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**European regulation and
policy governing biosimilar
products**

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Biological medicinal products as defined in European pharmaceutical law

- Biological source
- Method of manufacture
- Use of a combination of biological assay and physico-chemical methods for characterisation and control
 - Classical biological products
 - Recombinant proteins
 - Novel or advanced therapy medicinal products (gene and cell therapies and tissue engineered products)
 - Products cannot be characterised by physico-chemical means
- Approval is based upon an assessment of risk/benefit balance

New law re-validates the old law

- Regulatory path for approving similar biological medicinal product (biosimilar) was introduced in the new pharmaceutical law following consultation
- New law adopted in 2004 and came in operation in 2005
- “...Community legislature has since chosen explicitly to revalidate such an approach [Community interest in public health protection] in the new version of the abridged procedure introduced by Directive 2004/27...in the light of the objectives of the Community rules relating to marketing authorisation.” (*SmithKline Beecham*)
- The overriding objective is public health protection and patient safety.

New EU Legislation

- Preceded by:
 - “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 material used, molecular characteristics and therapeutic mode of action ... 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”
- Legal basis for approval of biosimilar products found in Article 10(4) coupling with dossier requirements in Annex I
- Article 10(4) however does not define what “biosimilar” is.

Current European legal position for biosimilar products:

- An assessment of quality and bioequivalence is not sufficient in the case of biological medicinal products
- Additional data, in particular the toxicological and clinical profile “shall be provided”
- Technical requirements are described in guidelines
- The Notice to Applicants (administrative guidance) reflects this position.

Approach taken by the new law on approval of biosimilar products

- Reflective of
 - the European law and policy that biological products are **different** from chemically synthesised products with respect to the mode of manufacture and control
 - the **precautionary** approach taken by the policy makers and the legislature as regards regulation of biological medicines
 - policy taken by the Commission that **public confidence** in the regulatory system is critical. This is confirmed by the Commission in its published policy on European strategy for development life sciences industry.

Guidance development- Who's Who

- **European Commission**
 - administrative and procedural guidelines
 - Notice to Applicants Working Group
- **European Medicines Agency**
 - co-ordinating body
 - assisted by advisory committee, Committee for Human Medicinal Products (CHMP) (and the veterinary equivalent)
 - standing working parties to advise on quality, safety, efficacy, biotech, pharmacovigilance
 - ad hoc expert groups to advise specific inter-disciplinary issues such as similar biological medicinal products

Guidelines relating to biosimilarity

- Guidance is being developed to set out relevant parameters for assessment of ‘similarity’ to implement the new law.

- Guidelines relating to broad principles on “similarity”
 - **Overarching guideline** on similar biological medicinal products (road map)
 - **General guidelines** relating to assessment of quality, pre-clinical and clinical testing
 - **Product class specific** guidelines

Guidelines relating to comparability and similarity

- Product class specific guidelines
 - recombinant erythropoietins
 - granulocyte-colony stimulating factor
 - somatropin
 - recombinant human insulin
 - lower molecular weight heparins (in preparation)

“Biosimilarity”- underlying principles in extant guidelines

- Standard generic approach is not appropriate for approval of this class of follow-on products given the complexity of biological/biotech products and processes involved
- ‘Similarity’
 - data requirement to determine the risk/benefit balance based on assessment of the criteria for safety, quality and efficacy
 - the general legal test for product approval applies with equal force for biosimilar products under the new law as it merely re-validates the over-riding objective of public health protection

Similar biological products- key issues (1)

- How much pre-clinical and clinical data are required?
 - primarily to address relevant safety and clinical performance of the product
 - data requirements depend on the product type and the claimed therapeutic indications and available disease specific guidelines
- Safety arising from immunogenicity
 - prospective planned immunogenicity studies using carefully selected and validated procedures
 - taking account of the process-related substances that may assist in mounting immunogenic responses
 - standardisation of assay

Similar biological products- key issues (2)

- Is the applicant required to undertake post-approval market surveillance?
 - pharmacovigilance and risk management plan required in product specific manner
 - pre-approval data package insufficient to predict long term safety
 - how to collect verifiable product-specific safety data?

Conclusion

- European law requires pre-clinical and clinical data to support approval of biosimilar products
- Consistent with the over-arching objective of public health protection, risk management plan and post-approval monitoring are required for all biosimilar products