

Follow-on Biologic Agents: Immunogenicity, Efficacy, and Safety
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On July 23, 2010, the FDA in the United States granted Sandoz approval of the first generic version of Lovenox (enoxaparin sodium injection, from sanofi-aventis). The FDA letter stated that the Office of Generic Drugs determined that the generic enoxaparin “meets the standards for approval (including those for active ingredient sameness and bioequivalence) and, therefore, is therapeutically equivalent to the reference drug (Lovenox).” The FDA’s (CDER) decision was rendered without any human clinical safety or efficacy data and thus has established a potentially tenuous precedence for the approval of follow-on biologics in the United States, employing a regulatory pathway which may be counterintuitive to patient safety and which is not in harmony with the European EMEA requirement for limited clinical trials prior to approval of follow-on biologics. The generic enoxaparin has been granted implicit interchangeability with Lovenox for use in a variety of clinical indications without clinical assessment. These include: the prevention of VTE in hip or knee replacement surgery; VTE prophylaxis in abdominopelvic surgery or acutely ill medical patients with severely restricted mobility and high risk for VTE; for warfarin bridging for inpatient treatment of acute VTE or outpatient treatment of acute DVT without PE; for the prevention of the ischemic complications of unstable angina and non-Q-wave myocardial infarction (in combination with aspirin); and for the treatment of acute ST-segment elevation MI managed medically or with subsequent percutaneous coronary intervention.

In a September, 2008, response to a Congressional inquiry the FDA’s Chief Scientist indicated that the process to assure “sufficient similarity between the follow-on biologic and the reference product” would include “optimum information regarding safety and efficacy considerations involving follow-on products.” The letter goes on to state in regard to interchangeability of the reference product and the follow-on biologic that “without clinical evidence that patients can be switched back and forth between two products without any detrimental effect, such changes should not be made unless directed by a physician.” This presentation will use the recent generic enoxaparin approval by the FDA as a case study to explore the immunogenicity, safety, and efficacy issues pertinent to the follow-on biologics.

Follow-on biologics are medications, which possess similar properties to existing biologic products; however, these are very complex proteins, which are not completely identical to each other, in contrast to generic drugs. Only a small portion of the various low molecular weight heparin molecules has been characterized and specifically have similar anticoagulant properties in vitro. It is clear that the anticoagulant component of heparin molecule is not responsible for inducing the immunogenicity complication labeled heparin induced thrombocytopenia (HIT) with (HITT) or without thrombosis. The 70% portion of the LMWH and unfractionated heparin molecule which has not yet been biochemically characterized is thought to be critical in the immunogenicity process. The only reliable approach to assess and compare the immunogenic potential of the generic enoxaparin to the brand name is to observe patient response in clinical trials. Furthermore, it is not clear whether the FDA will be monitoring source components of generic enoxaparin as closely as it does for the reference brand. This is

critical since we have recently observed over 250 patient deaths and an increased incidence of HIT, associated with contaminated unfractionated heparin source materials, which are used to manufacture LMWHs. The absence of clinical data for the generic enoxaparin, whether short term or longitudinal over time with post-marketing surveillance, increases the theoretical risks for immunogenicity and safety. Furthermore, the absence of any head to head clinical trials or even clinical trial use in any one specific indication creates doubt as to product interchangeability and bioequivalence since Lovenox has been used so ubiquitously for both arterial and venous thromboembolic states with different dosing regimens. In order to prove generic versus reference enoxaparin equivalence, Momenta and Sandoz developed a proprietary technology platform consisting of patented enzymes to compare proteolyzed source porcine mucosal derived unfractionated heparins and then also developed mass spectroscopic, nuclear magnetic resonance, and capillary electrophoretic techniques to compare and analyze the components of the reference product, its chemical structure and its carbohydrate moiety composition to their generic version. No in vivo comparisons were pursued.

In contrast, CBER is also developing its regulatory pathways for generic follow-on biologics. CBER has a different experience from CDER since it deals with many rare disease states and has observed unanticipated immunogenicity complications induced by biologic products which have ostensibly identical physicochemical characteristics in vitro and even in animal models. Only after clinical trials were conducted were alloantibodies observed for such products, including plasma-derived factor VIII concentrates and plasma derived and recombinant human thrombins. In addition, a recombinant erythropoietin product, which appeared bioequivalent to other reference recombinant products, has been withdrawn from the European market because of associated pure red cell aplasia. Thus, clinical trials, both up front and with longitudinal surveillance post-marketing, are critical to maintaining safety. Development of a clinical registry to monitor generic enoxaparin safety and to track physician prescribing trends would be an effective tool to amplify the voluntary FDA MedWatch mechanism for observing “danger signals” of approved drugs. This approach could also be extrapolated to other future generic and reference anticoagulant medications, which may be fast tracked through the FDA approval process.