Biologicals and biosimilars in the wind
- what is new?

- An update of biologics & biosimilar regulation

SciLifeLab Drug Discovery and Development Platform
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Disclaimer

- Venke Skibeli is a member of the Biosimilar Medicinal product Working Party under CHMP, European Medicines Agency (EMA).

- The views expressed in this review are the personal views of VS and should not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.
What is a biological?

- blood products
- advanced therapies
- rekombinant proteins
- vaccines
- enzymes
- heparin
- insulin
- Present basis for development of biosimilars
Evolution of expression systems for biologicals

- Living cells = natural heterogeneity / variation
Therapeutic protein structures

Aspirin
180 Daltons

Insulin
5 700 Daltons
51 aa

Growth hormone
22 000 Daltons
191 aa

Monoclonal antibody
150 000 Daltons

simple
complex
more complex
Considerably more complex

Exact structure of biologicals: unknown

The Approval process in the EU

EMA

- Almost all "innovative" medicines are licensed through the centralised procedure (CP)
  - Biologicals including biosimilars

- CHMP (Committee for Human Medicinal Products)
  - consensus or majority opinion
  (the votes from Norway and Island are not valid)

EU commission
  - decision
In EMA: Comparability/similarity of biologics is assessed by experts

- Two CHMP members ("Rapporteur" and "Co-Rapporteur") provide two independent initial assessments
  - Benefit/risk is thoroughly evaluated

- An expert group Biologics Working Party - BWP discusses the quality part of the dossier

- The working party for Biosimilars; BMWP - Biosimilar Medicinal product Working Party
  - Multidisciplinary team - experts within quality - non-clinical - clinical topics
Protection Periods

**Data Exclusivity**
- **8 years**
- Marketing Authorisation Reference Product
- Biosimilars Application

**Market Protection**
- **2 years**
- MA granted
- Pricing & Reimbursement
- Prepare to Launch

**Biosimilars Launch**
- **(1 yr)**
- Extra year of Market protection for new indication
- **The EU biosimilar story**

  - Omnitrop (somatropin) - submitted as «well established use/bibliographic (mixed) application» i 2001 - ‘old legislation’

  - Legislation for generics - not applicable

  - EMA adopted a legislation for biosimilars i 2003:
    - The EU- Directive 2001/83/EC
      - “European Drug Law.
    - Similar biological medicinal product
    - Art. 10(4)

  - New application in 2004

  - Omnitrop obtained MA in 2006
Evolution of Biosimilars in the EU

**Legislation**
- Directive 2001/83/EC
- Directive 2004/27/EC
- Directive 2003/63/EC

**Guidance**
- Overarching guideline
- Quality guideline
- Non-clinical/Clinical guideline
- Product-class specific guidelines

**Product evaluation**
- First biosimilars authorised – Omnitrope and Valtropin
- First biosimilar epoetins authorised
- First biosimilar filgrastims authorised
- First biosimilar mAbs authorised
What is a biosimilar? I

• **After protection periods** (like for generics)

• **Biosimilar products** – Similar biological medicinal product (EU, FDA, WHO)

  - The pharmaceutical form, strength and administration must be the same as for the reference product in the same indication

  - Current requirement for the Reference product:
    - must have an MA in the EU
What is a biosimilar? II

From EMA - revised general guidelines adopted in 2015:

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

- A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

Versus: “Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines” (Q&A on biosimilars)
Biosimilarity - general aspects

Development and conclusion on biosimilarity is a step-wise approach

1. **Step: quality** level, to establish high similarity in a comprehensive comparability exercise

2. **Step: non-clinical** level, great importance of functional assays to substantiate similar effects

3. **Step: clinical** level, lower sensitivity for demonstration of similarity, comparison should confirm biosimilarity as observed above
   - If not, can it be explained (why, how)?
   - What additional data can minimise concerns?

Risk of failure decreases
Basic principle for clinical development of biosimilars

- The aim of a biosimilar development programme is not to establish benefit of a treatment for the patient.

  - this has been done before for the reference product!

- The aim is to establish biosimilarity!

The „art“ is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, within current technical and scientific limitations (inherent variability).
Biosimilar regulation
- requirements for documentation
- decision on a **case by case** basis

- **Quality documentation**
  - The same as for all medicinal drugs **AND** comparability studies:
    - **same primary structure**

- **Non-clinical documentation**
  - Animal studies not regarded as informative
    - May be sufficient with **in vitro** studies in cells

- **Efficacy**
  - **Extrapolation of indications**
    - Within the same area of therapy
    - Between different areas of therapy
    - If the relevant mechanism of action and the target receptor(s) involved is the same

- **Safety**
  - Long time monitoring of safety & immunogenicity
    - Same strength, dose and same route of administration as the reference in the same indications

Manufacturing change for biologics

Biosimilars: the science of extrapolation

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(Blood. 2014;124(22):3191-3196)
Evidence for biosimilarity on a clinical level

- PK/PD-study - more sensitive than E/S-studies

- E/S studies should be performed in the most sensitive population:
  - So called „tailored“ studies more than abridged

The clinical study follows the idea that patients are „models“

- The clinical study is selected to represent the most sensitive model to study differences = tailored

- Thus, trial design might be (entirely) different from the normal guideline principles!
Documentation for biosimilars versus new active substances

**Biosimilars**

- Quality documentation
  - Analytical comparisons
  - Non-clinical tests
  - PK + PD
  - S & E
  - RMP

**New active substance**

- Quality documentation
  - Pharmacology and toxicology
  - Non-clinical tests
  - PK + PD
  - S & E
  - RMP
Documentation for biosimilars versus generics

Biosimilars

Pharmaceutical documentation

Analytical comparisons

Non-clinical tests

PK

S & E

RMP

Generics

Pharmaceutical documentation

PK

RMP
Steps in the manufacturing process for biologicals
The Comparability Exercise

- Technical expression:

- Show that two biologicals / biotech products are similar

1) **Scenario 1**: Change in the manufacturing process ("pre- and post-change"-product from the same manufacturer)

2) **Scenario 2**: A biosimilar is launched (compared to the reference)

- Scenario 1: Manufacturer owns all documentation and experience on the product
- Scenario 2: Most cases manufacturer has not access to data from the company owning the original (reference product)
“Similar but not identical”

- “Non-identicality” is a normal principle in biotechnology
- No batch of any biological is “identical” to the others

Epoetin alfa

“Inherent variability”
Changes of originator biologicals

Changes in the manufacturing process

(Data source: EPARs on EMA website)
Accepted differences in quality attributes

Change in the manufacturing process

This change for an originator mAb was approved without clinical data

A 20% difference in ADCC was accepted by CHMP as clinically not meaningful for biosimilar infliximab, based on additional functional data and justification.
What is a biosimilar?  
➢ epoetin alfa (MA in Europa)

Figure 4: In vivo biological activity of 20 consecutive batches of Binocrit

In vivo biological activity of 20 consecutive batches of Binocrit determined with the normocythaemic mouse assay according to the erythropoetin monograph of Ph. Eur. [10]. The method is routinely applied for release of drug substance.
- and what is **not** a biosimilar

„non-innovator epoetins“

➢ from other parts of the world
Immunogenicity

• **It is impossible to predict**
  - the incidence of unwanted immunogenicity
  - the characteristics of the immune response
  - the clinical consequences and significance of such immunogenicity

• **Immunogenicity of biosimilars**
  - is the reference product immunogenic?
    - Impossible to predict an increase or decrease

• The Applicant has to include immunogenicity data when submitting the dossier
A risk-based approach to immunogenicity
Immunogenicity of biosimilars
- examples on patient-related factors

- **Alemtuzumab** - indication multiple sclerosis, ADAs: **high level**
- (humanised MoAb)

- Binds to the surface antigen CD 52 on T- and B lymphocytes
- Induces a high incidence of ADA production in patients
- ADA production: **85% in patients; 92% neutralising**
- Efficacy: evaluated as no influence

Possible explanations:
- Transient ADAs
Examples of immune reactions caused by leachables/container-systems/packaging/storage

- **Epoetins „High-risk“ products**
  - Non-redundant natural counterparts ➔ Erythropoietin
  - **Epoetin alfa**
    - Change of excipients in the formulation, HSA ➔ polysorbate 80 & leaching of organic compounds from uncoated rubber stoppers
    - probably aggregation of the epoetin- molecules ➔ crossreacting ADAs
    - Causing antibody-mediated PRCA - pure red cell aplasia = the bone marrow does not produce red blood cells


The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes

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Normal BM containing polychromatophilic erythroblasts (arrows)

BM of a patient with Ab-mediated PRCA
What is the basic immunogenicity package?

**Low risk (e.g. insulin)**
- Frequent sampling only at the beginning
- Analysis at the end of a trial
- Shorter follow up
- Routine pharmaco-vigilance (for immunogenicity)

**High risk (e.g. epoetin)**
- More frequent sampling
- Real time analysis
- Longer follow up
- Cell-based neutralisation assay
- Intensified clinical monitoring
- Post-marketing immunogenicity study(ies)

- Incidence
- Persistence
- Titer
- Neutralisation
- Clinical impact
- Risk management
MAAs pipeline

MAAs by type of applications
MoAbs
-examples on monoclonal antibodies authorised in the EU

- **Rituximab (Mab thera):** chimeric mouse/humanised MoAb – binds and inhibits CD 20 on the surface of B-cells
  - Approved indications: Both cancer and rheumatic disease

- **Bevacizumab (Avastin):** humanised MoAb- binds and inhibits VEGF-A (angiogenesis)
  - Cancer indications

- **Ipilimumab (Yervoy):** fully humanised - immune checkpoint-inhibitor - modifiserer immunsystemet: Hemmer CTLA-4
  - Inicated for metastatic malign melanoma med spredning

- **Infliximab (Remicade):** chimeric humant/muse-MoAb
  - Biosimilar - approved late 2013- Remsima & Inflectra /Flixabi (2016)

- **Nivolumab (2015) - Opdivo/ pembrolizumab - Keytruda:** PD-1 inhibitors (programmed cell death-1)
  - Approved as monotherapi for metastatic melanoma (Keytruda) og metastatic NSCLC in 20
  - No biosimilars
Biosimilar Product Overview (April 2017) *

- 61 MAAs submitted
- 46 MAAs post-review
- 15 MAAs under review
- 34 Positive opinions
- 28 Valid MAs
- 10 Withdrawn (pre-approval)
  - Insulin (6)
  - Epoetin (1)
  - Pegfilgrastim (3)
- 2 Negative
  - Interferon alfa
  - Insulin
- 3 Withdrawn (post-approval)
  - Filgrastim (2)
  - Somatropin (1)
- 2 Negative
- 10 Withdrawn (post-approval)
  - Insulin (6)
  - Epoetin (1)
  - Pegfilgrastim (3)
- 3 Withdrawn (post-approval)
  - Filgrastim (2)
  - Somatropin (1)
- 3 Awaiting EC decision
  - Etanercept (1)
  - Rituximab (2)
- Adalimumab (2)
- Bevacizumab (2)
- Insulin glargine (1)
- Insulin lispro (1)
- Pegfilgrastim (2)
- Rituximab (3)
- Trastuzumab (4)

* Information on EMA website
Hot topics on biosimilars

- **Quality (comparability exercise)**
  - “The process is the product”

- **Immunogenicity**
  - Immunogenicity is perceived as a risk, especially upon switching from the reference product to a biosimilar

- **Extrapolation**
  - Difficulties to understand the concept of extrapolation
  - Unknown mechanisms of action
  - “Small differences in the structure may have a major impact on safety”.

- **Interchangeability** Some clinicians have problems with the expression: “similar but not the same”
Take home message

From the EMA perspective:
Biologics & Biosimilars approved in the EU are of good quality, efficacious and safe in use.
Interchangeability of Biosimilars: A European Perspective

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In our opinion, switching patients from the original to a biosimilar medicine or vice versa can be considered safe.
Thank you!

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Biosimilar Infliximab*

Concern: use in inflammatory bowel disease

- Identical primary, secondary and tertiary structure
- Comparable post-translational profiles
- Comparable in vitro functional characteristics
- Comparable pharmacokinetic profiles (250 patients with ankylosing spondylitis, 54 weeks, supportive efficacy and safety data)
- Comparable efficacy, safety and immunogenicity (606 patients with RA (rheumatoid arthritis))

* See European Public Assessment Reports: www.ema.europa.eu
Biosimilar infliximab - functional studies

Lower % of afucosylated glycoforms

Lower FcγRIIIa/b-binding

Lower ADCC activity
- Not seen under more physiological conditions

Impact on extrapolation to immune bowel disease - IBD?
CHMP decision on extrapolation for infliximab biosimilar*

All indications of the reference product were approved

- Neutralisation of soluble TNFα and trans-membrane TNFα mediates efficacy in Rheumatoid Arthritis and other forms of autoimmune arthritis

- By using a range of experimental models that are considered representative of the pathophysiological conditions and mechanisms of action of infliximab, convincing evidence was provided that the observed difference in afucosylated species was not clinically relevant

* See European Public Assessment Reports (EPARs) at www.ema.europa.eu