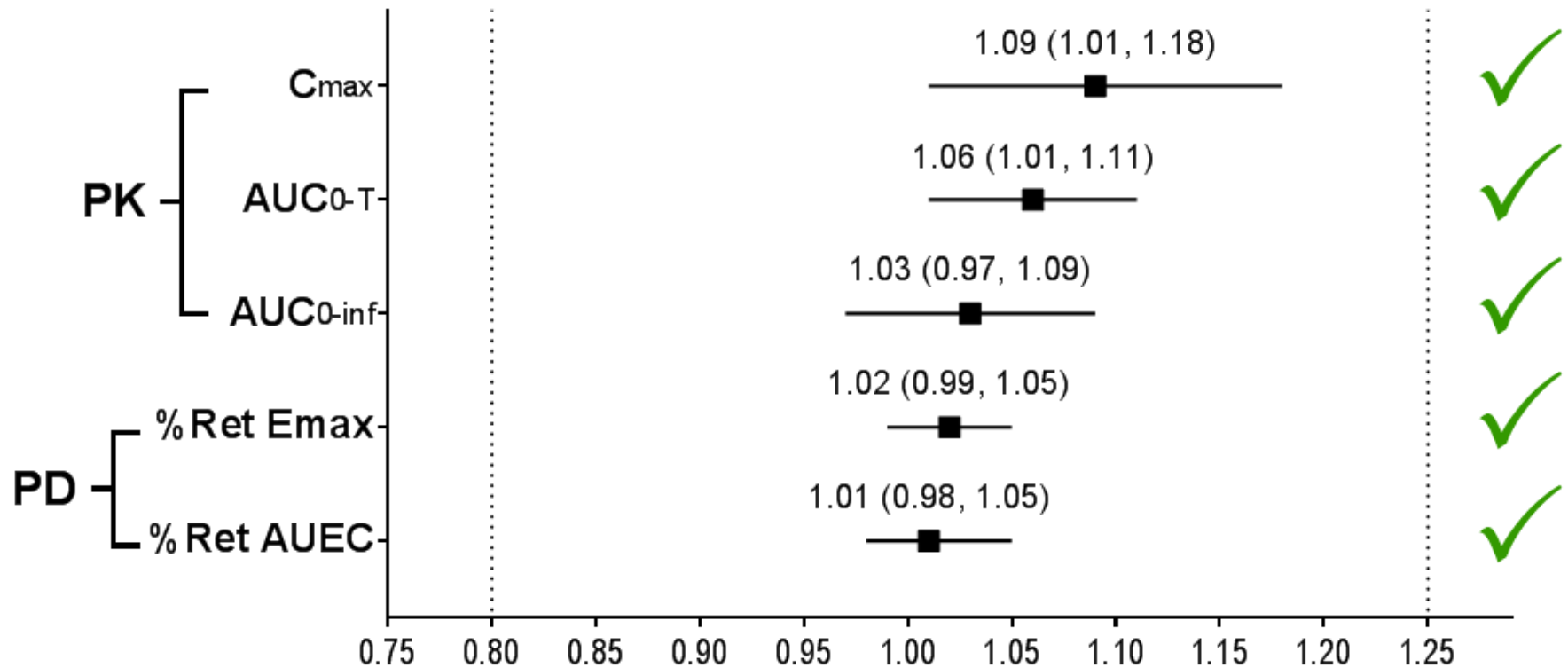


PD: reticulocyte count over 19 days



Single-Dose: EPOE-12-02 (SC)

PK and PD Similarity were Met



C_{max}: maximum concentration

AUC: area under curve

E_{max}: maximum effect

AUEC: area under effect curve

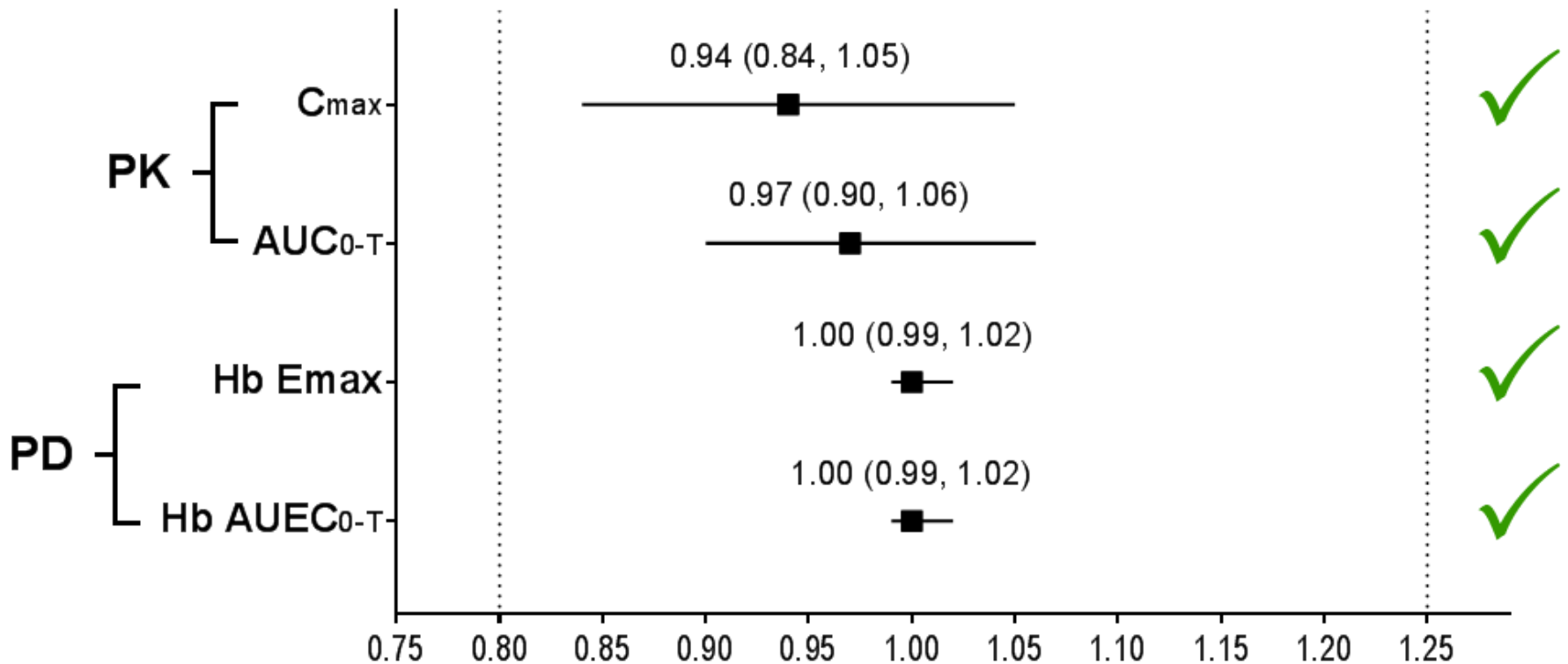
%Ret: reticulocyte count as a percentage of erythrocytes

Geometric Mean Ratio
(90% confidence interval)

"Epoetin Hospira"
US - Epogen

Multiple-Dose: EPOE-14-01 (SC)

PK and PD Similarity were Met



Cmax: maximum concentration
AUC: area under curve
Emax: maximum effect
AUEC: area under effect curve
Hb: hemoglobin level

Geometric Mean Ratio
(90% confidence interval)

"Epoetin Hospira"
US - Epogen

Clinical Pharmacology Summary



- The PK and PD study results support a demonstration of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen.
- The PK and PD study results add to the totality of the evidence to support a demonstration of biosimilarity between “Epoetin Hospira” and US-licensed Epogen.

Clinical Efficacy

Lola Luo, PhD

Clinical Statistical Reviewer

Division of Oncology and Hematology

Office of Biostatistics

U.S. Food and Drug Administration

Comparative Clinical Studies

Study ID	Design	Route	Number	Subjects	Dose	Schedule	Primary Endpoint
EPOE-12-02	Cross-over	Subcutaneous	81	Healthy subjects	100 U/kg	Single dose	PK and PD similarity (reticulocyte count)
EPOE-14-01	Parallel	Subcutaneous	129	Healthy subjects	100 U/kg	3 times / week for 4 weeks	PD similarity (Hb)
EPOE-10-13	Parallel	Subcutaneous	246	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose
EPOE-10-01	Parallel	Intravenous	612	Patients with CKD on HD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose

CKD: chronic kidney disease

PK: pharmacokinetics

PD: pharmacodynamics

Hb: hemoglobin

HD: hemodialysis

Good Clinical Practice Compliance

Study Site Closures



- EPOE-10-13 (SC)
 - 3 sites closed during conduct of the study
 - No additional sites identified in post-study GCP assessment
 - 10% (53/556) patients enrolled
 - 8% (20/246) patients in ITT population
- EPOE-10-01 (IV)
 - 7 sites closed during conduct of the study
 - 2 additional sites identified in post-study GCP assessment
 - 14% (140/1017) patients enrolled
 - 11% (65/612) patients in ITT population

Statistical Analysis Plan (SAP)

- Co-Primary Endpoints for the Comparative Clinical Studies:
 - Mean weekly hemoglobin (Hb) level during the last 4 weeks of the double-blind Maintenance Period.
 - Mean weekly dose per kg body weight during the last 4 weeks of the double-blind Maintenance Period.

- Equivalence Margin
 - Hb: $\pm 0.5\text{g/dL}$
 - Dose: $\pm 45\text{ U/kg/week}$

- Randomization:
 - 1:1 ratio
 - Double blind
 - Stratification by the titration period study drug dose (EPOE-10-13 only)

Sample Size Planned

	Parameter	Power	Equivalence Margin	SD	Predicted % Missing	Planned N
EPOE-10-13 (SC)	Hb (g/dL)	90%	± 0.5	0.94	35%	288
	Dose (U/kg/week)	90%	± 45	78		
EPOE-10-01 (IV)	Hb (g/dL)	90%	± 0.5	1.37	30%	564
	Dose (U/kg/week)	90%	± 45	118.11		

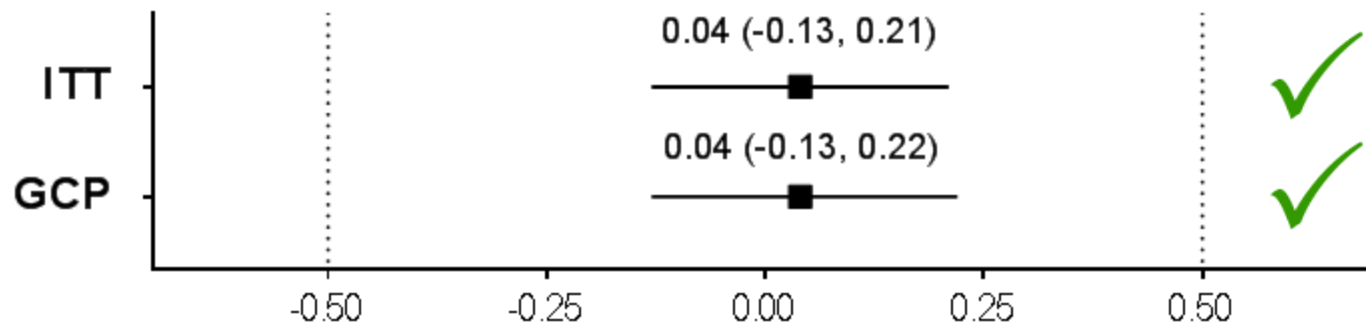
Statistical Methods

Analysis Population	Description	Clinical Study	“Epoetin Hospira”	US-Epogen /Procrit
Intent-to-treat (ITT)	All randomized subjects	EPOE-10-13 (SC)	124	122
		EPOE-10-01 (IV)	306	306
Good Clinical Practice (GCP)	ITT population excluding subjects from the closed sites	EPOE-10-13 (SC)	112	114
		EPOE-10-01 (IV)	268	279

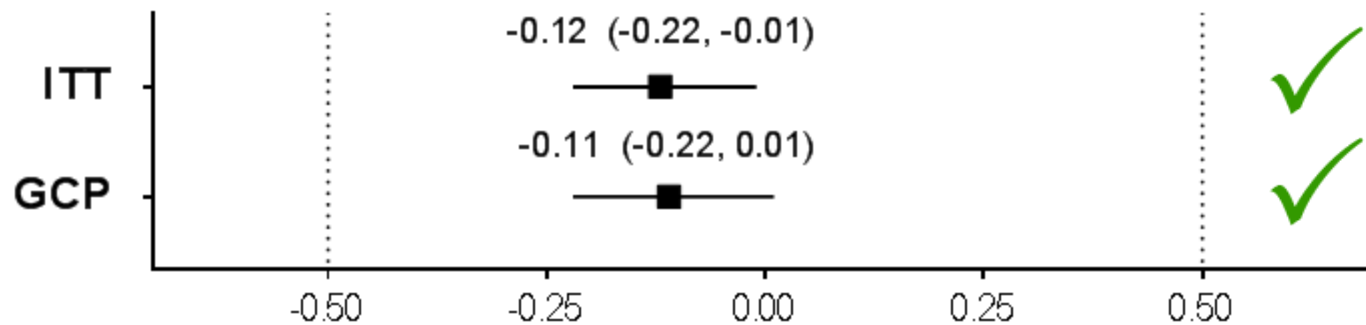
- A hierarchical testing procedure is used for the co-primary endpoints (mean Hb level → mean weekly dose/kg)
- An analysis of covariance (ANCOVA):
 - Treatment as the factor
 - Baseline value (Hb or dose) as covariate

Co-primary Endpoint: Difference in Mean Weekly Hemoglobin

EPOE-10-13 (subcutaneous)



EPOE-10-01 (intravenous)



Difference, in g/dL
(90% confidence interval)

("Epoetin Hospira" - US-Epogen)

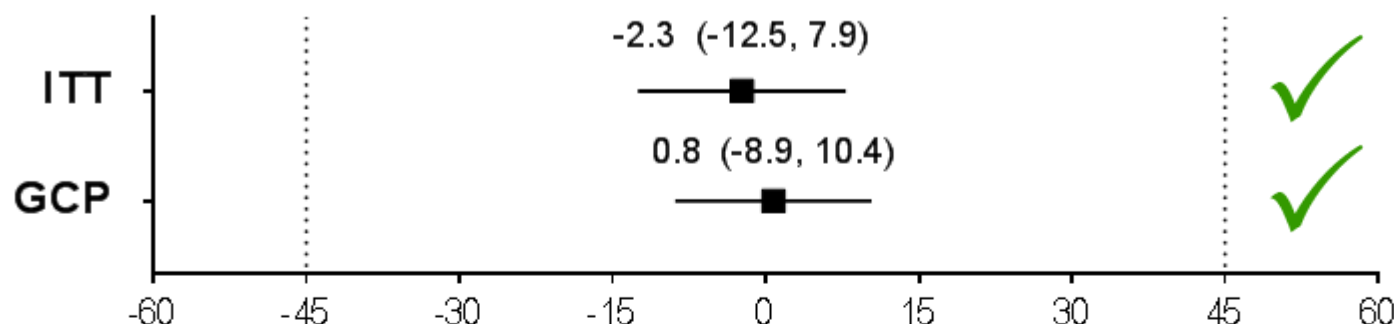
ITT: intent-to-treat

GCP: Good Clinical Practice

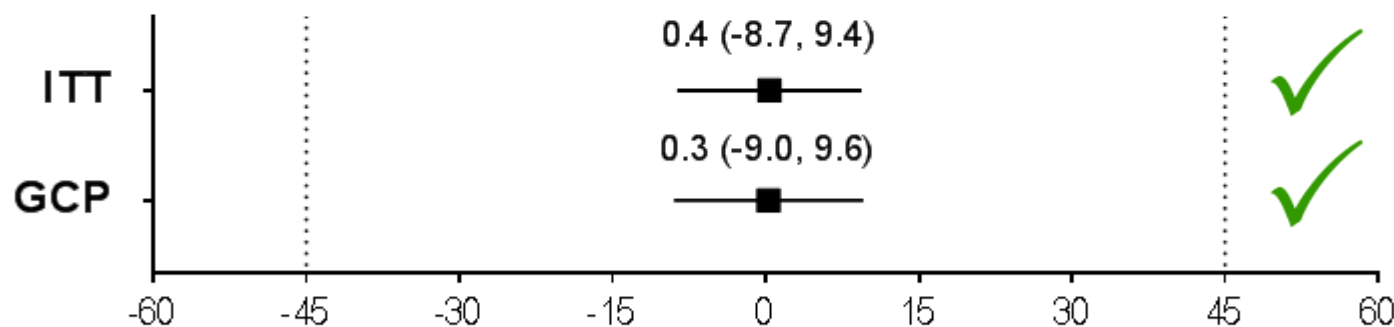
Co-primary Endpoint: Difference in Mean Weekly Dose



EPOE-10-13 (subcutaneous)



EPOE-10-01 (intravenous)



Difference, in U/kg/week ("Epoetin Hospira" - US-Epogen)
(90% confidence interval)

ITT: intent-to-treat
GCP: Good Clinical Practice

Efficacy Conclusions

- The 90% CIs for the difference between “Epoetin Hospira” and US-licensed Epogen/Procrit for both primary endpoints are within the equivalence margins for both EPOE-10-13 and EPOE-10-01 studies.
- These results were consistent between different sensitivity analyses and subgroups.
- These data support a demonstration of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit.

Clinical Safety

Lori Ehrlich, MD, PhD

Medical Officer

Division of Hematology Products

U.S. Food and Drug Administration

Safety analysis

EPOE-10-13 (SC) – maintenance period

	Original Analysis		Closed Sites Excluded	
	“Epoetin Hospira” N = 122 n (%)	US-Epogen/ Procrit N = 122 n (%)	“Epoetin Hospira” N = 110 n (%)	US-Epogen/ Procrit N = 114 n (%)
Subjects Reporting at Least One TEAE	85 (70)	86 (71)	79 (72)	79 (69)
Subjects Reporting at Least One Serious TEAE	23 (19)	33 (27)	19 (17)	29 (25)
Subjects Discontinuing Study Drug due to a TEAE	4 (3)	4 (3)	4 (4)	4 (4)
Subjects Reporting an TEAE Resulting in Death	3 (3)	2 (2)	3 (3)	2 (2)

SC: subcutaneous

TEAE: treatment-emergent adverse event

Safety analysis

EPOE-10-01 (IV)

	Original Analysis		Closed Sites Excluded	
	“Epoetin Hospira” N = 301 n (%)	US-Epogen/ Procrit N = 304 n (%)	“Epoetin Hospira” N = 264 n (%)	US-Epogen/ Procrit N = 277 n (%)
Subjects Reporting at Least One TEAE	232 (77)	229 (75)	207 (78)	210 (76)
Subjects Reporting at Least One Serious TEAE	75 (25)	82 (27)	64 (24)	77 (28)
Subjects Discontinuing Study Drug due to a TEAE	9 (3)	11 (4)	9 (3)	11 (4)
Subjects Reporting an TEAE Resulting in Death	5 (2)	6 (2)	3 (1)	6 (2)

IV: intravenous

TEAE: treatment-emergent adverse event

Additional Safety Findings

- Major events of interest (myocardial infarction, stroke, and thromboembolism) were observed in both arms with no imbalances.
- No cases of pure red cell aplasia (PRCA) were observed in these clinical studies.

Safety Conclusions

- Safety monitoring in clinical studies was adequate.
- No imbalances in safety profiles between patients who received “Epoetin Hospira” vs. US-licensed Epogen/Procrit.
- Sensitivity analysis excluding non-GCP compliant sites did not change the overall results.

Extrapolation Across Indications

Proposed indications are the same as US-licensed Epogen/Procrit:

- For the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion
- For the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL
- For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery

Support for Extrapolation

- Mechanism of action is the same across indications
- Similarity has been demonstrated with regard to:
 - Analytical attributes
 - Pharmacokinetics/pharmacodynamics
 - Immunogenicity
 - Efficacy and safety

Overall Summary of FDA Findings

Biosimilarity

- Highly similar to reference product, notwithstanding minor differences in clinically inactive components, and
- No clinically meaningful differences in safety, purity, and potency

Summary of FDA Findings

- Totality of analytical data, based on multiple orthogonal physicochemical and functional methods, support a demonstration of highly similar notwithstanding minor differences in clinically inactive components.
- Clinical data, including pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity data support a demonstration that there are no clinically meaningful differences.
- Residual uncertainties (differences in glycosylation and trisulfide species) were adequately addressed by other data, including clinical data.

Overall Conclusion

- Totality of the evidence supports a demonstration of biosimilarity between “Epoetin Hospira” and US-licensed Epogen/Procrit.
- Extrapolation to all indications for “Epoetin Hospira” is supported by demonstration of biosimilarity and, among other information, the scientific understanding of the mechanism of action across indications.