

United States FDA Approval Of Generic Lovenox®: A First Glimpse At Follow-On Biologic Sameness

On March 23, 2010, the landmark United States Patient Protection and Affordable Care Act (PPACA) was signed into law authorizing the Food and Drug Administration (FDA) to approve and categorize “copycat” versions of protein-based drugs as either “biosimilar” or “interchangeable.” An interchangeable follow-on biologic is largely analogous to the “sameness” status of an FDA approved Abbreviated New Drug Application (ANDA) for a small molecule drug. In this sense, both FDA approved “interchangeable biologics and ANDA approved small molecule drugs (i.e., generic drugs) may be freely substituted for their brand name counterparts without intervention by a health care provider. In fact, health insurance companies nearly always require lower cost generic substitution. Follow-on biologics alternatively approved as “biosimilar” are largely treated as new drugs and may only be substituted with the explicit approval of a medical professional.

While not a true biologic, Lovenox® (generic name *enoxaparin sodium*) demonstrates a high degree of structural complexity and manufacturing unpredictability commonly associated with protein-based drugs. Enoxaparin is essentially a lower molecular weight version of the polysaccharide anticoagulant known as heparin. Similar to the repeating amino acid subunits found in proteins, polysaccharides are composed of repeating sugar (i.e., carbohydrate) subunits.¹ Viewed broadly, enoxaparin is a “tweener drug” when it comes to molecular diversity and provides a first glimpse at future FDA approval of more complex follow-on biologics.

While the FDA criteria articulating the scientific/analytic boundaries between interchangeable and biosimilar follow-on biologics are largely unwritten, such criteria will likely be tailored to an individual protein drug or drug class. The PPACA allows (but does not require) the FDA to issue guidelines for the review of a particular biologic product or class of products, including appropriate tests that must be met to demonstrate equivalence. This is precisely what the FDA did when it recently granted Sandoz and Momenta Pharmaceuticals approval for the first ANDA for enoxaparin sodium.²

Lovenox® sales in 2009 were approximately \$2.5 billion in the United States, and \$4.0 billion worldwide.³ Seeking exclusive entry into this lucrative market prior to Sanofi-Aventis's patent expiration, generic rivals Teva and Amphastar each filed ANDAs with Paragraph IV Certification for enoxaparin over two years before Sandoz.⁴ While the relevant Sanofi patents have been subsequently affirmed as unenforceable⁵, both applications are still pending at the FDA.⁶ Citing safety concerns, the FDA initially rejected Sandoz's first ANDA for enoxaparin in 2007 for reasons linked to immunogenicity.

¹ While protein drugs are routinely comprised of up to twenty repeating amino acid subunits, heparin is comprised of up to three repeating sugar subunits.

² On August 26, 2005, Sandoz Inc. and Momenta Pharmaceuticals, Inc. jointly filed ANDA-77857 pursuant to §505(j) of the Federal Food Drug, and Cosmetic Act (FDCA) for generic enoxaparin. The FDA subsequently approved the ANDA on July 23, 2010. This article will consider Sandoz as the primary ANDA sponsor.

³ Sanofi-Aventis 2009 Annual Review.

⁴ Amphastar submitted their ANDA in March of 2003 with Teva filing afterwards.

⁵ See *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 525 F.3d. 1334 (Fed. Cir. 2008). The 180-day market exclusivity period expired on March 31, 2009.

⁶ As of August 31, 2010, the Teva and Amphastar ANDA applications have still not been approved.

Consequently, in August of 2010, Amphastar sought disclosure of confidential information about the source of contaminated heparin related to a recently filed civil lawsuit against U.S. suppliers of Chinese bulk heparin.^{7, 8} In light of the structural similarities with bona fide biologics, the fairly complex proprietary manufacturing protocols of enoxaparin, and the ongoing concerns with safety, the recent Sandoz ANDA approval provides guidance on how the FDA will regulate, and parties will ultimately litigate, more complex follow-on biologic applications.

Complex Non-Protein Drugs Like Lovenox[®] Are Surrogates For Follow-On Biologics

Since 1984, the ANDA review process has been focused on allowing generic versions of small molecule drugs that are the “same as” the active ingredient in the reference listed drug. The term “same as” means identical in “active ingredient(s), dosage form, strength, route of administration, and conditions of use.”⁹ Determining identical active ingredient(s) in a small molecule drug product is a fairly straightforward process using current chemical analytical methods.

However, precise chemical analysis of most protein-based drugs and some of the more complex non-protein drugs is not so simple. Due to their inherent unpredictability, high complexity, large size and myriad chemical modifications, biologics are often defined by their proprietary manufacturing protocols (e.g., chemistry, manufacturing and controls (CMC) data) rather than a easily defined end product. Enoxaparin is a fairly complex non-protein therapeutic comprised of low molecular weight heparin fragments isolated from a biological source (porcine intestinal mucosa). These fragments are isolated using proprietary manufacturing methods involving chemical and enzymatic disruption of high molecular weight bulk heparin. Despite lacking the highest complexities of most protein biologics, enoxaparin does have considerably more structural intricacy and variability than traditional small molecule drugs. For these reason, enoxaparin will serve as a surrogate for future FDA approval of follow-on biologics.

Manufacturing Methods Can Differ, But Source Material Should Be The Same

On July 23, 2010, the same day that Sandoz received FDA approval of their enoxaparin ANDA (and Teva and Amphastar did not), the FDA simultaneously published a comprehensive 45-page response to a 2003 Citizen’s Petition filed on behalf of Lovenox[®] manufacturer Sanofi-Aventis. The crux of the Sanofi Petition is that since it is not possible to completely chemically define Lovenox[®], it is impossible for the FDA to determine if generic enoxaparin is the “same as” the branded drug unless the generic is manufactured by the same or an “equivalent” process or, alternatively, successfully completes clinical trials. The FDA strongly disagreed. While at times contradictory, the FDA’s message in their written response is clear¹⁰ – for complex reference drugs that cannot be completely characterized by current analytical methods, approval of generic versions of those drugs is entirely possible without expensive clinical trials, complete molecular analysis, or identical manufacturing methods.

The FDA has acknowledged that the manufacture of enoxaparin is more unpredictable and variable than that of traditional small molecule drugs.¹¹ In a statement that resonates in the follow-on biologic arena, the FDA clearly articulated a policy that generic companies seeking approval for complex non-protein drugs do not necessarily need to reproduce the proprietary manufacturing processes of the

⁷ Alicia Mundy, “Baxter Faces New Challenge in Heparin Suit”, *Wall Street Journal*, August 16, 2010.

⁸ While most U.S. bulk heparin comes from China, the source of the bulk heparin used by Sandoz is not publicly known.

⁹ 21 C.F.R. § 314.92(a).

¹⁰ Docket No. FDA-2003-P-0273.

¹¹ Unpredictability and variability are hallmarks of protein-based biologic manufacturing.

reference-listed drug¹² – especially if the source biomaterial is the same. The FDA went on to list five overlapping criteria that an ANDA applicant *for enoxaparin* (ostensibly, not all drugs) can use to demonstrate active ingredient “sameness.” The first two criteria are significant because bioequivalence for follow-on biologics can be extrapolated inferred from these. These criteria are (1) the physical and chemical characteristics of the drug and (2) the nature of the source material and the method used to depolymerize the bulk heparin.

The first criterion is analytic in nature and is ultimately dependent on the second criterion. Complete analytic characterization of large proteins, sugars and combinations thereof (i.e., glycoproteins) is a daunting task and may ultimately be deemed irrelevant by the FDA.¹³ In the case of enoxaparin, the most pressing issue is the source of the bulk porcine heparin. For follow-on biologics, the more relevant issue(s) will likely include specific genetic strains of bacterial, plant, yeast and animal cells. Regarding the manufacturing methods for complex non-biologics such as enoxaparin, and possibly biologics, the FDA appears to be willing to grant a degree of latitude realizing that exactly reproducing trade secret manufacturing protocols is near impossible.¹⁴ Thus, if a generic drug maker is able to use highly similar genetic starting material or reasonably similar manufacturing methods (or both), it seems the FDA is more likely to approve the copycat version whether it is a marginally complex non-protein like enoxaparin or a highly complex recombinant protein biologic.

Partner With A Bioanalytical Company

While the details of the pending Teva and Amphastar ANDAs are not publicly known,¹⁵ one can only assume that the collaboration with a relevant bioanalytics company like Momenta provided a significant competitive advantage for Sandoz. Momenta is a U.S. based biotechnology company focused on the chemical characterization of complex sugars, glycoproteins and other biologically relevant mixtures. As enoxaparin is essentially a complex sugar polymer, it is not difficult to understand why the Sandoz ANDA gained favor with the FDA. The eventual public disclosure of FDA commentary related to the pending Teva and Amphastar enoxaparin ANDAs will likely provide further insight into the FDA approval process for follow-on biologics.

Looking forward, the complexity of biologics is largely based on the unpredictable chemical modifications that occur after the protein backbone has already been made. Such modifications are numerous and can include phosphorylation, glycosylation, methylation, SUMOylation and acetylation to name but a few. As protein glycosylation has been identified as a major source of variability in drug manufacturing, safety and efficacy, any follow-on biologic will almost certainly need to address the issue of glycoprotein biosimilarity. Collaborations between established generic drug programs and analytic biotechnology companies specializing in protein post-translational modifications will likely continue to provide a competitive advantage in the era of follow-on biologics.

¹² The PPACA requires follow-on biologic applicants to reveal proprietary manufacturing methods to reference listed drug patent holders. Commercial grade manufacturing protocols are often held as closely guarded trade secrets.

¹³ See FDA July 23, 2020 reply to Citizen’s Petition, pages 2, 3 and 30-33. Somewhat confusingly, a particular chemical ring “fingerprint” deemed pharmacologically significant by Sanofi was found by the FDA to be clinically irrelevant and speculative, yet partially necessary.

¹⁴ *Id.* at pages 28-30.

¹⁵ Including the source of the bulk heparin for the approved Sandoz enoxaparin ANDA.

**If you have any questions about this article or would like to discuss this topic further,
please feel free to contact:**

Robert Bakin, Ph.D.
(Phone) 571.215.3507
(Email) rbakin@tblawadvisors.com

Bernard Rhee, R.Ph., Esq.
(Phone) 443.519.5540
(Email) brhee@tblawadvisors.com

Technology & Business Law Advisors, LLC
1435 Autumn Leaf Road
Baltimore, Maryland 21286
USA

(Phone) 443.519.5540
(Facsimile) 866.941.8799
(Email) info@tblawadvisors.com

www.tblawadvisors.com