Clinical Trials for Biosimilars-
Principles & Challenges

Heike Schoen,
LUMIS International GmbH, Germany
Hyderabad October 27, 2014
AGENDA

- Biosimilars - still a new paradigm
- Regulations – facing increasing complexity
- Clinical trial challenges – Design and Effect
- Summary and Outlook
AGENDA

- Biosimilars - still a new paradigm
- Regulations – facing increasing complexity
- Clinical trial challenges – Design and Effect
- Summary and Outlook
Biosimilar developments

EUROPE currently largest biosimilar market

First Biosimilar was approved in Europe in 2006 (Omnitrope® developed by Sandoz, a Biosimilar of Genotropin® from Pfizer, rhGH)

Since then 17 Biosimilars have gained Marketing Authorization in Europe

US market to evolve through government initiative for health care reform, implementation of biosimilar guideline 2013

Pharmemerging Markets on a fast track through own regulatory pathways, developing biosimilars for local and global markets

Main Products:
- EPO to treat anemia after renal dialysis
- G-CSFs for lowered white blood cell counts after chemotherapy
- Human Growth Hormones
Expectations towards Biosimilars

- Provide cost savings in health care costs
- Increase patient access

Biosimilars 20-30% price reduction than Reference product (generics 70%)

Germany: 60 Mio EUR savings due to price reduction within first 12 months after entry of Biosimilar Epythropoietin

Top selling biologics (Herceptin, Enbrel, Humalog etc) lose patent protection at the end 2020

Increasing development of regulatory pathways to develop Biosimilars

Increasing competition to develop Biosimilars, Key players, national companies
Biosimilar – a complex development process

Amount of evidence for regulatory approval

Generic Drug Application
- Quality and Purity
- Bioequivalence
- 3-5 Mio USD
- 3-5 years

Biosimilar Drug Application
- Quality and Purity
- Biosimilarity
- Preclinical
- Immunogenicity
- Limited Clinical Trials
- 75-200 Mio USD
- 8-10 years

New Biologic Drug Application
- Full Preclinical and Clinical Dossier
- 1.2 Bill USD
- 12 years

Data from Lynne, 2014
Different Names same Meaning - same requirements

Europe (EMA): (2005/2013)
Similar biological medicinal product

WHO: Similar biological product (SBP)
/Reference Biological Product (RBP)

USA (FDA): Biological product/Biosimilar

National Regulation: terms can vary
(e.g. follow-on biologic)

Common Biosimilar concept:
To prove (highly) similarity to a Reference Product

Scientific principle
Quality characteristics
(analytical, physicochemical, manufacturing)
Non clinical data
Safety and efficacy

• At any step differences must be explained and justified, might require additional data
  (e.g. safety), head to head comparison

• If not similar to the reference product could lead to stand alone product development
AGENDA

- Biosimilars - a still new paradigm
- Regulations – Increasing complexity
- Clinical trial challenges – Design and Effect
- Summary and Outlook
Worldwide Biosimilar regulatory pathways

Biosimilars are a relatively new, emerging market. Regulatory guidelines and standards are still being developed in some countries and they are constantly evolving as technology develops.

The EMA published the first biosimilar regulatory approval pathway for the EU member states.

As more governments develop biosimilar pathways, the WHO and EU's established guidelines will continue to serve as a template, as demonstrated by Australia's unabated adoption of the EU guidelines.

The WHO biosimilar guideline, aimed at providing a consistent scientific standard, is the model for many newly developed biosimilar pathways.

Amgen: Biologics and Biosimilars
Biosimilar Marketing Authorisations  EMA 2013

28 MAAs submitted

1 negative

17 valid

Somatropin (1)
Epoetin (5)
Filgrastim (7)
Infliximab (2)
Follotropin alfa (2)

9 withdrawals

Insulin (6)
Epoetin (1)
Filgrastim (1)
Somatropin (1)

1 under review

Insulin glargine (1)
General Requirements to prove similarity

**EMA**
- Quality (chemistry, manufacturing and control, physiochemical properties, Impurities)
- Comparability-data
- Non-clinical
- Clinical

**WHO**
- Quality
- Analytical
- Non-clinical evaluation
- Clinical evaluation

**FDA**
- Analytical
- Non-Clinical
- Clinical pharmacology
- Clinical Safety & Efficacy

Stepwise approach – Product and process understanding for every comparability exercise
Clinical studies with test product of final manufacturing process
FDA: „totality of the evidence approach“
Reference Product

- Reference product needs to be authorized in the country
- Must always be the same
- Chosen reference product must be suitable to support the application for MA (completeness of data)
- Dosage form and route of administration of the Biosimilar and Reference Product must be the same
- A Biosimilar cannot be considered a Reference Product
- Limited clinical data of Reference Product might need to require additional data with Biosimilar
AGENDA

- Biosimilars - a still new paradigm
- Regulations – facing increasing complexity
- Clinical trial challenges – Design and Effect
- Summary and Outlook
Cinical trials - what is needed

„We understand the need of PK/PD studies, but why clinical trials if quality and non-clinical data show high similarity?“

„Wouldn`t be a safety study enough?“
What needs to be tested?

- Patient benefit
- Therapeutic effect
- Safety
- Efficacy
- Human Immunogenicity
- Pharmacokinetik
- Pharmacodynamik
- Adverse event profile

Might be requested as post marketing authorization trial
What needs to be evaluated?

- Human Immunogenicity
- Pharmacokinetics
- Pharmacodynamics
- Safety
- Efficacy

Randomized controlled clinical trial design to cover mainly uncertainty of unpredictably clinical consequences of minor differences

Level of similarity in pre-clinical data defines needed clinical trials

Clinical studies to be performed according to ICH-GCP
General Requirements for clinical trials

- Overall: No clinically meaningful differences between biosimilar and the reference product for safety and efficacy

- Stepwise approach - PK/PD Data – Efficacy clinical trials
- Scientific proven statistical concept to show similarity
- Sensitive endpoints to detect clinically meaningful differences in safety and efficacy between products
- Clinical trials to be assessed on case by case basis, depending on residual uncertainty
PK/PD studies

- Stepwise procedure before efficacy trials
- PK comparison of Reference and Biosimilar - single dose cross over study to characterize absorption, bioavailability and also elimination characteristics for products with short half life
- Parallel design if longer half-life
- Dose to be sensitive to detect differences
- Healthy volunteers if possible (AEs, risks) – homogenous patient population
- Add PD markers to PK studies
- Comparative PK/PD studies
**Efficacy Trial design – Equivalence testing**

Randomized controlled clinical trials – gold standard – hypothesis testing

Test drug does not show better or less efficacy
- Null hypothesis: treatments are not equivalent
- Alternative hypothesis: they are equivalent

Largest difference in efficacy that has no clinical relevance (lower and upper equivalence margin), two sided test within 95% CI

Finding of superiority leads to failure of equivalence trial

**EMA, WHO and FDA generally recommend equivalence trials**
Clinical trial design

Clinical endpoints

- Are not similar to endpoint of reference product (patient benefit)
- Need to detect potential differences in efficacy, not demonstrating efficacy
- Need to measure drug activities
  - e.g. Overall survival vs reduction/change of tumor mass (more sensitive)
- Use of Pharmacodynamik endpoints e.g. assessment of changes in tumor markers
  - Depend on understanding of mechanism of action, availability of PD measures and correlation with clinical outcomes

Individual definition of efficacy endpoint for each class of Biosimilar
Safety assessments - Immunogenicity

- Animal data not predictive for human immune response
- Refers to generation of Antibodies and neutralizing antibodies (NAbs) when using biologic drugs → to loss of efficacy (Nabs)
  → Autoimmune reaction to an endogenously produced protein
- To be investigated in patient population with high risk immune response/immun-related adverse event
- Sponsor to define and justify antibody testing strategy
- Duration of observation depend on Antibody development time
- Post-marketing studies for further characterization of immunogenicity
- Risk Management Plan
AGENDA

- Biosimilars - a still new paradigm
- Regulations – facing increasing complexity
- Clinical trial challenges – Design and Effect
- Summary and Outlook
Summary and Outlook

- Agents with increased complexity will enter global markets (e.g. monoclonal antibodies)
- Any difference between Biosimilar and Originator should always be explained and justified with perspective to clinical relevance; scientific proven concept
- In depth understanding of mechanism of action and manufacturing process needed

- Increase complexity of biologics should not lead to increase of costs to develop Biosimilar
- More data needed to understand longterm biosimilarity (Pharmacovigilance)
- Set of biosimilar class specific efficacy endpoints needed
Dhanyavaad! Thank you!