Agencija za lekove i medicinska sredstva Srbije

Efficacy and Safety Assessment of Biosimilars – Key Aspects

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Vršac, Nov 14-15, 2014

What is a “Biosimilar”?

Background: directive 2001/83/EC, as amended

Article 10(2b): generic medicinal product

Article 10(4): biosimilar medicinal product

Law on Medicinal Products and Medical Devices - Serbia (2010):
Biologically similar medicinal product is a medicinal product of biological origin similar to a reference medicinal product of biological origin which does not meet the requirements for a generic medicinal product concerning the differences in raw materials as well as the differences in manufacturing processes between that biologically similar medicinal product and the reference medicinal product of a biological origin

Development of Biosimilars

Data exclusivity period of several biopharmaceuticals has expired or it is about to expire.

Healthcare systems are forced to reduce expences by using cheaper medicinal products.

Biopharmaceuticals are often indicated for the therapy of life-threatening and serious illnesses. Patients in need should have access to effective and affordable treatments. Biopharmaceuticals have changed the quality of life for many patients.

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Generic vs. Biosimilar Medicinal Product

Generic approach means demonstration of bioequivalence with a reference product by appropriate bioavailability studies and is applicable to most chemically-derived products.

Biological medicinal product is a medicinal product whose active substance is made by or derived form a living organism.

Biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA.

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Concept of Biosimilars

Overarching guideline by EMA, October 2014: Guideline on similar biological medicinal products (CHMP/437/04) defines concept and principles of biosimilar approach.

Standard generic approach (BE study) is not sufficient to demonstrate similarity of biotechnology-derived products due to their complexity. Applicant would be required to perform non-clinical and clinical comparability studies.

Demonstration of the similar nature of the two biological medicinal products is required (quality characteristics, biological activity, safety and efficacy).

Biosimilar approach is more likely to be successfully applied to products that are highly purified and can be thoroughly characterised.

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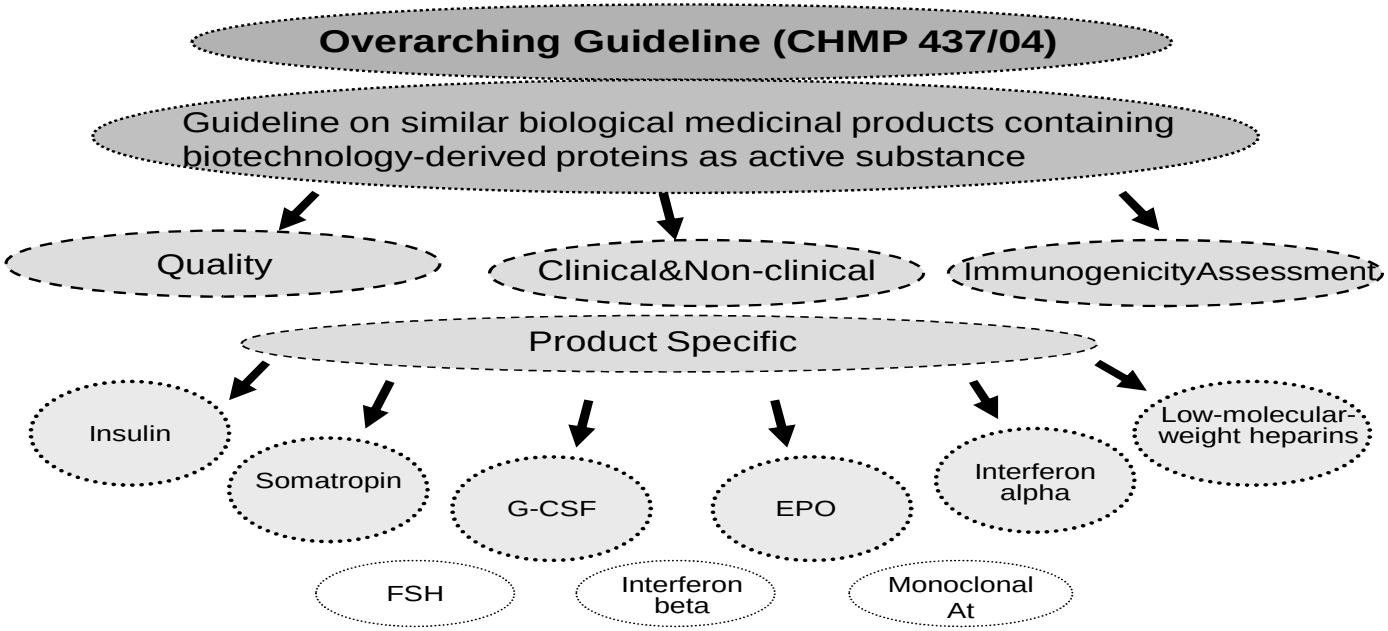
www.ema.europa.eu ⇒ human regulatory ⇒ scientific guidelines ⇒multidisciplinary ⇒ biosimilar



Biopharmaceuticals and Biosimilars: How Similar is Similar?

Active substance of a biosimilar must be similar, in molecular and biological terms, to the active substance of the reference product. Posology and route of administration of the biosimilar must be the same as those of the reference product. Any difference should not compromise safety.

“The process is the product”.

Stepwise approach is recommended throughout the development programme starting with a physicochemical and biological characterisation. Extent of the non-clinical and clinical studies depends on the level of evidence obtained in the previous steps.

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Reference Medicinal Product

Reference product must be authorised in the EU, on the basis of a complete dossier.

Single reference medicinal product should be used as the comparator throughout the comparability programme for quality, safety and efficacy studies.

Applicant should justify the choice of reference product.

It may be possible to compare the biosimilar in certain clinical and non-clinical studies with a non-EEA comparator which is approved by a regulatory authority with similar standards as EMA (e.g. ICH countries).

Biosimilar Means High-Quality Product

Biosimilar is manufactured and controlled according to its own development.

Requirements regard manufacturing processes, biosimilar comparability exercise for quality, analytical methods, physicochemical characterisation, biological activity, immnuochemical properties, purity and specifications. Performance and consistency of the manufacturing process of the biosimilar on its own should be covered.

It is not expected that all quality attributes of the biosimilar product will be identical to the reference product, but such differences should be justified with regard to their impact on safety and efficacy .

Non-clinical Issues of Biosimilarity

Gudeline on non-clinical and clinical issues is under revision.

In vitro studies: receptor-binding studies or cell-based assays, performed in order to establish comparability in reactivity.

In vivo studies should be performed in a species known to be relevant and designed to monitor pharmacodynamic effects, toxicity, toxicokinetics (determination of antibody titres, cross reactivity and neutralising capacity), specific safety concerns if relevant.

Studies should be comparative in nature and sufficiently long to allow detection of relevant differences in toxicity and immune responses.

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Clinical Issues of Biosimilarity

Aim of clinical data is to address slight differences shown at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product.

Product- and disease specific guidelines should be followed when appropriate.

It is recommended to generate the required quality, safety and efficacy data for the demonstration of biosimilarity using product manufactured with the commercial manufacturing process.

Clinical comparability exercise is a stepwise procedure that begins with PK and PD studies followed by clinical efficacy and safety trials or, in certain cases, confirmatory PK / PD studies.

PK and PD Studies

Comparative PK studies are an essential part of the biosimilar development programme. Criteria used in standard BE studies may be acceptable. Comparability limits for the main PK parameters should be defined prior to study and based on clinical judgment.

Similarity in terms of absorption and BA is of interest, but also differences in elimination characteristics between products.

PD effect of the test and the reference product should be compared in a population where the possible differences can best be observed. PD markers should be selected on the basis of clinical relevance.

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Clinical Studies for Demonstration of Biosimilarity

Efficacy trials: comparative clinical trials are necessary to demonstrate clinical comparability, with comparability margins prespecified and justified on clinical grounds.

Study population should be representative of approved indication and be sensitive for detecting potential differences between biosimilar and reference.

If biosimilarity has been demonstrated in one indication, extrapolation to other indications is possible with justification.

Clinical safety: comparative data should be collected pre-authorisation, but are usually insufficient to identify all differences. Possible concerns include infusion-related reactions and immunogenicity that may result from a manufacturing process.

Immunogenicity Assessment

Guideline is under revision. New EU legislation on biosimilars has strong emphasis on safety.

Clinical consequences are a loss of efficacy, serious general immune effects such as anaphylaxis, and a cross-reactivity with the endogenous counterpart.

Antibody response in humans cannot be predicted from animal studies. Only clinical trials can reveal immunogenicity.

Optimal antibody-testing strategy is required.

Immunogenicity issues are an essential part of Risk Management Plan (RMP).

Pharmacovigilance Aspects of Biosimilars

Pre-authorisation clinical data are not sufficient to identify rare AEs. Clinical safety of biosimilars must be monitored on an ongoing basis in the post-marketing setting.

Description of the PV system and RMP in accordance with current guidelines is mandatory in authorisation procedure.

RMP should include risk identification, risk monitoring, risk minimization and risk communication.

Important issues: traceability, interchangeability, substitution

Biosimilars in Europe (◊ approved in Serbia)

Centralised procedure is obligatory for biosimilars. Proof of approval through CP is needed when applying for MA of biosimilar in Serbia.

2006: **somatropin**

Omnitrope ◊, Valtropin - withdrawn for commercial reasons

2007: **erythropoietin**

Abseamed, Binocrit ◊, Epoetin alfa Hexal (epoetin alfa);
Silapo (◊ Eqralys), Retacrit (epoetin zeta);
Dynepo (epoetin delta) – withdrawn for commercial reasons
Biopoin, Eporatio (epoetin teta)

2008-2010: **filgrastim (G-CSF)**

Biograstim, Tevagrastim ◊, Ratiograstim, Zarzio ◊, Filgrastim Hexal, Nivestim ◊, Filgrastim Ratiopharm – withdrawn for commercial reasons

2013: **infliximab** (MAB)

Remsina, Inflectra – only in a few EU countries on the market

Interchangeability of Biosimilars?

Evaluation of biosimilar medicines by EMA do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Substitution policies are within responsibility of Member States.

Biosimilars are not biological generics. They are biological medicinal products SIMILAR to the one already approved in the therapy.

Decision to treat a patient with a reference or a biosimilar product should be taken following the opinion of a qualified healthcare proffesional.

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