

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

**INTRODUCTION & OBJECTIVES**

The 1<sup>st</sup> International Summit of SASAT for Generic Low Molecular Weight Heparins (LMWHs) was held in N. Delhi, in October 2007. In this summit a strong recommendation to develop newer guidelines for the development 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 Some substandard products were also withdrawn due to compositional variations and non-adherence to specifications. The primary objectives of this meeting were to review the current recommendations from major organizations and regulatory bodies, and to provide standards & guidelines for the safe approval of generic LMWHs.

Non-proprietary chemical drugs are called generic. LMWHs are biologic agents, therefore they are not true generic drugs. Regarding biological compounds, the US FDA stated that they prefer the term “follow-on” while EMEA prefers the term “biosimilar”. LMWHs are classified as biosimilar in Europe and a final guideline for biosimilar LMWH development is expected by early next year.

The 2<sup>nd</sup> International Summit of SASAT for LMWHs was held in N 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 provides proposed Regulatory Guidelines for Generic LMWH having incorporated recommendations from 3 key sources:

- (1) EMEA’s DRAFT Guideline on Similar Biological Medicinal Products Containing LMWH (April 2008);
- (2) ISTD’s Working Party on Biosimilar/follow-on LMWHs of the Scientific Subcommittee on Anticoagulation (Sept 2008);
- (3) SASAT’s 1<sup>st</sup> & 2<sup>nd</sup> International Summits for Generic LMWH (Oct 2007 & Oct 2008, respectively).

## EMA (European Medicines Agency) APRIL 2008

Table 1 is the 2008 Summary of the EMA Non-Clinical & Clinical Requirements for Similar Biological Medicinal Products Containing LMWHs.

Non-Clinical Studies		Clinical Studies		
Pharmacodynamic	Toxicology	Pharmacokinetic Pharmacodynamic	Clinical Efficacy	Clinical Safety
1. A number of in vitro tests (anti-Xa, anti-IIa activity) 2. Animal models for comparability studies	3. At least 1 repeat dose toxicity study for at least 4 weeks	1. Double-blind randomized, single-dose 2-way crossover in healthy volunteers	2. Double blind randomized parallel group study (prevention of Venous or Arterial Thromboembolism), or treatment of VTE	3. Data from efficacy trial (adverse events, HIT Type 2, liver function, osteoporosis)

## ISTH (International Society of Thrombosis & Haemostasis) SEPT 2008

ISTH has provided recommendations from its Working Party to ensure the quality of “generic” LMWHs as compared to the originator LMWHs in 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 HPLC and/or 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 & carboxyl groups must be described for the originator & 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 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 & chronic toxicity for biosimilar and originator LMWH.
13. Acute & repeated dosing studies for 2-3 animal species using different dosages comparing the biosimilar and the originator product.
14. Biosimilar and originator LMWH effects in an animal thrombosis model of the venous and arterial system and in a bleeding model.

#### *Pharmacodynamic Investigations in Volunteers*

15. Phase I clinical trials in human volunteers using prophylactic dosages for VTE over 5-7 days and 1 therapeutic dose BID for 5-7 days. Effects on anti-Xa activity, anti-thrombin activity, aPTT, tissue factor pathway inhibitor, or HI tabs, anti-Xa to anti-thrombin ratio, antithrombin activity, aPTT, tissue factor pathway inhibitor and the interaction of platelet factor IV 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 5-7 days. Same parameters as a Phase I study to demonstrate lack of differences between biosimilar and originator LMWHs.

#### *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 whether
  - a. A non-inferiority for each of the indications claimed with efficacy as primary endpoint.
  - b. Or a therapeutic equivalence in a sensitive indication as treatment of Venous Thromboembolism and/or Acute Coronary Syndrome with an opportunity to extrapolate to other indications in the same setting.
19. Compare to non-inferiority. Therapeutic equivalence could also detect a potential over efficacy which could lead to a non-significant 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; DVT and PE

treatment; ACS acute care and PCI; extracorporeal circulation; and chronic hemodialysis.

**SASAT (South Asian Society of Society on Atherosclerosis & Thrombosis)  
REGULATORY GUIDELINES FOR GENERIC LOW MOLECULAR WEIGHT HEPARIN  
(LMWH), OCT 2008**

In general, SASAT recognizes that:

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 & 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.

Non-Clinical Studies		Clinical Studies		
Pharmacodynamic	Toxicology	Pharmacokinetic Pharmacodynamic	Clinical Efficacy	Clinical Safety
<ol style="list-style-type: none"> <li>1. Physicochemical characteristics defined by ISTH</li> <li>2. Clearly defined in vitro tests (anti-Xa, anti-IIa activity, etc)(EMEA, ISTH)</li> <li>3. Animal models for comparability (EMEA &amp; ISTH)</li> </ol>	<ol style="list-style-type: none"> <li>4. Minimum of 1 repeat dose toxicity study for at least 4 weeks (EMEA)</li> <li>5. In vitro anticoagulant activity (ISTH)</li> </ol>	<ol style="list-style-type: none"> <li>1. Double-blind randomized, single-dose 2-way crossover clinical trial in healthy volunteers (EMEA)</li> </ol>	<ol style="list-style-type: none"> <li>2. A minimum of two double-blind, randomized parallel group studies (1 study for venous thromboembolism (VTE), such as DVT or PE; <u>and</u> 1 study for arterial thromboembolism, such as CVA prophylaxis in atrial fibrillation)</li> </ol>	<ol style="list-style-type: none"> <li>3. Data from efficacy trial (adverse events, HIT Type 2, liver function, osteoporosis); same as Clinical Efficacy (i.e. two clinical trials with 1 study for VTE <u>and</u> 1 study for arterial thromboembolism)</li> </ol>

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

- LMWHS represent a critical group/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 the newer guidelines including the 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 public input on the development of newer guidelines for the approval process of these drugs.
- SASAT recommend the development of International monographs on each of the individual LMWH

- SASAT has organized special forums to address the issues related to the generic antithrombotic drugs since 2000. Some of these are organized in conjunction with the other organizations 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 12<sup>th</sup> this year in New Delhi, India.
- SASAT's position on the issue related to generic LMWHs is summarized in this white paper which will be published in the form of an article after the review of the publication committee.

## **REFERENCES**

*From EMEA's Guideline on Similar Biological Medicinal Products Containing LMWH (April 2008)*

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2. Guideline on similar biological medicinal products (CHMP/437/04/draft).
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)
4. Concept paper on similar biological medicinal products containing low molecular weight heparins –(non) clinical issues.
5. Note for guidance on toxicokinetics: A Guidance for assessing systemic exposure in toxicological studies (CPMP/ICH/384/95).
6. Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00).
7. Guideline on risk management systems for medicinal products for human use (EMEA/CHMP 96286/2005).
8. Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for expedited Reporting (CPMP/ICH/377/95).

*From ISTH's Working Party on Biosimilar LMWH of the Scientific Subcommittee on Anticoagulation (Sept 2008)*

9. References to be added pp 11-15 of ISTH's 24SEP08 document

*From SASAT's 1<sup>st</sup> & 2<sup>nd</sup> International Summits for Generic LMWH (Oct 2007 & Oct 2008, respectively)*

10. Fareed J and Walenga JM. "Why differentiate low molecular weight heparins for venous thromboembolism?" Presented at NATF/SASAT Round Table 9/28/2008.
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Follow-on 'Generic' Biologic Compounds." Presented at NATF/SASAT Round Table  
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