



Making Medicines Affordable

EUROPEAN GENERIC MEDICINES ASSOCIATION



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EGA's position on the comparability and regulation of biosimilars

Informal consultation of working group on regulatory evaluation of therapeutic biological medicines

WHO 19-20 April 2007, Geneva



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- Introduction
- Comparability concept
- Biosimilar development
- Recommendations for WHO guidelines
- Conclusion



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Introduction





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Biosimilars

- Protein products, which are sufficiently similar to an approved product to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and efficacy of the approved protein product
- Regulatory framework in the EU and the US
 - EU legislation in place - overarching guidelines and individual guidelines for selected products available
 - Approval pathway available for proteins licensed as drugs under the Food, Drug and Cosmetic Act, section 505
 - No approval pathway available for proteins licensed as biologics under the Public Health Service Act, section 351



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Comparability concept

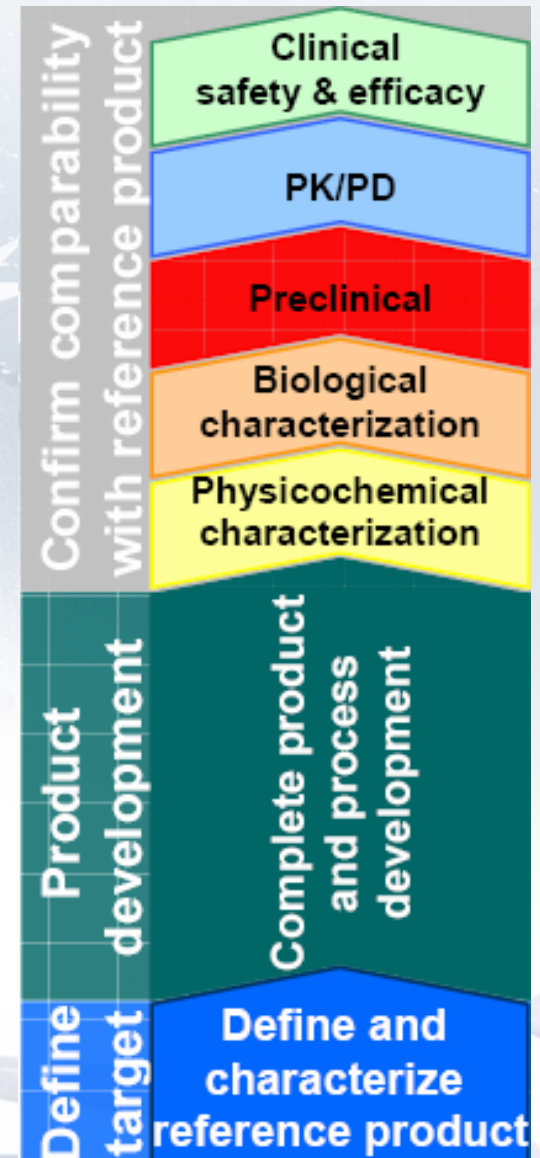




Biosimilar development

Differences and common grounds to originators

- The goals of drug development for both originator and biosimilar products are
 - Safety
 - Efficacy
 - Quality
 - Reproducibility
- Biosimilar products also require
 - Extensive comparability to an approved reference product
- The concepts of comparability and quality by design are important for all sponsors and enable process changes for improved processes, more efficient manufacture





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Value and Limitations of Comparator Studies with an Originator Product

- **Comparator studies with the originator product can not substitute for**
 - complete CMC development
 - full physicochemical characterization
 - full biological characterization
 - full release testing
 - basic non-clinical testing
 - clinical trials
- **Comparator studies may allow to**
 - limit preclinical testing
 - limit dose-ranging studies
 - limit population(s) in clinical phase III testing
 - extrapolate to broader indications based on sound scientific rationales
 - Development programs must be science- and data-driven and will be different from product to product.



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Biosimilar development

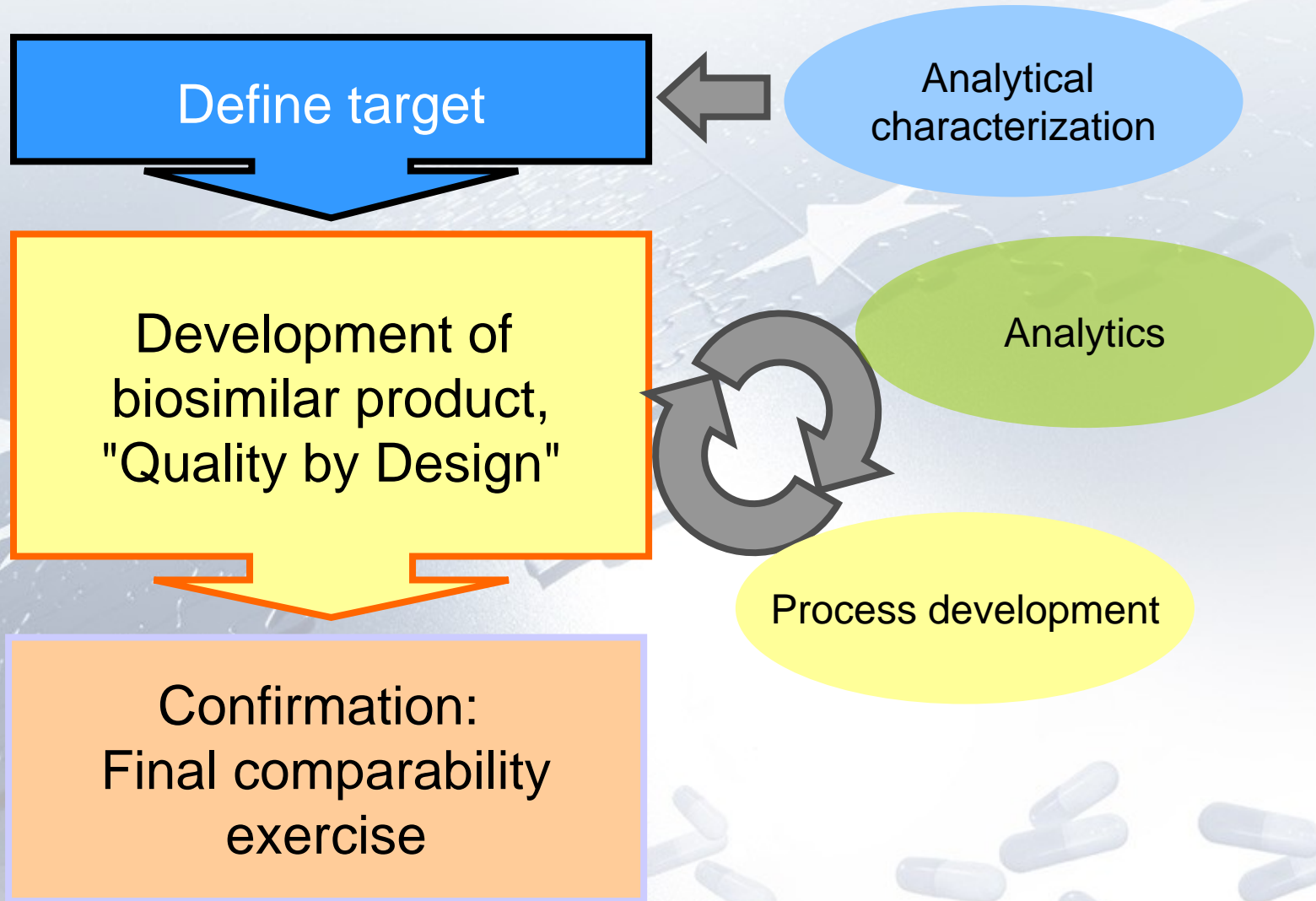




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The development of a biosimilar product is targeted to match the reference medicinal product through the application of state-of-the-art science and technology in head-to-head studies

Biosimilars: The reference product defines the target





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Quality By Design

- Manufacturing process is pro-actively designed to achieve a product equivalent to the reference product (quality, safety & efficacy)
 - Extensive characterization of reference product (multiple batches)
 - Broad set of orthogonal state-of-the-art analytical tools
 - Accounting for formulation, packaging materials, etc.
 - In vitro biological testing, in vivo PK/PD studies, clinical trial
- Continuous feedback between process development and high performance analytical techniques result in the required specific selection of
 - Cell line
 - Raw materials, media
 - Upstream and downstream process parameter
 - Control of critical variables
 - Formulation, primary packaging, delivery system



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Non-Glycosylated Proteins

- Current methods allow complete characterization of the chemical structure of non-glycosylated proteins

Parameter	Test	Resolved species
Primary structure incl. disulfide bridging	Orthogonal peptide mapping with UV and MS detection Mass spectrometry: <ul style="list-style-type: none">- MS/MS sequencing- LC-ESI-MS- MALDI-TOF-MS N-terminal Edman sequencing	Complete evaluation of primary sequence and post translational modifications possible
Higher order structure	Circular dichroism 1D-NMR Bioassay	Folding



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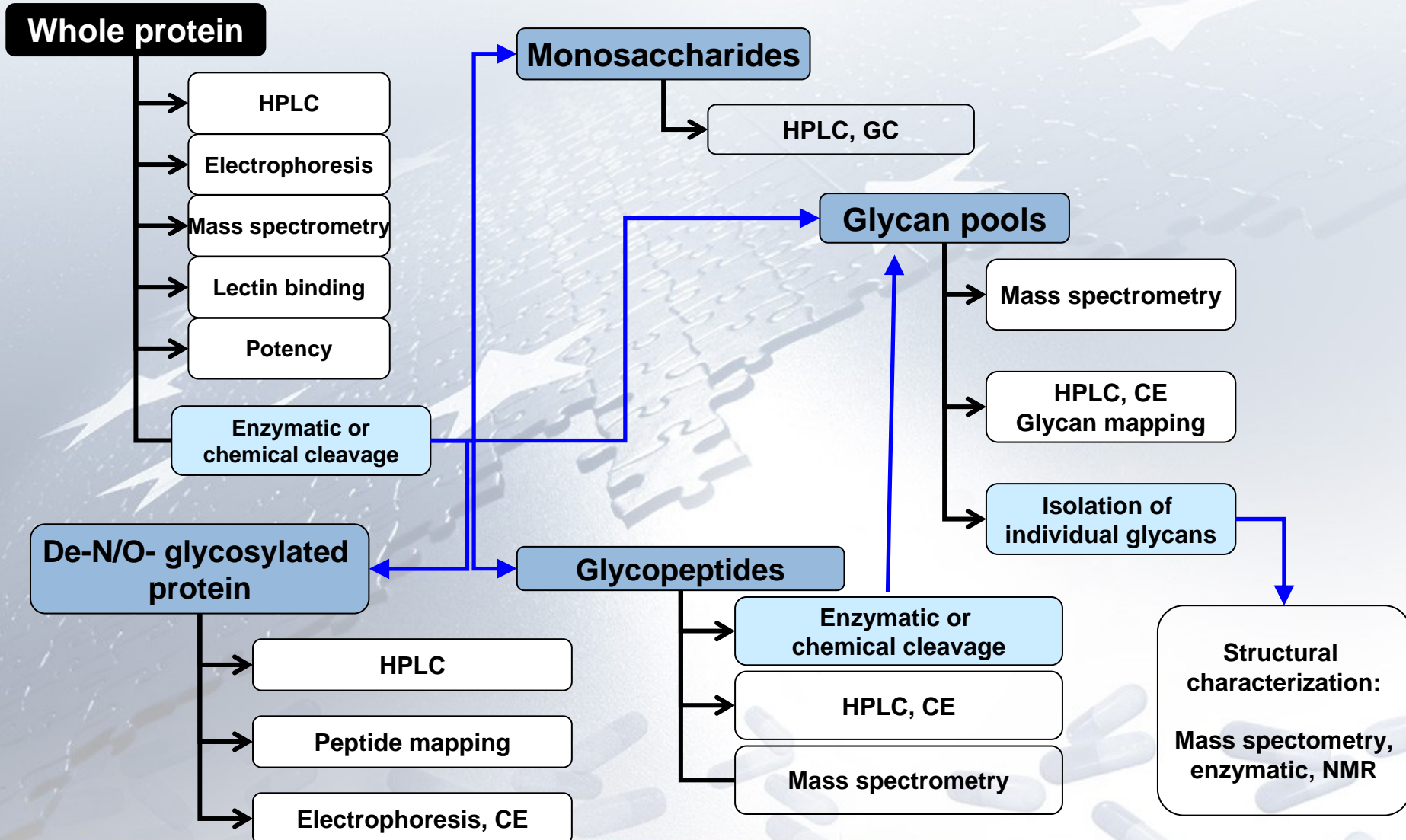
Glycosylated Proteins

- Therapeutic glycoproteins consist of mixtures of proteins with the identical amino acid sequence and different glycovariants
- Required parameters to define the glycosylation:
 - Quantitative composition of the individual glycan structures
 - Structural identification of the single glycans
 - Complete chemical structure
 - Site occupancy
- Glycoproteins can readily be characterized by current state-of-the-art analytical methods



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The analysis of complex glycoproteins requires a combination of multiple analytical methods



Advances in Analytical Technologies for Glycan Proteins (Examples)

Technique	Properties	Advances	Added value
HPLC, Capillary electrophoresis	Glycan separation	Stationary phases, instrumentation; miniaturization	Increased resolving power, improved precision; increased sensitivity, hyphenation to MS
ESI-MS MALDI-MS	Glycan structure	Ionization modes, mass analyzers MS/MS and MS ⁿ capabilities, Data evaluation	Increase of mass resolution and sensitivity Structural characterization of main structure and of modifications
Enzymatic sample preparation	Glycan structure	Enzymatic toolbox	Structural characterization

How Close is Close Enough? Demonstrating Comparability

- The criteria for the comparison of the biosimilar candidate and the reference product are based on
 - Understanding batch-to-batch variability of the reference medicinal product
 - Classification of the product variants into product-related substances or impurities (ICH Q6B)
 - Level of understanding the relevance of subtle differences on safety/efficacy (ICH Q5E)

- The manufacturing process for the biosimilar is systematically designed to meet the required comparability criteria



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Recommendation for WHO guidelines

Potential WHO guidelines on biosimilar products?

- Development of a concept paper and general recommendations regarding the minimum requirements regarding quality, non-clinical, clinical and post marketing surveillance
- ↳ Facilitate global standards for follow-on biologics
- Definition of general principles and requirements on the topics of interchangeability and substitution based on
 - Complexity of the product
 - Understanding of the mode of action
 - Clinical experience



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Conclusion



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Conclusions

- Current analytical technology enables physicochemical characterization which along with preclinical and clinical studies provide data to demonstrate comparability
- Manufacturing and characterization of biosimilars, like all other biologics, will comply with established high scientific and regulatory standards
- Current EU biosimilar guidelines in place
- WHO guidance would be welcome to facilitate global standards for the regulation of follow-on biologics
 - Development of a concept paper and general recommendations regarding the minimum requirements
 - Definition of general principles and requirements on the topics interchangeability and substitution based on comparability