

SASAT (South Asian Society on Atherosclerosis & Thrombosis) Proposal for Regulatory Guidelines for Generic Low-molecular Weight Heparins (LMWHs)

Evi Kalodiki, MD, PhD, and Wendy Leong, PharmD, MBA,
on behalf of the SASAT and Task Force on Generic LMWHs

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Introduction and Objectives

The first International Summit of South Asian Society on Atherosclerosis & Thrombosis (SASAT) for generic low-molecular weight heparins (LMWHs) was held in New Delhi, in October 2007. In this summit, a strong recommendation to develop newer guidelines for the validation of generic versions of LMWHs were proposed. As of 2008, several generic LMWHs have become available and widely prescribed in 17 countries. Wide compositional variations have been noted among the generic LMWHs. Some sub-standard products were also withdrawn due to compositional variations and nonadherence to specifications. The primary objectives of this meeting were to review the current recommendations from major organizations and regulatory bodies and to provide standards and guidelines for the safe approval of generic LMWHs.

Nonproprietary chemical drugs are called generic. Low-molecular weight heparins are biologic agents, therefore they cannot be true generic drugs. Regarding biological compounds, the United States Food and Drug Administration (USFDA) stated that they prefer the term "follow-on" while European Medicines Agency (EMA) prefers the term "biosimilar". Low-molecular weight heparins are classified as biosimilar in Europe and final guidelines for biosimilar LMWH development is expected in 2009.

The second International Summit of SASAT for LMWHs was held in New Delhi in October 2008. In addition to the position on the generic products this summit addressed the problem of heparin contamination that has emerged since April 2008.

This SASAT WHITE PAPER on Regulatory Guidelines for Generic LMWH has incorporated recommendations from 3 key sources:

1. EMA's DRAFT Guideline on Similar Biological Medicinal Products Containing LMWH (April 2008)¹⁻⁸;
2. ISTH's (International Society of Thrombosis and Haemostasis) Working Party on Biosimilar/Follow-on LMWHs of the Scientific Subcommittee on Anticoagulation (September 2008)⁹;
3. SASAT's first and second International Summits for Generic LMWHs (October 2007 and October 2008, respectively).¹⁰

European Medicines Agency, April 2008

Table 1 is A Summary of the EMA Non Clinical and Clinical Requirements for Similar Biological Medicinal Products Containing LMWHs.

International Society of Thrombosis and Haemostasis, September 2008

The International Society of Thrombosis and Haemostasis has provided recommendations from its Working Party to ensure the quality of "generic" LMWHs as compared to the originator LMWHs in

From the Loyola University Medical Center, Maywood, Illinois.

Address correspondence to: Jawed Fareed, 2160 S First Avenue, Maywood, IL 60153; e-mail: jfareed@lumc.edu.

Table 1

NonClinical Studies		Clinical Studies		
Pharmacodynamic	Toxicology	Pharmacokinetic, Pharmacodynamic	Clinical Efficacy	Clinical Safety
A number of in vitro tests (anti-Xa, anti-IIa activity); animal models for comparability studies	At least 1 repeat dose toxicity study for at least 4 weeks	Double-blind randomized, single-dose 2-way crossover in healthy volunteers	Double-blind randomized parallel group study (prevention of VTE or arterial thromboembolism), or treatment of VTE	Data from efficacy trial (adverse events, HIT type 2, liver function, osteoporosis)

NOTES: EMEA = European Medicines Agency; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular weight heparins; VTE = venous thromboembolism.

key areas such as physicochemical characteristics, in vitro anticoagulant activities, animal pharmacology, pharmacodynamic investigations in volunteers, pharmacodynamics in patients with renal dysfunction, and clinical trials to demonstrate safety of “generic” LMWHs. The recommendations are summarized below.

Physicochemical Characteristics

1. Origin of starting material (animal, country) to be described for the originator and biosimilar/follow-on LMWHs.
2. Biosimilar/follow-on LMWHs must be produced exactly as described in the monograph of the originator product.
3. All experiments must be performed in comparison to the originator product.
4. Biosimilar/follow-on LMWHs must be profiled by high-performance liquid chromatography (HPLC) and/or nuclear magnetic resonance (NMR) with typical units of heparin and the active pentasaccharide sequence.
5. Batch-to-batch analysis demonstrating no difference between biosimilar/follow-on and originator LMWHs.
6. Quantity of negatively charged sulfate groups and carboxyl groups must be described for the originator and the biosimilar/follow-on LMWHs.
7. Antithrombin affinity chromatography technique.
8. Heparin cofactor II activity.
9. Heparan sulfate, glycosaminoglycans, or other impurities should be minimal as detected by NMR and other techniques.

In Vitro Anticoagulant Activities

10. Biological activity of biosimilar LMWH to inhibit factor Xa, thrombin, and activated partial thromboplastin time (aPTT) in human pool

plasma must be in the same range as the originator LMWH.

11. Protamine neutralization or titration and platelet factor 4 interaction should not differ for the originator and biosimilar LMWH using multiple lots of each LMWH.

Animal Pharmacology

12. Acute and chronic toxicity for biosimilar and originator LMWH.
13. Acute and repeated dosing studies in 2 to 3 animal species using different dosages comparing the biosimilar and the originator product.
14. Biosimilar and originator LMWH effects in an animal model of venous and arterial thrombosis and in a bleeding model.

Pharmacodynamic Investigations in Volunteers

15. Phase I clinical trials in human volunteers using prophylactic dosages for VTE over 5 to 7 days and 1 therapeutic dose twice daily (bid) for 5 to 7 days. Effects on anti-Xa activity, antithrombin activity, aPTT, tissue factor pathway inhibitor, or HI tabs, anti-Xa to antithrombin ratio, and the interaction of platelet factor 4 have to be investigated.

Pharmacodynamics in Patients With Renal Dysfunction

16. Pharmacodynamic data in patients with renal impairment for VTE prophylaxis comparing the originator and biosimilar LMWH once daily subcutaneously for 5 to 7 days. Same parameters as a Phase I study to demonstrate lack of differences between biosimilar and originator LMWHs.

Table 2

Nonclinical Studies		Clinical Studies		
Pharmacodynamic	Toxicology	Pharmacokinetic, Pharmacodynamic	Clinical Efficacy	Clinical Safety
Physicochemical characteristics defined by ISTH clearly defined in vitro tests (anti-Xa, anti-IIa activity, and so on; EMEA, ISTH); animal models for comparability (EMEA and ISTH)	Minimum of 1 repeat dose toxicity study for at least 4 weeks (EMEA) in vitro anticoagulant activity (ISTH)	Double-blind randomized, single-dose 2-way crossover clinical trial in healthy volunteers (EMEA)	A minimum of 2 double-blind, randomized parallel group studies (1 study for VTE, such as DVT or PE, and 1 study for arterial thromboembolism, such as CVA prophylaxis in atrial fibrillation)	Data from efficacy trial (adverse events, HIT type 2, liver function, osteoporosis); same as clinical efficacy (ie, 2 clinical trials with 1 study for VTE and 1 study for arterial thromboembolism)

NOTES: CVA = cerebrovascular accident; DVT = deep vein thrombosis; EMEA = European Medicines Agency; HIT = heparin-induced thrombocytopenia; ISTH = International Society of Thrombosis and Haemostasis; LMWH = low-molecular weight heparins; PE = pulmonary embolism; SASAT = South Asian Society on Atherosclerosis & Thrombosis; VTE = venous thromboembolism.

Clinical Trial to Demonstrate Biosimilar LMWH Safety

17. Efficacy and safety of biosimilar LMWH to originator LMWH to be demonstrated in clinical trials.
18. Methodology of clinical trials would be prospective, randomized double blind versus originator to show
 - a. noninferiority for each of the indications claimed with efficacy as primary endpoint or
 - b. therapeutic equivalence in a sensitive indication such as treatment of venous thromboembolism (VTE) and/or acute coronary syndrome (ACS).
19. Compared to noninferiority, therapeutic equivalence would also detect a potential over efficacy, which could lead to a nonsignificant increasing risk of bleeding, and is therefore more sensitive to establish net clinical benefit. Most relevant indications are VTE prophylaxis for post-operative and medical patients with acute illness; deep vein thrombosis (DVT) and pulmonary embolism (PE) treatment; ACS acute care and percutaneous coronary intervention (PCI); extracorporeal circulation; and chronic hemodialysis.

South Asian Society on Atherosclerosis & Thrombosis Regulatory Guidelines for Generic LMWH, October 2008

In general, SASAT recognizes the following:

1. Biologic drugs, such as LMWH, are derived from living systems or organisms.

2. SASAT emphasizes that biologic antithrombotic drugs such as LMWH may not be duplicated as a generic biosimilar/follow-on using traditional generic approval processes.
3. SASAT recognizes that generic biologic LMWH may not simply be approved with pharmacokinetic bioavailability data and requires more complex analysis for safety and efficacy.
4. SASAT wishes to highlight the immunogenic profiling of LMWHs.
5. If a generic LMWH is accepted a post marketing surveillance should be done.

Table 2 is a Summary of the SASAT Proposal for Regulatory Guidelines/Recommendations for Generic LMWH.

Position Statement from SASAT on the Development of Generic Low Molecular Weight Heparins

- LMWHs represent a critical group of high risk of drugs which are more complex than most of the other drugs (hybrid of natural origin/chemical process).
- Unlike unfractionated heparins, LMWHs are made by different processes with significant product specifications and represent distinct drug entities.
- SASAT agrees that the newer guidelines including the use of updated technology to characterize these agents should be included to demonstrate their chemical equivalence to the innovator product.
- SASAT endorses the position of EMEA on the need for public input on the development of newer guidelines for the approval process of these drugs.

- SASAT recommends the development of International monographs on each of the individual LMWHs.
- SASAT has organized special forums to address the issues related to generic antithrombotic drugs since 2000. Some of these are organized in conjunction with the other professional groups such as the ICATH, IUA and NATF.
- SASAT has worked with other peer organizations to develop applicable guidelines for the development of generic antithrombotic drugs including LMWHs.
- Recognizing the introduction of generic LMWHs SASAT, has convened an International First Summit on this topic in October 2007, New Delhi, India. A second summit took place on October 12th this year in New Delhi, India.
- The recommendations from these meetings will be jointly published with the North American Thrombosis Forum in 2009. The recommendation from the meeting with the North American Thrombosis Forum will be incorporated in the final document.

Members of the Task Force

Andrew Nicolaidis, Cyprus
 Gundu Rao, India
 Renu Saxena, India
 Rakesh Wahi, USA
 Omer Iqbal, USA
 David Vanthel, USA
 Wolfram Raake, Germany
 Russel Hull, Canada
 Job Harenberg, Germany
 Jawed Fareed, USA

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3. Guideline on clinical investigation of medicinal products for prophylaxis of high intra and postoperative venous thromboembolic risk (CPMP/EWP/707/98 Rev. 1 - draft).
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6. Note for guidance on nonclinical locale tolerance testing of medicinal products (CPMP/SWP/2145/00).
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