

# Biosimilar medicinal products – focus on non-clinical and clinical aspects

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# Content of the presentation

- Similar biological medicinal products
- Specific problems for biotech products
- Requirements
  - EU
  - US



# Similar biological medicinal products



# Similar biological medicinal products (1)

- Similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between biosimilar products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established

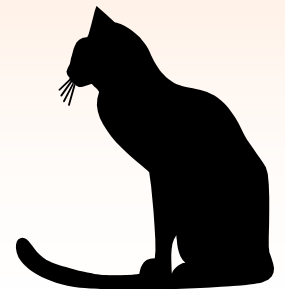


# Similar biological medicinal products (2)

- Until very recently, no legal framework has existed for similar biological medicinal products
- This deficiency has been rectified in the new EU legislation, but in US still no legal framework exist
- It is more difficult to obtain approval for similar biological medicinal products because of the properties of biotech products



# Specific problems for biotech products



# Specific problems for biotech products (1)

- Difficult to guarantee the quality, safety and efficacy of a «biotech product»
- Complex series factors may affect the expression of a foreign gene within host cell
- Genetic Instability: inherent character of biological systems i.e. mutations, selection etc.



# Specific problems for biotech products (2)

- Impurities :
  - Starting materials (reagents used for the fermentation process )
  - Presence of important quantities of the host cell natural proteins
  - Presence of structural impurities close to the protein of interest
  - Viral or bacterial contamination (depending on the expression system or environment)
  - Endotoxines from bacterial expression systems
  - DNA from eukaryotic expression systems



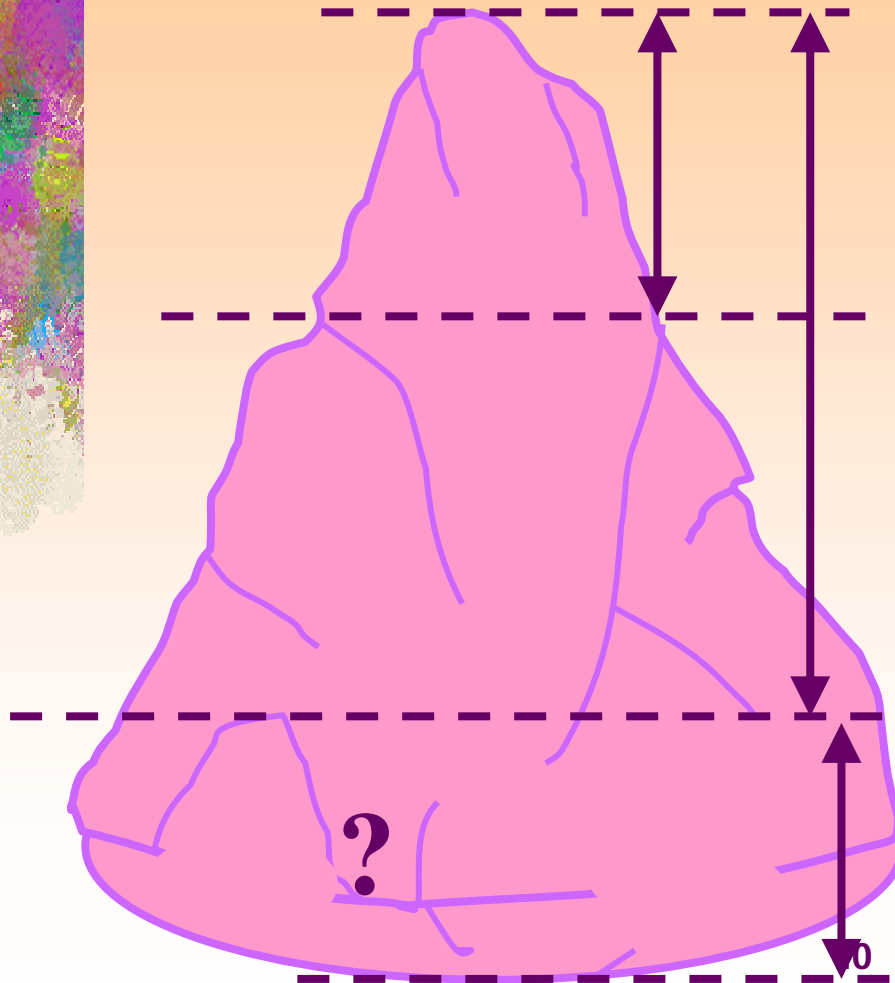


# Specific problems for biotech products (3)

- The three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile, can be significantly altered by changes which may initially be considered to be 'minor' in the manufacturing process
- Structural modifications may lead to
  - differences in their biological activities
  - immunological differences
- Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products



# Specific problems for biotech products - FDA view



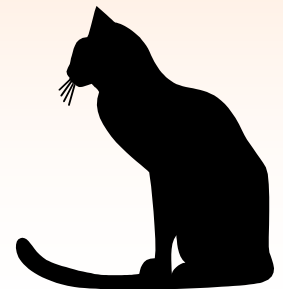
- Release tests

- Characterisation

- Process



# EU Requirements



# Directive 2004/27

- Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecular characteristics and therapeutic modes of action
- When a biological medicinal product does not meet all the conditions to be considered as a generic medicinal product, the results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both



# View of the European Commission

- Small, well-identified molecules will most likely follow a procedure similar to the procedure established for conventional generics
- In contrast, biosimilarity will probably not be possible for large molecules with a complex spatial configuration, and full pre-clinical and clinical studies will be necessary; the data required will be in proportion to the complexity of the molecule

Dr. Philippe Brunet of the European Commission in an article about the legislative review published in the French pharmaceutical journal *Les Pharmaceutiques* (n°112 of December 2003)



# Draft EMEA Guidance on biosimilar products (1)

- Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the reference medicinal product
- These studies to demonstrate biosimilarity are more likely to be applied to highly purified products, which can be thoroughly characterised (such as some biotechnology-derived medicinal products)



# Draft EMEA Guidance on biosimilar products (2)

- Although not legally forbidden, the 'biosimilar' approach is more difficult to apply to other types of biological medicinal products which by their nature are more difficult to characterise, such as biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained (such as gene and cell therapy products)



# Draft EMEA Guideline on biosimilar products (3)

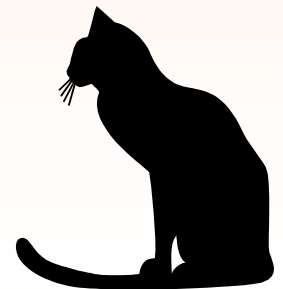
- Whether a medicinal product would be acceptable using the 'biosimilar' approach depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences
- The requirements to demonstrate safety and efficacy are essentially product-class specific
- Non-clinical/clinical data package is determined on a case-by-case basis, for situations where there is no product-class specific guidance





# Draft EMEA Guideline on biosimilar products (4)

- In order to support pharmacovigilance monitoring, the specific product given to the patient should be clearly identified



# Reference product (1)

- The active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product
  - e.g., no comparison between interferon alpha and interferon beta
- The same reference product should be used throughout the comparability program for quality, safety and efficacy studies



# Reference product (2)

- The pharmaceutical form, strength and route of administration of the similar biological medicinal product should be the same as that of the reference medicinal product
- When the pharmaceutical form or the strength or the route of administration are not the same, the results of appropriate non-clinical/clinical trials must be provided in order to demonstrate the safety/efficacy of the similar biological medicinal product



# Comparability – Quality Issues

- Comparison based on testing and characterisation of active substance and finished product is not sufficient
- Many factors should be considered in a comparability exercise
  - Expression/vector system
  - Production and purification processes
  - Facility/equipment
  - Analytical techniques



# Comparability – Clinical Issues

- In case the reference product has more than one indication, the efficacy and safety has to be justified or demonstrated for each indication separately
- Justifications should be based on clinical experience, literature data for the reference product, mode of action (receptors), pre-clinical data, and immunogenicity



# Product-specific guidance

- Granulocyte-Colony Stimulating Factor
- Erythropoietin
- Insulin
- Somatropin



# Preclinical PD data

- *In vitro* studies: Suggested are receptor binding assays and cell-proliferation assays
- *In vivo* studies: Rodent models (neutropenic and non-neutropenic, r-GSF), mouse assays (erythropoietin, EPO), weight-gain and/or tibia growth assay in rats (somatropin) are recommended
- N.B. Studies at high doses may be difficult, as usually only formulated reference product is available



# Toxicological studies

- One repeated dose toxicity study in a relevant species (e.g rat for somatropin)
- Duration varies between 28 days (rG-SF, insulin, somatropin) and 3 months (EPO)
- Local tolerance data in one species needed (can be part of repeated-dose tox)
- Normally safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required





# Clinical – PK data

- Important parameters are AUC,  $C_{\max}$ ,  $t_{1/2}$ , and clearance
- Cross-over design is not appropriate for proteins with a long half-life, pegylated proteins, or proteins for which formation of anti-drug antibodies is likely
- General principles for demonstration of bioequivalence apply
  - Probably refers to range of 80-125% for AUC and  $C_{\max}$



# Clinical – Efficacy

- Not always needed (e.g. insulin)
- One or two (e.g. EPO) clinical studies
- Two-arm or three-arm design (including placebo)
- Duration of comparative phase can vary between 12 weeks (EPO) and 6-12 months (somatropin)



# Clinical – Safety

- Recommend number of patients for EPO is 300
- For other products number could be lower depending on duration of usage, rarity of the disease, etc.
- Duration of study can vary between 6 months (G-CSF) and 12 months (somatropin, EPO, insulin)
- Pharmacovigilance plan to address immunogenicity and rare adverse events
  - pure red cell aplasia connected with EPO

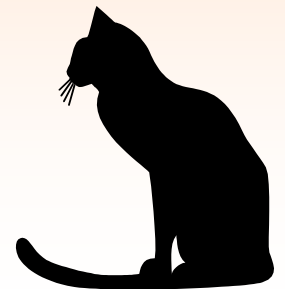


# Clinical – Immunogenicity

- Immunogenicity must always be investigated
- Normally an antibody response in humans cannot be predicted from animal studies
- In case of chronic administration one-year follow-up data needed
- If a different immune response is seen compared with the innovator product, further analyses to characterise antibodies and implications for efficacy, safety and PK are necessary



# US Requirements



# US situation – “Follow-on proteins” (1)

- Rep. Henry Waxman (yes, from Hatch-Waxman) stated at a conference that there is “still a long way to go” before a regulatory framework for biogeneric drugs is developed
- No scientific consensus on how to establish that a generic (biologic) is the same as the original biological product



# US situation – “Follow-on proteins” (2)

- It is difficult to establish bioequivalence for biotech drugs because the manufacturing processes are inherently different from those for new chemical drugs
- There is no currently recognized mechanism for approving generic versions of biological products, and there is relatively little direct competition in the biological marketplace



# US situation – “Follow-on proteins” (3)

- In many ways, this important sector of the market continues to operate as the market for other pharmaceutical products operated before 1984
- Legislators are already beginning to lay out a path that involves a much more case-by-case approval process for biological drugs than for traditional drugs





# US situation – FDA (1)

- The FDA held a public meeting on “follow-on proteins” in September 2004 and was co-sponsoring a workshop in February 2005 on related scientific issues
- Brand name manufacturers maintain that full preclinical and clinical testing is needed to ensure that a follow-on protein is equivalent to an innovator product
- Generic firms counter that advanced analytical and manufacturing systems permit development of similar biopharmaceuticals with abbreviated testing



# US situation – FDA (2)

- **FDA stated that its policy has evolved over many years and continues to evolve based on:**
  - the ability of analytical techniques to characterise products
  - current manufacturing practices and controls
  - clinical and regulatory experience
  - legal requirements



# US situation – FDA (3)

- However, the manufacturers become increasingly impatient, and Sandoz has filed a lawsuit against the FDA on September 13th, 2005
- Sandoz has filed an application for Omnitrope (somatotropin) on July 30, 2003, but the FDA still has not taken any decision



# Possible FDA acceptance of interchangeable protein products (1)

- **Highly purified**
- **Primary structures proven**
- **Physico-chemical tests for secondary and tertiary structure determination**
- **Clinically relevant bioassays**
- **Mechanism of drug action is known**
- **Validated biomarkers available**
- **Extensive experience/ human data available from multiple manufacturers**



# Possible FDA acceptance of interchangeable protein products (2)

- **Need for animal studies depends on**
  - **Relevant species**
  - **Unique species availability**
  - **Animal model of disease**
  - **Impact of immunogenicity on study conduct and interpretation**
  - **Assay capabilities (availability/sensitivity) for PK/PD**
  - **Predicting human immunogenicity (limited)**



# Possible FDA acceptance of interchangeable protein products (3)

- **Human PK studies necessary**
  - Bioavailability may be process dependent
  - If product is a suspension
  - 80-125% bioequivalence criteria can be used (may be difficult to achieve)
  - Animal PK/PD studies can only substitute if they are predictive and human PK/PD studies are not feasible due to safety issues



# Possible FDA acceptance of interchangeable protein products (4)

- **Human PD studies**
  - **If PD measurements are clinically relevant**
  - **If human PK is not feasible, less sensitive, or if drug conc. is not correlated with biological activity**
  - **May eliminate the need for clinical studies**



# Possible FDA acceptance of interchangeable protein products (5)

- **Immunogenicity:**
  - Induction of antibodies can lead to
    - No effect
    - Compromise further therapy (e.g. Factor VIII, interferon-alpha)
    - Alter PK
    - Cross-react with native protein and induce adverse events
  - Antigenicity of molecular variants could be product and process-related





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Thank you for your attention

Questions?

