



Current EMEA Position on Biosimilars Low Molecular Weight Heparins (LMWHs): European Perspective

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Generic pharmaceutical products are very common in the EU since they are well proven and less expensive. A generic product must be the same as the reference product with respect to: active substance, content, pharmaceutical formulation and bioequivalence. However special requirements are asked for similar biological/biotechnology-derived products. The generic approach is not appropriate and adequate. The physico-chemical characterisation of low molecular weight heparins (LMWHs) is limited due to the high complexity of the molecules and the limited knowledge of safety and efficacy for each fraction. Therefore bioequivalence studies alone are not sufficient to establish therapeutic equivalence between LMWHs.

The EMEA has established a working party (BMWP) to create guidelines on similar biological medicinal products with respect to LMWHs. The final version was published by CHMP Committee for Medicinal Products for Human Use, London, 19 March 2009 with the following title:

GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING LOW-MOLECULAR-WEIGHT-HEPARINS, EMEA/CHMP/BMWP/118264/2007.

The date for this to be effective is October 2009.

Definitions

What is a biological medicine?

A biological medicine is a medicine whose active substance is made or derived from a living organism.

What is a similar or biosimilar medicine?

A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised.

How is a biosimilar medicine evaluated?

As the biological medicine has been authorised for several years, there is available information, which does not need to be reproduced. The reference product has to be as safe and effective as the original product

EMEA requirements for non-clinical and clinical studies

The EMEA is requesting non-clinical and clinical studies (always in reference with the original product) for the development of biosimilar LMWHs in the following manner:

1. Pharmacodynamic studies

-in vitro studies (e.g. anti-Xa and anti-IIa activity) -in vivo studies (appropriate pharmacodynamic models; e.g. stasis induced thrombosis, Wessler model, laser induced thrombosis)

2. Toxicological studies

One repeat dose toxicity study in a relevant species (e.g the rat). Study duration should be at least 4 weeks and should be in accordance with the “Note for guidance on repeated dose toxicity (CPMP/SWP/11042/99)”. Safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing of a biosimilar biological medicinal product.

3. Clinical studies

- Pharmacokinetic /Pharmacodynamic studies One double blind randomized single dose two way crossover study in healthy volunteers using s.c. administration.
- Clinical Efficacy One adequately powered, randomised, double blind, parallel group clinical trial -prevention of venous or arterial thromboembolism -high VTE-risk (hip and knee surgery) -in the VTE-prevention setting, the clinically most relevant endpoint consists of proximal deep vein thrombosis (DVT), pulmonary embolism (PE) and VTE related death.

4. Clinical safety

- Care should be taken to compare the type, frequency and severity of adverse reactions (major bleeding, type of HIT type II, platelet count, thrombocytopenia, liver function, osteoporosis e.g.)

Extrapolation

Demonstration of comparable efficacy and safety in surgical patients at high risk for VTE as recommended may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant.

Reference Product

The chosen reference product must be a medicinal product authorized in the European Community on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83 EC. The pharmaceutical form, strength and route of administration of the biosimilar product should be the same as of the reference product.

The biosimilar approach

The success of a biosimilar medicinal development program depends largely on the ability to characterize the product and to demonstrate the similar nature of the concerned product in terms of quality, safety and efficacy.

References:

1 EMEA/CHMP/BMWP/118264/2007 Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins (London, 19 March 2009).

2 Schepper ,K.

Clinical Requirements for the Development of Biosimilar Products Part I : Pharm. Ind. 70, Nr. 7, 825-829 (2008) Part II: Pharm. Ind. 70, Nr. 8, 925-928 (2008)

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