

M-ENOXAPARIN: A TECHNOLOGY-ENABLED GENERIC DRUG

M-Enoxaparin, Momenta’s most advanced product candidate, is designed to be a generic version of Sanofi-Aventis’ low molecular weight heparin (LMWH) product, Lovenox® (enoxaparin sodium injection). Lovenox is one of the most widely prescribed LMWHs in the world and is used for the prevention and treatment of deep vein thrombosis (DVT) and treatment of acute coronary syndromes (ACS). In 2005, Sanofi-Aventis reported worldwide sales of Lovenox of approximately \$2.7 billion. Lovenox is a heterogeneous mixture of complex sugar chains which, we believe, prior to the application of our technology, had not been thoroughly characterized. Momenta’s ability to analyze and sequence complex mixtures of sugars has allowed us to characterize Lovenox and develop a generic version of Lovenox that we believe will demonstrate chemical “sameness” to Lovenox and meet the FDA requirements for generic marketing approval.

Momenta has entered into an exclusive collaboration with Sandoz, the generics division of Novartis, to jointly develop and commercialize M-Enoxaparin. An Abbreviated New Drug Application, or ANDA, for M-Enoxaparin was submitted in August 2005.

WHAT IS A GENERIC DRUG?

A generic drug is comparable to an innovator (branded) drug product and has the same active ingredient(s), dosage form, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are identical in chemical composition to their branded counterparts, they are typically sold at a discount to the branded product.

GENERIC VERSIONS OF COMPLEX DRUG PRODUCTS

For selected drugs which consist of complex mixtures, defining the active ingredients and demonstrating chemical “sameness” is very challenging due to technical limitations. Determination of the “sameness” of the active ingredients for a generic drug product is based on demonstrating chemical equivalence of the active components of the generic version to those of the branded product. The FDA defines active ingredients as “any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease.” While the standard for demonstrating chemical equivalence is relatively straightforward for small molecule drugs, it is inherently more difficult to define active ingredients for complex drugs, especially those composed of complex mixtures.

Below are some examples of drugs which exist as complex mixtures. This table is not meant to be a complete description of all complex mixtures but highlight selected distinctions between categories.

	Active Ingredients	Regulatory Application for Approval	Regulatory Application for Generic Approval	Source Material
Heparins	Complex sugars	NDA	ANDA	Extracted from porcine mucosa
Therapeutic Glycoproteins/ Monoclonal Antibodies	Proteins and complex sugars; proteins	BLA*	No abbreviated regulatory path currently exists in U.S.	Manufactured in living cells
Botanicals/ Other mixtures	Various	NDA	ANDA	Extracted from plant or natural matter

* Most therapeutic proteins / antibodies are approved as Biologics License Applications, or BLAs.

Momenta believes recent advances in technology, such as its work in complex sugars, can be applied to chemically define the active ingredients in complex mixtures and create technology-enabled generic versions of complex drug products.

ABBREVIATED NEW DRUG APPLICATION (ANDA) PROCESS

Generic drugs are submitted to the FDA's Office of Generic Drugs through the ANDA process. Generic drug applications are termed "abbreviated" because they are not required to duplicate the clinical (human) testing or, generally, preclinical testing necessary to establish the underlying safety and effectiveness of the branded product. Rather, to be approved, a generic drug must be shown to have chemical "sameness" and bioequivalence to the branded product (or reference listed drug product) upon which the ANDA is based. ANDAs can be filed for most drugs that are listed in the FDA's publication *Approved Drug Product with Therapeutic Equivalence Evaluations*, commonly referred to as the "Orange Book."

The ANDA process is differentiated from the 505(b)(2) approval process which is the pathway that selected follow-on protein products, such as Omnitrope, have utilized for approval. Section 505(b)(2) of the Food, Drug, and Cosmetic Act permits an applicant seeking approval of a drug to rely on information from published scientific literature or on the fact that the agency has already found a similar drug to be safe and effective. Approval under Section 505(b)(2) may or may not require human clinical trials and does not enable interchangeability or substitutability with a branded product.

CREATING AN ABBREVIATED APPLICATION PROCESS FOR BLA APPROVED PRODUCTS

Currently there is no established statutory or regulatory pathway which provides the FDA with the authority to utilize an abbreviated approval process for generic versions of BLA products, including most therapeutic glycoproteins and monoclonal antibodies. Most therapeutic protein drugs were approved by the FDA under the Public Health Service Act. Unlike products approved through the use of NDAs, there is no provision in the Public Health Service Act that would permit approval of a follow-on, or generic, protein product using an abbreviated application. Establishment of such a pathway would require FDA to establish standards as well as for the U.S. Congress to enact new legislation.

BRINGING AN ANDA APPROVED GENERIC DRUG TO MARKET

Upon successful completion of all FDA approval requirements, the FDA will issue either a Full Approval or a Tentative Approval for marketing of the generic product. A Full Approval enables commercialization of the generic version. Tentative Approval is granted by the FDA when it has completed its technical review of the ANDA and found it acceptable for approval, but there is an outstanding issue of patent exclusivity that prevents commercialization. Full Approval is then granted when either patent litigation is resolved in the favor of the patent challenger, a period of 30 months has expired since the commencement of the patent challenge, or after the expiry of other patents/ exclusivity protections, whichever is first. Generic drug applicants that are the first to file a substantially complete ANDA containing a "paragraph IV" certification are eligible for and are typically awarded a 180-day period of generic market exclusivity which may delay subsequent generic approvals.

COMMERCIALIZING A GENERIC DRUG

If a generic version of a drug demonstrates "sameness" of active ingredients and meets the other requirements for ANDA approval, it is deemed by the FDA to be "therapeutically equivalent" to the innovator product, meaning that it is expected to have the same clinical effect and safety profile when used under the conditions specified in its labeling. Therapeutically equivalent drugs receive an "A" rating in the FDA's Orange Book and are generally substitutable for the innovator drug by both hospital and retail pharmacies. Many health insurance plans require automatic substitution of "A" rated generic products when they are available. As a result, the commercialization strategy for a therapeutically equivalent generic drug does not require extensive marketing and sales efforts but rather is based largely on direct substitution at the pharmacy level.

