



Thoughts on Approval Guidelines for Generic Heparins and Low Molecular Weight Heparins

*Written Communications to the FDA
from the North American Thrombosis Forum*

The North American Thrombosis Forum (NATF, www.NATFonline.org) is an independent non-profit organization comprised of scientists, clinicians, and patient advocates. NATF is dedicated to improving health care through clinical and basic research, clinical and patient education, and public health advocacy. Our focus is on Public Health issues with a primary aim to improve patient safety. Thromboembolic disease currently results in the disability or death of more than 600,000 U.S. citizens each year. As such, the disease imposes a heavy human burden and high economic cost to the health care system. Improving prevention, diagnosis, and treatment of thrombotic disorders is a major goal of NATF. Ensuring sustained access to reliable, safe, and effective medicines to patients is of critical importance.

NATF is keenly aware of and in agreement with the effort to provide lower cost medicines, including biologics, for our nation's patients. However, the complexity of biological products such as heparins and low molecular weight heparins (LMWHs) and the potential for multiple unrecognized effects of putative biosimilars require that new standards and criteria be put in place to assure that such biosimilars are safe and effective. **Our concerns derive solely from a patient safety standpoint and do not involve issues regarding exclusivity or drug costs.**

NATF's efforts on follow-on biologics or biosimilars were initiated in the Spring of 2009, when a critical working group was convened to discuss the proposed legislation on this issue. The group discussed concerns that both the House and Senate Bills focused on the length of exclusivity, with little or no emphasis on potential safety issues that could develop if follow-on biologics are approved without stringent clinical testing. The meeting led to the development of a strategy for NATF to communicate and educate members of Congress of our concerns for patient safety regarding the approval and marketing of follow-on biologics.

NATF devoted much of the Spring and Summer of 2009 to implementing this strategy. The success of our efforts is demonstrated by the growing interest and concern over the patient safety issues associated with potential biosimilars, as evidenced by the responses and interactions from our Congressional meetings. While we are encouraged by the responses to our efforts, we note that a number of issues remain unresolved. These issues include:

- Comparability of product to innovator product vs. "reference" material;
- Clinical testing in high risk patients;
- Post-approval monitoring;
- Alignment or harmonization with the European Medicines Agency (EMA) guidelines.

Biologics are not like conventional pharmaceuticals; they are more complex substances. Each biologic drug has different starting materials and manufacturing processes, so that the final product always varies physically and chemically in subtle but important ways. Additionally, a biologic produced by and purified from a different culture system and animal source, including undetectable viral and prion contaminants. Although a biologic might appear similar to the innovator product in laboratory tests, inherent variability could lead to important differences in potency, safety, or effectiveness when administered to a patient.



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There is potential for unanticipated adverse events or immune responses to a biologic drug. In one well-known example of an antihemophilic factor preparation, many patients developed antibodies against this product and suffered serious adverse effects. Minor changes in the manufacturing process were responsible for an immune response not seen with the former product. Also, there is the possibility of impurities or contaminants that are not readily identified or quantified. Intentional adulteration of heparin, undetected with routine tests to assess drug potency, occurred only a year ago and claimed the lives of several hundred victims before it could be identified.

The legislative bills currently being considered by the US Congress assume that all biologics are protein-based. In this context, the recently issued guidelines of the European Medicine Agency (EMA) provide an excellent outline of the steps necessary for safe approval of LMWH generic products (*Document EMA/CHMP/BMWP/118264/2007 "Guideline on Non-Clinical Clinical and Clinical Development of Similar Biological Medicinal Products Containing Low-Molecular-Weight-Heparins"*). Unlike the majority of generic biologics, 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, a distinction clearly noted by EMA. Alignment or harmonization with the EMA guidelines by the FDA will help focus on the unique and inherent complexities of carbohydrate-based agents.

The EMA document emphasizes the critical issue that approval of follow-on biologics requires well-designed and properly conducted clinical trials demonstrating safety and efficacy of biosimilars. While we encourage abbreviated trials, they should never be at the cost of patient safety. Also, potency and biological effects of the biosimilar and approved product must be equivalent. Transparent criteria need to be set to demonstrate whether biosimilars can be substituted for approved products (interchangeability) and if biosimilars themselves must be excluded as reference products. Lastly, long-term safety must be established and rigorously monitored in patients treated with biosimilars.

As an advocacy group of scientists, clinicians, and patients working to combat thrombosis or blood clotting disorders, we are intent on having healthcare reform that makes safety a top priority for patients who will take these follow-on biologics. Therefore, we question why approvability of biosimilars to molecules as complex as heparins or LMWHs would have lower safety standards in the U.S. than it currently has in Europe. Clearly, the availability of cheaper biosimilars will be a great benefit to our patients, but only if the patients are not risking their lives by taking these drugs. Patients with clotting disorders have immediate and critical medical needs which if not met with established standard of care (clinical and pharmaceutical care) put the patient at risk of death or compromised future health. Heparins and LMWHs are pharmaceuticals used in a clinical setting that does not have as much room for 'error' as treatment with statins for example which are used for their long-term effects. The lack of sufficient protection for patient safety in the current biosimilar legislation affects all biologics, including cancer therapies and hormonal treatments.



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Biologics are not like conventional drugs and, therefore, it is essential that we assure adequacy of the approval process for follow-on biologics to ensure these medicines are not just less expensive, but equally safe and effective as the original molecules. Although a biologic might appear similar to the innovator product in laboratory tests, inherent variability could lead to important differences in potency, safety, and/or effectiveness when clinically used.

NATF believes it is essential that the approval process for biosimilars or follow-on biologics ensures that these medications are not just less expensive, but equally safe and effective.

We look forward to discussing these issues with you or members of your staff. We will follow up to schedule a meeting date with you and Ilene Sussman, PhD, Executive Director of NATF. Please do not hesitate to contact Dr. Sussman (617-525-8326 or isussman@natfonline.org) or one of us with any questions on this important matter.