Drug, Healthcare and Patient Safety

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REVIEW

Update on the safety and bioequivalence of biosimilars – focus on enoxaparin

This article was published in the following Dove Press journal:
Drug, Healthcare and Patient Safety
10 June 2013
Number of times this article has been viewed

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Abstract: Generic forms of chemically-derived drugs must exhibit chemical identity and be bioequivalent in healthy human subjects. The use of generic drugs results in a considerable savings of healthcare expenditures. Biologic drugs are produced in living systems or are derived from biologic material and extend beyond proteins to include antibodies, polysaccharides, polynucleotides, and live viral material. Such drugs pose a challenge to characterize as they tend to be larger in size than chemically-derived drugs, can exhibit a variety of post-translational modifications, and can have activities that are dependent on specific conformations. Biosimilars are not true generics, but rather, exhibit a high degree of similarity to the reference product and are considered to be biologically and clinically comparable to the innovator product. Therefore, the development process for biosimilars is more complex than for a true generic. Guidance is now available from the US Food and Drug Administration and from the European Medicines Agency for the development of biosimilar drugs. Biosimilar drugs are expected to have a major impact in the management of various diseases in coming years.

Keywords: generic, biosimilar, low molecular weight heparin

Introduction

For many years, drug products were largely limited to single well-defined molecular entities, produced through chemical synthesis. This changed in 1982 when the first biotech drug, Humulin (a human insulin drug produced by genetically engineered bacteria), was approved by the US Food and Drug Administration (FDA). Since then, numerous biotech drugs have been approved in the US, averaging 23 per year from 2001–2011. These drugs make up an ever increasing share of the pharmaceutical market, with yearly sales reaching $92 to $130 billion.[1,2] A number of biologic drugs used to treat rheumatoid arthritis, various cancers, or diabetes are now among the world's top selling medicines in terms of dollars.[3] Additionally, biological drugs make up a large proportion of new product approvals by the FDA,[4] with the prediction that this could rise to 70% of all new drug approvals by 2025.[5,6]

Small molecule drugs

Small molecule drug products typically have molecular weights in the range of 100 to 1000 Da and exhibit known chemical structures that can be readily characterized using chemical assays or analytical instrumentation. Such drugs are produced through well-defined chemical reactions and it is possible that multiple synthetic pathways can be utilized to produce the same end-product. Such products are easy to purify and contaminants, if present, tend to be easy to identify and eliminate. Small molecule

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drug products exhibit high degrees of purity and tend to be stable products.

Generic drugs

In 1984, the United States Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch-Waxman Act, created an abbreviated regulatory pathway for the approval of generic drugs.[7] At the time, chemically-derived, small molecule drugs were the norm. Manufacturers submitting an Abbreviated New Drug Application (ANDA) are required to demonstrate that the active ingredient is identical chemically to the corresponding branded product and that the branded and proposed generic product is bioequivalent in healthy subjects. Such drugs need to exhibit the same strength, dosage form, and route of administration as the reference drug. If these criteria are met, it is assumed that the generic product's safety and efficacy are also equivalent to that of the branded product. Another important consideration is that drugs approved through the ANDA pathway are considered to be interchangeable with the branded product unless specifically stated otherwise.[8]

Today, it is estimated that almost 80% of the prescriptions in the US are filled using generic products. With the average cost of generic drugs being 80%–85% less than the brand name counterpart[9] in 2010, the use of generic drugs resulted in a savings of approximately $158 billion.[9] Despite this, there are still questions as to whether all generic drugs are in fact identical to their respective reference products. Recent experience showing inequality between generic and branded forms of extended release bupropion[10] suggests that stricter evaluation of generic formulations of drugs with complex formulations or narrow therapeutic indices may be needed to ensure bioequivalence and clinical equivalence.

Biologic drugs

Biologic drugs are produced in a living system through the use of recombinant DNA technology (bacteria, plant, or animal cells) or are derived from biologic material and encompass antibodies, proteins, polysaccharides, polynucleotides, and live viral material. Such drugs include recombinant clotting factors, hormones, cytokines, growth factors, enzymes, clotting factors, antibodies or antibody fragments, and toxins that are used for the treatment of a variety of conditions including cancer, arthritis, or hemophilia.[11]

Characteristics of biologic drugs are summarized in Table 1. Biologic drugs tend to be much larger in size (proteins containing hundreds of amino acids) and exhibit a more complex structure compared to chemically synthesized drugs.

Table 1 Characteristics of biologic drugs

1. Manufactured in or derived from microorganisms, plant cells, or animal cells.
2. Large, complex molecules or mixtures of molecules that can be difficult to fully characterize.
3. Encompass antibodies, polysaccharides, polynucleotides, proteins, and live viral material.
4. Increased potential for immunogenicity compared to small molecule drugs.
5. Potentially less stable than small molecule drugs.

The biologic function of a protein, for instance, is dependent not only on its primary amino acid structure but also on the way in which it is folded (secondary and tertiary structures). A variety of post-translational modifications including glycosylation, phosphorylation, sulfation, and lipidation can impact the conformation of a protein. The type or extent of post-translational modifications can vary depending upon the way in which a given protein is produced.[12] The use of different host cells to express the protein of interest can affect the final product. Recombinant proteins need to be isolated from the host cell in which they are produced. This adds to the complexity of the production process and increases the possibility that the final product could be contaminated with cellular debris or host cell derived proteins and other contaminants from the media. Protein-based drugs tend to be less stable than chemically synthesized small molecules, being sensitive to heat and shear stress. Some biologic drugs such as glatiramer acetate (Copaxone) and the low molecular weight heparins (LMWH; ie, enoxaparin) contain multiple components, adding to the complexity of characterization and making the determination of the true active ingredient difficult.

While biologic drugs are clinically effective, the high cost of treatment is a concern. Therefore, the availability of "generic" versions of biological drugs would be desirable as this could result in savings of billions of dollars on a yearly basis.[13,14] However, producing a "generic" biological drug (a biosimilar) is far more complex than producing a generic chemically-derived, small molecule drug.

Biosimilars

Biosimilars (also known as subsequent entry biologics, biogenerics, or biocomparables) are not true generics in the sense that they are not exactly the same as the innovator product, but rather are only considered biologically and clinically comparable to the innovator product. Like true generics, biosimilars are meant to be used at the same dose and for the same indication as the reference product. This means that

the characterization of a biosimilar is meant to demonstrate a high degree of similarity to the reference product rather than demonstrate clinical benefit.[15] Such a high degree of similarity of complex biological products requires a multi-stepped approach utilizing state-of-the-art analytical assays to demonstrate physiochemical comparability followed by preclinical and clinical studies to demonstrate biosimilarity.[16]

In the European Community, there have been 14 biosimilars approved for use, one of which was subsequently withdrawn.[17] These include products containing epoetin alfa, epoetin zeta, somatropin, and filgrastim as their active substances. In addition, it is reported that applications for biosimilar human insulin, folliptropin alpha, and infliximab are currently under review.[18] In the US, a number of follow-on biologic drugs have been approved,[16] but none were true biosimilars as defined in the "Biologics Price Competition and Innovation Act of 2009". The follow-on versions of menotropin and enoxaparin were approved under the ANDA pathway and follow-on versions of menotropin, hyaluronidase, glucagon, calcitonin and somatropin were approved under the 505(b)(2) regulatory pathway.

Characterizing generic versions of small-molecule drugs is considerably easier than characterizing biologic drugs due to several key characteristics.[19] The characterization of a biosimilar drug is more extensive than the characterization of a generic small-molecule drug. The ultimate characteristics of biologic drugs are influenced by: choice of source material (cell line), production process, purification process, and the final pharmaceutical formulation. Differences in protein folding, aggregation, and glycosylation might manifest clinically as decreased potency/efficacy, altered pharmacokinetic behavior, or increased immunogenicity. Some such differences have been previously reported for epoetin alfa preparations from different manufacturers.[20,21] Since manufacturing processes are complex and never fully disclosed, biopharmaceuticals are considered impossible to exactly replicate, leading to the idea that "the product is the process".[22] This can sometimes prove difficult to achieve as shown with the oft cited example of erythropoietin where a small change in product formulation (switch in the use of stabilizers) led to a significant change in product safety (increased incidence of pure red cell aplasia).[23]

The key issue is to determine whether sufficient relevant similarities in chemical composition, biologic activity, and pharmacokinetic aspects exist so that all relevant aspects of safety and efficacy can be reliably predicted based on knowledge of the innovator product. Along these lines, a number of questions arise related to the development of biosimilar drugs. Where do we set the threshold for similarity? What level of evidence is required to demonstrate biosimilarity? How best to protect patient safety? Can biosimilars be considered interchangeable? To what extent will post-marketing surveillance be required?

Regulatory issues

As part of the United States Patient Protection and Affordable Care Act of 2012,[24] the Public Health Service Act was amended to include an abbreviated approval pathway for biological products that are demonstrated to be highly similar (biosimilar) to or interchangeable with an FDA-licensed biological product. This is referred to as the "Biologics Price Competition and Innovation Act of 2009" or the 351(k) pathway. According to the FDA, a biosimilar is a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of the safety, purity, and potency.[25]

Totality of evidence approach

As part of this process, the FDA has issued draft guidelines describing the risk-based "totality of evidence" approach that they intend to use to evaluate biosimilarity. This guidance suggests a step-wise approach to demonstrating biosimilarity that includes comparisons of structure, function, animal toxicity, human pharmacokinetics/pharmacodynamics, immunogenicity, and safety/effectiveness between the proposed biosimilar and the reference product. Such an approach integrates multiple measures to develop "fingerprints" that can be used to characterize complex products. The type and extent of analyses that will be required to demonstrate biosimilarity will be determined on a product-specific basis. The extent of animal and clinical testing that will be required will depend on the amount of residual uncertainty in the product's sameness. That is, the amount of additional in vivo data that is required for approval may be reduced in cases where the structure can be characterized and there is sufficient clinical experience with the innovator drug.

The European Medicines Agency (EMA) has issued broad guidelines that are applicable to all similar biological medicinal products that include guidance on stability testing, quality issues, and preclinical safety testing. Additionally, product specific guidelines have been published (although not all are yet in effect) for products containing follicle stimulation hormone, recombinant interferon alpha, recombinant

interferon beta, monoclonal antibodies, recombinant erythropoietin, LMWH, recombinant colony stimulating factor, somatropin, and recombinant human insulin.[26]

It is accepted that innovator biologic drugs can show some batch-to-batch differences in terms of structural properties or biologic potency. The development of a biosimilar drug requires more effort than developing a generic small molecule drug in that a detailed analysis of the reference product must be made by the manufacturer of the biosimilar to define the target range for any given parameter within which the biosimilar must fall. If any parameters are outside the reference range for the innovator, it must be shown not to impact clinical behavior of the drug.[15] This is similar to the analysis that would be performed by the innovator company if a change in the production process for the innovator drug was made.

Safety of biosimilars

Beyond product specific safety concerns (ie, bleeding with LMWH), the primary safety concern with biosimilar drugs, as with biologic drugs in general, is the potential for immunogenicity. Immunogenic responses to biologic drugs can occur as a result of multiple factors. Immunogenicity increases as the extent of change in the amino acid sequence changes. Structural alterations that arise from differences in storage conditions, purification, or formulation of the product or the presence of impurities can trigger an immunogenic response.

Unfortunately, assessing the potential for immunogenicity is not easy as in vitro assays and animal models have limited ability to predict the human response.[27] Additionally, the underlying disease state of the patient can impact the development of the immune response. As such, clinical data is the best indicator of immunogenic potential. In cases where the incidence of an immunogenic response is low, the best means of identifying potential problems is through careful post-marketing surveillance. For such a system to be effective, however, there needs to be clear identification of the particular product administered to a given patient. Thus, in addition to the drug's generic name, adverse event reports should indicate a brand name or manufacturer name to identify the product.[28]

The impact of an immunogenic response can vary widely. Some antibodies may not alter the clinical effectiveness of the drug. Others may cause allergic or anaphylactic type responses. Neutralizing antibodies are of particular concern as they can limit the effectiveness of the therapy or may neutralize the endogenous protein.[29]

Another safety concern associated with the use of biosimilars revolves around the concept of interchangeability. As stated earlier, small molecule generic drugs are automatically considered to be interchangeable unless otherwise stated. Since biosimilars are not exact copies of the innovator drug, it must be demonstrated that the risk associated with switching from or alternating between innovator and biosimilar is not greater than the risk associated with remaining on the innovator therapy and that the clinical benefit remains the same. Seemingly simple issues such as batch-to-batch consistency also become important aspects in determining the frequency of immunogenic reactions, interchangeability, and similarity of the biosimilar to the innovator.

Biosimilar granulocyte colony stimulating factor

Six biosimilar versions of filgrastim (Neupogen®, Amgen Inc, Thousand Oaks, CA, USA) have market authorization at the European Union level.[30] A number of studies have been published that compare chemical/physicochemical properties[31,32] or clinical behavior[33–36] of one of more biosimilar filgrastims with Neupogen. These studies have indicated that primary structure, purity, and molecular characteristics of the biosimilar and originator products are comparable. Similarly, the biosimilar and branded drugs were bioequivalent in terms of efficacy (duration of severe neutropenia, time to neutrophil count recovery) and exhibited statistically similar safety profiles.

Biosimilar human growth hormone

Two biosimilar versions of somatotropin (Genotropin®, Pfizer Inc, New York, NY, USA) have market authorization at the European Union level.[30] Published studies have shown that the biosimilar and the originator drugs are comparable in terms of pharmacokinetics,[37] therapeutic efficacy,[38] and incidence of adverse effects.[39]

Biosimilar erythropoietin

Five biosimilar versions of erythropoietin (epoetin alpha or epoetin zeta) have market authorization at the European Union level.[30] While biosimilar preparations of erythropoietin have been shown to be equally effective as the originator drug,[40–42] there are concerns related to the generation of neutralizing antibodies[43] and the development of pure red cell aplasia.[23,44]

Biosimilar LMWHs

Although not considered biologic products as defined by US PHS Act section 351(i), LMWHs are complex drug

products sourced from biologic material. The development of biosimilar LMWHs illustrates clearly the complicated issues associated with defining biosimilarity of complex drug products as discussed below. European regulatory agencies consider LMWHs as true biosimilars whereas the US FDA treats these agents as generic drugs. The criteria used by the FDA to define the sameness of the enoxaparin preparations are summarized in Table 2.

Source material (LMWHs)

The starting material for the production of LMWHs is unfractionated heparin. While heparin can be isolated from a variety of species and tissues, clinical grade heparin is primarily isolated from porcine intestinal mucosa.[45] Heparin is a complex mixture of glycosaminoglycan chains that vary in molecular weight from approximately 3000 to 30,000 Da.[46] For heparin chains of any given size, there is another level of heterogeneity in that the components that make up the heparin chains are not identical. Heparin chains are made up of alternating glusosamine (basic) and hexuronic (acidic) sugars; the hexuronic acids can be either epimer iduronic or glucuronic acid. Further, these chains exhibit differential patterns of sulfation and acetylation.[47,48] The structure of heparins isolated from different species or tissues is known to exhibit structural differences.[49,50]

These structural attributes of heparin govern its pharmacologic profile in that heparin chains of varying length (molecular weight) exhibit varying pharmacologic effects.[51–53] For example, it is well appreciated that there is a minimal heparin chain length required to promote thrombin inhibition.[54] In addition, pharmacokinetic behavior is influenced by chain length, with shorter heparin chains exhibiting a higher bioavailability and slower clearance than larger chains.[46] Such differences in pharmacokinetic and pharmacologic effects (as will be illustrated below) have led to the classification of LMWHs from different manufacturers as individual drugs.[55]

The content and location of sulfate groups along the saccharide chains impact the ability of heparin to interact with various proteins. The most notable illustration of this is the presence of a particular 3-O sulfate group required for interaction of heparin with antithrombin.[56] This 3-O sulfate group is present on only a small percentage of heparin chains. It is known that various structural features of heparin including average molecular weight, the extent of sulfation, iduronic acid content, and level of acetylation vary between species and can be altered by factors such as diet, source tissue collection, and processing.[57] As the relative content of these structural features is carried through from starting heparin to LMWH product, control and characterization of the starting material (unfractionated heparin) is crucial to produce a biosimilar LMWH.

Characterizing the various components that make up a heparin LMWH preparation requires considerable analytical effort. While techniques are available to break down the oligosaccharides into their component saccharides, simply knowing the content of these components is not sufficient to define similarity as their linkage, and thus relative position in the oligosaccharide chain, will determine the ultimate biologic effect of that oligosaccharide chain,[58,59] remembering that a myriad of different oligosaccharide chains make up a LMWH.

Table 2 FDA criteria for demonstration of sameness of enoxaparin active ingredient[72]

1. Equivalence of physicochemical properties.
2. Equivalence of source material and the method of depolymerization.
3. Equivalence of disaccharide building blocks and oligosaccharide sequence.
4. Equivalence in biochemical and biologic assays.
5. Equivalence of in vivo pharmacodynamic profile.

Abbreviation: FDA, US Food and Drug Administration.

Production process (LMWH)

LMWHs can be produced using a variety of cleavage reactions.[60] In addition to a reduction in molecular weight, the cleavage of heparin chains results in structural changes at the site of cleavage as well as to the saccharide backbone that are dependent upon the reaction conditions. The use of β-elimination reactions (either chemical or enzymatic) leads to the generation of a double bond at the non-reducing terminal. Additionally, there are side-reactions that lead to changes in the saccharide units. Such changes include a reduction in 2-O sulfation, epimerization of terminal sugar residues and the formation of 1,6-anhydro sugars. The extent of such changes, particularly the formation of 1,6-anhydro sugars, are known to be dependent on reaction conditions such as pH and temperature.[61] Thus, the measurement of such parameters can be used as a means to confirm that the production process used to make the biosimilar is comparable to that used to make the innovator. Additional microchemical changes which may not be so obvious can also be inflicted during the manufacturing process. Because of the variations in chain composition and their relative abundance, such changes are not easy to detect.

Potency characterization (LMWH)

Small molecule drugs typically target single sites. LMWHs, in contrast, are multi-target drugs whose effects are mediated

through a variety of cofactors.[62] Although the potency of LMWHs and their dosing are based on their anti-factor Xa activity, additional actions such as the inhibition of thrombin and the release of mediators from the vascular endothelium such as tissue factor pathway inhibitor contribute to the overall biologic effect of the drug.[62] Complicating the potency characterization is the fact that different oligosaccharide chains can mediate different activities. Only chains containing a particular AT-binding pentasaccharide can inhibit factor Xa and thrombin and such oligosaccharides must be longer than 16 saccharides in order to inhibit thrombin.[63] AT-binding pentasaccharide containing chains make up approximately 25%–30% of the oligosaccharides in a LMWH preparation. Therefore, measuring pharmacopoeial potency of LMWHs (anti-Xa and anti-thrombin activity) only measures the biologic effects of a fraction of the oligosaccharide chains in the preparation. Saccharides with and without the AT-binding pentasaccharide can still exhibit biologic effects such as the release of tissue factor pathway inhibitor. Characterizing potency based on one parameter is insufficient as the ratio of all of the antithrombotic activities of a LMWH is not consistent across different LMWH preparations.[51,62] The in vitro potency as determined by conventional methods may not always be proportional to the in vivo effects due to the endogenous interactions and indirect effects of these polypharmacologic agents. For these agents some additional in vivo potency evaluation may be useful.

Bioequivalence (LMWH)

Bioequivalence of small molecule drugs can be shown in a straightforward manner by measuring circulating blood levels of the drug at several time points following administration. For LMWHs, this is more difficult as chemical assays to determine blood levels do not exist due to the heterogeneity of the product. Rather, drug concentrations are estimated based on pharmacodynamic levels of activity.[64] Each biologic activity can exhibit different pharmacokinetic behavior as different sized oligosaccharide chains are absorbed and cleared at different rates.[65]

Immunogenicity (LMWH)

Like other biologic drugs, heparins can elicit an immune response. This condition is known as heparin-induced thrombocytopenia (HIT). In heparin treated patients, antibodies can develop against a complex of heparin bound to platelet factor 4 (PF4), a protein found in platelet alpha-granules. While it is appreciated that immunogenicity is influenced by the relative size of the PF4-heparin clusters (heparin > LMWH > fondaparinux), the exact epitopes that trigger antibody formation are not known.[66] Simply measuring the incidence of antibody formation is not sufficient to determine biosimilarity as a far greater proportion of treated patients develop PF 4-heparin antibodies than go on to develop clinical HIT. It has also been shown that the incidence of antibody formation is not only dependent on the size of the heparin chain, but also on the clinical population being treated.[67]

Although most antibodies that develop against the PF4-heparin complex do not cause a biologic effect, in a small fraction of patients these antibodies are functional in that they can bind to Fc receptors on the platelet surface, leading to platelet activation that can be measured by laboratory assays. A fraction of "functional" antibodies will facilitate the development of venous or arterial thrombosis which can lead to ischemia or death. The relative proportion of patients falling into each category (no antibody, non-functional antibody, functional antibody, clinical HIT) differ according to the patient population being treated.[68]

The incidence of developing HIT in patients treated with LMWH is less than that seen with heparin treated patients, with the incidence of developing PF4-heparin antibodies estimated at 2%–8% and the incidence of clinical HIT estimated as 0%–0.9%.[67] Little is known regarding why heparins elicit an antibody response in some patients and not in others or why only some patients who have developed antibodies go on to thrombose. There is some suggestion that particular ratios of heparin to PF4 are needed to develop the antigenic epitope.[69,70]

While cross-reactivity of a heparin preparation can be determined with in vitro techniques, such assays are not able to demonstrate whether the antigenicity of different preparations is clinically different. Several attempts have been made to mimic HIT with an animal model, with varying success. In a model in which mice were immunized with human anti-PF4-heparin antibodies, administration of heparin or LMWH led to a thrombocytopenic response similar to that seen in humans, but there was no development of thrombosis.[71] Human data, obtained through clinical trial or post-marketing surveillance, remains the best way of determining the immunogenicity of LMWH.

Demonstration of efficacy (LMWH)

The development of most biosimilars is expected to require some demonstration that its efficacy is comparable to that of the innovator drug. In the case of the LMWH enoxaparin, the FDA did not require clinical data outside of demonstrating

equivalence of the in vivo pharmacodynamic profile (in terms of anti-factor Xa and anti-thrombin activity),[72] relying instead on in vitro potency data and extensive physicochemical data to demonstrate equivalence in physicochemical properties, source material, mode of depolymerization, disaccharide building blocks, and oligosaccharide sequence. This is in contrast to the current EMA guidelines[73] that recommend that clinical efficacy and safety be demonstrated in at least one adequately powered, randomized, double-blind, parallel group clinical trial. This recommendation is based on the knowledge that a clear correlation between pharmacodynamic parameters (anti-factor Xa or anti-thrombin activity) and clinical outcome has not been established. A number of peer groups have also expressed opinions on the development of biosimilar LMWHs.[74,75]

Summary

Biologic drugs are either derived from biologic material or are produced through the use of recombinant DNA technology. Such drugs include vaccines, replacement proteins (enzymes, blood clotting factors) or cytokines, hormones, and antibodies used to treat a variety of conditions including leukemias and rheumatoid disorders. Biosimilars are copies of biologic drugs whose patent protection has ended and are analogous to a generic version of a chemically-derived drug. Biosimilars, however, are much more complicated to develop than a generic version of a chemically derived drug owing to their complex structure and inherent variability.

To develop a biosimilar, a multi-step approach has been described by regulatory agencies and others.[34] Such an approach requires iterative physicochemical and biological characterization to develop the production process and validation of biosimilarity through preclinical, pharmacokinetic/pharmacodynamic and/or clinical trials. Although there are isolated reports in the literature demonstrating instances where bioactivity of a non-innovator did not meet the specifications for the innovator,[76] issues with potency are not expected if the biosimilar is developed according to the recommended multi-step approach.

The primary safety concern with the use of biosimilars as with innovator biologic drugs is the potential for immunogenicity. Immunogenic potential can be difficult to predict as in vitro assays and animal models often do not correlate with the human response which can be impacted by the disease state or other patient-specific factors. There is also the concern that immunogenicity could be enhanced if there are repeated switches between innovator and biosimilar (or multiple biosimilars), calling into question whether biosimilars can be considered interchangeable.

Another potential safety issue relates to the extrapolation of efficacy or safety data to other indications in which the innovator drug is approved for use. LMWHs, for example, are used in the treatment of both venous and arterial thrombosis, conditions where the pathophysiologic mechanisms involved in clot formation differ. Additionally, as mentioned earlier, the incidence of the immunogenic response to heparins varies in different patient populations. Thus, additional data may be required to confirm biosimilarity across all indications.

Current perspective

Biosimilar drugs will have a major impact in the management of various diseases in coming years. Although the current discussion and guidelines are focused towards biosimilars of protein origin, additional biosimilar agents, such as glycosaminoglycans, nucleic acid derivatives, complex lipoproteins, and complex organic macromolecules of natural origin will emerge. Simple chemical characterization of such agents without requiring biologic and clinical studies may not be optimal to assure their safety and efficacy. Thus additional guidelines are needed for the rational development of biosimilar drugs.

Disclosure

The authors have received financial support in the form of a research grant to Dr Jeanine Walenga from Sanofi (Paris, France) for the study of biosimilar low molecular weight heparins. The authors are fully responsible for all content and editorial decisions related to the development of this manuscript.

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