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Biosimilars: Considerations With Low Molecular Weight Heparins

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H&O What are biosimilars, and for what reasons are they being developed?

CMJ Biosimilars are copies of existing biopharmaceuticals that differ from the originals in that they are made with a different cell line and undergo a different manufacturing and purification process. Contemporary biopharmaceuticals are principally proteins that originate from or are structurally related to macromolecules found in biological systems. These are most commonly produced by recombinant technologies in tightly controlled processes that use cell culture bioreactors. The cell-based systems and processes are complex and unique to the producer and product.¹ From a regulatory perspective, heparins and heparin derivatives are actually drugs rather than biologics. Because discussions of biosimilar biopharmaceuticals (follow-on biologics) have focused on the legislative activity that is required for their licensure in the United States, it is important to create a context in which to understand the issues surrounding heparin “biosimilars.”

Based on experience with generic, low molecular weight (LMW) pharmaceuticals approved for use by the US Food and Drug Administration (FDA) after passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), the “Hatch-Waxman Act,” biosimilar biopharmaceuticals are envisioned as lower cost versions of the expensive biopharmaceuticals. It is a widespread view, although hardly universal, that cost savings

from biosimilars are a necessary element in healthcare cost containment. However, cost savings may not be as large as envisioned. A report from the US Federal Trade Commission estimates that the cost of biosimilars is likely to be only 30% lower than the existing products, rather than the 50–90% reductions in price obtained from generic drugs.²

Currently, biosimilars are not specifically licensable by the FDA. The FDA has the authority to approve copies of simple drugs under the Hatch-Waxman Act and thus has regulated the availability of generic drugs since 1984. However, because of the historical complexities of its legislative authorizations,³ the FDA has had limited or no legal authority to approve copies of biosimilar biopharmaceuticals. Recognizing the complexity of heparins and LMW heparins, the FDA has evaluated them more like biologics than drugs. The 3 currently licensed LMW heparins have distinguishable chemical and pharmacological properties⁴ and have been approved as individual drugs, not as interchangeable biopharmaceuticals. These LMW heparins have indications for use that are specific to each—off-label uses notwithstanding—as their package inserts indicate.⁵

Several legislative proposals (eg, H.R. 1427, 1548, S. 726, 1679, 1796) have been introduced in the past 2–3 years to address the need for FDA authorization to approve biosimilars; these proposals include an abbreviated approval pathway (similar to that using an abbreviated new drug application [ANDA] for generic drugs) for follow-on biopharmaceuticals. The early proposals contained ambiguities that raised concerns within the medical and scientific communities regarding the safety of an abbreviated approval process for biosimilar biopharmaceuticals. Of particular concern was primary reliance on *in vitro* comparative chemical analysis and only pharmacodynamic and pharmacokinetic data, which are generally the same requirements as for simple generic drugs that are licensed under the Hatch-Waxman Act. A second major cause for concern resulted from ambiguity in the criteria that would be used to determine if an innovator product and its copy biosimilar are interchangeable. The current legislative proposals (eg, H.R. 3200, 3590, 3962, 4038), now embedded within the broad-scope healthcare bills, have addressed and alleviated some of these concerns. These proposals, however, include other considerations, such as payment policies, and the biosimilars component is no longer a primary focus. Although the fate of the

current legislative proposals is uncertain, the sections that address authorization of the FDA for biosimilars could be separated from the larger bills and handled independently by the Congress, essentially returning to their earlier status as independent bills. The House and Senate versions of the sections relevant to biosimilars are now sufficiently similar that the possibility for bipartisan passage of legislation to enable the FDA to review and approve biosimilars may be possible. The current situation is that follow-on biologics are products awaiting a “pathway” for their approval; several submissions for approval, including those that position LMW heparins as “biosimilar drugs” already lie in wait. The FDA has been working on criteria for assessing “biosimilarity” and assuring safety and efficacy of such products,⁶ including immunogenicity; in December 2009, the FDA issued a draft guidance for industry related to immunogenicity (Assay Development for Immunogenicity Testing of Therapeutic Proteins). Concerns remain, however, because of uncertainties regarding the criteria to be used for determining “interchangeability” (ie, legal direct substitution of a biosimilar for a licensed innovator biopharmaceutical). This is particularly important if only in vitro chemical and potency data and limited pharmacodynamic and pharmacokinetic data are accepted to support a determination of “biosimilarity” and “interchangeability.” Without evidence from an appropriate clinical trial, which may be an abbreviated one, the opportunity for unintended consequences seems inevitable. The European Medicines Agency already has in place a regulatory pathway for biosimilar biopharmaceuticals and has issued guidelines for LMW heparin biosimilars that include appropriate clinical trials.⁷

The reasons for developing and producing biosimilars are multiple and different for innovator and biosimilar producers, patients, consumers, and payers for healthcare. For producers, market growth can be anticipated through expansion of use of biosimilars because of their lower costs and the aging of the US population. A pathway for approval of biosimilars will create a business opportunity for generic drug companies not previously involved in innovative biopharmaceuticals to produce biosimilars at lower prices because of their lower development costs. For payers, a reduction in the cost of healthcare will be welcomed. As expected, the perspectives differ between the biotechnology companies responsible for innovative biopharmaceutical products and the “generic” drug-producing companies intending to enter this market. These differences are clearly reflected in the debates surrounding the period of market and data exclusivity. Longer periods benefit producers of licensed biopharmaceuticals; shorter periods benefit biosimilars producers. Ensuring safety for patients will ultimately depend on the FDA. A comprehensive and enlightening discussion of the economic and

financial bases for these perspectives can be found in 2 reports: *Avoiding No Man's Land, Potential Unintended Consequences of Follow-on Biologics*⁸ and *The Proposed Approval Pathway for 'Biosimilars' and its Potential Implications for Various Stakeholders*.⁹

H&O How is the manufacturing process of biosimilars different from that of conventional pharmaceuticals?

CMJ Biopharmaceuticals are more complex than generic drugs. Most of the biopharmaceuticals are proteins, macromolecules that use recombinant technologies and cellular “factories” for their production. Exact copies of the licensed biopharmaceuticals are unlikely to be produced by biosimilar producers. Differences must be expected. Processes are very unlikely to be identical, except when the biosimilar producer is actually the innovator producer, a strategy employed by some major pharmaceutical companies that has already been introduced for other drugs. Post ribosomal modifications such as glycosylation, acylation, phosphorylation or sulfation, γ -carboxylation, and hydroxylation can differ depending on the cell culture systems employed for their production. Differences in amino acid sequence and post-ribosomal modifications can result in new epitopes that act as immunogens. The purification processes needed to produce biopharmaceuticals can themselves produce contaminants from the cellular systems used. In contrast, conventional pharmaceuticals are primarily produced by classical chemical synthesis and purification processes. Many of the small molecule drugs are produced in solvents that are incompatible with and do not promote growth of microorganisms, again in contrast to the aqueous solutions necessarily employed in production of biopharmaceuticals. Although all legislative proposals recognize the inherent molecular complexity of biopharmaceuticals, the descriptions of biosimilar biopharmaceuticals are general, perhaps even vague, and thus the most important aspects of safety will depend on the criteria employed by the FDA in its approval guidelines and approval processes.⁶

Heparin derivatives are different from both protein biopharmaceuticals and small molecule drugs. Protein and nucleic acid biopharmaceuticals will exhibit narrow molecular weight ranges. Proteins are heterogeneous as the result of “noise” in polypeptide translation and post-ribosomal modifications, particularly glycosylation, but such heterogeneity is limited when compared with heparins. Nucleic acids products similarly possess limited heterogeneity as the result of imperfect transcription or when chemically synthesized less than 100% yields at each step in the synthesis of oligo or polynucleotide chains. Again, such heterogeneity is less than heparin or

heparin-derived biopharmaceuticals. Protein biopharmaceuticals are nominally unique molecules with a definable amino acid sequence; nucleic acid–based pharmaceuticals have defined nucleotide sequences. Heparin-derived biopharmaceuticals and unfractionated heparins are inherently chemically heterogeneous and do not have defined monosaccharide sequences nor defined sulfation or acetylation of the uronic acid and glucosamine residues throughout the glycosaminoglycan chains. Heparin thus exhibits undefinable homogeneity, different from other biopharmaceuticals. It originates from mixtures of glycosaminoglycans, principally in the intestinal mucosa and is subject to breed and diet sources of heterogeneity. Because unfractionated heparin is the starting material for LMW heparins, their heterogeneity initially originates from the LMW heparin's sources. Purification of heparin from intestinal mucosa is, in its early stages, a crude and almost primitive process. Nevertheless, unfractionated heparin, a biopharmaceutical that can be purified adequately, and has been used for approximately 70 years, is safe when appropriately monitored. When appropriately used, heparin remains an invaluable anticoagulant and antithrombotic that is indispensable for many medical procedures (eg, extracorporeal dialysis and blood oxygenation). Even though US Pharmacopeia (USP) heparin and European Pharmacopeia (EP) heparin are molecularly heterogeneous, because of the evolved preparation processes, they can be produced with a high degree of consistency between lots and among producers. Unfractionated heparins from different producers are not, however, of identical potency, although greater consistency among them can be expected in the future as the result of revisions of the monographs for heparins by the USP and the EP that raise the minimum acceptable potency.¹⁰

H&O Why does the development of biosimilar LMW heparins warrant higher concern for safety compared with other drug-derived biosimilars?

CMJ The higher level of concern for LMW heparins is derived from several considerations in addition to the already mentioned heterogeneity of the starting material used for LMW heparin production. Primarily, the major concern is based on the fact that heparin and LMW heparins are currently covered under drug regulations rather than biologic regulations at the FDA. Consequently, heparin is not explicitly considered in the proposed legislation. However, the FDA apparently has deferred consideration of applications for at least one heparin biosimilar pending receipt of legal authority to consider the substance with the same care that is employed for biologics. Currently licensed LMW heparins are approved as individual drugs

and their approval is supported by data from extensive clinical trials. If legislation were to permit prior drug-model abbreviated applications, without well-designed and adequate clinical trials, differences that might only be evident clinically in high-risk patients could easily go unrecognized until adverse events are reported. The tragedy of the adulterated heparin that resulted in more than 200 deaths, however, makes it seem unlikely that the FDA will not require rigorous evidence for safety and efficacy, particularly if a claim of interchangeability is to be granted. Safety will be a particularly important consideration because LMW heparins have been associated with bleeding in patients with renal impairment¹¹⁻¹³ and patients receiving a neuraxial anesthetic.¹⁴ It is also notable here that the principal adverse biochemical reaction associated with the hyper-sulfated chondroitin sulfate is contact system activation with the formation of bradykinin and consequent hypotension.¹⁵ Although this reaction has not been identified with any heparins prior to this situation, it may be reasonable to now ask if existing heparins or “new” heparin biosimilars might not affect kininogen proteolysis via contact system activation, and lead to risk previously unanticipated.

A second consideration arises from risks associated with unrecognized differences in efficacy (in vivo anticoagulant, antithrombotic, anti-inflammatory, or anti-metastatic activity).¹⁶ If the in vitro chemical data (only recently required by the USP monograph for unfractionated heparin) and in vitro potency assessment indicate differences, extrapolation of anticoagulant activity to these other activities would be unwarranted. Revisions to the monographs for LMW heparins are currently under consideration by the USP, but because the reference material for LMW heparin is limited to one approved product in the United States, it is unclear how it might be used by companies who submit products for consideration as biosimilar to LMW heparins other than enoxaparin.

A third consideration arises from the differences among LMW heparins in their clearance from the circulation; renal clearance has the most pronounced difference, and varies according to the molecular weight of the heparin preparation. In this regard, knowledge of the average molecular weight alone is inadequate, and the range of molecular weights and the distribution of the molecules within the molecular weight ranges need to be considered.¹⁷⁻¹⁹ Concerns and contraindications related to renal insufficiency are well documented and are particularly relevant in older patients.²⁰

A fourth cause for concern is the diversity of functions and functional ability associated with various heparins and LMW heparins. The use of these biopharmaceuticals, as well as other anticoagulant drugs, is challenged by the need to balance the risk of hemorrhage against the risk of

thrombus formation. Anticoagulant and antithrombotic actions are commonly considered to be predominantly, albeit not exclusively, the result of enhancement of the activity of antithrombin in protease inactivation (eg, thrombin and factor Xa). Although these are the 2 target proteases against which *in vitro* activity and potency are commonly measured, they are only 2 of the proteases inactivated by antithrombin and for which inactivation is accelerated by heparin and LMW heparins. The ability to enhance antithrombin inactivation of proteases is dominated by the specific effect of a unique pentasaccharide sequence within some heparin and LMW heparin molecules which imbues them with high affinity for antithrombin compared with heparin molecules that do not contain this sequence. Although this pentasaccharide sequence dominates the affinity of the heparin for antithrombin, the actual affinity is affected by disaccharide sequences on both ends of the pentasaccharide sequence within a heparin or LMW heparin molecule²¹ and the location of the pentasaccharide sequence in the heparin chains. The differences due to these properties can be as high as 100 times, and the fraction of the molecules containing these “enhanced” sequences are only generally known for a single LMW heparin. Also, other protease inhibitors’ ability to inactivate thrombin (eg, heparin cofactor II) do so without a clearly defined specific sequence within a heparin molecule, but can be very potently enhanced by heparins and other glycosaminoglycans.²² All of these differences in properties must be expected to change the appropriate dosages for such products.

Heparin-induced thrombocytopenia, a consequence of the formation of an immunogen as the result of the complex between heparin and platelet factor 4, is generally less problematic with LMW heparins. However, evidence for the dependence on the structure of the LMW heparin is not extensive, and thus inference from the existing evidence to biosimilar LMW heparins may not be justifiable. Reaction with existing antibodies to platelet factor 4–heparin complexes perhaps is the greatest unknown, particularly if interchangeability is approved without adequate verification that the “biosimilar LMW heparin” does not differ from the licensed product that it intends to replace. In this regard, it seems appropriate to invoke the aphorism once said by astronomer Carl Sagan: “Absence of evidence is not evidence of absence.”

A fifth cause for concern would arise if pressures on companies who are to produce biosimilar heparin derivatives force them to look for less costly raw materials than those used in unfractionated heparin of porcine origin. Bovine lung heparin, although not licensed for use in the United States, could be such an alternative starting material. Until pharmacopeial changes were made in response to the crisis created by adulteration

of the heparin active pharmaceutical ingredient,²³ manufacturing to specification permitted substitution of glycosaminoglycans such as chondroitin sulfate that had been chemically hyper-sulfated to pass the then-existing release requirements. Although this possibility is now very much less likely, the “clever” blending of products might conceivably breach the newly established controls.

And finally, several “biosimilars” for enoxaparin have been developed and marketed in countries outside the United States, at least one of which was recalled from the market. Although this can be little more than a cautionary note, the expectation is that because these biosimilar heparins have already been developed, they seem likely to be submitted to the FDA for consideration for sale in the United States. Bulk product of enoxaparin, for example, seems to be sold under this name from China and India (<http://www.alibaba.com/showroom/Enoxaparin.html>).

H&O What are the differences seen among LMW heparins?

CMJ Several differences are well established for the LMW heparin products currently on the market in the United States.²⁴ Firstly, LMW heparins are produced from unfractionated heparin by chemical depolymerization using 4 different chemical agents: nitrous acid (dalteparin), alkaline depolymerization (enoxaparin), heparinase digestion (tinzaparin), and peroxidative cleavage (ardeparin). The actual conditions under which these depolymerization processes are carried out are unlikely to be the same, even if the general chemical reactions are the same on paper, and thus the chance that the products will be formed in different amounts is almost certain (eg, molecular weight distributions and fraction of pentasaccharide-containing molecules). Data show that the amounts of the high-affinity, pentasaccharide-containing molecules in these LMW heparins are different, thus attesting to this inference. The molecular weight distributions, range, and relative amount of the product within narrow segments of the molecular weight also differ. These differences affect the pharmacokinetic and pharmacodynamic behaviors, and thus the assumption of “interchangeability” of a biosimilar LMW heparin—if the same common names were to be permitted—could be dangerous to patient safety. As already noted, regulation to assure safety and efficacy by the FDA will be a technical challenge, particularly when the expectations for substantially lower costs for biosimilars are widespread because of the experience with generic small-molecule drugs.

Secondly, there is an ever increasing body of evidence showing that the heparins affect processes other than hemostasis/thrombosis, and thus the risk of differences that are initially unidentified is a concern. Although links

between coagulation and malignancy have been discussed for a long time, sufficiently clear and specific relationships have not emerged in other than some in vitro studies. Although not surprising given the complexity of “cancer” generally, it may be that only improved post-marketing surveillance of uses of LMW heparins—both innovator and biosimilar products—will be able to warn of adverse, unintended consequences.

Much hinges on whether or not abbreviated clinical trials are required by the FDA for licensure of biosimilar biopharmaceuticals, heparin derivatives in particular. As noted already, because heparins and heparin derivatives are legally included under drug regulations, rather than biologic regulations, clarification of this historical anomaly remains to be made. The political, economic, legal, and regulatory considerations may make placing heparin among the biologic agents rather than in the drug categories difficult.

H&O What precautions should researchers/physicians take when investigating or using LMW heparins?

CMJ Should biosimilar LMW heparins appear quickly after the legislation authorizing the FDA to approve them is passed, it will be important to examine the evidence for substitutability and interchangeability provided by the suppliers. Such evaluations will likely be made by those responsible for the decisions regarding their organizations’ formularies, and in the face of pressure to reduce costs, the final decisions may be made by individuals who lack sufficient knowledge of these particular issues. If biosimilar LMW heparins were to be approved without demonstration of interchangeability in clinical trials, then the need for pharmacovigilance would likely be much greater than usual for these biopharmaceuticals. It can be hoped that ensuring safety of “biosimilar LMW heparins” does not require another tragedy similar to the one seen with unfractionated heparin to get the attention of the medical community and the regulatory authorities.

Perhaps the prevailing situation regarding approval of biosimilar biopharmaceuticals is most easily described by the following rhetorical questions: “Do we know all of the biological activities associated with heparin and LMW heparins?” “Would we be comfortable as patients receiving a biosimilar LMW heparin that had been approved as interchangeable without clinical trial validation?” “Can we afford the added costs, both human and economic, of unanticipated adverse events that are traceable to moderately less expensive biosimilar biopharmaceuticals that have been judged licensable on the basis of in vitro and pharmacologic data only?”

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