Implementation of a U.S. Biosimilar Pathway
And Experience in Europe

National Conference of State Legislatures
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Global Biosimilar Strategic Planning & Operations
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Amgen believes that when you put patients first, sound policy will follow

Amgen supports a responsible, science-based regulatory pathway for biosimilars that meets our guiding principles of:

- Patient safety
- Sound scientific analysis
- Fair incentives for the development of new therapies
Biosimilars are not generics; biologics are larger & more complicated than chemical drugs

<table>
<thead>
<tr>
<th>Small Molecule</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td><strong>Insulin</strong></td>
</tr>
<tr>
<td>Approx. 180 daltons</td>
<td>Approx. 5,800 daltons</td>
</tr>
<tr>
<td>21 atoms</td>
<td>788 atoms</td>
</tr>
<tr>
<td><strong>Somatropin</strong></td>
<td><strong>IgG1 antibody</strong></td>
</tr>
<tr>
<td>191 amino acids</td>
<td>&gt;1000 amino acids</td>
</tr>
<tr>
<td>~22,000 daltons</td>
<td>~150,000 daltons</td>
</tr>
<tr>
<td>3091 atoms</td>
<td>&gt;20,000 atoms</td>
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The Challenge With Biosimilars Is Knowing Which Differences Matter Clinically

Biotechnology is a compilation of technologies to design, produce, purify, and analyze proteins

- Molecular biology and rDNA technology
- Fermentation and cell culture technology
- Large scale protein recovery & purification
- Reliable analytics for large proteins
Biologics manufacturing requires multiple disciplines working together

U.S. biosimilar pathway amends the Public Health Service Act and covers key requirements
The U.S. law defines new standards and terms

**Standard:** Biosimilarity determined on the basis of 1) analytical studies, 2) animal studies, including toxicity, and 3) clinical studies, including immunogenicity and PK/PD sufficient to demonstrate that the product is "highly similar" to the reference product and safe, pure and potent for one or more approved conditions of use.

**Definition:** The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. 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.

**Standard:** Biosimilar can be expected to produce the same clinical result as the reference product in any given patient. For products administered more than once, the risk (in terms of safety or diminished efficacy) of switching can't be greater than the risk of using the reference product alone.

**Definition:** For a product that meets the above standard, the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.

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The European pathway was designed with science as the primary consideration

**European Commission Directive**
**June 2003**
Directs EMA to create a regulatory pathway for biosimilars by establishing new Annex on an application for MA with specific dossier requirements for "similar biological medicinal products".

**EMA & CHMP Guideline: Similar Biological Medicinal Products**
**October 2005**
Outlines requirements for Marketing Authorization Applications (MAA) based on the demonstration of the similar nature of the two biological medicines.

"Due to the complexity of biological / biotechnology-derived products the generic approach is scientifically not appropriate for these products" — EMA
Guideline on Similar Biological Medicinal Products, Section 2.1: Application of "Similar Biological Medicinal Products" Approach
European Medicines Agency scientific guidelines have set detailed approval standards

**TOPIC KEY THEMES**

**Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues**
- Similar, but not identical
- Justify any differences
- Greater differences require more clinical data

**Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues**
- Equivalent Efficacy
- Similar safety (non-inferior)
- Similar immunogenic potential
- Product level non-clinical and clinical requirements
- Recommended study designs, post-marketing commitments


### EMA reviews demonstrate a science-based standard

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic/Common Name</th>
<th>Owner of Trade Name</th>
<th>Reference Product</th>
<th>Decision</th>
<th>Decision Date</th>
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</thead>
<tbody>
<tr>
<td>Desmopressin®</td>
<td>somatropin</td>
<td>Sandoz</td>
<td>Genotropin®</td>
<td>Approved</td>
<td>April 12, 2006</td>
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<tr>
<td>Velosyn®</td>
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<td>BioFar pray</td>
<td>Humatrope</td>
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<td>Biopharm</td>
<td>methionine asfb</td>
<td>Infexis</td>
<td>Rejected</td>
<td>Joined Feb, 2006</td>
<td></td>
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<tr>
<td>Bencro™ Epoetin alpha head</td>
<td>epoetin alpha</td>
<td>Novartis</td>
<td>Epire</td>
<td>Approved</td>
<td>Aug. 20, 2007</td>
</tr>
<tr>
<td>Betacor®</td>
<td>epoetin beta</td>
<td>Hospira</td>
<td>Eprex®</td>
<td>Approved</td>
<td>Dec. 18, 2007</td>
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<tr>
<td>Eoestin</td>
<td>epoetin alpha</td>
<td>RetouchGenMeda</td>
<td>Eprex®</td>
<td>Withdraw</td>
<td>Mar. 15, 2011</td>
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<tr>
<td>Insulin 30/70 Mix Marvel</td>
<td>biphasic insulin</td>
<td>Marvel</td>
<td>Humulin</td>
<td>Withdraw</td>
<td>Jan. 16, 2003</td>
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<td>Transgenetix</td>
<td>Filgrastim</td>
<td>Taas Ralaphem</td>
<td>NEUPOGEN® (Filgrastim)</td>
<td>Approved</td>
<td>Sep. 18, 2003</td>
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<td>Zzacor®</td>
<td>Filgrastim</td>
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<td>Feb. 6, 2009</td>
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<td>Hospira</td>
<td>NEUPOGEN® (Filgrastim)</td>
<td>Approved</td>
<td>Jun 10, 2010</td>
</tr>
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According to The United States Patent and Trademark Office on the search tool at [http://www.uspto.gov/](http://www.uspto.gov/) and accessed on June 29, 2011, the following marks are registered or otherwise listed in the US:

- Eprex® is a registered trademark of JOHNSON & JOHNSON CORPORATION
- NEUPOGEN® is a registered trademark of Amgen, Inc.
- Retacrit® is a registered trademark of Hospira, Inc. CORPORATION DELAWARE
- Tevagrastim® is a registered trademark of TEVA Pharmaceutical Industries Ltd.
- Novartis® is a registered trademark of Novartis US Limited CORPORATION GREAT BRITAIN


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Amgen Policy Discussion. Geoff Eich, 8/7/2011
Europe is addressing pharmacovigilance challenges with “multi-source” biologics

<table>
<thead>
<tr>
<th>Year</th>
<th>Product(s)</th>
</tr>
</thead>
</table>
| 1998 | Eprex® (epoetin alfa)  
|      | NeoRecormon (epoetin beta) |
| 2001 | Eprex® (epoetin alfa)  
|      | NeoRecormon (epoetin beta)  
|      | Aranesp® (darbepoetin alfa)* |
| 2009 | Eprex® (epoetin alfa)  
|      | NeoRecormon (epoetin beta)  
|      | Aranesp® (darbepoetin alfa)*  
|      | Dynepo® (epoetin delta) (withdrawn)  
|      | Mircera® (peg-epoetin beta)  
|      | Ratioepo (epoetin theta)  
|      | Biopoin (epoetin theta)  
|      | Binocrit™ (epoetin alfa)  
|      | Abseamed (epoetin alfa)  
|      | Epoetin alfa Hexal (epoetin alfa)  
|      | Silapo (epoetin zeta)  
|      | Retacrit® (epoetin zeta) |

Amgen believes three levels of traceability for both biologics and biosimilars are essential to allow health authorities to trace an event to its root cause:

- Drug class
- Individual manufacturer's product
- Manufacturer's lot number

According to The United States Patent and Trademark Office's on-line search tool at [http://www.uspto.gov/](http://www.uspto.gov/) and accessed on June 29, 2011, the following marks are registered or otherwise listed with that office:

- Aranesp® is a registered trademark of Amgen, Inc.
- Mircera® is a registered trademark of Hoffmann-La Roche Inc. CORPORATION NEW JERSEY
- Dynepo® is a registered trademark of Aventis Pharma Holding GmbH CORPORATION FED REP GERMANY
- Ratioepo, Biopoin, and Mircera® are registered trademarks of Amgen, Inc.
- Silapo (epoetin zeta) and Retacrit® (epoetin zeta) are registered trademarks of Amgen Inc.


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Differences between full and biosimilar applications highlight areas of EMA emphasis

| CMC | Drug substance  
|     | Manufacture  
|     | Characterisation  
|     | Control  
|     | Reference standard  
|     | Container  
|     | Stability  
| Drug product | Description  
|     | Development  
|     | Manufacture  
|     | Control  
|     | Reference standard  
|     | Container  
|     | Stability  
|     | Comparability data  
|     | Analytical comparison with reference product  

| Nonclinical | Pharmacology  
|            | Primary pharm.  
|            | Secondary pharm.  
|            | Safety pharm.  
|            | Interactions  
| Pharmacokinetics | ADME  
|                | Interactions  
| Toxicology | Single dose  
|            | Repeat dose  
| Genotoxicity | Carcinogenicity  
| Reproduction | Local tolerance  

| Clinical | Pharmacology  
|         | Pharmacokinetics  
|         | Single dose  
| Efficacy and safety | Dose finding  
|                | Schedule finding  
| Pivotal  
|            | Indication 1  
|            | Indication 3  
|            | Indication 4  
| Post-marketing studies | Safety in all indications  
|                | Efficacy in other indications  
|                | Immunogenicity  


Amgen Policy Discussion. Geoff Eich, 8/7/2011
Clinical development for two EU biosimilars highlights the need for class-specific approaches

### Zarzio® (filgrastim)
- **Pivotal Efficacy Studies**
  - 40 HV (sc) vs. Neupogen PD
  - 26 HV (iv) vs. Neupogen PD
  - 56 HV (sc) vs. Neupogen PD

### Binocrit® (epoetin alfa)
- **PK/PD Studies in Healthy Volunteers**
  - 6 subjects single dose sc vs. Epredix
  - 76 subjects multi-dose iv vs. Neorecombin
  - 72 subjects multi-dose sc vs. Neorecombin

### Pivotal Efficacy & Safety Study
- **Supportive Efficacy**
  - 170 breast cancer patients (sc)
  - Efficacy, Safety & Immunogenicity

Total in studies before approval:
- 146 healthy volunteers
- 170 breast cancer patients

**EU ESA Indications**

- Renal anaemia – on dialysis (IV only)
- Renal anaemia – not on dialysis (IV only)
- Anaemia in cancer chemotherapy
- Increasing yield for autologous transfusions
- Reducing need for allogeneic transfusions
- Anaemia in premature infants

**Extrapolated indication(s)**

*Please see full US safety information, including boxed warnings for Aranesp® (darbepoetin alfa) at the end of this presentation or at www.aranesp.com.*

Many EU Member State Regulators (e.g. UK & France) link pharmacovigilance & substitution

Prescribing of biosimilars

“When prescribing biological products, it is good practice to use the brand name. This will ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist.”

“Products (biosimilar and reference) that have the same international non-proprietary name (INN) are not to be presumed identical for the reasons given above.”

Reporting suspected ADRs for biosimilars

“To ensure that any ADR that you report is assigned to the correct product, it is important that the product name rather than the substance name is used for reporting.”

Both regulatory agencies are acknowledging the need for product identification and accurate attribution of adverse events


An EMA Pharmacovigilance Working Party communication highlights the challenge

Epoetin - Risk of pure red cell aplasia

Record name of epoetin product (brand name or scientific name with name of manufacturer) in patient file.

In June 2009, a clinical trial to evaluate the safety and immunogenicity of a biosimilar epoetin product in the treatment of anaemia associated with chronic renal failure in paediatric patients was stopped because of the occurrence of FPRC cases. While investigations on the cause of FPRCs in these cases are still ongoing, the PVWP recommends in important that accurate medication histories are maintained for patients treated with epoetin, i.e. recording the trade name or the scientific name with the name of the manufacturer in the patient file. The identification and traceability of epoetin products used in patients will help to assess if FPRC cases and other reported cases of adverse reactions are related to any quality specifications of a certain epoetin product. The PVWP recommends that the product information of all epoetins includes a map to indicate patient immunization records.


Amgen Policy Discussion. Geoff Eich, 8/7/2011
FDA is currently considering public input on important aspects of the law

- Biosimilarity
- Interchangeability
- Patient Safety and Pharmacovigilance
- Supportive Data
- Definition of a Biologic Product
- Guidance
- Exclusivity
- User fees

Amgen believes that when patients are put first, sound policy will follow

1. Use well-designed clinical trials to establish biosimilarity

2. Ensure product, manufacturer and lot number are known for each biological given to a patient

3. Set scientific and practical criteria for interchangeability

It is not whether you can analyze structural differences; what matters is the result in the human body
Questions?