



*The online version of this article, along with access to discussion threads on NATF's eForum, is available at: [www.natfonline.org/follow\\_on\\_biologics.php](http://www.natfonline.org/follow_on_biologics.php) (July, 2010)*

The Food and Drug Administration (FDA) announced the approval of the first generic low-molecular-weight heparin (enoxaparin) on July 23, 2010. Information on this announcement is available at the FDA's website:

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm>.

In general terms, the benefits of generic medications have been appreciated by patients and society for over 25 years since the passage of the Hatch-Waxman Bill that created the abbreviated new drug application or ANDA pathway. These benefits are the result of providing known safe and effective medications based upon a brand product's clinical data and track record at substantially lower prices.

The first application for a generic LMWH was submitted to the FDA in 2005. Over the last several years multiple pharmaceutical companies have submitted their versions of LMWH to the FDA for review and potential approval using the ANDA pathway. The decision for the approval of a generic enoxaparin was unexpected by many healthcare professionals and organizations because of the lack of even a single controlled clinical trial.

The significant time since filing of the 'generic' LMWH to approval is evidence that FDA required substantial time to sort through many of the molecular complexities of the active components of LMWHs; to evaluate the quality control, consistency, and reproducibility of the manufacturing processes utilized to produce the active drug from biologic origin; to consider how to quantitate the pharmacologic properties of the generic drug in the absence of standardized assays except for *in vitro* inhibition of factor Xa, which does not always equate with drug effectiveness or safety; to assess the immunogenic potential of the generic applicant to the brand name and to determine if the cause(s) of over 250 patient deaths, associated with contaminated unfractionated heparin which is used to manufacture LMWH, would jeopardize patient safety when the generic drug is administered.

In the midst of these hurdles, many perspectives and concerns have been raised and tensions escalated, by the competing (and often self-serving) forces in the health care debate. Pharmaceutical companies are attempting to protect their patent positions and profit margins. Politicians seek less expensive health care while attempting to maintain fairness in the business environment. Healthcare professionals, including physicians,

pharmacists and nurses, agree that health care costs should be reduced but will not sacrifice patient safety. Reimbursement organizations see an opportunity to lower the cost of care in one fell swoop with generic medications, which can be used interchangeably and substitute for brand name established reference drugs in their formularies.

Not-for-profit professional advocacy organizations, such as the North American Thrombosis Forum (NATF), have attempted to inform and educate their physician, scientist, and patient constituencies in the health care debate about the implications of introducing generic complex biologics into the marketplace. Over the past 2 years NATF has included presentations at its Summit and Forum meetings to highlight the intricate nature of LMWH production, their anticoagulant actions, and the wide variety of patient conditions surrounding their use in the treatment and prevention of arterial and venous thrombosis. NATF believes these activities have been crucial since the voice of patient safety appears to have been superseded and squelched by the business, political, and economic exigencies in the follow-on biologics discussions.

The FDA has reviewed complex drugs in the past, approving generic agents like phenytoin, warfarin, and levothyroxine. Despite concerns, doubts, and protests, many of which still linger today, most of these generic agents have been administered routinely, safely, and effectively for patient care. Complex biologics, like LMWHs, represent a different challenge to the FDA because there are far more aspects of the clinical and scientific puzzles to consider. Unlike other generic drugs, which can be synthesized or biochemically copied, the most important components in a biological such as enoxaparin are not understood or characterized and cannot be copied identically in the laboratory. The only way to establish parity of structure and equivalence of function and safety for the biologics is through carefully conducted clinical trials. This piece of information was not available to the FDA when it considered the suitability of the generic enoxaparin for approval. In the non-biologic medication sphere, the components to be considered for efficacy and safety standards were established and validated within the FDA. That is not the case thus far for generic LMWH. With the enormous amounts of scientific and clinical information associated with the reference commercial name brand LMWH and the generic form of enoxaparin, the FDA chose to evaluate enoxaparin "sameness" based on the source material, the manufacturing process, immunogenicity, the end product chemistry, and the generic agent's anticoagulant activity in the test tube and in a living organism.

Importantly, by establishing these criteria for LMWHs, the FDA has defined the pathway for approval of the next wave of generic biologic products. These agents will likely have much broader implications and indications, impacting those patients with diabetes, cardiovascular disease, and cancer. While many experts advocated comparing the generic agent to the brand name product in one or more clinical trials to ensure safety and efficacy, the FDA did not feel these additional steps were necessary. It is concerning to note this decision is not in harmony with the approval criteria adopted by the EMEA for biosimilar LMWH.

Clinicians can now prescribe this generic enoxaparin and expect the exact same levels of anticoagulation (and hopefully antithrombotic) outcomes, as were reported with the brand name products, which completed rigorous, multiple, adequately powered and clinically controlled trials to gain approval from the FDA.

We urge physicians and patients who find responses varying from what was expected to report them using the FDA's Medwatch program available at: <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>. Since many states have mandatory generic substitution laws where a pharmacist must replace the prescribed brand name medication with a generic equivalent, clinicians must be increasingly attentive for unexpected or untoward effects.

In this early period, it is logical for those familiar with brand name LMWH to question this FDA judgment, to identify therapeutic failures, and episodes of adverse events. These experiences only become valuable when they are collected in a systematic fashion and ultimately lead to drugs being withdrawn from the market.

In summary, the FDA has approved a generic version of LMWH without any clinical validation. Because of the complexity of LMWHs it is important for clinicians and patients to be vigilant for unexpected or variations in response to any generic medications and report to the FDA as soon as possible. With this landmark decision, patients can expect the introduction of more generic biologic medications.