"Biosimilar" medicinal products
EU experience and perspectives

Jean-Hugues Trouvin, Pharm. D, PhD.
Scientific adviser for biological products, AFSSAPS
BWP chairman, EMA, London

Disclaimer

✓ Although being a member of EMA committees and working parties, my presentation might not be the view of the CHMP and the EMA, nor that of the French Medicines Agency (Afssaps).
✓ This presentation reflects only personal views and binds in no way the organisations mentioned above.
Outlook

✓ Why "Biosimilars"
✓ The challenges of being a biological product
✓ The concept of “biosimilarity” and development of the EU regulation
✓ The biosimilar guidelines
✓ Current experience
✓ Unresolved issues
✓ Conclusions

Why the concept of biosimilar emerged in Europe -1-

✓ In the early 2000s, for some biological products, marketing authorisation protection were to expire soon: hGh, EPO, G-CSF, etc.

✓ Would the generic approach be applicable?

✓ Acknowledgment that biological products are complex macromolecules
Why the concept of biosimilar emerged in Europe -2-

- Complexity at three levels:
  - Molecular (biological product)
  - Origin, production process and heterogeneity
  - Characterisation and quality control of the quality attributes contributing to Safety and Efficacy

- Recent examples of safety-efficacy consequences after a change in production process

- The bioequivalence parameter used for assessing generics is not sufficient and relevant for biologicals

Definition of a biological medicinal product

- A biological medicinal product is a product, the active substance of which is a biological substance.

- A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control.

- Biological medicinal products:
  - immunological medicinal products
  - medicinal products derived from human blood, human plasma or human urine
  - medicinal products defined in Part A of the Annex to Regulation 2309/93 (Biotechnology derived products)
  - advanced therapy medicinal products as defined in regulation 1394/2007
Biological products and their challenges

✓ Complex structure

✓ Complex production process

✓ Complex quality profile:
  ▪ analytical testing
  ▪ Immunogenic properties
Complex structure

- IgG, ~660AA, MW: ~150 000 Da
- Interferon alfa, 165AA, MW: 19 625 Da
- Aspirin, MW: 180 Da

Molecular weight

<table>
<thead>
<tr>
<th>Product</th>
<th>Molecular weight (kDa)</th>
<th>Number of amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>0.151</td>
<td>N/A</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>4.5</td>
<td>32</td>
</tr>
<tr>
<td>Epoetin-α</td>
<td>30.4</td>
<td>165</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>264.0</td>
<td>2,332</td>
</tr>
</tbody>
</table>

Protein structure

(a) Primary structure
-Ala–Glu–Val–Thr–Asp–Pro–Gly–

(b) Secondary structure
\[\begin{align*}
\text{α helix} & \\
\text{β sheet} & 
\end{align*}\]

(c) Tertiary structure

(d) Quaternary structure


3D structure of epoetin alfa

Post-translational modification

✓ After translation the protein backbone is further processed in the cell:
  - Glycosylation
  - Sulphatation, Amidation, etc.

✓ Glycosylation is also complex: more than one glycosylation form (isoforms) → glycan pattern and microheterogeneity

✓ Sometimes, proteins are chemically modified (post production modification)
  - PEGylation
  - Conjugation

glycosylation > complex carbohydrate structures -1-

carbohydrates
- sialic acid
- gal
- glucNAc
- man
- fuc

glycans

protein
glycosylation
> complex carbohydrate structures -2-

An “Isoform” is a Complex Mixture of Glycosylated Species

Sialylation of Glycan Structures on Epoetin alfa

\[
\begin{align*}
\text{Isoform 12} &= (4) (4) (4) (0) \\
\text{Additional combinations of structures} &= + \text{other permutations and combinations including structures with sulfates and lactosamine extensions.}
\end{align*}
\]

By permission Andrew Fox, Amgen
Microheterogeneity of EPO Products -1-

Isoelectric focusing profiles of EPO preparations from various manufacturers.


Microheterogeneity of EPO Products

- IEF pattern and sialic acid content of the two EPO isoform preps may appear very similar → but

- Bioactivity is different

Glycosylation and Monoclonal antibody isoforms

Monoclonal antibodies biological activity glycosylation-dependant

Dr. Prost, LFB, by permission
**Impact of glycosylation on Mc Ab bioactivity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GlcNAc/Mannose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sialic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A 527-amino acid residue protein containing 17 S-S bridges and 3 glycosylation sites</td>
<td>Possible sources of heterogeneity (experimentally observed variations only !)</td>
<td>Additional O-Glycosylation</td>
<td>Proteolysis at Arg</td>
<td>Oxidation of Cys or Met residues</td>
<td>Deamidation of Asn residues</td>
<td>By permission, J. Mascaro</td>
</tr>
<tr>
<td>N-terminal sequence length variation (non-recombinant t-PA only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Spontaneous modifications: instability, aggregation

Monomer ↔ Multimer ↔ Small aggregate

Large aggregate → Precipitation

Molecular structure: source of variability and heterogeneity

These complex structural elements contribute:
- to the bioactivity → Clinical efficacy
- to the biodistribution → Clinical pharmacokinetics
- to the immunogenicity profile → Clinical safety

Source of variability:
- Substitution
- Oxidation
- Deamidation
- Truncated form
- N- and C-terminal heterogeneousness
- ... Type of modification:
- Glycosylation (–N & O-linked)
- Methylation / Acetylation / Acylation
- Phosphorylation / Sulfatation
- ...
Biological products and their challenges

✓ Complex structure

✓ Complex production process

✓ Complex quality profile:
  - analytical testing
  - Immunogenic properties

Complexity of the production process

✓ A biological substance “is a substance that is produced by or extracted from a biological source… EU Dir. 2003/63”
  - Biological natural source (extraction and variability of the sources)
  - Biotechnology methods → Cell substrate
    - For cultivation (growth) of bacteria, virus, etc.
    - As expressing/producing cells:
      - genetically modified to express a foreign gene
      - Induction of secretion
  - Transgenic animals
  - Transgenic plants
Complexity of the production process -1-

- Cloning into DNA Vector
- Transfer into Host Cell, Expression
- Large-Scale Fermentation
- Downstreaming

E.g., bacterial or mammalian cell

From J. Mascaro - Roche

Complexity of the production process -2-

Cell culture conditions

Spinners  Bioreactor

Cell culture conditions may affect several quality attributes yield, glycosylation, integrity, etc.
Complexity of the production process -3- Purification steps

Purification process may affect several quality attributes
Selection of variants, process-related impurities, etc.

The process: key elements to consider

✓ Production system
  ▪ Extraction
  ▪ Expression system
✓ Purification system
  ▪ Purity profile
  ▪ Product-related substances
  ▪ Process-related substances
✓ In Process controls
✓ Batch release specifications

All these elements contribute to the "purity-impurity" profile
“The process is the product.”

Each company has its own unique cell line, process and manufacturing platform

- Eli Lilly & Co.: Expression system: E. Coli
  - Expressed molecule: Pro-Insulin (35 AA bridge)
  - Leader sequence
  - Other sequences as needed
- Novo Nordisk: Expression system: S. cerevisiae
  - Expressed molecule: Insulin precursor (1 AA bridge)
  - Leader sequence
  - Other sequences as needed

Quality of biological products

- Protein of interest
- Peptid variants
- 3D structure
- Post-translational variants
- Degradation
- Process-related impurities

Source: Talk Inger Møllerup, Novo Nordisk A/S
Joint EMEA/DIA Workshop on Biosimilars, Paris 2005
Biological products and their challenges

✓ Complex structure

✓ Complex production process

✓ Complex quality profile:
  - analytical testing
  - Immunogenic properties

Characterization: structure and physico-chemical properties

✓ Complex molecular structures and various quality attributes to be monitored:
  - Identity
  - Purity / contaminants
  - Variants and product-related substances
  - Conformation / aggregation
  - Biological activity

✓ Wide range of analytical tools to be considered:
  - UV absorption
  - Circular dichroism spectroscopy
  - Fourier transform IR
  - Fluorescence spectroscopy
  - NMR spectroscopy
  - Calorimetric approaches
  - Immunochemical assays: ELISA; immunoprecipitation; biosensors
  - Biological activity: in cell lines and animals
  - Chromatographic techniques: various types of HPLC; peptide mapping
  - Electrophoretic techniques: SDS-PAGE; IEF; CZE
  - Field flow fractionation
  - Ultracentrifugation
  - Static and dynamic light scattering
  - Electron microscopy
  - X-ray techniques
  - Mass spectrometry

Adapted from Crommelin DJA, et al. Int J Pharm 2003;266:3-16.
### Analytical testing and quality attributes

<table>
<thead>
<tr>
<th>Method</th>
<th>Size</th>
<th>Charge</th>
<th>1° struct.</th>
<th>2°/3° struct.</th>
<th>Purity</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Size exclusion</td>
<td>-</td>
<td>++++</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Ion exchange</td>
<td>+++</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Reverse phase</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Electrophoresis</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>SDS-Page</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>IEF</td>
<td>-</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>W-Blot</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Assays</td>
<td>Immunoassays</td>
<td>-</td>
<td>-</td>
<td>+/−</td>
<td>+/−</td>
<td>-</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>In vivo assay</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+/−</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

(from R. Thorpe, personal communication)

### The Analytical chemistry challenge: glycoform analysis

The analysis of complex (glyco)proteins requires a combination of multiple and orthogonal analytical methods.

Whole protein:
- HPLC
- Electrophoresis
- Mass spectrometry
- Lectin binding
- Potency

Monosaccharides:
- Mass spectrometry
- Lectin binding

De-N/O-glycosylated protein:
- HPLC
- Peptide mapping
- Electrophoresis, CE

Glycopeptides:
- Enzymatic or chemical cleavage
- HPLC, CE
- Mass spectrometry

Glycan pools:
- Mass spectrometry
- HPLC, CE
- Glycan mapping

Mass spectrometry:
- HPLC, CE
- Glycan mapping

Structural characterization:
- Mass spectrometry, enzymatic, NMR

DIA-MERC 2011, Amman - Biosimilars
Quality profile: what do we know of the iceberg?

Need for a relevant control strategy at all stages

Complex structure

Complex production process

Complex quality profile:
- analytical testing
- Consequences on the immunogenic properties
The key question: Immunogenicity

✓ All therapeutic proteins have the potential to be immunogenic

✓ Risk factors for immunogenicity:
  ▪ Nature of the active substance
  ▪ Previous history of the product (class effect)
  ▪ Target patient population
  ▪ Mode/route of administration
  ▪ Product- and process-related impurities: “purer” preparations of proteins are less likely to give rise to immune reactions
    ➢ Important to consider presence of other “related” or “unrelated” substances that may play the role potential adjuvant
    ➢ Less immunogenicity if greater homology (similarity) with the endogenous human protein

The key question: Immunogenicity

✓ The immune system can detect alterations in proteins missed by analytical methods
✓ Immunogenicity of biopharmaceuticals may have serious clinical consequences
  ▪ Non-neutralizing Antibodies → no impact on clinical efficacy
  ▪ Neutralizing antibodies → inhibition (up to complete loss) of the therapeutic effect
✓ Prediction of (non) immunogenic potential from quality data is inappropriate
The key question: Immunogenicity

✓ This question is considered as a key issue for proteins of therapeutic interest
✓ Should always be addressed in the framework of clinical trials
  ▪ The animal model is not predictive
  ▪ Must take into account the different target populations (indications)
  ▪ To establish correlations between appearance of antibodies and (loss of) efficacy
  ▪ Need to establish detection methods and assays for antibodies
✓ Need to establish the clinical meaning of the detected immune reaction against the therapeutic protein
✓ Need to include, within the pharmacovigilance programme, a follow-up of the immunogenic response

Biological products and their challenges

✓ Complex structure
  → impact on the safety and efficacy profile

✓ Complex production process
  → impact on the quality profile and consistency

✓ Complex quality profile
  → difficulties to monitor and quality control the final product
  → Immunogenicity potential
The question

✓ Considering all the “biological challenges”

✓ Is the « generic » approach possible for biological products?

✓ The answer would be:   ➔  NO

From innovators to « biosimilars »
Biosimilars: European Legislative framework

✓ Directive 2004/27
  ■ Article 10.4 Biological Medicinal Products:

Where a biological Medicinal Product which is similar to a reference biological product does not meet the conditions in the definition of a generic medicinal product owing to differences relating to raw materials or differences in manufacturing processes of the biological medicinal product. The results of appropriate pre-clinical and clinical trials relating to these conditions must be provided.

Biosimilars – development of guidelines

✓ Need guidelines to accompany the « biosimilar » status.
✓ The first guideline (2000) was dealing with the question of « comparison »
  ■ Following a change introduced in the manufacturing process of a biological medicinal product
  ■ For a biological product prepared by a new manufacturer
The biosimilar concept: the comparability exercise

How much do we need to know for a biological?

How much „similarity“ do we need?

The key words of the "Comparability Exercise" -1-

✓ "Comparability" in terms of
  - quality,
  - safety
  - efficacy

✓ Generally, same pharmaceutical form, strength and route of administration

✓ (non)Clinical data requirements depend on
  - Extent of possible characterisation (quality attributes)
  - Observed / potential differences in the quality attributes
  - Clinical experience with the substance and its class
  - But also ….. case by case approach
The key words of the "Comparability Exercise" -2-

- All studies are comparative
- Reference product authorized in the EU
- Same reference product for all aspects of the comparability exercise
- Pivotal studies: use final formulation derived from the final process

Series of guidelines developed

- Overarching guideline
- Quality guideline
- Non-clinical and clinical guidelines
- Product specific guidelines (annex)
  - Somatropin
  - Epoetin
  - Granulocyte-colony stimulating factor (G-CSF)
  - Insulin
  - Low molecular weight heparins
  - IFN α (draft)
  - IFN b (position statement)
« Overarching guideline » (CHMP/437/04)

✓ Scope: Any biological medicinal product
  ▪ Biotechnology derived protein
  ▪ Immunologicals (e.g. vaccines and allergens): unlikely, but case by case…
  ▪ Blood products or recombinant alternatives: reduced clinical dossier not acceptable
  ▪ Others (e.g. gene, cell therapy): considered in the future in light of scientific knowledge and regulatory experience gained at the time…
✓ "Generic approach": not appropriate to biologics due to complexity of molecular structure and/or production
✓ Biosimilarity to be established at all levels: Q / S / E
✓ Importance to clearly identify the product to support pharmacovigilance monitoring
✓ When pharmaceutical form or strength or route of administration are not the same: must be supported by non-clinical/clinical trials
✓ Reference medicinal product: must be authorised in the Community on the basis of a complete dossier

Quality guideline

✓ Quality guideline (CHMP/BWP/49348/2005)
  ▪ Comparability exercise versus reference product
    ➢ Comparison against official data (e.g. pharmacopeial monographs or against other published scientific data): not sufficient
    ➢ Quality attributes:
      – not expected to be identical.
      – Limits: not wider than the range of variability of the reference product
      – Differences: to be justified in relation to safety and efficacy.
    ➢ Reference product:
      – Comparability for medicinal product + active substance
      – Same reference for all three parts of the dossier (Q/S/E)
      – To be clearly identified (brand name, pharmaceutical form, formulation and strength …)
      – Shelf life of the reference product to be considered
  ▪ Manufacturing process of the biosimilar product:
    ➢ Own development + state of the art information
    ➢ Own process related impurities
    ➢ Suitability of the proposed formulation to be demonstrated, even if same as reference product.
    ➢ Generate clinical data for the comparability study with product manufactured with the final manufacturing process (i.e. representing quality profile of the batches to be commercialised)
Non-clinical studies

- Comparative in nature; designed to detect differences
- In vitro studies:
  - Usually necessary to assess any possible differences in reactivity
- In vivo studies:
  - Pharmacodynamic effect/activity
  - Non-clinical toxicity: ≥1 repeat-dose including toxicokinetics
  - If specific concerns (e.g., local tolerance) may be addressed in the same repeat dose toxicity study
- Usually safety pharmacology, reproduction, mutagenicity and carcinogenicity not required

Efficacy -1-

- Pharmacokinetics (PK) studies
  - Generally, for all routes of administration applied for
  - Absorption and clearance and/or half life (elimination rate may differ)
  - Pre-specified equivalence margins, (acceptance range for generics may not be applicable)
- Pharmacodynamics (PD) studies
  - Clinically relevant PD marker
  - Combined PK/PD study (information on dose-response relationship)
  - Dose in the linear part of the dose-response curve
Similar biological medicinal product
Non-clinical / Clinical

✔ Efficacy -2-
- Confirmatory comparative trial(s)
  - Equivalence margins
    » Pre-specified
    » Adequately justified, primarily on clinical grounds
- Comparative PK/PD studies may suffice to demonstrate clinical comparability, if
  - PK of the reference product is well characterized
  - Sufficient knowledge of PD properties
  - ≥1 PD marker(s) accepted as surrogate marker(s) for efficacy
  - Equivalence margin appropriately justified
  - Dose-response sufficiently characterised

Similar biological medicinal product
Non-clinical / Clinical

✔ Extrapolation of the clinical indications
  - Each claimed indication should be justified, or if necessary demonstrated separately
  - Extrapolation to other indication(s) depends on
    - clinical experience
    - available literature data
    - same mechanisms of action or receptor(s) involved in all indications
Similar biological medicinal product
Non-clinical / Clinical

✓ Clinical Safety and pharmacovigilance
  ▪ Safety clinical data to be provided, even if comparable efficacy
  ▪ Undesirable effects: comparison of type, frequency and severity
  ▪ Not all differences can be detected pre-licensing
  ▪ Risk specification to be provided (including issues related to tolerability)
  ▪ Risk management programme / Pharmacovigilance plan to be provided:
    ➢ Focus on rare adverse reactions
    ➢ Specific PhV measures for the reference product usually to be adopted

Similar biological medicinal product
Non-clinical / Clinical

✓ Immunogenicity
  ▪ Important issue for protein therapeutics
  ▪ Must always be investigated within all clinical trials
    ➢ Cannot be predicted from animal studies
    ➢ Should be considered in different therapeutic indications (i.e. for each indication)
  ▪ Requires validated assay for determination of binding/neutralising antibodies
  ▪ Optimal antibody testing strategy
    ➢ periodicity and timing of sampling,
    ➢ interference with antigen,
    ➢ qualified assay(s) (sensitivity, specificity)
    ➢ Clinical implications of antibodies
    ➢ Chronic administration
  ⇒ usually one-year data pre-licensing
### Similar biological medicinal product

**Biosimilar MAA (status November 2008)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Product Name</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Omnitrope (somatropin)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
<tr>
<td>2.</td>
<td>Valtropin (somatropin)</td>
<td>Biopartners</td>
<td>Authorised</td>
</tr>
<tr>
<td>3.</td>
<td>Alpheon (interferon alfa)</td>
<td>Biopartners</td>
<td>Negative</td>
</tr>
<tr>
<td>4.</td>
<td>Bionocrit (epoetin alfa)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
<tr>
<td>5.</td>
<td>Epoetin alfa Hexal (epoetin alfa)</td>
<td>Hexal</td>
<td>Authorised</td>
</tr>
<tr>
<td>6.</td>
<td>Abseamed (epoetin alfa)</td>
<td>Medice</td>
<td>Authorised</td>
</tr>
<tr>
<td>7.</td>
<td>Silapo (epoetin zeta)</td>
<td>Stada</td>
<td>Authorised</td>
</tr>
<tr>
<td>8.</td>
<td>Retacrit (epoetin zeta)</td>
<td>Hospira</td>
<td>Authorised</td>
</tr>
<tr>
<td>9.</td>
<td>Insulin Marvel Short (insulin)</td>
<td>Marvel Life Science</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>10.</td>
<td>Insulin Marvel Intermediate (insulin)</td>
<td>Marvel Life Science</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>11.</td>
<td>Insulin Marvel Long (insulin)</td>
<td>Marvel Life Science</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>12.</td>
<td>Filgrastim Ratiopharm (filgrastim)</td>
<td>Ratiopharm</td>
<td>Authorised</td>
</tr>
<tr>
<td>13.</td>
<td>Ratiograstim (filgrastim)</td>
<td>Ratiopharm</td>
<td>Authorised</td>
</tr>
<tr>
<td>14.</td>
<td>Biograstim (filgrastim)</td>
<td>CT Arzneimittel</td>
<td>Authorised</td>
</tr>
<tr>
<td>15.</td>
<td>Tevagrasim (filgrastim)</td>
<td>Teva</td>
<td>Authorised</td>
</tr>
<tr>
<td>16.</td>
<td>Filgrastim Hexal (filgrastim)</td>
<td>Hexal</td>
<td>Authorised</td>
</tr>
<tr>
<td>17.</td>
<td>Zarzio (filgrastim)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
</tbody>
</table>
Some questions on the biosimilar status

Would the concept be applicable to “all biologicals”?  

- The regulation applies to “biological medicinal products” → any type of biologics could be licensed as a biosimilar,  
- For scientific reasons, the approach will be more likely successful for products which can be thoroughly characterised, such as proteins produced by recombinant DNA technology  
- More difficult to apply to other types of biologics:  
  - by nature are more complex (e.g. vaccines),  
  - for which there is little regulatory experience gained so far (e.g. gene therapy).
Interchangeability – Substitution

✓ As regards substitution or interchangeability
  ▪ on a scientific basis, biosimilars should not be assimilated to generics
  ▪ as such the term biogeneric is not considered appropriate in the EU.
  ▪ Interchangeability is not a point that EU legislation currently addresses. This policy question is left to the initiative of the National competent authorities.

Similar biological medicinal product

Conclusion

✓ Similar biological medicinal product
  ▪ Legal framework introduced in 2003
  ▪ Applicant may choose to file as stand-alone application
  ▪ Biosimilar approach: reduction of non-clinical and clinical data compared to a full dossier

✓ Comparability exercise:
  ▪ Similar ≠ identical
  ▪ Studies should be comparative Q + S + E
  ▪ Reference product must be authorized in the EU
  ▪ Same reference product for all aspects of the comparability exercise
  ▪ Pivotal studies: use the final process material
"Biosimilar" does not mean "generic"

- In « biosimilar », you get BIO and SIMILAR
  - SIMILAR indicates the administrative and regulatory status
  - BIO means and reminds that this is a biological product, with all its complexity and consequences in terms of safety and efficacy
    - not recommended to switch patients from a biological product to another without therapeutic justification
    - No reason, for biosimilars, to deviate from general recommendations for biologics
    - The « biosimilarity » concept (as well as the « comparability » programme) are not aimed at concluding that the two products are «identical»
### Note explicative “Erythropoietine”

**EMEA/CHMP 94526/05**

<table>
<thead>
<tr>
<th>Preclinical studies</th>
<th>Comparative non-clinical studies  28-day toxicology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human PK &amp; PD studies</td>
<td>Single dose in healthy volunteers using SC and IV Include PD evaluation (reticulocytes) in PK studies</td>
</tr>
<tr>
<td>Efficacy studies</td>
<td>2, randomised, double blind studies in nephrology Both routes of administration (SC and IV) Dose and Hb levels to be collected</td>
</tr>
<tr>
<td>Extrapolation</td>
<td>Yes – equivalence in renal anaemia may allow extension to other indications, if justified by applicant</td>
</tr>
<tr>
<td>Safety</td>
<td>Safety from efficacy studies is adequate for approval 12-month, comparative immunogenicity data</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>PRCA to be addressed Safety in cohort of patients from all indications (ie. including extrapolated indications)</td>
</tr>
</tbody>
</table>
### Note explicative “G-CSF”

**EMEA/CHMP 31329/05**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical studies</td>
<td>Comparative non-clinical studies</td>
</tr>
<tr>
<td></td>
<td>28-day toxicology</td>
</tr>
<tr>
<td>Human PK &amp; PD studies</td>
<td>Single dose in healthy volunteers using SC and IV ANC and CD34* in healthy volunteers</td>
</tr>
<tr>
<td>Efficacy studies</td>
<td>2-arm (vs. reference product) OR 3-arm (vs. reference product + placebo) equivalence trial in CIN OR PD study in healthy volunteers (if justified)</td>
</tr>
<tr>
<td>Extrapolation</td>
<td>Yes – Equivalence in CIN will allow extrapolation to other indications, if mechanism of action is the same</td>
</tr>
<tr>
<td>Safety</td>
<td>Evaluate AE’s and immunogenicity in CIN study 6-month follow-up</td>
</tr>
<tr>
<td>Post-Approval Commitments</td>
<td>Specific monitoring for LoE in extrapolated indications</td>
</tr>
</tbody>
</table>

*Note: SC stands for subcutaneous, IV for intravenous, ANC for absolute neutrophil count, CD34* for CD34 positive cells, AE for adverse events, LoE for level of evidence.*