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Generic Low Molecular Weight Heparins: Where Do We Stand?

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Unfractionated heparin and different brands of commercially available low molecular weight heparins (LMWHs) have made a major impact on the management of thrombotic disorders in the past 50 years. While the generic versions of unfractionated heparins have been developed in accordance to the initial manufacturing guidelines and subsequent Food and Drug Administration (FDA) mandates, the different brands of LMWHs are considered distinct drugs due to the significant differences in their patent process. Therefore unlike the unfractionated heparins, commercially available LMWHs are not considered the same. Because of the major differences in their drug substances, other substances and molecular/composition, the therapeutic profile of different LMWHs also differ. The regulatory agencies such as the FDA and World Health Organizations (WHO) consider each of the LMWHs as a distinct drug requiring clinical validation data for specific indications.

The LMWHs are now the standard of care drugs, with profound impact on the management of arterial and venous thrombosis, with an aggregate sales of over 3 billion dollars. As the patents for the manufacturing of these drugs are now expired or near expiring, most generic companies have targeted to market copycat versions of the branded LMWHs, such as enoxaparin and dalteparin. Such companies as Sandoz, Hospira, Ratio Pharma, Teva Pharmaceutical and Baxter Health Care, to name a few, are trying to enter this race. Several other smaller suppliers from Asian and North American regions have also introduced products from such manufacturers as Gland Pharma (India) and Ital-Pharmaco (Italy). Many other European and Asian companies are trying to manufacture the generic LMWHs.

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Unlike unfractionated heparin, the LMWHs differ significantly from one another and therefore the therapeutic exchange of these products is not recommended at this time (1-3). Similarly, because of the lack of proper guidelines and the non-approved status of the generic versions of LMWHs such as enoxaparin and dalteparin, the generic interchange of LMWHs is also not recommended in countries with international patent protection laws and regulatory compliance. In both Europe and the USA, several companies have applied for the marketing rights for enoxaparin brand (Sanofi-Aventis, Paris, France) and dalteparin brand (Pfizer/Eisai, USA). The current guidelines for the generic version of LMWHs acceptance are inadequate at this time. There is a need for preparing proper guidelines for the acceptance or rejection of the therapeutic and/or generic equivalence criteria. This would be extremely important and timely (4-6). Several initiatives from professional organizations, such as the International Union of Angiology (IUA), European Medicines Equivalence Agency (EMEA), and WHO have been proposed

During the past year, there have been several communications from the public, pharmaceutical companies, and regulatory agencies expressing various concerns over the guidelines to develop generic LMWHs. There are extreme opinions from various groups in favor and against the current guidelines and acceptance criteria. There are claims from the pharmaceutical sector regarding the absolute requirements to characterize the LMWHs fully prior to their becoming generic. Some of the letters have been addressed to the US FDA by scientific and pharmaceutical sectors by experts in this field. While the US FDA has not taken an official stand on this matter, EMEA has taken a position to develop newer guidelines and seek public opinion and input on this matter. Since there are no current guidelines on the regulations applicable to the LMWHs the generic manufacturers wish to enforce the current generic acceptance rules for the LMWHs. However, LMWHs are hybrid drugs including both biologic and chemical attributes with complex composition. Therefore, newer guidelines are needed for acceptance. In the absence of clear guidelines for the acceptance of generic versions of these drugs, there appears to be major confusion at the basic and pharmaceutical level. On the one hand, the generic suppliers would like approval of their generic products by submission of an abbreviated new drug application (ANDA), thus bypassing the clinical trial validation requirement. Other groups including those producing the innovator products contend that additional chemical and biological characterization is needed.

Some of the generic versions of LMWHs are already available in Asia and South America and represent substandard products. These products do not conform to current product and regulatory compliance guidelines. For this reason some of the generic LMWHs manufactured in South Asia have been removed from the market. Moreover, there are no established guidelines to approve or disapprove these drugs in Europe or the US. Therefore, additional guidelines regarding the characterization of these products may be needed, and any unilateral claim from manufacturers that structural information obtained from specific analytical profiling may result in an ideal generic product is not valid. Claims from the suppliers that generic LMWHs are identical to branded products are not supported by any publication or other documentation that we are aware of at this time. Chemical characterization of a complex heterogeneous sulfated carbohydrate mix-

ture may be similar; however, the pharmacodynamics of such a mixture is a cumulative biologic response (6-8). Until data on pharmacodynamics are available, the product(s) cannot be claimed similar. Therefore in addition to the chemical characterization, molecular profiling of these drugs may be necessary.

It is indeed true that until now, the FDA has not approved a generic version of a complex sugar generic product. We do not believe that LMWHs can be fully characterized in terms of chemical, biochemical, biophysical or biologic actions by any single group as these products are derived from porcine mucosal sources which require biologic characterization. There are many factors including the starting material that are important determinants of the final product and that may show batch-to-batch variation (6-8). Any claims that a generic manufacturer will have a significant regulatory advantage over other generic suppliers may not be valid.

It has been known for some time that non-anticoagulant components of heparin exert additional biological actions. Some of these have been described in several reports. To fully characterize the biological effects of LMWHs and their components is a very difficult task. Interestingly, neither the innovator nor generic products have been characterized in terms of their anticoagulant and non-anticoagulant components. Heparin has been used for over 50 years; however, its chemical and biologic attributes are not fully understood even at this time. Knowledge of the structure of heparin (sequences and other properties) has been useful but these properties do not fully characterize heparin in terms of its pharmacologic effects.

Some scientists and consultants for generic manufacturers undoubtedly have a good track record in analytical techniques for carbohydrate analysis. However, the relevance of the data produced by them to generic equivalence is questionable. As a matter of fact, there are certain specific attributes in LMWHs such as the presence of modified structures including 5 membered rings, galactouronic acid and ethereal benzyl groups, which are not taken into account.

An ideal LMWH should be a replica of heparin and there should be no structural alterations. Unfortunately manufacturing of LMWH requires harsh enzymatic and/or chemical processes that generate certain process specific structural changes in the final product. The biologic role of these microchemical changes within the structure of heparin is minor, however, the presence of specific structures can be used to confirm the process used for their manufacturing. It is for this reason that claims regarding the 1,6 anhydromanno group as a specific signature of enoxaparin have been made. As a matter of fact, such specific structural attributes are also present in the starting material of porcine mucosal heparin. Thus, if LMWHs are to be chemically characterized, one should also characterize all starting batches of unfractionated heparin as well. This underscores the importance of the batch and product consistency from different manufacturers of heparin. In China, the global source of porcine heparin, crude heparin is collected from hundreds of manufacturers and the pooled products are sold to pharmaceutical companies. There is no guarantee on the uniformity of the starting material. If there is a characterization needed for regulatory purposes it should be instituted at this stage.

Several carbohydrate chemists dedicated to carrying out structural work on heparins have already published some key steps in characterizing heparins. It is indeed true that sophisticated techniques such as nuclear magnetic resonance and mass spectrometry can be used to further characterize any molecule; however, their relevance to drug development is limited. In the case of the individual LMWHs, specific molecular attributes such as the presence of a double bond, constricted rings and anomeric structures are sufficient to differentiate these agents from one another. In addition, affinity based methods to investigate the binding profile provides useful data on the interactions of LMWHs. Even if this data is generated it can not be used as a substitute for the cumulative biologic responses which can only be obtained from animal models and especially from clinical trials.

We believe that some of the current available generic LMWHs may not be equivalent to branded products; however, there are several other manufacturers of generic LMWH whose products may pass the current regulatory stipulations. Thus, there is a clear need for additional regulatory stipulations focusing on the pharmacodynamic equivalence of these products. Until such guidelines are available a generic interchange is not valid. Regarding the therapeutic interchange, it is unlikely that a particular laboratory test may be sufficient in developing guidelines to interchange one product to another product.

References have been made to the typical standards of FDA for sameness (bioavailability) for more complex structures. In the case of LMWHs, bioavailability has a limited meaning as additional microchemical changes add to chemical diversity of these agents and therefore has limited value when discussing the pharmacodynamics of LMWHs Since the LMWHs represent an unique hybrid between a biologic and chemical process, the regulatory bodies currently may not have appropriate standards, as this is a totally new area. Some of the generic manufacturers have repeatedly made several unqualified statements regarding the FDA as if it has already favored their approach and is likely to give them favorable considerations. To our knowledge, the FDA does not have any favored position on this matter at this time.

When the LMWHs were initially developed, they were thought to be equivalent. There was a strong debate in the scientific community regarding the differentiation of LMWHs produced by different manufacturing processes. The regulatory bodies and professional groups ultimately accepted the fact that each of the commercially available LMWHs is a distinct drug. Therefore, therapeutic exchange between different LMWHs was not acceptable. Unlike other generic drugs, the currently available LMWHs such as enoxaparin and dalteparin are approved for specific clinical indications. Enoxaparin happens to have the most indications because of the extensive clinical validation carried out with this LMWH. If the generic industry requests the FDA for an unqualified approval for a generic enoxaparin, it would be inconsistent with regulatory compliance to grant this approval without requiring biologic and clinical validation of the generic product. Therefore, any claim, based purely on analytical characterization of a generic LMWH that the regulatory bodies will preferentially grant them approval to introduce a generic "equivalent" product for multiple indications is purely speculative. Each of the different LMWHs has various structural attributes, which can also be adjusted to meet regulatory standards (current or future). However, the real sameness can only be established in bioequivalence studies that represent a complex array of bioassays. There are more than one hundred ways to characterize heparins in biochemical, biophysical, molecular and structural methods. Moreover, the pharmacological characterizations can include over three hundred parameters. Therefore, drug development and academic research is to be differentiated. Eventually proper drug development guidelines focusing on patient safety, efficacy and peer consensus will provide the adequate approaches. At this time, some of these claims appear academic. However these may have an impact on structural characterization only. The functional characterization of these drugs is more important and will require additional work.

Despite the fact that a compendium on the analytical profile of heparins and related GAGS is not available, sophisticated analytical methods and techniques such as countercurrent distribution, circular dichroism, high resolution NMR, mass spectral analysis and ligand binding mapping have been used. More importantly, the functional profiling of these agents in terms of protein and peptide binding, modulation of enzymes, ability to release endogenous mediators such as TFPI, pharmacodynamic interactions and pharmacokinetic behavior may not be similar even though the chemical analyses indicate sameness. The long term toxicity profile along with potential accumulation of these effects is equally important. Therefore, chemical characterization alone without biologic profiling and toxicologic considerations of a complex multicomponent drug is not sufficient for optimal and ethical development. The regulatory bodies such as EMEA, US FDA and European Pharmacopeia (EP)

are currently aware of these complexities and are urged to take steps in developing relevant guidelines for a proper review of the generic versions of LMWHs in order to avoid future harm to patients.

The public is aware of the need for the introduction of affordable medications that will be available to all those in need. Generic conversion of branded drugs within certain guidelines is one approach to accomplish this. Generic versions of synthetic organic agents can be manufactured and can pass the compliance requirement under current stipulations. However, currently there are no published guidelines for complex polycomponent drugs such as the heparins. As LMWHs are hybrids of a biological product with chemical modifications, there is a need for developing valid guidelines based on not only chemical characterization but more importantly biochemical, pharmacological and preclinical equivalence. Only then can additional decisions regarding the need for clinical assessment be addressed.

We are aware of TEVA, AMPHASTAR and MOMENTA's application for the authorization to commercialize generic enoxaparin in the US and do not know what the US FDA will decide. However, the current generic guidelines are inadequate and should be redefined. From our discussion, extensive chemical characterization of the innovator product is not the ultimate answer, because the LMWHs are complex mixtures of oligosaccharides which are hybrids of both biologic and chemical processes and thus pharmacologic actions can only be assessed in animal models and clinical trials. Thus, true bioequivalence requires further definition. More importantly, sameness can only be proven in biologic settings and population pharmacodynamic studies. Unlike most generic drugs which are simpler and mostly used for specific indications the LMWHs have broad indications. Also, not all LMWHs are approved for the same indications. We do not believe that the premarin case study is the best precedent for understanding the FDA's current policy on generics of complex mixtures. While there are no scientific reports related to the LMWH generic conversion it is quite evident that the major interest in this process is driven by business opportunity. The claims on both sides are unilateral. Several groups are in the process of reviewing all of the relevant documentation and will be discussing this matter in scientific meetings of the International Society of Thrombosis and Hemostasis, International Union of Angiology and the International Academy of Clinical and Applied Thrombosis and Hemostasis during the coming months (July-December 2007). Together with the specific monographs, consensus reports and other documents from regulatory agencies, this information will be helpful in developing valid guidelines.

It should be stressed that technologic advances have provided us with tools to characterize chemicals and biologicals in infinite ways. To what extent should such a characterization impact a biologically derived heterogeneous mixture of oligosaccharides whose pharmacologic actions are based upon a cumulative effect on blood cells, vasculature and plasmatic processes? The answer to this question remains unknown at this time and may require a great deal of integrated studies and carefully developed guidelines which will include animal experiments and qualified clinical trials.

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Key Questions Related to the Development of Generic Versions of LMWHs

Jawed Fareed, PhD

1. How valid are the regulatory guidelines for the approval of generic drugs to be applied to drugs produced by newer methods including combined biologic and clinical methods?
2. Should LMWHs be considered as heparin and should the same regulations be applied for their approval as for heparin and other biologics?
3. Are the discussions related to protein products applicable to carbohydrate derived drugs such as the LMWHs?
4. Is there any modifications of the regulatory guidelines for the approval of hybrid products such as the LMWHs?
5. Should the complete clinical and structural characterization of a hybrid biologic/chemical product be a pre-requisite for the approval of a generic equivalent product? If so, what are the hallmarks for the innovator product?
6. Are additional characterization in terms of product specifications required to approve the generic versions of LMWHs?
7. Are there generic versions of LMWHs currently available?
8. How are these drugs manufactured and approved for clinical use?
9. Are there any safety and efficacy concerns with the use of these drugs?
10. Should the generic brand of a product require clinical validation?
11. Is the bioequivalence requirement adequate for the clinical equivalence for all indications?
12. There are extreme opinions on the need of complete characterization of the innovator product to carryout clinical trials on the generic equivalent. Are these necessary?
13. Are the differences between the branded LMWHs significant enough to consider each of these drugs to be classified as different?
14. Utilizing the patents for each of these agents, is it possible to manufacture the generic versions of such branded LMWHs as Dalteparin, Enoxaparin, Fraxiparin, Tinzaparin, Certoparin, Parnaparin, and Bemiparin?
15. Are there additional unique features in each of these LMWHs which attribute additional uniqueness for these products, not covered in the patent, that can only be described as product art and manufacturing refinements?
16. Are the batch differences within a branded product significant enough to suggest that within a branded name LMWHs marked variations in product profiles can be observed?
17. It is claimed that branded products are unique and only partially characterized suggests that individual low molecular weight heparins are unique and the patent described process may not provide sufficient information to make a generic version of each drug. Therefore, additional physicochemical analyses using newer technology has provided specific data which can be used to characterize different products.
18. Are there any guidelines from regulatory bodies and/or professional societies to evaluate the generic versions of LMWHs to set up acceptance or rejection criterion?
19. Who are the manufacturers of the generic versions of Enoxaparin? Do they have adequate knowledge to produce comparable products?

Please address questions and comments to: NATF; 1620 Tremont Street, Suite 3022; Roxbury Crossing, MA 02120, USA, Phone: (617) 525-8326, or email: info@NATFonline.org.

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As a Fledgling Organization, we rely upon your participation, energy, spirit of volunteering, and philanthropy that characterize the culture of North America. With your support, NATF sponsors several multidisciplinary thrombosis education programs annually: 1) "Proactive Prophyalxis," a multidisciplinary symposium geared to healthcare professionals, patients, and caregivers, and 2) the NATF "Thrombosis Summit," an annual event focused to meet all five NATF mission points.

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