

CONSENSUS STATEMENT

A Consensus Conference on complex biologics and low molecular weight heparins

Under the auspices of the North American Thrombosis Forum (NATF), the International Union of Angiology (IUA) and the South Asian Society of Atherosclerosis and Thrombosis (SASAT)

Co-chairmen: J. Fareed, V.F. Tapson

Moderators: D.A. Hoppensteadt, I. Sussman

Facilitator: C.A. Carter

Recording secretary: E. Kalodiki

Faculty and their organizations: I. Sussman (NATF); D.A. Hoppensteadt, E. Kalodiki (IUA); S. Parker (The American College of Chest Physicians-ACCP); *J. Harenberg, *R. Hull (The International Society on Thrombosis and Haemostasis-ISTH); J. Fareed, *G. Rao (SASAT); D.F. Lovinger (The Society of Hospital Medicine); L.D. Ried (The American Pharmacists Association-APhA); *A. Kakkar (European Medicinal Agency-EMA); L. Talarico, *F. Ofosu (Regulatory Perspective of the food and drugs administration-US FDA); H.I. Bussey, *J. Fanikos, J.B. Groce, N. Skinner (Professional Practice); M. Ahluwalia, C. A. Carter, O. Iqbal, C.M. Jackson, W.P. Jeske, M. George, E. Ramacciotti, V.F. Tapson, D. Van Thiel, R. Wahi, J. Walenga (Expert attendees).

Disclaimer

In recognition of the ongoing global issues and developments in the management of thrombosis and related disorders, scientific and professional organizations are continually striving to identify, discuss and develop consensus opinions. The issues related to the healthcare reform initiatives that are currently occurring in several countries with particular reference to the development of biosimilar agents, and more specific the heparin related agents are of major concern. Unlike the conventional generic drugs, the heparin related agents such as low molecular weight heparins (LMWH) represent a complex mixture of sulfated carbohydrates of natural origin rendering these as multi-component and polyfunctional agents difficult to reproduce.

NATF, IUA and SASAT convened a meeting at the headquarters of the ACCP on February 18 2010, with representatives of the above societies,

The individuals indicated by * participated by phone and voted at the end.

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organizations and professionals. However, ACCP deferred their vote until the issues were brought to their entire board.

The objective of the meeting was to generate a consensus of position and a Call to Action on the important issues of patient safety associated with the newer complex biologics. More specific to:

1. develop a consensus statement to communicate priorities for patient safety issues related to complex biologics and "generic" LMWH;
2. develop recommendations that foster collaboration and public health initiatives amongst organizations and interested parties;
3. review and discuss the current regulatory approval pathways for complex biologics and the status of healthcare reform initiatives relative to complex biologics;
4. review the positional statements and communications regarding biosimilars/follow-on complex biologics from various organizations and develop a common pathway to address identified safety issues;
5. develop a consensus on the guidelines for the approval process for biosimilar and complex biologic anticoagulants in the form of this white paper;

6) alert the healthcare community on potential safety issues related to the anticoagulant group of agents and the potential impact of biosimilar LMWH.

Terminology, definitions and concerns

Biosimilars is the term used in Europe while Follow-On-Biologics (FOB) is used by the US Food and Drug Administration (FDA). Based on their characteristics the following concerns arise:

1. biosimilar discussions are primarily targeted for proteins;
2. the recommendations for proteins/biosimilars are not applicable for complex carbohydrates;
3. LMWHs are polytherapeutic agents unlike other biosimilars;
4. they have higher molecular weight;
5. they are sensitive to the manufacturing process;
6. minor impurities/differences may result in serious health implications;
7. their approval pathways are different than for small molecule generics.

It was agreed that the term generic or biogeneric is not appropriate for these agents. Generic should be reserved for drugs that are manufactured chemically by a well known, defined and completely reproducible procedure.

Position statements

PDA perspective

Dr Lilia Talarico with her experience as a former officer gave the FDA regulatory perspective. A LMWH cannot be used interchangeably, unit for unit, with heparin, nor can an individual LMWH be used interchangeably with another. In the USA, innovator LMWH are classified as drugs under the New Drug Application (NDA) process. As a result, the development of a potential FOB compound would be as a “drug” under Section 505 of the Food and Cosmetic (FD & C) Act. Under this Section, there are two available pathways for a FOB entry, the 505(j) and 505(b)(2). The 505(j) pathway, which is commonly referred to as the abbreviated NDA (ANDA), requires the demonstration of bioequivalence through pharmacoki-

netic (PK) studies. The 505(b)(2) is intended to be a hybrid of the full NDA and the ANDA. This pathway requires additional data pertaining to safety and efficacy typically in the form of clinical studies.

The position of the various organizations as put forward by their representatives, appear below.

Position statement from the North American Thrombosis Forum (NATF)

1. the regulatory approval process to be developed by the FDA for biosimilars should be just as rigorous and comprehensive as it was for the reference pharmaceutical drug to ensure safety and efficacy and to define structure and function;
2. the FDA approval process must be flexible enough to accommodate scientific progress and clinical realities;
3. FDA must have the discretion to implement different regulatory guidelines for different types of biologics;
4. interchangeability should not be “preordained” for a biosimilar; it is a designation which must be earned not presumed;
5. the biological activity of FOB must use same unit of biologic activity as the reference product;
6. Potency or “activity units” of FOB and the reference must be equivalent so that they will exhibit comparable PK properties *in vivo*.

Position statement from the Scientific Committee of IUA

1. the administrative board of IUA has charged the scientific committee of IUA to discuss the issues related to the development of generic LMWHs;
2. special meetings were held during the IUA World Congress in Rome 2004, Lisbon 2006 and Athens 2008. Another meeting will take place during 24th IUA Congress in Buenos Aires in April 2010;
3. the IUA recognizes the difficult issues related to the development and approval of generic versions of LMWH;
4. the IUA has reviewed several reports on the introduction of substandard versions of biosimilar LMWH in South America and South East Asia;
5. the IUA identified the need to develop revised guidelines specific for the development of biosimilar equivalents of LMWH;

6. it also identified the need for peer review and additional input to further improve these recommendations to address the safety and efficacy issues;

7. therapeutic interchange among these products is not appropriate. The choice of LMWH should reflect the level of clinical evidence and the approval of the regulatory authorities for each indication".¹

Position statement from South Asian Society of Atherosclerosis and Thrombosis (SASAT)

1. LMWH represent a critical group of drugs which are more complex than most of the other drugs. They are hybrids of natural origin and chemical process;

2. unlike unfractionated heparins, LMWH are made by different processes, with significant product specifications and represent distinct entities;

3. SASAT agrees the newer guidelines should include the updated technology, to characterize these agents and demonstrate their chemical equivalence;

4. SASAT recommends the development of international monographs on each LMWH by the US, the European, Japanese and other pharmacopoeiae;

5. since 2000 SASAT has organized special sessions to address the issues related to the generic antithrombotic agents;

6. recognizing the introduction of generic LMWHs, SASAT, has convened three international summits in India: October 2007 and 2008 and November 2009 and published their conclusions.²

Other published statements

The International Society of Thrombosis and Hemostasis (ISTH) has stated that "based on the heterogeneity of LMWHs, biosimilar LMWHs have to demonstrate their non-inferiority compared with the originator products in preclinical and clinical investigations".^{3,4}

The American College of Chest Physicians (ACCP) position is that "because LMWHs are prepared by different methods of depolymerisation, they differ to some extent in pharmacokinetic properties and anticoagulant profiles, and are not clinically interchangeable".⁵⁻⁸

The Society of Hospital Medicine agreed that the term generic should not be used. Their primary concern is safety and efficacy and this should be supported by clinical trials.

The American Pharmacists Association (APhA) presented their position as published in 2007:⁹

1. APhA encourages the development of safe, effective and affordable therapeutically equivalent generic versions of biologic drug products, including clinical trials that assess safety;

2. APhA encourages the FDA to develop a scientifically-based process to approve therapeutically equivalent generic versions of biologic drug products;

3. APhA should actively support legislation to hasten the development of an efficient regulatory process to approve therapeutic equivalent generic versions of biologic drug products;

4. APhA should initiate educational programs for pharmacists and other health care professionals concerning the determination of therapeutic equivalence of generic versions of biologic drugs/products.

The European Medicinal Agency (EMA) position emphasizes the need for at least one clinical trial for a biosimilar LMWH.¹⁰

The American College of Cardiology (ACC) and the American Heart Association (AHA) have already published their position that "although LMWHs share many pharmacological similarities, they also vary in important respects, and it is important to consider each drug individually rather than as members of interchangeable compounds".¹¹

The collective professional practice position was that they agreed to the above statements. In addition they pointed out that the public needs to be educated and give their informed consent on choosing their therapeutic agents. Unlike chemical pharmaceuticals, substitution between biologics, including biosimilars, can have clinical consequences and create health concerns for patients.¹²

A position paper on biosimilars by the Austrian Society of Hematology and Oncology concludes that "a final assessment of the safety of biosimilars has to take into account indication, dosage, route of application and duration of treatment and can only be made after comprehensive post-marketing studies".¹³

Conclusions

Based on the above discussion and documentation research, the consensus of the participants was that FDA should go further than EMEA and request one trial for each indication of each biosimilar LMWH.

The final consensus statement of the conference was that there is a need to Call to Action, which should concentrate on implementing the following four points:

1. patient safety and product efficacy are the critical concerns and must not be compromised;
2. patient safety and product efficacy must be demonstrated in valid phase III clinical trials designed for specific indications;
3. approval guidelines must ensure that any biosimilar and its reference innovator product be interchangeable for each intended use based upon scientific and clinical data;
4. appropriate guidelines for biosimilars should be developed for each specific class of therapeutic agents (*e.g.*, proteins, complex sugars, nucleic acids).

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Corresponding author: E-mail: e.Kalodiki@imperial.ac.uk