



Regulatory Guidelines Update Generic Low Molecular Weight Heparins. Assumed Requirements of the European Medicinal Agency (EMA).

Dr. Wolfram Raake, Munich (Germany)

A biological medicine is a medicine whose active substance is made by or derived from a living organism. While a biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised.

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

Regarding similar biological medicinal products. The biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. Also there is a spectrum of molecular complexity among the various products. Due to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for those agents. Similar biological medicinal products are not generic medicinal products, since there are subtle differences from different manufacturers, which may not be fully apparent until greater experience is obtained. Therefore the new specific similar biological product has to be clearly identified before given to the patient. Also the active substance of a similar biological medicinal product must be similar in molecular and biological terms to the active substance of the reference product.

Introduction (background).

More specifically regarding heparins. Heparin is a sulphated glycosaminoglycan. It is sourced from domestic animals, mainly from porcine intestinal walls. LMWHs are prepared from unfractionated heparin by various depolymerisation processes. Due to the chemical heterogeneity, conventional pharmacokinetic studies cannot be performed. There are several licensed LMWHs that differ in their source material, manufacturing process, pharmacodynamic properties and therapeutic indications. In addition LMWHs offer certain advantages compared to the unfractionated heparin. They have longer dose intervals and more predictable pharmacokinetics and pharmacodynamics.

The committee for medicinal products for human use (CHMP) issued its guidelines on similar biological medicinal products containing LMWHs. They compiled their 1st draft in March 2007 and they placed as deadline for comments i.e. the end of consultation Oct 2008.

According to the draft EMEA guideline (London, 24 April 2008), the essential requirements for the generic LMWHs are:

1. Performance of non-clinical studies before initiating clinical development.
2. Performance of pharmacodynamic studies (in vivo), between the similar biological medicinal product and the reference LMWH. For example for anti-Xa and anti-IIa activity. Standardised assays should be used; in accordance with the European Pharmacopoeia.
3. Performance of in vivo studies:

- a. On an appropriate in vivo pharmacodynamic model (e.g. by evaluation of pharmacodynamic markers such as anti-Xa and anti-IIa activity and TFPI). If feasible, this evaluation can be performed as part of the described repeat dose toxicity study and/or

- b. On a suitable animal venous or arterial thrombosis model (e.g. stasis induced thrombosis (Wessler model), laser induced thrombosis, jugular vein clamping model).

4. Performance of 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/1042/99)”. Special emphasis should be laid on the determination of effects on blood coagulation / hemostasis and on potential development of osteoporosis. Data on local tolerance can be performed as part of the described repeat dose toxicity study.

Safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing of a similar biological medicinal product containing LMWH.

5. Performance of clinical Pharmacokinetic / Pharmacodynamic studies. Due to the heterogeneity of LMWHs conventional pharmacokinetic studies cannot be performed. Instead, the absorption and elimination characteristics of LMWHs should be compared by using pharmacodynamic tests as surrogate markers for PK/PD assessment such as anti-FXa and anti-FIIa and TFPI activity. These pharmacodynamic properties of the similar biological medicinal product and the reference product should be compared in a randomized, single dose two way crossover study in healthy volunteers using s.c. administration.

Regarding clinical efficacy a similar biological medicinal product (LMWH) should show

equivalent efficacy and safety to a reference product approved in the EU. One adequately powered, randomised, double blind, parallel group clinical trial should be performed on the prevention of venous or arterial thromboembolism (the most sensitive model should be selected). This should be on high VTE risk (patients with hip and knee surgery) or in the VTE-prevention setting, the clinically most relevant endpoint consists of proximal deep vein thrombosis (DVT) pulmonary embolism (PE) and VTE-related death. The number of proximal DVT's, PE and deaths should support the biosimilarity of the two products and the overall follow-up should be at least 60 days to detect late thrombotic events.

Regarding the clinical safety this should be assessed separately. Even if the efficacy is comparable, the safety profile may exhibit a difference. Care should be taken to compare the type, frequency and severity of adverse reactions and any major bleeding should be carefully assessed. Monitoring of platelet count should be performed to assess any type II heparin induced thrombocytopenia (HIT). Also liver function testing is recommended. 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.

Table 1 is a survey on the non-clinical and clinical requirements for similar biological medicinal products containing LMWHs

Non clinical studies		Clinical studies		
PD	Toxicology	PK / PD	Clinical efficacy	Clinical safety
- a number of in vitro tests (aXa, aIIa) - animal models for comparability studies	- at least 1 repeat dose toxicity study for at least 4 weeks	- double blind randomized, single dose two way crossover in healthy volunteers	- double blind randomized parallel group study (prevention of venous or arterial thromboembolism)	- data from efficacy trial (adverse events, HIT Type II, liver function, osteoporosis)

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 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 products in terms of quality, safety and efficacy.

Regarding the generic LMWHs development costs, in general it is expected that the generic medicinal products are cheaper than the originals. However, production and manufacturing of a biosimilar medicinal product are much more labor and cost intensive than the production of a common chemical generic compound. The EMEA demands preclinical and clinical studies in comparison with original product.

The EMEA [Committee for medicinal products for human use (CHMP)] has published the final guideline EMEA/CHMP/BMWP/118264/2007, London, 19 March 2009: **Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins**, date for coming into effect: October 2009.