



CONSENSUS MEETING: CALL TO ACTION ON ISSUES OF COMPLEX BIOLOGICS AND PATIENT SAFETY

- Patient safety and product efficacy are the critical concerns and must not be compromised.
- Patient safety and product efficacy must be demonstrated in valid Phase III clinical trials designed for specific indications.
- Approval guidelines must ensure that any biosimilar and its reference innovator product be interchangeable for each intended use based upon scientific and clinical data.
- Appropriate guidelines for biosimilars should be developed for each specific class of therapeutic agents (e.g., proteins, complex sugars, nucleic acids).

The rationale behind and intent of each of the criteria is explained below:

1. Patient safety and product efficacy are the critical concerns and must not be compromised.

Biologics are not like conventional pharmaceuticals; they are complex substances. Each biologic agent has different starting material and manufacturing processes, so that the final product always varies physically and chemically in ways that are important, albeit, subtle. Although a biologic may appear to be indistinguishable to the innovator product in laboratory testing, inherent variability could lead to important differences in potency, safety, or effectiveness when administered to a patient.

Patients with thrombotic disorders have immediate and critical medical needs, which if not met with established standard of care, put the patient at risk of death or compromised future health. Heparins and LMWHs are used in an urgent or emergent clinical setting that does not have much room for “error” compared with treatment with other therapeutic agents (e.g., insulin, growth hormone), used for their long-term effectiveness. Therefore, biosimilar heparins and follow-on LMWHs must not have compromised safety and efficacy compared with innovator products.



2. Patient safety and product efficacy must be demonstrated in valid Phase III clinical trials designed for specific indications.

Questions remain regarding why the approvability standard for biosimilars as complex as heparins or LMWHs would have lower safety standards in the U.S. than in Europe, where the European Medicines Agency (EMA) emphasizes that approval of biosimilars requires well designed and properly conducted clinical trials demonstrating safety or efficacy of biosimilars

(<http://natfonline.org/april%202009/EMEGuidelines.pdf>, <http://natfonline.org/docs/14%20Recommendations%20on%20LMWHs%20Biosimilars%20by%20ISTH%20July%202009.pdf>). Although NATF encourages abbreviated clinical trials, these must remain valid trials designed for specific indications.

- Clinical trials must not be abbreviated at the cost of patient safety.
- Potency and biological effects of the biosimilar and the approved product must be equivalent in order to allow interchangeability.
- Long-term safety must be established and rigorously monitored in patients treated with biosimilar heparin and heparin derivatives.

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.

Insofar as substitution of the biosimilar for the innovator product is considered, this should require chemical, biochemical, pharmacologic, and clinical data that ensure the products are, in fact, interchangeable. This means that physicians can fully rely on the performance and labeling of the innovator product to predict outcomes with the biosimilar. The criteria for determining interchangeability must be transparent and explicit.

4. Appropriate guidelines for biosimilars should be developed for each specific class of therapeutic agents (e.g., proteins, complex sugars, nucleic acids)

The legislative bills currently being considered by the U.S. Congress presume that all biologics are protein-based. Unlike the majority of biosimilars, which are of protein origin, LMWHs are carbohydrate-based large and complex molecules with a unique set of manufacturing challenges that differ from the more clearly characterized protein-based pharmaceuticals. Properties required to be indistinguishable for approval must be those relevant to the unique structures of each specific class of therapeutic agents.



CONSENSUS MEETING

The International Union of Angiology (IUA), South Asian Society of Atherosclerosis & Thrombosis (SASAT) and North American Thrombosis Forum (NATF) are collaborating to facilitate discussion and mobilize a Call to Action regarding the emerging issues of complex biologics and generic low-molecular-weight heparins relative to patient safety. The common concern of IUA, SASAT and NATF is that a clinically unqualified approval of generic low-molecular-weight heparins may potentially compromise patient safety and clinical practice. A Consensus Meeting was held on February 18, 2010 at the headquarters of the American College of Chest Physicians in Northbrook Illinois to update these issues with the input of a distinguished group of experts and organizations who have had a major interest in these areas.

The objective of this meeting was to mobilize a Call to Action regarding the issues complex biologics and patient safety. The goals of the meeting were to:

- Develop a consensus statement that communicates priorities for patient safety issues relative to complex biologics and generic low-molecular-weight heparins.
- Develop recommendations that foster collaboration in public health initiatives amongst organizations and interested parties.
- Discuss scientific issues pertaining to the complexities related to biosimilar drugs and differentiate these from conventional drugs.

Participating organizations included the American College of Chest Physicians, American Pharmacists Association, International Society on Thrombosis & Haemostasis, International Union of Angiology, North American Thrombosis Forum, Society of Hospital Medicine, and South Asian Society on Atherosclerosis & Thrombosis.

BACKGROUND

The issues related to contaminated heparin and the complexities of the structural and biologic actions of glycosaminoglycan related drugs have added a new dimension to our understanding of the overall clinical effects of these drugs with far reaching impact on the safety and efficacy and the need for proper guidelines in the standardization and optimization of their clinical use. The recently debated issues on biosimilar drugs which are primarily directed to proteins and their recombinant equivalent have further complicated this matter. Complex carbohydrates such as low-molecular-weight heparins represent depolymerized derivatives of natural heterogeneous polymers with several chemical modifications which can impact their biologic actions. Therefore the current guidelines for conventional generic product approval may not be applicable for their approval as generic biologics. This is a more complex issue than previously thought and



may lend itself to the introduction of substandard drugs. To avoid this, it is important to alert the regulatory bodies and healthcare providers.

In recognition of the ongoing global issues and developments in the management of thrombosis and related disorders, scientific and professional organizations such as the IUA, SASAT, and NATF have continually had discussions to identify and develop consensus opinions on this issue. The initiatives related to the healthcare reform with particular reference to the development of biosimilar drugs, in particular, the heparin related agents are of major focus. Unlike the conventional generic drugs, the heparin related drugs such as low-molecular-weight heparins represent a complex mixture of sulfated carbohydrates of natural origin rendering these as multi-component and polyfunctional drugs which may be difficult to be genericized.