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#### Immunogenicity: Impact on the Design of Clinical Trials for Biosimilars

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#### **Presentation Outline**

- Biosimilars: First wave products
- Immunogenicity: A general safety concern
- Guidance for Biosimilars: Immunogenicity assessment
- Post-approval Studies: Objectives
- Conclusions



### **Biosimilars** First wave products



#### What is a Biosimilar Product?

- In Europe, biosimilar, or similar biological medicinal product, is a biological medicinal product "similar" to a licensed reference medicinal product'
- Biological medicinal products, e.g.: medicinal products containing biotechnology-derived proteins as active substance, immunologicals such as vaccines, bloodderived products, monoclonal antibodies, etc.

The terminology 'follow-on protein product' (FOPP) is widely used in the USA

### How to Confirm Similar Nature?

Comparability studies are needed to generate evidence substantiating the similar nature, in terms of

- Quality
- Safety
- Efficacy

of the similar biological medicinal product and the chosen reference product

Biosimilar guideline CHMP/437/04



#### First-Wave Biosimilar Products under Development

Active Biological Substance	Treatment Area
Somatropin	Human Growth Hormone Replacement
Interferon Alfa	Hepatitis C
Interferon Beta	Multiple Sclerosis
Insulin	Diabetes
Erythropoietin (EPO)	Anaemia
Granulocyte-Colony Stimulating Factor (G-CSF)	Neutropenia



#### **Biosimilar Approvals**

Biosimilar	INN	Reference product	Approval date
Omnitrope (Sandoz)	Somatropin	Genotropin (Pfizer)	12 April 2006
Valtropin (Biopartners)	Somatropin	Humatrope (Eli Lilly)	24 April 2006
Binocrit (Sandoz)	Epoetin alfa	Eprex/Erypo (Janssen-Cilag)	28 August 2007
Epoetin alfa Hexal (Hexal)	Epoetin alfa	Eprex/Erypo (Janssen-Cilag)	28 August 2007
Abseamed (Medice)	Epoetin alfa	Eprex/Erypo (Janssen-Cilag)	28 August 2007



### **Immunogenicity** A general safety concern





#### Immunogenicity: Frequency and Severity Vary Widely

Frequency	Therapeutic protein	Consequences
Frequent >1/10	anti-TNFα (up to 61%)	Loss of efficacy, infusion reactions
	rh FVIII (20%-40%)	Loss of efficacy
	rh Insulin (~44%)	None/ Loss of efficacy
Common	rh GH (3%-7%)	None/Enhanced?/Loss of efficacy
1/10 - 1/100	rh G-CSF (3%)	None
Uncommon 1/100 - 1/1000	anti-CD20 ( <u>&lt;</u> 1%)	Unknown
Rare 1/1000 - 1/10 000	anti-HER2 ( <u>&lt;</u> 0.1%)	Unknown
Very rare <1/10 000	rh Erythropoetin	Pure Red Cell Aplasia



# Factors Influencing Immunogenicity of Biopharmaceuticals

#### Patient-related factors

- Genetic factors
- Age

#### Disease- and treatment-related factors

- Underlying disease
- Immune status, including immunomodulating therapy
- Intensity of treatment (dose, dosing interval and duration of treatment)
- Route of administration (s.c. > i.m. > i.v. )
- Product-related factors
  - Source of protein
  - Manufacturing process (impurity profile, contaminants)
  - Formulation and stability characteristics (degradation products, aggregates)



## **Guidance for Biosimilars**

#### Immunogenicity assessment





### EU Directives Concerning Biosimilar Products

- Directive 2004/27/EC Art. 10.4 (Amending Directive 2001/83/EC)
- Directive 2003/63/EC Annex I, Part II, Nr. 4 (Amending Directive 2001/83/EC)
  - Definition 'similar biological medicinal product'
  - More information is required as 'essential similarity' cannot be met
  - Need for additional nonclinical/clinical data
  - "Case by case" approach following relevant guidelines
  - No automatic extrapolation to other indications



### EMEA Guidelines for Biosimilar Products

Overarching Guideline (CHMP/437/04) "Guideline on Similar Biological Medicinal Products"

#### introduces concept, outlines basic principles, provides "user guide"





### Principles for Evaluation of Immunogenicity

- The immunogenicity of a similar biological medicinal product must always be investigated.
- Normally an antibody response in humans cannot be predicted from animal studies.
- The assessment of immunogenicity requires an optimal antibody testing strategy, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies and pharmacokinetics or pharmacodynamics, relevant for clinical safety and efficacy in all aspects.
- It is important to consider the risk of immunogenicity in different therapeutic indications separately.

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES (EMEA/CHMP/42832/2005)

### **Testing Strategy Well Defined**

The applicant should present a rationale for the proposed antibody-testing strategy. Testing for immunogenicity should be performed by state of the art methods using assays with appropriate specificity and sensitivity. The screening assays should be validated and sensitive enough to detect low titre and low affinity antibodies. An assay for neutralising antibodies should be available for further characterisation of antibodies detected by the screening assays. Standard methods and international standards should be used whenever possible. The possible interference of the circulating antigen with the antibody assays should be taken into account. The periodicity and timing of sampling for testing of antibodies should be justified.

- In view of the unpredictability of the onset and incidence of immunogenicity, long term results of monitoring of antibodies at predetermined intervals will be required. In case of chronic administration, one-year follow-up data will be required pre-licensing.
- The applicant should consider the possibility of antibodies to process-related impurities.

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#### **Evaluation of the Clinical Significance of the Observed Immune Response**

- If a different immune response to the product is observed as compared to the innovator product, further analyses to characterise the antibodies and their implications to clinical safety, efficacy and pharmacokinetic parameters are required.
- Special consideration should be given to those products where there is a chance that the immune response could seriously affect the endogenous protein and its unique biological function.
- Antibody testing should be considered as part of all clinical trials protocols. The applicant should consider the role of immunogenicity in certain events, such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy. The sponsor needs to discuss possibilities to encourage the reporting of relevant adverse events, including events related to loss of efficacy.

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES (EMEA/CHMP/42832/2005)



#### Immunogenicity: Biosimilar Guideline Annexes

#### Insulin:

The safety concerns with a similar rh-insulin relate mainly to the potential for immunogenicity. The issue of immunogenicity can only be settled through clinical trials of sufficient duration, *i.e.* at least 12 months using subcutaneous administration. The comparative phase of this study should be at least 6 months, to be completed pre-approval. Data at the end of 12 months could be presented as part of post-marketing commitment. The primary outcome measure should be the incidence of antibodies to the test and reference medicinal product.

The plans for these trials should take into account:

- Justification of study population including history of previous insulin exposure
- Definitions of pre-specified analyses of the immunogenicity data with respect to effects on clinical findings (glycaemic control, insulin dose requirements, local and systemic allergic reactions)

(EMEA/CHMP/32775/2005)



#### Immunogenicity: Biosimilar Guideline Annexes (cont'd)

- Somatropin: The applicant should provide comparative 12-month immunogenicity data of patients who participated in the efficacy trial(s) with sampling at 3-month intervals and testing using validated assays of adequate specificity and sensitivity. (EMEA/CHMP/94528/2005)
- Erythropoetin: The applicant should provide at least 12-month comparative immunogenicity data pre-authorisation. Retention samples for both correction phase and maintenance phase studies are recommended. For detection of anti-epoetin antibodies, a validated, highly sensitive assay should be used. (EMEA/CHMP/94526/2005)
- G-CSF: Immunogenicity data should be collected according to the principles described in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CPMP/42832/05). (EMEA/CHMP/31329/2005)



#### Draft Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins

- Further systematic immunogenicity testing might become necessary after marketing authorization, and may be included in the risk management plan.
- The extent of immunogenicity data to be collected in the post-marketing setting will depend on various factors including:
  - Disease-related factors like its prevalence, the vulnerability of the patients, availability of alternative therapies, duration of treatment, etc.
  - Pre-authorization immunogenicity findings including impact on efficacy and safety
  - Experience on immunogenicity with similar proteins or related members from that class of proteins, including proteins manufactured with similar production processes.
- However, biotechnology-derived proteins should be considered individually, and therefore the possibility for extrapolation from other related proteins is limited and needs to be fully justified.



Pharmacovigilance Plans outlined in Product-Specific Annexes of EMEA Biosimilar Guidelines

#### Insulin, Somatropin:

"Plan should take into account risks identified during product development and potential risks, especially as regards **immunogenicity**, and should detail how these issues will be addressed in post-marketing follow-up"

#### Epoetin:

"In order to further study the safety profile of the similar biological medicinal product, particularly rare serious adverse events such as **immune mediated PRCA**, safety data should be collected from a cohort of patients representing all approved therapeutic indications"

#### • G-CSF:

"Attention should be paid to immunogenicity and potential rare serious adverse events, especially in patients undergoing chronic administration. Lack of efficacy should also be monitored, especially in individuals undergoing haematopoietic progenitor cell mobilization"



## **Post-Approval Studies** Objectives

### Why Post-Approval Studies?

- To detect rare side effects that would not be captured in the clinical development program
- To investigate specific safety issues related to the product-class
- To investigate the product properties in day-today clinical setting
- Pharmacovigilance planning
- Pharmacoeconomic studies



Is There Any Difference Between Post-Approval Program of Biosimilar and Reference Product?

- In the development of the post-approval risk-management program of the biosimilar product it is important to distinguish between product-specific safety issues and safety issues that are apparent for the product-class to which the biosimilar product belongs
- In general, the risk assessment of the biosimilar and the reference product will be comparable
- This enables the manufacturers of biosimilar products to focus their post-approval study programs on issues that are well-known and established



#### **Size of Post-Approval Studies**

- Sample size will depend on the frequency of the adverse reaction
- For an incidence rate of 
  <u>></u> 1% the number of ca. 300
  patients might be sufficient to detect at least one case
- For a very rare adverse reaction such as PRCA it was assessed that at least 20,000 patient years of exposure in each study arm would be needed to detect a 4-fold higher rate (4 in 10,000 versus 1 in 10,000) with 50% power (PRIMS registry)



#### Conclusions

- Immunogenicity is a general safety concern that all therapeutic proteins have in common
- The potential to induce unwanted immune responses is similar for new biotechnological entities and biosimilar products
- In general, the risk assessment of the biosimilar and the reference product will be comparable
- Pre- and post-approval programs of biosimilar products will usually focus on the product-class specific safety issues of the reference product that are well-known and established
- Substantial guidance for immunogenicity assessment is already incorporated in the various guidelines for biosimilar products today
- The new Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins (EMEA/14327/2006) will be a valuable extension of the existing guidance