Biosimilars

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Disclosures

• Research Support
  (paid to UMass Medical School)
  – Abbott Laboratories
  – Ardea
  – Fidia Farmaceutici SpA
  – Lilly
  – Roche Pharmaceuticals
  – Sanofi-Aventis

• Consulting
  – Amgen
  – Baxter Healthcare Corp.
  – Bristol-Myers Squibb Co.
  – Celgene Corp.
  – Crescendo Bioscience
  – Epirus Biopharmaceuticals
  – Genentech
  – Horizon Pharma
  – Janssen
  – Molecular Partners AG
  – Pfizer, Inc.
  – Savient
  – Sun Pharma
  – UCB
Overview

• Definitions
• Biosimilars: Marketed & in Development
• Biopharmaceuticals
  – Structure
  – Changes in Manufacture
  – Regulatory Aspects
• Biosimilars: Abbreviated Approval Pathways

What Is A Biosimilar?
Biopharmaceuticals

- Medications manufactured using live organisms
  - Blood and plasma products
  - Non-recombinant proteins (purified from natural sources)
  - Recombinant proteins
  - Monoclonal antibodies (produced in cell culture)
  - Vaccines
  - Cultured cellular and tissue products


Biologics Price Competition and Innovation Act of 2009
[ § 7002 of Patient Protection and Affordable Care Act of 2010 (H.R. 3590)]

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

“(2) The term ‘biosimilar’ or ‘biosimilarity’, in reference to a biological product that is the subject of an application under subsection (k), means—

(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and

(B) 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.
Biosimilars

• Also called
  – ‘Follow-on’ Protein Products -US
  – Subsequent Entry Biologicals (SEB) - Canada
  – Biocomparables - Mexico

• Never identical to reference product (unlike small molecule generic drugs)

• Exhibit a range of structural similarities to the original product
  – Generally similar (e.g., some natural products)
  – Highly similar (e.g., some recombinant proteins)
  – Precisely identical (e.g., some peptides)


Biosimilars:
Marketed & in Development
Expiration of US Patents For Biologic Agents Used To Treat Rheumatic Diseases

*Initial US patent for etanercept was due to expire in October 2012, but a new patent was issued that is valid until November 2028.

**Any EU member country can grant a supplementary protection certificate that extends the duration of patent protection for a medication in that country for up to 5.5 years after the original expiration date.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>United States</th>
<th>European Union*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>October 2019</td>
<td>December 2017</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>December 2016</td>
<td>April 2018</td>
</tr>
<tr>
<td>Anakinra</td>
<td>February 2022</td>
<td>May 2009</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>February 2024</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>November 2028</td>
<td>November 2015</td>
</tr>
<tr>
<td>Golimumab</td>
<td>February 2024</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>September 2018</td>
<td>August 2014</td>
</tr>
<tr>
<td>Rituximab</td>
<td>September 2016</td>
<td>November 2013</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>December 2015</td>
<td>July 2010</td>
</tr>
</tbody>
</table>

## Marketed “Biosimilars” Based On Biologic Agents Used To Treat Rheumatic Diseases

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Manufacturer (location)</th>
<th>Marketed in</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab biosimilar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reditux™</td>
<td>Dr. Reddy’s Laboratories (India)</td>
<td>Bolivia, Chile, India and Peru</td>
</tr>
<tr>
<td>Kikuzubam™</td>
<td>Probiomed (Mexico)</td>
<td>Bolivia, Chile, Mexico, and Peru</td>
</tr>
<tr>
<td><strong>Etanercept biosimilar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yisaipu</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>China</td>
</tr>
<tr>
<td>Etanar®</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>Colombia</td>
</tr>
<tr>
<td><strong>Infliximab biosimilar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remsima™ (CT-P13)</td>
<td>Celltrion (South Korea)</td>
<td>Approved in South Korea (EMA application pending)</td>
</tr>
</tbody>
</table>


### Biosimilar Etanercept: Yisaipu

- **DESCRIPTION**
  - **Proprietary Name:** Recombinant Human Necrosis Factor-αReceptorII: IgG Fc (rTNFR:Fc) Fusion Protein for Injection
  - **Brand Name:** Yisaipu
  - **Composition:** Yisaipu is formulated in single-use vials containing 12.5mg or 25 mg rTNFR:Fc, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine. Reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection.

**Biosimilar Etanercept: Etanar™**

**PRODUCTO NUEVO**

**ETANAR**

Polvo lyofilizado para inyección

Inhibidor del factor de necrosis tumoral (TNF)

*(Etanercept)*

**COMPOSICIÓN:** Cada vial de ETANAR contiene 25 mg de polvo lyofilizado para inyección. Cada caja de ETANAR contiene 4 vueltas con 4 ampollas de agua destilada para preparar la solución. 8 agujas y 8 tornadas impregnadas con alcohol. ETANAR debe conservarse a una temperatura entre 2 y 8 °C, protegido de la luz.

**DESCRIPCIÓN:** ETANAR es etanercept, un inhibidor del factor de necrosis tumoral (TNF), producto de biotecnología, indicado en el tratamiento de casos severos de enfermedades reumáticas como artritis reumatoide del adulto, artritis reumatoide juvenil y artritis psoriásica. El etanercept es el receptor recombinante humano del factor de necrosis tumoral a. El etanercept es una proteína artificial que combina el receptor soluble humano de TNF con la porción Fc (fragmento cristalizado) de inmunoglobulina humana IgG1. El etanercept se obtiene por biotecnología de ADN recombinante de células de ovario de hámster chino a la que se ha transferido ADN humano del receptor de TNF y del fragmento Fc de inmunoglobulina G1 (IgG1). La secuencia de aminoácidos de ETANAR es idéntica a la que se reporta en el WHO Drugs Information, Volumen 13, No. 2 publicado por la Organización Mundial de la Salud en 1999 para etanercept.


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**Biosimilar Rituximab: Reditux™**

**Product Portfolio:**

*Proprietary Products*

Generic Biopharmaceuticals

- 2 products in the market: Grafene™ (generic Filgrastim) & Reditux™ (generic Rituximab)
- 8 products in pipeline

http://www.drreddys.com/products/biosimilars.html
Biosimilar Rituximab: Kikuzubam™

- 2011: 23 biocomparables were registered & marketed in Mexico
- October 19, 2011: Publication of Mexican guidelines for biocomparables in Diario Oficial de la Federación
- April 20, 2012: Implementation of biocomparables guidelines announced by Federal Commission for the Protection Against Sanitary Risks (COFEPRIS)
  - Just before the biocomparables guidelines took effect in Mexico, Probiomed won a US$14.4 million contract to provide Kikuzubam™ to the Mexican State Employees’ Social Security and Social Services Institute (ISSSTE)

http://www.gabionline.net/layout/set/print/content/view/full/1906

Biosimilar Infliximab: Remsima™

July 24, 2012

Celltrion wins approval for world-first biosimilar

http://whowired.com/110635
Biosimilar TNF Inhibitors in Development To Treat Rheumatic Diseases

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Manufacturer (location)</th>
<th>Current status†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab biosimilar</td>
<td>Boehringer Ingelheim Pharmaceuticals (Germany)</td>
<td>Clinical trials (Phase I in New Zealand)</td>
</tr>
<tr>
<td>BI695501</td>
<td>TSH Biopharm Co., Ltd. (Taiwan)</td>
<td>Clinical trials (Phase III in Taiwan)</td>
</tr>
<tr>
<td>Etanercept biosimilar</td>
<td>Hanwha Chemical (South Korea)</td>
<td>Clinical trials (Phase III in South Korea)</td>
</tr>
<tr>
<td>HD203</td>
<td>LG Life Sciences Ltd. (South Korea)</td>
<td>Clinical trials (Phase I in South Korea)</td>
</tr>
<tr>
<td>LBEC0101</td>
<td>Avesthagen (India)</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>PRX-106 (plant cells)</td>
<td>Protalix Biotherapeutics (Israel)</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>Infliximab biosimilar</td>
<td>PRX-106 (biosimilar etanercept)</td>
<td>Clinical trials (Phase I)</td>
</tr>
</tbody>
</table>

*BioXpress Therapeutics SA (Switzerland) is currently developing biosimilars for abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab & tocilizumab.
†As of November 2012.


Biosimilar TNF Inhibitor in Development

- Proprietary recombinant protein expression system (ProCellEx®) uses genetic engineering and plant (carrot and tobacco) cell culture to produce biologically equivalent complex proteins
  - Lower cost to manufacture monoclonal antibodies in plants
  - Closed bioreactor system using sterilized, large flexible plastic containers
  - Produces proteins with
    - Amino acid structure practically equivalent to that of the human protein
    - Glycan structure very similar, although not identical,
    - Biological activity maintained
- PRX-106 (biosimilar etanercept) in development
  - PRX-106 administered i.p. significantly improved clinical parameters in collagen-induced arthritis model

## Rituximab Biosimilars in Development To Treat Rheumatic Diseases

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Manufacturer (location)</th>
<th>Current status‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>TL011</td>
<td>Teva Pharmaceutical Industries (Israel)</td>
<td>Clinical trials (Phase III in Bulgaria, Czech Republic, Georgia, Germany, Hungary, Macedonia, Poland, Romania, Russian Federation, Serbia, Spain, Ukraine) – prematurely ended</td>
</tr>
<tr>
<td>GP2013</td>
<td>Sandoz Biopharmaceuticals (Switzerland)</td>
<td>Clinical trials (Phase I/II in Argentina, Austria, Brazil, France, Germany, India, Italy, Spain and Turkey)</td>
</tr>
<tr>
<td>BI695500</td>
<td>Boehringer Ingelheim Pharmaceuticals (Germany)</td>
<td>Clinical trials (Phase I in Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Denmark, Estonia, France, Germany, Greece, Guatemala, Hungary, Ireland, Italy, Mexico, Netherlands, New Zealand, Norway, Peru, Poland, Portugal, Russian Federation, Serbia &amp; Montenegro, South Africa, Spain, Sweden, Ukraine, UK, US)</td>
</tr>
<tr>
<td>CT-P10</td>
<td>Celltrion (South Korea)</td>
<td>Clinical trials (Phase I in South Korea)</td>
</tr>
<tr>
<td>PF-05280586</td>
<td>Pfizer (US)</td>
<td>Clinical trials (Phase I in US, Australia, Canada, Colombia, Mexico, Russian Federation, South Africa, UK)</td>
</tr>
<tr>
<td>MK-8808</td>
<td>Merck (US)</td>
<td>Clinical trials (Phase I in US, Belarus, Bulgaria, Colombia, Hungary, Poland, Russian Federation, Spain, UK)</td>
</tr>
<tr>
<td>MAb (plant cells)</td>
<td>iBio (US)</td>
<td>Preclinical studies</td>
</tr>
</tbody>
</table>

*BioXpress Therapeutics SA (Switzerland) is currently developing biosimilars for abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab & tocilizumab.

‡As of November 2012.


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### Rituximab Biosimilars in Development

- **Proprietary gene expression technology (iBioLaunch™)** that induces plants rapidly to produce high levels of proteins
  - High yields of biologically-active antibody without contaminating animal cell products
  - Significantly lower cost to manufacture monoclonal antibodies in whole plants

http://ibioinc.com/home/products/;
Biopharmaceuticals:
Structure & Changes in Manufacture

Four Levels of Protein Structure

(a) Primary structure
Carboxyl end
\[ \text{R} \text{C} - \text{H} - \text{H} - \text{H} - \text{H} - \text{O} - \text{H} - \text{R} \]
Amino end
\[ \text{O} - \text{H} - \text{H} - \text{R} - \text{H} - \text{H} - \text{R} \]

(b) Secondary structure
Hydrogen bonds between amino acids at different locations in polypeptide chain

(c) Tertiary structure
Heme
\[ \beta \text{ polypeptide} \]

(d) Quaternary structure
Heme group

# Properties That May Affect Bioactivity of Proteins

<table>
<thead>
<tr>
<th>Wanted</th>
<th>Unwanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct folding into tertiary structure (S-S bonds)</td>
<td>Incorrect folding</td>
</tr>
<tr>
<td>Assembly of subunits into quaternary structure</td>
<td>Aggregation</td>
</tr>
<tr>
<td>Glycosylation</td>
<td>Amino acid modification (e.g., citrullination, deamidation, carbamylation)</td>
</tr>
<tr>
<td></td>
<td>Proteolytic cleavage</td>
</tr>
</tbody>
</table>

# Protein Heterogeneity

- Amino acid substitution
- N- and C-terminal modifications
- Mismatched S-S bonds
- Folding
- Truncation
- Aggregation
- Multimer dissociation
- Denaturation
- Acetylation
- Fatty acylation
- Deamidation
- Oxidation
- Carbamylation
- Carboxylation
- Formylation
- γ-Carboxyglutamaylation
- O-linked glycosylation
- N-linked glycosylation
- Methylation
- Phosphorylation
- Sulphation
- PEGylation
How Similar Is A Biosimilar?

Range of Structural Relationships Between Biosimilars & Original Product

• Most biosimilars are not identical to the original product
• Exhibit a range of structural similarities
  – Proteins produced by recombinant DNA
    • Share primary amino acid sequence
    • Different post-translational modifications
  – Proteins purified from natural sources
    • May have slightly different amino acid sequences
    • Different post-translational modifications
‘Second-generation’ Biopharmaceuticals

• Structurally different from originally licensed biopharmaceutical
• Intended to improve performance while preserving mechanism of action
• Not considered to be ‘follow-on’ products

Changes in Biopharmaceutical Production

• Different commercial lots of an innovator biologic agent may vary slightly
  – Subtle changes in production process inevitably occur throughout lifetime of a biopharmaceutical
    • Produced using different batches of medium
    • Manufactured at different sites
• Changes in production process over time
  – Small modifications may result in gradual changes in a biopharmaceutical
  – When large alterations occur, analytical and clinical studies must be conducted to compare new product with that manufactured before the change
Acceptable Changes in Glycosylated Biopharmaceuticals

- Chemical characterization of different commercial lots of rituximab and etanercept produced between 2007 and 2011 revealed variations in both C-terminal lysine content and glycosylation.

- Increase in unfucosylated G0 glycans in later batches of rituximab resulted in more potent ADCC.

- Despite these differences, each product was marketed with no change in label throughout this time.


Biopharmaceuticals: Changes in Manufacture

- Changes in production have resulted in decreased immunogenicity:
  - Avonex® (interferon β1a produced by Biogen Idec in a new cell line) had decreased immunogenicity compared to the interferon β1a that had been produced in the original Chinese hamster ovary cell line by Bioferon Biochemische Substanzen GmbH & Co.


- Changes in formulation or packaging have resulted in increased immunogenicity with clinical consequences:
  - Eprex® (rhEPO, Ortho Biotech)
    - Formulation change (switching protein stabilizer from human serum albumin to polysorbate 80) and
    - New packaging system (pre-filled syringe with rubber plunger for s.c. administration)
    - Resulted in formation of anti-EPO Ab that cross-reacted with endogenous EPO → 175 cases of pure red cell aplasia between 1998 and 2004

Biopharmaceuticals:
Regulatory Aspects

Worldwide Status of Regulations for the Approval of Biosimilar Agents*

*As of April 2012.

Biopharmaceuticals: Regulatory Aspects in the United States


- Established modern system of generic drugs
- Amended Federal Food, Drug, & Cosmetic (FDC) Act
- Two abbreviated pathways for the approval of generic drugs, including natural source products and recombinant proteins
  - Section 505(b)(2) eliminates unnecessary duplication of preclinical and some human studies in the New Drug Application (NDA) for a generic drug
    - Allows direct comparison of the generic drug with a product already approved for the same indication in brief clinical trials of 3- to 6-months in duration
  - Section 505(j) sets forth process by which the producer of a generic drug that is identical to a previously approved product can file an Abbreviated New Drug Application (ANDA) to seek FDA approval of the generic compound
    - Allows applicant to rely on the FDA’s previous finding of safety and efficacy for the already approved drug
    - Allows 180 day exclusivity to companies that are the “first-to-file” an ANDA against holders of patents for branded counterparts
Biopharmaceuticals Differ Significantly From Small Molecule Drugs

Aspirin
mw = 180.16 Da

Monoclonal antibody
mw = 150,000 Da


Some Biopharmaceuticals Approved in US as 505(b)(2) Generic Drugs

<table>
<thead>
<tr>
<th>Name (Descriptive and Trade)</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin, rDNA (Fortical)</td>
<td>Unigene, Upsher-Smith</td>
</tr>
<tr>
<td>Glucagon, rDNA (GlucaGen)</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>Hyaluronidase, rDNA (Hylenex)</td>
<td>Halozyme Therapeutics; Baxter</td>
</tr>
<tr>
<td>Hyaluronidase, bovine (Amphadase)</td>
<td>Amphaster Pharmaceuticals</td>
</tr>
<tr>
<td>Hyaluronidase, ovine (Vitrase)</td>
<td>ISTA Pharmaceuticals</td>
</tr>
<tr>
<td>Somatropin, rDNA (Omnitrope)</td>
<td>Sandoz/Novartis</td>
</tr>
</tbody>
</table>

- Approvals relied, in part, on available knowledge about safety and effectiveness of structurally similar, already approved products:
  - Structural characterization
  - Comparative PK & PD data
  - Immunogenicity & safety data
  - Short (3- to 6-month) clinical trials comparing biosimilar directly to innovator rDNA product for same indication.
US Statutes Governing FDA Approval or Licensing of Protein and Peptide Drugs

• Section 505 of Federal Food, Drug, & Cosmetic (FDC) Act (21 USC § 355)
  – Natural source products & recombinant proteins
  – "Hatch-Waxman Act" provided 2 abbreviated approval pathways in 1984
    • Section 505(b)(2)
    • Section 505(j)

• Section 351 of the Public Health Service (PHS) Act (42 USC § 262)
  – Large, complex biologic agents
  – Requires 2 adequate RCTs for approval
  – Had no abbreviated approval pathway

Biosimilars: Abbreviated Approval Pathways in the European Union & United States
EMA Guideline on Biosimilars

- Required to compare biosimilar with reference product:
  - Preclinical in vitro assays & in vivo animal studies
  - Clinical studies in patients
- If available, single- and multiple-dose PK studies & PD studies using biomarkers relevant to the clinical efficacy of the drug
- In most cases, ‘comparative clinical trials’ are also needed
  - To demonstrate clinical equivalence between the biosimilar and the already approved reference product
  - To assess potential immunogenicity with chronic dosing
- Careful post-approval pharmacovigilance monitoring is expected
- Extrapolation of efficacy data for the biosimilar to another indication, if reference product acts by the same mechanism in each disease state


EMA Guideline on Biosimilar Monoclonal Antibodies

- Studies to demonstrate PD & PK comparability of the mAbs.
  - In vitro studies to compare functional properties of a potentially biosimilar monoclonal Ab to those of innovator mAb.
  - Additional in vivo animal studies might be required, if mAbs are produced in different cell expression systems or differ substantially in formulation.
- At least one RCT to demonstrate similar clinical efficacy
  - Double-blind, parallel-group, comparative design to assess PD or clinical parameters.
  - Powered to demonstrate therapeutic equivalence
- Collection of additional data on long-term immunogenicity & safety of biosimilar mAb following approval

EMA Guideline on Biosimilars: 2011 Proposed Revisions

- Reduce size and number of animal studies required for evaluation of biosimilars.
- Streamline design of clinical testing in patients
  - When reference biopharmaceutical is approved for several indications, phase 2 studies of a biosimilar should be conducted in the disease setting that is most responsive to the innovator therapy
  - Non-inferiority trial design (trials designed to demonstrate therapeutic equivalence or superiority would require much larger numbers of participants)
- Extrapolation of safety & efficacy data from one indication to other indications
- 1-year follow-up immunogenicity data are expected to be requested for biopharmaceuticals intended for chronic administration

Patient Protection and Affordable Care Act of 2010 (H.R. 3590)

- Passed by US Senate on December 24, 2009
- Passed by US House of Representatives on March 21, 2010 (219 for & 212 against)
- Signed into law as Public Law 111-148 by President Barack Obama on March 22, 2010
- Section 7002 of H.R. 3590 (referred to as Biologics Price Competition and Innovation Act of 2009) amends Section 351 of the Public Health Service Act to create an abbreviated Biological License Application (BLA) for ‘highly similar’ biological products
Biologics Price Competition and Innovation Act of 2009: Abbreviated Biological License Application

• Permits a biosimilar to be evaluated against only a single reference biological product
• To be considered for an abbreviated BLA, each of the following must be the same for the biosimilar and the innovator product:
  – Presumed mechanism of action
  – Route of administration
  – Dosage form
  – Potency
• Biosimilar may only be reviewed and approved for indications for which the FDA already has approved the innovator product

To demonstrate that a biosimilar is ‘highly similar’ to the reference product, ‘notwithstanding minor differences in clinically inactive components’, data must be obtained from:
  – Analytical studies and
  – Animal studies and
  – At least one clinical trial, which must be conducted in patients with a disease for which the innovator product is licensed

• Clinical study must:
  – Demonstrate ‘safety, purity, and potency’ of the biosimilar
  – Evaluate its PK and PD
  – Include an assessment to establish that the biosimilar is not more immunogenic than the innovator reference product
• Same REMS required of innovator biologic agent licensed under the PHS Act are applied to biosimilar
FDA “Totality of the Evidence” Approach To Assessing Biosimilars

- FDA scientists will integrate various types of information to provide an overall assessment that a biologic is biosimilar to an approved reference product
- Highly similar analytical & PK/PD data suggest a lower risk of clinical differences
- Comparative equivalence clinical studies (no Phase 2)


- A biosimilar agent need not be licensed for all routes of administration, doses and indications for which the reference product is approved
- Extrapolation of data from a clinical trial of the biosimilar conducted in one disease to support approval for additional indications, for which reference product is already licensed
- Does not specify requirements for clinical trial
  - Size or duration
  - Non-inferiority or equivalence design

Biosimilars: Clinical Trial Design Issues

- Since the biosimilar must be almost identical to the originator biopharmaceutical, an active comparator clinical trial must demonstrate equivalence within a prespecified margin (“goalposts”)
  - If the ‘biosimilar’ is superior to the originator biopharmaceutical ('bio-better'), it is not biosimilar
  - Thus, non-inferiority trial design is not adequate to assess biosimilarity

- Biosimilar must be studied at the same dose that is licensed for the originator biopharmaceutical
  - Dose-ranging studies (phase 2) are not needed for biosimilars

- Data can be extrapolated from a clinical trial of the biosimilar conducted in one disease to support approval for additional indications, for which the originator biopharmaceutical is already licensed

Phase 1 Double-Blind RCT of CT-P13 vs. Remicade® in Ankylosing Spondylitis

- 250 patients with active AS randomized 1:1 to receive either CT-P13 or Remicade® (5 mg/kg 2-hour IV infusion per dose)
  - Dose-loading phase: Weeks 0, 2, & 6
  - Maintenance phase: Weeks 14, 22, & 30

- Assessments
  - Ratios of geometric means of primary PK parameters between Weeks 22-30 were subjected to ANCOVA analysis at 90% CIs
  - ASAS20 & ASAS40 at Week 30
  - Safety (incidence of AEs)

- Primary endpoint: Ratio of geometric means of PK parameters in CT-P13 & Remicade® arms (Weeks 22-30)
  - AUC; 1.05 (90% CI 0.94 to 1.16)
  - Cmax,ss; 1.02 (90% CI 0.95 to 1.09

<table>
<thead>
<tr>
<th>AEs (to Week 30)</th>
<th>CT-P13 (n=128)</th>
<th>Remicade® (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>83 (64.8%)</td>
<td>78 (63.9%)</td>
</tr>
<tr>
<td>Infections</td>
<td>24 (18.8%)</td>
<td>22 (18.0%)</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>5 (3.9%)</td>
<td>6 (4.9%)</td>
</tr>
<tr>
<td>TB</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

Phase 3 Double-Blind RCT of CT-P13 vs. Remicade® in Rheumatoid Arthritis

- 606 patients with active RA despite previous DMARDs randomized 1:1 to receive either CT-P13 or Remicade® (3 mg/kg 2-hour IV infusion per dose) + MTX & folic acid
  - Dose-loading phase: Wks 0, 2, & 6
  - Maintenance phase: Wks 14, 22, & 30
- Primary endpoint: Proportion of patients achieving ACR20 at week 30
  - Equivalence between treatments defined using exact binomial test with 95% CIs within margin of ±15%
- Secondary endpoints
  - ACR50/70
  - Frequency of AEs

Related AEs (up to Week 30) | CTP-13 (n=302) | Remicade® (n=304) |
--------------------------|----------------|-------------------|
Total                     | 106 (35.2%)    | 108 (35.9%)       |
Infections                | 46 (15.3%)     | 51 (16.9%)        |
Infusion reactions        | 20 (6.6%)      | 25 (8.3%)         |
TB                        | 3 (1.0%)       | 0                 |

Biologics Price Competition and Innovation Act of 2009: Interchangeability

- If a biosimilar is determined to be ‘interchangeable,’ a pharmacist would be allowed to substitute the biosimilar for a prescribed biological therapy without involving the prescribing physician.
- Unlike small-molecule drugs, a biopharmaceutical that is repeatedly interchanged with a similar biological agent may exhibit immunogenicity that could compromise the efficacy and safety of both medications.
- It is extremely important that there not be frequent switching between the original protein product and the biosimilar because even subtle differences, such as impurities introduced during manufacturing, may trigger an immune response to the biosimilar.

Biologics Price Competition and Innovation Act of 2009: Economic Benefits for Manufacturers

- Protection for manufacturer of innovator product
  - Period of ‘exclusivity’ during which follow-on products may not be approved
    - BLA for approval of a follow-on biological product may not be submitted for 4 years after initial approval of reference product
    - FDA may not approve a BLA for a follow-on biological product until 12 years after reference product was first licensed
  - Period of exclusivity may be extended by 6 months if studies of innovator biological product in children are requested by HHS Secretary and carried out
- Incentive for manufacturer of ‘interchangeable’ biosimilar
  - Period of ‘exclusive marketing rights’ for manufacturer of ‘interchangeable’ biosimilar
    - 1 year of exclusive marketing rights to first biosimilar that is approved as being ‘interchangeable’ with reference product
    - Period of exclusivity may be extended for up to 42 months, if patent litigation is ongoing between manufacturer of biosimilar and manufacturer of innovator product
Biosimilars: Concerns for the Rheumatologist

- Will a biosimilar be as effective as the originally licensed biopharmaceutical?
- Will a biosimilar be as safe as the originally licensed biopharmaceutical?
- If a pharmacist substitutes a biosimilar for a prescribed biopharmaceutical, will the patient be adversely affected?
- Will the availability of biosimilars reduce the high cost of targeted biological therapies for our patients?