**Biosimilars - An Update**

*Focused on Quality Considerations*

Steven Kozlowski, M.D.
Director, Office of Biotechnology Products
OPS/CDER / U.S. FDA

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012

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**Statute**

- The Biologics Price Competition and Innovation Act (BPCI Act) was passed as part of healthcare reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.
- The BPCI Act creates an *abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable* with an FDA-licensed reference product.

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**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 on certain existing scientific knowledge about the safety, purity, and potency of the reference product.
- This new licensure pathway permits a "biosimilar" biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

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**Biosimilar Draft Guidances**

**Overarching Goal:** Efficient, predictable and transparent regulatory pathway

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Sci. Cons.)
2. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Q&A)
3. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Quality)

*Always consider entire text and context of guidance excerpts*

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**Biosimilarity**

- *Biosimilar or biosimilarity* means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;"
- and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.*

*How close is close enough?*

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**Speakers**

- **Quality Considerations for Biosimilars**
  - Marjorie Shapiro, Ph.D. Division of Monoclonal Antibodies/OBP/OPS/CDER/FDA
- **PhRMA Perspectives**
  - Robert J. Mattaliano, Ph.D., Group VP, Biologics Development, Genzyme Corporation
- **GPhA Perspectives**
  - Mark McCamish, MD, Ph.D. Global Head Biopharmaceutical Development, Sandoz International, GmbH
Quality Considerations for Biosimilars

Marjorie Shapiro, Ph.D.
Division of Monoclonal Antibodies/OBP/OPS

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012
Definition of Biosimilar/Biosimilarity in BPCI Act

Biosimilar or biosimilarity is defined in Section 351 of the PHS Act to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product”.

Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.
Scientific Considerations Draft Guidance

The stepwise approach should start with extensive structural and functional characterization of both the proposed product and the reference product, which serves as the foundation of a biosimilar development program.
Highly Similar Analytical and PK/PD Data = Lower Risk of Clinical Differences

Two approaches to achieve biosimilarity:

- 351(a) package
  - Analytical
  - Nonclinical
  - Clin Pharm
  - Additional Clinical Studies

- 351(k) package
  - Analytical
  - Nonclinical
  - Clin Pharm
  - Additional Clinical Studies
Quality Considerations Draft Guidance

• Focuses on analytical studies that may be relevant to assessing the similarity between a proposed biosimilar protein product and a reference product.

• General principles:
  – Importance of extensive analytical, physicochemical and biological characterization
  – Product/process impurities, expression system
  – Identification of lots used in the various analyses for biosimilarity determination
  – Advances in manufacturing science and Quality-by-Design approaches may facilitate “fingerprint”-like analysis
Hierarchy of Protein Structure

Primary structure
- Lys
- Lys
- Gly
- Gly
- Leu
- Val
- Ala
- His

Secondary structure
- \( \alpha \) Helix

Tertiary structure
- Polypeptide chain

Quaternary structure
- Assembled subunits

All need to be evaluated as part of analytical similarity studies
Protein Heterogeneity

- Amino Acid Substitution
- N- and C-terminal mods
- Mismatched S-S bonds
- Folding
- Truncation
- Aggregation
- Multimer Dissociation
- Denaturation
- Acetylation
- Fatty acylation
- Deamidation
- Oxidation

- Carbamylation
- Carboxylation
- Formylation
- \(\gamma\)-Carboxyglutamylolation
- O-linked Glycosylation
- N-linked Glycosylation
- Methylation
- Phosphorylation
- Sulphation
- PEGylation
Types of N-linked glycans

- **Complex tetra-antennary glycans**
  - Sialic Acid Terminus
  - Lactosamine

- **Hybrid glycans**
  - High mannose glycans
  - Complex tetra-antennary glycans

- **High mannose glycans**
  - Mannose residues linked to asparagine (Asn)
  - Glycosylation patterns vary

- **Complex tetra-antennary glycans**
  - Longer antennae with additional sugars
  - More diverse in structure and function

- **Hybrid glycans**
  - Combination of high mannose and complex glycans
  - Includes galactosylation and fucosylation

These structures play crucial roles in various biological processes, including protein stability, cell adhesion, and immune system interactions.
Antibody Glycans

Gomord et al. Plant Biotechnology Journal 2010
Analytical Tools to Evaluate Proteins

- Amino acid sequence and modifications:
  - MS, peptide mapping, chromatographic separations

- Folding:
  - S-S bonding, calorimetry, HDX and ion mobility MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, fluorescence

- Subunit interactions:
  - Chromatography, ion mobility MS

- Heterogeneity of size, aggregates, charge, hydrophobicity:
  - Chromatography resins; gel & capillary electrophoresis, light scatter, IM-MS, Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy

- Glycosylation
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS

- Bioactivity
  - Cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction

- Impurities
  - Proteomics, immunoassays, metal & solvents analysis
Choice of Analytics

• It is expected that appropriate analytical test methods will be selected based on:
  – the nature of the protein being characterized,
  – knowledge regarding the structure, and
  – heterogeneity of the reference and proposed biosimilar product, including
    » known and potential impurities, and
    » characteristics that are critical to product performance

• Use of stability studies to reveal subtle or hidden differences
Source Materials

- Mice
- Humans
- Bacteria
- Insect cell-culture
- Mammalian cell-culture
- Plant cell-culture
- Transgenics
- Yeast
Expression Systems

• **Differences** between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered.

• The type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities.
Protein Impurities – The *E. coli* Proteome

Host cell proteins can be detected, identified, and quantified. Similar impurities profiles decrease risk of product difference.
Know Your Protein!

- Need to understand what is important for biological function of protein

- If multiple MOAs, need to understand MOA for specific indication and critical quality attributes for that MOA

- Need to understand impact of potential post translational modifications
  - Oxidation of met and deamidation of asn may impact function or immunogenicity of some proteins but not others

- Need to understand how combinations of quality attributes interact to impact clinical performance.

- Case-by-case evaluation of different post translational modifications and any potential clinical impact
Approach to Reverse Engineering for Developing a Biosimilar Product

• Analyze cell substrates
  – Design so that host cell protein profile will match
• Reverse engineer upstream manufacturing
  – Media composition and fermentation parameters
  – Growth characteristics
  – Match product attributes
• Reverse engineer downstream purification
  – Match product variants and process impurities
• Formulation
  – Match stability profile
Fingerprinting

• It may be useful to compare products using a meaningful fingerprint-like analysis algorithm
  – that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods.

• Advances in manufacturing science and Quality-by-Design approaches may allow a better match to a reference product’s fingerprint.

• May allow a more selective and targeted approach to subsequent animal and/or clinical studies.
Data Collection During New Biological Entity Product Development

Preclinical Toxicology Studies

- Short term
- Long term

IND Enabling | Phase I | Phase II | Phase III
---|---|---|---

Clinical Studies
- Dose ranging
- Safety

Dose ranging
- Safety
- Efficacy

Efficacy
- Safety

Product Quality

Adapted from a slide by Tony Mire-Sluis
# Product Quality Assays During New Biological Entity Product Development

## Development Decision | IND | BLA

<table>
<thead>
<tr>
<th>Research</th>
<th>Developmental Research</th>
<th>IND Enabling</th>
<th>Phase I</th>
<th>II</th>
<th>III</th>
<th>IV Post Marketing</th>
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<tr>
<td>Early purification studies</td>
<td>Protein selection</td>
<td>Limited Structural characterization</td>
<td>In depth characterization assay development</td>
<td>Lot release</td>
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<td>Limited viral clearance</td>
<td>Specification setting</td>
<td>Stability</td>
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<td>Limited stability</td>
<td>Manufacturing scale up</td>
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Data Collection During Biosimilar Product Development

Preclinical Toxicology Studies
Short term

351(k) package

IND Enabling | Initial Clinical Studies | Additional Clinical Studies
---|---|---
Clinical Studies | Immunogenicity
PK/PD | Additional Clinical Studies

Product Quality

Depends on extent of analytical similarity and PK/PD similarity prior to this point
Preferred Biosimilar Product Quality Development Process

Development Decision | IND | BLA
---|---|---
Biosimilar Initial Advisory Meeting | BPD Type 1/2/3 | BPD Type 4

Developmental Research
- Purchase reference product lots
- Analyze reference product lots
- Develop biosimilar construct and cell line
- Manufacturing process development

IND Enabling
- In depth characterization assay development
- Preliminary analytical/functional similarity studies
- Formulation studies
- Analytical and functional similarity studies
- Qualified/validated release and stability assays

Initial Clinical Studies
- Continuous characterization
- Specification setting
- Final Mf scale
- Stability
- Viral Clearance

Additional Clinical Studies
- Final analytical and functional similarity studies
- Specification setting
- Stability

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Development Framework:
Comparative Analytical Characterization Continuum

• Cannot be biosimilar

• Similar
  – Needs additional information to determine if highly similar (e.g., additional analytical data, or other studies to determine if minor differences are “clinically inactive components”)

• Highly similar
  – Permits a selective and targeted approach to determine if biosimilar

• Highly similar with fingerprint-like similarity
  – Permits a more selective and targeted approach to determine if biosimilar
Acknowledgements

• Steve Kozlowski
• Leah Christl
• Emily Shacter
• Tony Mire-Sluis
A PhRMA Member View on Biosimilars
Analytical and Quality Considerations

Robert J Mattaliano, Ph.D., Group VP, Biologics Development

Jade (with her mother) Fabry disease USA

FDA Advisory Committee on Pharmaceutical Science and Clinical Pharmacology
August 8, 2012
Genzyme's Mission - to discover and deliver transformative therapies for patients with rare and special unmet medical needs, providing hope where there was none before.

• Founded in 1981 and pioneered treatments for rare diseases
• Serving patients in over 100 countries
• Strong relationships with patients and patient communities
• Driven by Science
  • Broad range of technology platforms
  • Closely integrated with clinical, commercial, regulatory, patient advocacy
• We now benefit from the reach and resources of Sanofi, one of the world’s largest pharmaceutical companies

Next-generation therapies for Gaucher, Fabry and Pompe diseases

Research in Niemann-Pick B, Lupus, MS, Parkinson’s and Cystic Fibrosis
Biologics versus Small Molecule Drugs

Biologics

- Larger, complex, dynamic structures
- Diverse populations of molecules not easily characterized
- Produced using a biological process
- Complicated manufacturing
- Example: Monoclonal antibodies

Small Molecule Drugs

- Synthetic
- Manufacturing processes using defined chemical reactions
- Smaller, simpler structures – can be fully characterized by standard analytical techniques
- Example: Aspirin

Aspirin
~180 daltons

Insulin
51 amino-acids
~5,800 daltons

Somatropin
191 amino-acids
~22,000 daltons

IgG1
>1000 amino acids
~150,000 daltons

Images not to scale

Not All Biologics Are Created Equal
Gradations of Complexity

- Small Molecule Drugs
- Synthetic Peptides
- Insulins
- LMW Heparins
- Growth Factors
- Monoclonal Antibodies
- Enzymes
- Viral Vectors
- Vaccines
- Cells
- Coagulation Factors
- Cytokines
- Vaccines
- Monoclonal Antibodies
- Growth Factors
- LMW Heparins
- Insulins
- Synthetic Peptides
- Small Molecule Drugs

Dominant Metric:
- Analytics
- Analytics and Process
- Process

Molecular Complexity

Process Specific Dependency

Analytical Certainty
Probing the Quality and Consistency of Biologics
Quantitative and Qualitative Tools - Many Form the Basis for Release Tests

• **Protein Structure**
  - Primary Sequence Confirmation
  - Identity
  - Disulfide Bonding Pattern
  - Secondary, Tertiary and Quaternary Structures
  - Molecular Weight Analyses
  - Glycan Attachment Sites

• **Drug-related Substances and/or Impurities**
  - Electrophoretic Purity (reducing and non-reducing denaturing conditions)
  - Chromatographic Purity (various stationary phases)
  - Soluble Oligomer and Aggregate content
  - Particle Content

• **Process-related Substances and/or Impurities**
  - Host Cell Impurities
  - Host Cell DNA
  - Process related Impurities (e.g., Protein A, metals, solvents)
  - Process Extractables, Leachables

• **Post-Translational Modifications**
  - Individual Monosaccharide Content (e.g., NANA, NGNA, fucose, phosphorylated mannose)
  - Oligosaccharide Profiling, Site Specific Glycoform Analysis
  - Amino Acid Modifications (e.g., deamidation, oxidation)
  - Degree of Proteolytic Fragmentation

• **Function / Potency**
  - Bioassays
  - Receptor Binding
  - Cellular uptake/processing
  - Enzymatic Activity/Kinetics

• **Stability**
  - Biologic and Impurity attributes under proposed storage conditions
  - Thermal-, pH-, Photo-Stability under controlled stress conditions

• **General Methods**
  - Appearance, Concentration, pH, Endotoxin, Sterility

• **Non-Clinical Analyses in Relevant Animal Models**
  - Pharmacokinetics
  - Biodistribution
  - Pharmacodynamics
Apparent Molecular Complexity
Depends on the Method Being Used

Separation Based
Molecular Mass

SDS-PAGE

Separation Based
Molecular Charge

Isoelectric Focusing

<table>
<thead>
<tr>
<th>Molecular Mass</th>
<th>200 kD</th>
<th>116 kD</th>
<th>97 kD</th>
<th>66 kD</th>
<th>55 kD</th>
<th>36 kD</th>
<th>31 kD</th>
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- SDS-PAGE
- Isoelectric Focusing
ICH Topic Q6B
Specifications:
Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical and clinical studies.
Protein amino acids are often covalently modified in the cell to critically confer structure, function and stability.

15 of 20 amino acids have known modifications:
- 10 residues (Arg, Asp, Cys, Glu, His, Lys, Met, Ser, Thr, Tyr) have reactive N, O, or S atoms
- 2 residues (Asn, Gln) contain reactive amide containing side chains
- 3 residues which are less reactive (Trp, Pro, Gly)
- 5 residues (Leu, Ile, Val, Ala, Phe) with no reported modifications

Post-Translational Modifications include:
- Disulfide bond formation - Methylation
- N-Glycosylation, O-Glycosylation - Poly-glycination, -glutamination
- Deamidation, Asp Isomerization - C-hydroxylation
- Oxidation - Transglutamination
- Phosphorylation - Sulphation
- Carboxylation - Lipidation

The type and degree of PTM’s varies with expression cell type and specific production process.
Post Translational Modifications
Consider Glycosylation

Glycosylation Variants Inform Targeting and Clearance

- Sialic Acid
- Galactose
- N-acetyl Glucosamine
- Mannose
- Fucose
- Phosphate

significant glycan structures / site

10 10 5 11 4 7 10

~ $1.54 \times 10^6$ possible variants based on predominant site specific glycans alone
Sophisticated Models May Imply a Higher Level of Understanding of Molecular Complexity

Model of glucosidase acid alpha based on the structure of maltase-glucoamylase complexed to an active site inhibitor (Sim et al, 2008 JBC). Courtesy of R. Wei, C. Pan
Making Gains on Our Understanding of Diverse Populations of Structurally Complex Molecules

- Our industry has been greatly enabled by advances in analytical technologies and methods

- Unfortunately, our ability to probe the inherent complexities of many biologics remains imperfect

- Seemingly small changes to a biologics structure or population diversity may have unintended clinical consequences

- Consequently, the specific production process, controls and clinical experience often define product safety and efficacy

- What distinguishes innovators from biosimilar manufacturers are insights regarding critical quality attributes and experience producing a particular product
Identifying Biologics Critical Attributes is Key
A single amino acid essential for a MAb function

- MAb-ligand crystal structure solved
- Limited engineering alternatives
- Strategy => Adapt the Process Control Strategy
- Refine Process Design Space
On-Going and Emerging Areas of Investigation

- Impact of codon optimization (i.e., codon bias)\(^1\)
- Different types and levels of post-translational modifications (e.g., glycosylation)
- Understanding molecular flexibility / surface dynamics
- Controlling the diversity of complex molecular populations
- Mitigating physical instabilities (e.g., aggregates, particles)
- How trace impurities may facilitate immunogenic responses\(^2\)
- Reactivity of product contact disposables (e.g., extractables, leachables)

Biologics Are Not Monomolecular Entities
Two Central Questions Arise Regarding Biosimilars

To what extent can innovator product sampling provide a sufficient picture of reference biologic complexity and manufacturing history to assess biosimilarity?

Can comparative analytical testing assure no meaningful differences from a reference biologic clinical safety, purity, and potency?
In February 2012, FDA issued three draft guidance documents on biosimilar product development to assist industry in developing these products.

- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Draft)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Draft)
- Biosimilars: Questions and Answers Regarding Implementation of the BPCIA (Draft)

When finalized, these guidances will represent the FDA’s current thinking on these topics.
Recognizing One’s Limitations

The Definition*

“the biological product is **highly similar** to the reference product, notwithstanding minor differences in clinically inactive component”, **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”.

Recognizing an analytical program’s limitations is equally important as, if not more important than, recognizing its strengths.

*Scientific Considerations in Demonstrating **Biosimilarity** to a Reference Product  (FDA Draft Guidance, February 2012)
FDA’s Stepwise Approach to Demonstrate Biosimilarity
Assuring Patient Safety is Paramount

Analytical Studies
Demonstrate that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components

Animal Studies
Including assessments of toxicity, PK/PD, and immunogenicity, in accordance with ICH S6 guidelines

Clinical Studies
Demonstrate safety, purity, and potency in conditions of use for which the reference product is currently used, including assessment of immunogenicity and PK/PD

• FDA proposes to use risk-based, totality-of-the-evidence approach to evaluate all available data and information
• However, FDA has the discretion to determine that an element above is unnecessary for approval
How Will Biosimilar Sponsors Identify Critical Quality Attributes?

Established Process w/ Defined Critical Quality Attributes (CQAs)

Comparability

- Development
- Physicochemical Analysis
- Preclinical/ Clinical Testing
- Manufacturing

Established Quality, Safety & Efficacy Profile

Product CQAs Are Directly Linked to Clinical Experience

Manufacturing Change

Proposed Biosimilar

- Development
- Physicochemical Analysis
- Preclinical/ Clinical Testing
- Establishment of Similar Quality, Safety & Efficacy

Reference Product

- Development
- Physicochemical Analysis
- Preclinical/ Clinical Testing

Established Quality, Safety & Efficacy Profile

Head-to-Head, Comparative Studies

Biosimilarity
Sorting Out Which Attributes Are Critical
Example - N-terminal Heterogeneity/Cyclization

- Common post-translational modification (e.g., MAb H, L chains)
- Thermodynamically favored
- Catalyzed by glutaminyl cyclase (many plants and animals, including humans)
Cyclization of N-Terminal Glutamine to Pyroglutamic Acid May Be Directly Impacted by Manufacturing Process Intermediate Hold Times

Could increasing N-terminal glutamine facilitate susceptibility to proteolysis, favor antigen presentation and enhance immune response?

Estimated % Molecules with Gln at N-Terminus

Process History
Experimental Confirmation is Key
Example - N-terminal Heterogeneity/Cyclization

- Removal of N-terminal pyroglutamic acid had no measurable effects on higher order structure, activity, ligand binding, cellular uptake, aggregation, degradation, pharmacodynamics or biodistribution

- Hypothetical concerns of N-terminal heterogeneity on immunogenicity
  - Conflicting literature with respect to relative immunogenicity for N-terminal glutamine vs. pyroglutamic acid using peptide models

- Sera from patient with neutralizing or high titers did not cross react with N-terminal epitopes of the biologic; thus, no apparent role for N-terminus in immunogenicity
Identifying Critical Attributes
Example – Sialylation Positional Differences on Complex Glycans

- GlcNAc
- Mannose
- Galactose
- Fucose
- NANA

Graphs showing:
- Specific Activity (U/mg) vs. Moles Sialic Acid
  - N = 17, R² = 0.013, P = 0.66
- Specific Activity (U/mg) vs. % Bisialylated Biantennary Glycan
  - N = 17, R² = 0.50, P = 0.001
Even When Biologics Are “Highly Similar”
Expect the Unexpected

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<th>B</th>
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* Percentage of Reference Value
Even When Biologics Are “Highly Similar” Expect the Unexpected

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* Percentage of Reference Value
Considering The Implications of Change (e.g., Biologics Source, Process, Clinical Indication)

Model Systems

Molecular Mechanisms

- How well do we understand the disease, indication?
- Etiology and pathology, associated structural and functional defects

- How well do we understand the drug, critical quality attributes and production process?
- Identity, purity, potency, ADME, safety, manufacturability, specificity

- How well do we understand the mechanism of action with respect to the disease/indication we are targeting?
- Strength of target validation in the context of the clinical disease

- How well can we follow the effect of our drug on the disease/indication we are targeting?
- Biomarkers, imaging, type of specimens
PhRMA’s Overarching Principles on Regulatory Pathways for Biosimilars

• Patient safety should be paramount when evaluating proposed biosimilar products

• The statutory standard for biosimilarity rests in the negative — in establishing the absence of clinically meaningful differences
  • An abbreviated licensure pathway is appropriate only when a biological product has been demonstrated to be highly similar to, and devoid of any clinically meaningful differences from, a single FDA-approved reference product

• A clear, scientifically rigorous process for evaluation of potential differences between a proposed biosimilar and its reference product is essential to ensure, for patients, the quality, safety, and efficacy of the biosimilar
Some Concluding Thoughts

• We should be humble about what we don’t know
• Being wrong may have serious consequences for drug efficacy and patient safety
• We are making progress linking some, but not all, biologics properties to critical quality attributes
• The lenses and model approaches through which we examine biologics have room for improvement
• Innovators have detailed information on numerous drug product lots which can be directly linked to clinical experience
• Given the gradation of biologics complexity, a one size fits all strategy for biosimilars will not be possible
FDA ACPS-CP
UPDATE ON BIOSIMILARS

On Behalf of GPhA

Mark McCamish, MD, PhD
Global Head Biopharmaceutical Development
Sandoz International

FDA White Oaks Conference Center, Silver Spring, MD, 8 August 2012
## OVERVIEW

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<th>Why biosimilars?</th>
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<td>Abbreviated clinical trial designs</td>
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<td>Successful commercialization broadens patient access</td>
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GROWING DEMAND DRIVES COSTS... AND THREATENS TO LIMIT PATIENT ACCESS

Estimated daily treatment costs\(^1\) in USD per day

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<th>Small molecule drugs</th>
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\(^1\) Source: NY Times, March 2010

The “Biologics Boondoggle”

“A breast cancer patient’s annual cost for Herceptin is $37,000…

People with rheumatoid arthritis or Crohn’s disease spend $50,000 a year on Humira…

…and those who take Cerezyme to treat Gaucher disease….spend a staggering $200,000 a year…

“...the top six biologics already consume 43% of the drug budget for Medicare Part B”

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BY 2016, 7 OF THE TOP 10 PHARMACEUTICALS WORLDWIDE WILL BE BIOLOGICS¹

<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>2016 Rev. (USD bn)</th>
<th>2010 Rev. (USD bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HUMIRA</td>
<td>Biologic</td>
<td>10.0</td>
<td>6.7</td>
</tr>
<tr>
<td>2. AVASTIN</td>
<td>Biologic</td>
<td>7.7</td>
<td>6.2</td>
</tr>
<tr>
<td>3. RITUXAN</td>
<td>Biologic</td>
<td>7.6</td>
<td>6.1</td>
</tr>
<tr>
<td>4. ENBREL</td>
<td>Biologic</td>
<td>7.1</td>
<td>7.3</td>
</tr>
<tr>
<td>5. CRESTOR</td>
<td>Small molecule</td>
<td>7.5</td>
<td>6.0</td>
</tr>
<tr>
<td>6. SERETIDE/ADVAIR</td>
<td>Respiratory / device</td>
<td>6.7</td>
<td>7.9</td>
</tr>
<tr>
<td>7. REMICADE</td>
<td>Biologic</td>
<td>6.2</td>
<td>6.5</td>
</tr>
<tr>
<td>8. HERCEPTIN</td>
<td>Biologic</td>
<td>6.3</td>
<td>5.2</td>
</tr>
<tr>
<td>9. REVLIMID</td>
<td>Small molecule</td>
<td>6.1</td>
<td>2.5</td>
</tr>
<tr>
<td>10. LANTUS</td>
<td>Biologic</td>
<td>5.3</td>
<td>4.7</td>
</tr>
</tbody>
</table>

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¹ Source: Evaluate Pharma, Sandoz analysis
OVERVIEW

- Why biosimilars?
- Scientific approach to biosimilar development
- Abbreviated clinical trial designs
- Successful commercialization broadens patient access
FINGERPRINTING AND ENOXAPARIN

- FDA developed 5 criteria for fingerprinting evaluation of enoxaparin
  - Equivalence of physiochemical properties
  - Equivalence of heparin source material and mode of depolymerization
  - Equivalence in diasaccharide building blocks, fragment mapping and sequence of oligosaccharide species
  - Equivalence in biological and biochemical assays
  - Equivalence of in vivo pharmacodynamic profile

FDA: “The five criteria ensure that generic enoxaparin will have the same active ingredient components as those of Lovenox’s enoxaparin (within the context of its variability) even though the contribution of each component has not been fully elucidated. Therefore, pharmacological activity of the active ingredient of the generic enoxaparin and that of Lovenox can be expected to be the same.”

BIOLOGICS ARE MORE COMPLEX THAN SMALL MOLECULES AND MABS MORE COMPLEX THAN SIMPLE BIOLOGICS

Monoclonal Antibody (IgG)

Aspirin®

- small chemical molecule
  - Molecular weight = 180 Daltons
  - 0 amino acids

Calcitonin

- simple biologic
  - Molecular weight = 3,455 Daltons
  - ~ 32 amino acids
  - w/o host cell modifications
  - produced in yeast, bacteria

- complex biologic
  - Molecular weight = 150,000 Daltons
  - ~ 1300 amino acids
  - w/host cell modifications (glycosolations, etc)
  - produced in mammalian cells
BIOSIMILARS MUST BE SYSTEMATICALLY ENGINEERED TO MATCH THE REFERENCE PRODUCT

1. Target directed development
   - Reference product
     - Target range
   - Drug product development
     - Purification process development
     - Bioprocess development
     - Recombinant cell line development
   - Analytics
     - Process development

2. Confirmation of biosimilarity
   - Clinical
   - PK/PD
   - Preclinical
     - Biological characterization
     - Physicochemical characterization

Leveraging biological variability
“ACCEPTABLE CHANGES IN QUALITY ATTRIBUTES OF GLYCOSYLATED BIOPHARMACEUTICALS”

- Monitoring batches of an approved mAb revealed a shift in quality
- Shift in glycosylation (structure) pattern results in different potency in cell-based assays (function)
- Indication of a change in the manufacturing process
- Sandoz observed such shifts in several original products


Difference to post-change version sometimes greater than to biosimilar
EMA’S BMWP\(^1\) CONTINUES TO EMPHASIZE THE REGULATORY BASIS OF THE APPROVAL OF BIOSIMILARS

- Biosimilars are intended to be used at the same dose(s) and dosing regimen(s) as the reference product
- Focus is on the **demonstration of (bio)similarity** not patient benefit *per se*
- Extensive comparability exercise to ensure similar quality, safety and efficacy
- **Scientific principles underlying the comparability exercise** required for changes in the manufacturing process of a given biological product and the development of a biosimilar are the same
- Similar physicochemical characteristics prerequisite for reduction in non-clinical and clinical data requirements

\(^1\)Martina Weise, MD, BfArM, April 2012 @ EGA International Symposium on Biosimilars
SIMULTANEOUS QUALITY SHIFTS IN EU AND US REFERENCE PRODUCTS
## POST-SHIFT EU AND US REFERENCE ANALYTICALLY INDISTINGUISHABLE

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Post-shift Rituxan range</th>
<th>Post-shift MabThera range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Charge</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0K</td>
<td>68.5 – 74.5 (N=5)</td>
<td>67.0 – 74.7 (N=14)</td>
</tr>
<tr>
<td><strong>APs</strong></td>
<td>19.8 – 24.5 (N=5)</td>
<td>18.8 – 22.0 (N=14)</td>
</tr>
<tr>
<td><strong>BPs</strong></td>
<td>6.3 – 10.4 (N=5)</td>
<td>5.8 – 11.0 (N=14)</td>
</tr>
<tr>
<td><strong>1Q</strong></td>
<td>2.1 – 4.0 (N=5)</td>
<td>1.3 – 4.4 (N=14)</td>
</tr>
<tr>
<td><strong>Purity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEC</td>
<td>98.7 – 99.0 (N=12)</td>
<td>98.1 – 99.1 (N=38)</td>
</tr>
<tr>
<td><strong>Aggr.</strong></td>
<td>0.9 – 1.1 (N=12)</td>
<td>0.8 – 1.8 (N=38)</td>
</tr>
</tbody>
</table>
## POST-SHIFT EU AND US REFERENCE ANALYTICALLY INDISTINGUISHABLE

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Post-shift US Rituxan Range</th>
<th>Post-shift MabTher Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycosylation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactosylation</td>
<td>53.9 – 59.3 (N=8)</td>
<td>50.3 – 64.1 (N=33)</td>
</tr>
<tr>
<td>Sialylation</td>
<td>0.6-3.1 (N=8)</td>
<td>0.5-3.9 (N=33)</td>
</tr>
<tr>
<td>Mannosylation</td>
<td>1.9 – 3.7 (N=8)</td>
<td>1.3 -3.8 (N=33)</td>
</tr>
<tr>
<td>bG0-F</td>
<td>0.9 - 1.8 (N=8)</td>
<td>0.8 – 1.7 (N=33)</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADCC</td>
<td>105 – 129 (N=8)</td>
<td>97 – 132 (N=28)</td>
</tr>
<tr>
<td>CDC</td>
<td>103 – 119 (N=7)</td>
<td>95 – 127 (N=27)</td>
</tr>
<tr>
<td>Binding</td>
<td>97 – 102 (N=3)</td>
<td>96 – 107 (N=22)</td>
</tr>
</tbody>
</table>

All trademarks are the property of their respective owners.
Sandoz started to analyze Enbrel ® US and EU in 2007
A parallel quality shift in Enbrel was observed in both regions
The quality shift is independent of the pharmaceutical form
## EU AND US ENBREL ANALYTICALLY INDISTINGUISHABLE
(PARAMETERS INDEPENDENT FROM PRODUCT AGE)

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Quality Attribute</th>
<th>Enbrel DP Post-shift range</th>
<th>Enbrel DP Post-shift range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality</td>
<td>Osmolality [osmol/kg]</td>
<td>0.314-0.322 (N=10)</td>
<td>0.316-0.324 (N=11)</td>
</tr>
<tr>
<td>Charge</td>
<td>Overall sialylation (AEX)</td>
<td>1.53 – 1.61 (N=11)</td>
<td>1.48 – 1.64 (N=17)</td>
</tr>
<tr>
<td>Glycosylation</td>
<td>bG0 [%]</td>
<td>17.6 - 22-7 (N=13)</td>
<td>16.9 - 31.3 (N=19)</td>
</tr>
<tr>
<td></td>
<td>bG1 [%]</td>
<td>16.3 - 17.2 (N=13)</td>
<td>15.5 - 17.7 (N=19)</td>
</tr>
<tr>
<td></td>
<td>bG2 [%]</td>
<td>29.5 – 34.2 (N=13)</td>
<td>23.7 – 36.1 (N=19)</td>
</tr>
<tr>
<td>Sialylation N-glycans</td>
<td>0S [%] non-sialylated</td>
<td>47.2 - 57.7 (N=8)</td>
<td>44.9 - 61.2 (N=15)</td>
</tr>
<tr>
<td></td>
<td>1S [%] mono-sialylated</td>
<td>36.6 - 40.2 (N=8)</td>
<td>31.6 - 42.7 (N=15)</td>
</tr>
<tr>
<td></td>
<td>2S [%] di-sialylated</td>
<td>8.6 - 12.4 (N=8)</td>
<td>7.2 - 12.3 (N=15)</td>
</tr>
</tbody>
</table>

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EU AND US ENBREL ANALYTICALLY INDISTINGUISHABLE
(PARAME...S INDEPENDENT FROM PRODUCT AGE)

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Quality Attribute</th>
<th>Enbrel DP Post-shift range</th>
<th>Enbrel DP Post-shift range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>US Enbrel</td>
<td>EU Enbrel</td>
</tr>
<tr>
<td>Glycosylation</td>
<td>bGX(-F) [%]</td>
<td>20.3 – 22.4 (N=10)</td>
<td>20.5 – 22.5 (N=19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alpha-Gal [%]</td>
<td>0.2 – 0.5 (N=13)</td>
<td>0.0 – 0.6 (N=19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Man5 [%]</td>
<td>2.7 – 3.8 (N=13)</td>
<td>1.8 – 3.3 (N=19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purity</td>
<td>Proline amide [%]</td>
<td>1.2 – 3.5 (N=13)</td>
<td>1.5 – 3.7 (N=17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acidic variants (CEX) [%]</td>
<td>0 - 7.5 (N=13)</td>
<td>0 - 8.4 (N=19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basic variants (CEX) [%]</td>
<td>49.5 - 54.2 (N=13)</td>
<td>42.2 - 53.4 (N=19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>TNF-alpha RGA [%]</td>
<td>81 – 94 (N=4)</td>
<td>82 – 106 (N=13)</td>
</tr>
</tbody>
</table>

bGX(-F) = afucosylated complex N-glycans
Alpha-Gal = α-1,3-galactosylated complex N-glycans

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EU AND US ENBREL ANALYTICALLY INDISTINGUISHABLE
(PARAMETERS ARE DEPENDENT ON PRODUCT AGE)

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Quality Attribute</th>
<th>Enbrel DP Post-shift range</th>
<th>Enbrel DP Post-shift range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purity</td>
<td>Aggregates [%] (SEC)</td>
<td>1.3-2.2 (N=13)</td>
<td>1.5-3.6 (N=18)</td>
</tr>
<tr>
<td></td>
<td>Degradation / Fragmention [%] (SEC)</td>
<td>1.8-4.2 (N=13)</td>
<td>2.6-4.1 (N=18)</td>
</tr>
<tr>
<td>Purity</td>
<td>Purity main Peak (SEC) [%]</td>
<td>94.2-96.9 (N=13)</td>
<td>93.3-95.0 (N=18)</td>
</tr>
<tr>
<td>Clipping - N-terminal heterogeneity</td>
<td>L1(1-34) [%] Intact molecule</td>
<td>90.8-92.7 (N=6)</td>
<td>65.0-90.2 (N=13)</td>
</tr>
<tr>
<td></td>
<td>L1(2-34) [%] N-term. Leu clipped</td>
<td>2.4-3.8 (N=6)</td>
<td>3.4-22.9 (N=13)</td>
</tr>
<tr>
<td></td>
<td>L1(3-34) [%] N-term. Leu+Pro</td>
<td>4.2 - 5.8 (N=6)</td>
<td>6.4 - 12.4 (N=13)</td>
</tr>
</tbody>
</table>

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CLIPPING OF N-TERMINUS OF ETANERCEPT IS CORRELATED WITH AGE OF PRODUCT

- Age decreases purity and increases clipping
- Age explains the current non-overlapping data

![Graphs showing the relationship between days of remaining shelf-life and % N-terminal variant for different molecules and clipping states.]
QUALITY BY DESIGN PROCEDURES – DIRECTLY APPLICABLE TO BIOSIMILARS

The QbD umbrella

Guidelines: ICH Q8, Q9, Q10, Q11; variation guideline; Concepts: Design space, process space, design specs; critical quality attributes, control strategy, developability
ICH Q8 Design space

- Desired Product Performance
- Process Parameters
- Process Design: Unit operations, control strategy, etc.
- Process Performance: Cpk, robustness, etc.

Quality by Design

Product Knowledge

Product Specifications

Product Attributes: Dosage form, stability, formulation, etc.

Continuous Improvement

Process Understanding

Process Controls

Moheb Nasr, Ph.D., former Director, Office of New Drug Quality Assessment, OPS/CDER
QBD BIOSIMILAR PRODUCT SPECIFICATIONS IMPACTED BY VARIABILITY IN ORIGINATOR PRODUCT

- Analytical methods are sensitive to differentiate between
  - Batch to batch
  - Batches before and after a change of the manufacturing process
  - Batches from different sites

- Analytical methods can determine whether batches sourced in different countries are identical or not
  - Microheterogeneity of protein structure
    - Purity profiles
    - Glycan distribution

WHAT DOES FDA MEAN? PART II

Fingerprinting

- A subset of information from a complex structure allows identification
  - Allows for extrapolation of attributes that are not measured

Used to identify a single member of a population
- Can this strategy be used for a population or distribution?
- Enoxaparin (a drug product)

Used when members of a group are manufactured using same process (e.g. embryogenesis & growth)
- Will this only work when processes are highly defined like enoxaparin?
- Are biotech manufacturing processes too variable and limited to allow for such an approach for our products?
FINGERPRINT MABS/FUSION PROTEINS AS FDA MIGHT SEE IT

Primary structure e.g.:
- LC-MS intact mass
- LC-MS subunits
- Peptide mapping

Higher order structure e.g.:
- NMR
- CD spectroscopy
- FT-IR

Impurities e.g.:
- CEX, cIEF acidic and basic variants
- LC glycation
- Peptide mapping deamidation, oxidation, mutation, glycation
- SEC/FFF/AUC aggregation

PTMs e.g.:
- NP-HPLC-(MS) N-glycans
- AEX N-glycans
- MALDI-TOF N-glycans
- HPAEC-PAD N-glycans
- MALDI-TOF O-glycans
- HPAEC-PAD sialic acids
- RP-HPLC sialic acids

Biological activity e.g.:
- Binding assay
- ADCC assay
- CDC assay

Combination of attributes e.g.:
- MVDA, mathematical algorithms

A comprehensive set and combination of orthogonal analytical methods revealing structure-function relationships, delivering in depth comparability information and allowing extrapolation towards non-measured attributes.
MABS ARE COMPLEX ... BUT CAN BE THOROUGHLY CHARACTERIZED USING STATE-OF-THE-ART ANALYTICS

Biological characteristics

- Antigen binding

Physicochemical characteristics

- **N-terminal heterogeneity**
  - Pyroglutamate formation
  - Other modifications

- **Amino acid modifications**
  - Deamidation, Oxidation, Glycation, Isomerization

- **Fragmentation**
  - Cleavage in hinge region, Asp-Pro

- **Oligosaccharides**
  - Fucosylation, Sialylation, Galactosylation,…

- **Disulfide Bonds**
  - Free thiols, disulfide shuffling, thioether

- **C-terminal heterogeneity**
  - Lysine processing, Proline amidation

---

**Fab**

- **Effector functions**
  - Complement interaction
  - Fc Receptor interaction

**Fc**

- **Heavy chain**
  - Complement interaction
  - Fc Receptor interaction

- **Light chain**
  - Oligosaccharides
  - Disulfide Bonds
ORTHOGONAL BIOASSAYS ADDRESSING MULTIPLE FUNCTIONS

Antibody dependent cellular cytotoxicity (ADCC)
Complement dependent cytotoxicity (CDC)

Effector cells (NK cells)
Target cell
FcγRIIIa

Membrane attack complex
Programmed cell death (Apoptosis)

Blocking / Inhibiting RB

Soluble Target
STRUCTURE FUNCTION RELATIONSHIPS Refined in Biosimilar Development: Adjusting ADCC in Clone Selection

Range of originator on market too narrow to deduce S/F-relationship

Variability observed during cell line development enables elucidation of quantitative S/F-relationship
OVERVIEW

- Why biosimilars?
- Scientific approach to biosimilar development
- Abbreviated clinical trial designs
- Successful commercialization broadens patient access
OVERVIEW OF FDA APPROACH TO BIOSIMILARITY

TOTALITY OF EVIDENCE, STEPWISE, AND RISK BASED APPROACH

- **PK/PD**
  - Preclinical: Biological characterization
  - Clinical: PK and PD (where there is a relevant PD measure) studies are generally expected

- **Flexibility regarding need for animal studies**
  - Animal toxicity studies may not be warranted
  - Useful if safety uncertainties remain before first-in-man studies

- **Analytical characterization is the foundation**
  - The more comprehensive and robust the data, the stronger the justification for selective and targeted approach to animal and human testing

- **Understanding of reference product is important**: MOA, SAR, clinical knowledge, availability of clinically relevant PD measure, etc.

- **Scope and magnitude depends on extent of residual uncertainty from below steps**
  - No need to independently establish safety or efficacy
  - Immunogenicity data is minimally expected
## USING GCSF AS AN EXAMPLE: PHYSICOCHEMICAL COMPARABILITY

<table>
<thead>
<tr>
<th>Molecular Attribute</th>
<th>Methods</th>
<th>Zarzio®</th>
<th>Reference Product</th>
<th>International Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition, Primary Structure</td>
<td>Peptide map (LC-MS), Peptide Mass Fingerprint (MALDI-MS), MALDI-TOF, Sequencing</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Higher-order Structure, Conformation</td>
<td>Far and Near UV CD Spectroscopy, Thermal Stability, NMR, SPR, ELISA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Polarity, Charge, Isoforms</td>
<td>RP-HPLC, CZE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Size, Aggregates, Physical Conditions</td>
<td>SDS-PAGE/Coomassie, SEC, AF4, AUC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Binding</td>
<td>Cell Assays, SPR, ELISA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Biological Activity</td>
<td>Cell Assays, In-Vivo Assay</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

NB: Fligrastim is a non-glycosylated protein thus much easier to characterise proving physicochemical equivalence
MULTIPLE PHASE I STUDIES CONFIRM BIOEQUIVALENCE

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Randomized, double-blind, 2-way crossover</td>
<td>Randomized, double-blind, 2-way crossover</td>
<td>Randomized, double-blind, 2-way crossover, with two dose groups</td>
<td>Randomized, double-blind, 2-way crossover</td>
</tr>
<tr>
<td>Study population</td>
<td>Healthy volunteers</td>
<td>Healthy volunteers</td>
<td>Healthy volunteers</td>
<td>Healthy volunteers</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>40</td>
<td>26</td>
<td>56</td>
<td>24</td>
</tr>
<tr>
<td>Age range of volunteers</td>
<td>Age range: 25-45 years Race: 100% Caucasian Sex distribution: 52.5% male and 47.5% female</td>
<td>Age range: 23-30 years Race: 100% Caucasian Sex distribution: 54% male and 46% female</td>
<td>Age range: 21-54 years Race: 100% Caucasian Sex distribution: 59% male and 41% female</td>
<td>Age range: 21-53 years Race: 100% Caucasian Sex distribution: 54% male and 46% female</td>
</tr>
<tr>
<td>Dose</td>
<td>10 µg/kg</td>
<td>5 µg/kg</td>
<td>2.5 or 5 µg/kg</td>
<td>1 µg/kg</td>
</tr>
<tr>
<td>Frequency of dosing</td>
<td>Multiple s.c. injections for seven days</td>
<td>Single i.v. injection</td>
<td>Multiple s.c. injections for seven days</td>
<td>Single s.c. injection</td>
</tr>
</tbody>
</table>

Four randomized, double-blind, single and multiple dose, crossover studies using doses from 1 to 10 µg/kg body weight were conducted in 146 healthy female and male subjects.

European Public Assessment Report (EPAR)
**PHASE I: STUDY EPO6-102 PK RESULTS**

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Ratio (%) and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>99.68 [96.95 – 102.47]</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>99.83 [95.76 – 101.98]</td>
</tr>
</tbody>
</table>

- **Dose:** 5 µg/kg IV single-dose
- **Curves superimposable for Zarzio® and Neupogen®**
- **Zarzio® and Neupogen®** show bioequivalence after a single IV dose

PHASE I: STUDY EPO6-102 PD RESULTS

- ANC Ratio (%) and 95% CI
  - $30.0 \pm 20.0 \pm 10.0 \pm 0.0$

- AUEC = area under the effect on ANC-time curve

- Dose: 5 µg/kg IV single-dose
- ANC curves superimposable for Zarzio® and Neupogen®
- Zarzio® and Neupogen® show comparable pharmacodynamics after a single IV dose

PHASE I: STUDY EPO6-101 PD RESULTS

Development of absolute neutrophil count (ANC)

- **Zarzio®**
- **Neupogen®**

- Dose: 10 µg/kg SC for 7 days
- CD34+ count = surrogate marker for efficacy in stem cell mobilisation
- Curves for both ANC and CD34+ cells superimposable for Zarzio® and Neupogen®

Development of CD34+ cells

Plateau after 5th injection: spc for stem cell mob is 5 injections

PK/PD BE DEMONSTRATION IS PIVOTAL: WHAT IS NECESSARY TO CONFIRM EFFICACY AND SAFETY
PHASE III STUDY EP06-301

Design
• Open, single-arm, multi-center study evaluating the safety and efficacy of EP2006 in breast cancer patients
• n = 170 chemotherapy-naïve patients with high risk stage II or stage III/IV breast cancer
• Chemotherapy: 4 cycles of *doxorubicin (60 mg/m²) and docetaxel (75 mg/m²) every 3 weeks
• EP2006 was administered (30 MUs <60kg, 48 MUs >60kg) from day 2 of each cycleANC reached 10x10⁹/l post nadir or for up to 14 days

Main criteria for evaluation of safety
• Incidence, occurrence and severity of adverse events
• Detection of anti-rhG-CSF antibody formation

Main criteria for evaluation of efficacy
• Incidence and duration of grade 4 neutropenia
• Incidence of febrile neutropenia

* EORTC 2006 rate as 40% risk of febrile neutropenia
PHASE III STUDY: EFFICACY

Mean ANC curve for each cycle

Typical to see lowest nadir following cycle 1

Mean ANC by cycle and day

ANC : Healthy 3-5 x 10^9, grade 4 CIN 0.5 x 10^9, grade 3 CIN 1 x 10^9, grade 2 CIN 1.5-1 x 10^9

47% had grade 4 neutropenia at cycle 1 compared to 83% observed by Green et al and 79% by Holmes et al.
SANDOZ FILGRASTIM - SUMMARY OF CLINICAL EXPERIENCE

**In vitro pharmacology and preclinical studies**
- 4 week subchronic toxicity (rats)
- Local tolerance (rabbits)
- PK/PD (rats)

**Comprehensive molecular analysis**
- In vitro bioassay demonstrates full biological functionality
- Demonstration of structure and purity

**PK / PD**
- Comparable PK / PD shown in 5 phase I studies (174 volunteers)

**Clinical**
- Clinical safety and efficacy shown in innovative phase III study
- Registry IV in SCN with 5 year follow up
- Pharmacovigilance plan

**PAC**
- > 2 million patient days total

Sandoz’ filgrastim is not approved in the US.
INNOVATION REQUIRED IN BOTH TECHNICAL DEVELOPMENT AND CLINICAL DEVELOPMENT

Key challenges

**Time & Investment**
- **Significant expense** (USD 100 - 250m)
- **Long time** to develop (7-8 years)

**Technical Development**
- **Achieving “highly similar”** to match originator molecule profile
- **Matching** final dosage form of originator

**Clinical Development**
- **Use of novel endpoints and populations** to confirm biosimilarity (not *de novo* safety/efficacy)
- **Clinical trial design** to support extrapolation across indications, interchangeability & commercial success
Overview

- Why biosimilars?
- Scientific approach to biosimilar development
- Abbreviated clinical trial designs
- Successful commercialization broadens patient access
UK EXAMPLE: BIOSIMILARS EXPAND ACCESS TO G-CSF¹

UK G-CSF volume growth
Percent change vs. previous year

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Sandoz’ filgrastim is not approved in the US.

- **G-CSF prevents hospital re-admissions** due to infections
- **Many physicians have moved G-CSF back to 1st-line cancer treatment** due to lower biosimilars cost
- **Sandoz’s filgrastim (G-CSF)** “Patient Support Kits” expand patient access:
  - Patients self-administer at home
  - Substantial efficiency savings

¹ Granulocyte colony stimulating factor

SOURCE: IMS, NHS