Quality and Regulatory Aspects of Biosimilars

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13th May 2016
Outline of Presentation

• What are biosimilars?
• Regulation of biosimilars
• Principles of biosimilar medicines
• How to demonstrate biosimilarity
• Pharmacovigilance
• Naming
• The future?
What are biosimilars?

- Biosimilars are biological medicinal products
  - 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 physico-chemical and biological testing, together with the production process and its control.
What’s a biosimilar?

A close copy of an authorised biological product – any biological product.

Oh a generic!!! Not entirely!

Biosimilar idea has evolved from generics – so the concept is the same!

- Active substances of generics are exact copies of the approved product and are considered identical.
- A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised biological medicine (reference) in the EEA.
### Complexity of biological medicines

<table>
<thead>
<tr>
<th>Conventional ‘small molecule’ pharmaceuticals</th>
<th>Biotechnology derived biopharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Mw &lt; 1kDa</td>
<td>High Mw (&gt;50kDa)</td>
</tr>
<tr>
<td>Usually organic chemical synthesis</td>
<td>Produced from live cells/organisms</td>
</tr>
<tr>
<td>Single chemical entity, high homogeneity/purity</td>
<td>Complex heterogeneous mixtures, broad specifications</td>
</tr>
<tr>
<td>Parenteral and non parenteral routes</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Non-antigenic (predominantly)</td>
<td>Often immunogenic</td>
</tr>
</tbody>
</table>
Increasing complexity!
Manufacture of recombinant proteins

Manufacturing of recombinant Proteins is complex

DNA Vector

Cloning into DNA Vector

Transfer into Host Cell
Expression
Cell Development

Large-Scale Fermentation

Downstreaming

Formulation

e.g., bacterial or mammalian cell

Source: Slide by Nanna Aaby Kruse, Mediacadeny, Oct 2011
"The process is the product"

- fluctuations in the manufacturing process
  (e.g., pH, temperature, culture media):

- changes in the manufacturing process

  • "One process – one product" paradigm

Biotechnological medicinal products are "individuals"

Biotechnological medicinal products are more than the drug substance

Small changes can have high impact

How does this fit with biosimilar products???
Manufacture of recombinant proteins

Manufacturing of recombinant Proteins is complex

A second manufacturer uses…

(Probably) a different DNA vector

Cloning into DNA Vector

The same amino acid sequence (maybe the same genetic sequence)

A different downstreaming protocol

Transfer into Host Cell Expression Cell Development

A different fermentation process

Downstreaming

Large-Scale Fermentation

Different in-process controls

Formulation

Maybe a different formulation

Different Process → different product

Source: Slide by Nanna Aaby Kruse, Mediacademy, Oct 2011
What’s a biosimilar?

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised biological medicine product (reference) in the EEA.

• 2003 – amendment to EU 2001/83/EC introduced term ‘similar biological medicinal product’
• 2005 - Guideline on similar biological medicinal products published by EMA – introduced the term ‘biosimilar’
• Continued publication of guidelines by EMA
Legal basis: Directive 2001/83/EC

- **Article 10(1)** allows for the authorisation of generics
- **Article 10(4)** - Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.
- **Annex I** - The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.
Biosimilars: A brief history

- 80's: rDNA insulin
- 90's: Comparability guidelines
- 00's: EU + WHO Biosimilar guidelines
- 2015: Global interest in biosimilars accelerating
CHMP Guideline Framework on Similar Biological Medicinal Products.

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS (CHMP/437/2004)
Overarching Guideline

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE:

“Product Specific Guidelines”
- Erythropoietins
- G-CSF
- Somatotropins
- Insulins
- Monoclonal antibodies
- Low molecular weight heparins
- Interferon beta
- Interferon alpha
- Follicle stimulating hormone
Principles of biosimilar medicines (CHMP/437/04)

- Contain a version of the active ingredient
- Concept applicable to any biological medicine
- Concept suited to products that are highly purified and thoroughly characterised (e.g. biotechnological medicines)
- **Comparability exercise**: demonstrates similarity to reference in terms of quality characteristics, biological activity, safety and efficacy
- Same posology and route of administration as reference
- Deviations in strength, form, excipients and presentation require justification
Principles of biosimilar medicines (CHMP/437/04)

• Comparable safety and efficacy
• Differences that enhance safety can be justified
• Indication extrapolation if justified
• Once approved no need to repeat demonstration of biosimilarity to reference (e.g. manufacturing process change)
• Pharmacovigilance requirements – Art 102(e) of Directive 2001/83/EC
Principles of biosimilar medicines
(CHMP/437/04)

• Development programme: stepwise approach
• Comprehensive physiochemical and biological characterisation required
• Aim of clinical data: address slight differences in previous steps
• Clinical data cannot be used to justify substantial differences in quality data
Quality: foundation of biosimilars

- Define Target Profile
- State of art analytical tools
- Structured development: QbD
- Critical Quality Attributes – systematically Controlled
- Non-critical attributes – greater tolerance

• Slide: Presentation by Peter Richardson, EMA at DIA Biosimilars conference, London 2015
There has been a shift toward greater emphasis on the quality package to demonstrate biosimilarity.
Rapid advances in analytical sciences!

Increasing armamentarium and sensitivity of analytical tools

The Sensitivity of Mass Spectrometer (MS) Methods is Progressing Rapidly

<table>
<thead>
<tr>
<th>Year</th>
<th>Detection limit of peptide (pmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>100</td>
</tr>
<tr>
<td>1993</td>
<td>10</td>
</tr>
<tr>
<td>1997</td>
<td>1</td>
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<td>0.1</td>
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<td>2003</td>
<td>0.01</td>
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<tr>
<td>2005</td>
<td>0.001</td>
</tr>
<tr>
<td>2008</td>
<td>0.0001</td>
</tr>
<tr>
<td>2011</td>
<td>0.00001</td>
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- 10 000 fold increase in sensitivity in 10 years
- 10 million fold increase in sensitivity in 20 years!

*Slide presented by Tony Mire-Sluis (Amgen) at CASSS Mass Spec 2012*

M. Weise, EBG Biosimilars 2016
EU Regulatory approval pathway for Biosimilars

- Manufacturer needs to demonstrate that there are no clinically meaningful differences between the biosimilar and the Reference i.e. Integrated Compatibility exercise on Q, S, E versus Originator

CTD Modules

- Originator Application
  - Clinical
  - Non-clinical
  - Quality

- Biosimilar Application
  - Clinical + Comparability
  - Non-clinical + Comparability
  - + Comparability exercise

Integrated Comparability Exercise

* a step by step approach, the extent of the Non-clinical and clinical testing can be decided depending on the similarity on the quality profile
Where to start?

• European Reference product – Extensive information required
• Use to define Quality Target Product Profile (QTPP)*
  – Publicly available information
  – Extensive characterisation (use multiple batches of reference product to get range of parameters)
  – QTPP forms basis of development

* QTPP: A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product
What next?

• Manufacture the biosimilar product
  – Design manufacturing process to match QTPP
  – Full quality dossier required.
  – Use state of the art technologies
  – In accordance with relevant ICH and CHMP guidelines
  – Targeted development of biosimilar to match the reference product
  – Careful consideration to the manufacturing process as the process defines the product e.g. host cell line, transfection process, cell culture media, hold times, drug product excipients, primary packaging.

The biosimilar manufacturer will not have access to the manufacturing process of the originator therefore its makes this process very difficult.