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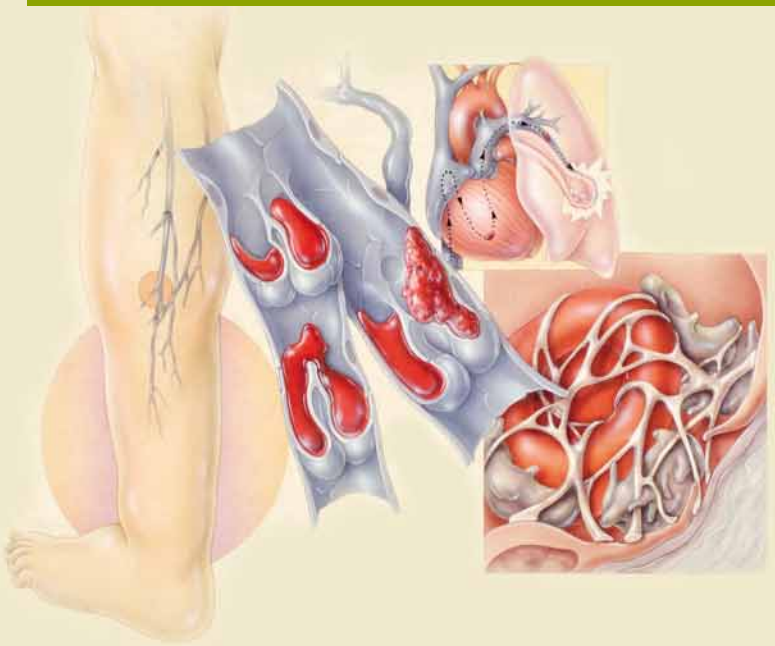
Low-Molecular-Weight Heparins: Patient Safety and Clinical Data Requirements for Follow-on "Generic" Biologic Compounds

HIGHLIGHTS OF A ROUNDTABLE



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James Boyd Groce III, PharmD, CACP is a consultant to sanofi-aventis and Eisai. **Victor F. Tapson, MD, FCCP** has received funding for clinical grants from Bayer and sanofi-aventis. **Jawed Fareed, PhD** is a consultant to Mitsubishi Pharma. **Philip Marcus, MD, MPH, FCCP** has nothing to disclose. **Gourang P. Patel, PharmD, MSc, BCPS** is on the advisory boards of sanofi-aventis and Pfizer. **Lilia Talarico, MD** has nothing to disclose.

Introduction

Prevention of thromboembolism (VTE) and its manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE) is one of the principal issues in the care of hospitalized patients. VTE is often silent; its presence has too often been recognized when PE is found at autopsy.

Prevention of VTE by appropriate prophylactic measures is recommended in evidence-based guidelines. Until low-molecular-weight heparins (LMWHs) became available in the 1990s, anticoagulants used for VTE prophylaxis included unfractionated heparin (UH) and other agents, such as vitamin K antagonists. LMWH has proven to be reliably safe and effective in VTE prophylaxis in both medical and surgical patients. VTE prophylaxis has also been shown to be cost-effective when drug and associated costs are compared with the costs of not preventing the sequelae of PE and lengthened hospital stay.[1]

As the patents begin to expire on the branded LMWH products, efforts are underway to develop and receive regulatory approval for what would be called "generic" versions of the branded products if they were chemical drugs. However, the description "generic" as commonly applied to follow-on products to branded chemical drugs cannot, and is not being used in the literature or by regulatory bodies to describe follow-on products to drugs of biologic origin. The LMWHs are drugs of biologic origin.

The LMWHs are derived from UH, which has a biologic source—most commonly, cells from porcine intestines. The UH molecule is about 15 kDa in size and is a complex mixture of oligosaccharide chains made up of sugar units. LMWH molecules are produced in a manufacturing process that depolymerizes the oligosaccharide chain and produces a molecule about 3.7 kDa in size. Each LMWH is made by a unique manufacturing process that is proprietary for each manufacturer. Each LMWH molecule can be characterized by specific differences in molecular structure, biochemical and pharmacologic profiles, and clinical effect.[2]

Although the LMWH molecules are distinct in biochemical, pharmacologic, and clinical profiles, understanding is still incomplete regarding the relationship between molecular structure and clinical activity—for example, why 60% to 70% of a LMWH molecule does not contribute to anticoagulant activity. Immunogenicity—a principal side effect of LMWH—may be associated with the molecular structure that does not contribute to anticoagulation.

As the probability increases that follow-on ("generic" or "biosimilar") LMWH drugs will be developed and approval for them will be sought, it becomes important to establish criteria for a well-defined LMWH. These should include[3]:

- Reproducibility of pharmacologic activity beyond anti-factor Xa and anti-factor IIa activity despite complexity of molecular structure and biologic origin
- Reliability of clinical use in any clinical setting studied in (1) sufficiently large patient populations and (2) special patient populations.

The question of describing biologic drugs that would be called "generic" if they were chemical drugs has been addressed by regulatory bodies in the United States and Europe. The term "biosimilar" has been adopted by the European Medicines Agency (EMEA). The US Food and Drug Administration (FDA) prefers the term "follow-on" to describe drugs that are developed and marketed as alternatives to branded biologic drugs. The terminology would apply to monoclonal antibodies and other products of biologic origin. The FDA has stated that the term "follow-on" describes a product that may be close, but not identical, to the reference drug.

A process exists within the FDA for application, review, and approval of generic chemical drugs. At present, no process exists within the FDA for reviewing and approving applications for follow-on biologic drugs such as LMWH, based on previous FDA approval of a branded product. Approval of follow-on biologics such as LMWH is not specifically permitted under existing law. Congressional action will be required to make necessary amendments in the relevant legislation.

Considerations that will have to be addressed when approval is sought for a follow-on biologic drug such as LMWH include:

- Full characterization of the reference (branded) drug
- Available analytic tests to assess safety
- Assessment of clinical efficacy in specific clinical situations
- Reproducibility of the manufacturing process, with consideration of product complexity and proprietary restrictions on the manufacturing process
- Adequacy of bioassay technology to compare the branded and follow-on products
- Immunogenic potential of the follow-on drug.

Safety must be a major issue in review of application for follow-on biologics. LMWH drugs in use today are regarded as having high risk in clinical practice, as are other anticoagulants such as UH and warfarin.[4] The known risks in clinical practice may be additive with currently unknown risks of follow-on LMWHs because of differences in biologic origin of source material, manufacturing processes, molecular structure, clinical effect, and side effects such as immunogenicity.

The question of therapeutic interchange will continue to be important for follow-on LMWHs as it is currently for branded products. Therapeutic interchange is regarded as inappropriate for branded LMWHs on the basis of differences in biochemical and pharmacologic profiles and clinical effect identified in well-designed clinical trials.[5]

There are examples that illustrate how even minor changes in the formulation of a biologic agent can have significant clinical consequences (eg, a small change in formulation of epoetin-α resulted in development of neutralizing antibodies to both the drug and native erythropoietin in some patients).[6]

Use of follow-on LMWH agents will require vigilance:

- Being aware that follow-on (biosimilar) products are not identical to their reference products and that there may be unknown or untested safety issues
- Insisting on extensive testing of safety/efficacy—immunogenicity in particular—both preapproval and postapproval
- Adoption of postapproval mechanisms to facilitate detection of rare adverse events associated with each manufacturer's follow-on product
- Distinct International Proprietary Names and trade names for each follow-on product to help prevent mistakes in prescribing and to facilitate reporting of adverse events.

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Background, Scope of the Problem, and Therapeutic Options

Philip Marcus, MD, MPH, FCCP and Victor F. Tapson, MD, FCCP, Co-Chairs

When the current, branded low-molecular-weight heparin (LMWH) agents go off patent, will there be products described variously as "generic" or "biosimilar," and will they be safe in clinical use?

The anticoagulant properties of LMWH have made the currently available branded drugs particularly useful in the prevention of venous thromboembolism (VTE) and its clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE). Of course, VTE must be recognized and not missed or mistaken for some other entity; for example, a patient was admitted with a diagnosis of chronic obstructive pulmonary disease (COPD) exacerbation and proved to have a fatal PE (**Figure 1**).

If every LMWH drug is different from every other LMWH drug in multiple ways, can there ever be a biosimilar ("generic") version of LMWH that meets essential criteria for patient safety? This question is addressed by every speaker in this roundtable, and, until it is resolved satisfactorily, the question will remain open.

Prevention of VTE by appropriate prophylactic measures is recommended in evidence-based guidelines, such as those of the American College of Chest Physicians.[1,2] The guidelines are well known, but not always whole-heartedly adopted and enforced by hospitals or rigorously employed by physicians.

In too many instances, PE is diagnosed at autopsy. In a 1989 study, Sandler and Martin[3] found that autopsy revealed (1) PE to be the cause of death in 239 of 2,388 patients (10%), of whom 15% were less than 60 years of age and 60% did not have cancer, (2) 83% had a DVT at autopsy, of which 19% were symptomatic, (3) 3% of patients with DVT at autopsy had undergone an antemortem examination, and (4) a majority of those who died of PE were medical patients. The findings confirm what physicians generally know: that most DVTs are silent, and not finding one on physical examination does not prove that a DVT is not present.

A number of studies have shown that any hospital stay increases risk for VTE, DVT, and PE. An old, but still useful, study diagrams the natural history of DVT (**Figure 2**), illustrating why prophylaxis can help prevent the unpredictable evolution of DVT into PE.[4]

We know from studies, and from our own experience, that the patient who has a DVT is likely to be predisposed to DVT in future events, such as a hospital stay or a long airplane flight. Risk for sequelae of DVT can increase in years following the initial event; sequelae for which a patient can be predisposed include postthrombotic syndrome with chronic edema, a condition for which the physician must be alert in order to recognize it, and PE.[5]

Goldhaber et al[6] reported a 2004 retrospective analysis showing that 71% of 5,451 patients with documented DVT had not received any form of prophylaxis; 60% were medical patients and 40% were surgical patients. Interestingly, of the patients who received DVT prophylaxis, 60% received pharmacologic prophylaxis (38% unfractionated heparin [UH] and 26% LMWH). Surprisingly, DVT was four times more common with use of UH than with LMWH.

Because LMWH—particularly the most commonly used agent, enoxaparin—is a reliable prophylactic agent for prevention of VTE, we see that we must deal substantively with the following question: Will there be a safe and effective biosimilar ("generic") LMWH? In partial answer, we already know that the answer is "no" insofar as the term "generic" is suitable for describing follow-on chemical drugs, but not for biologics.

Failure to prescribe VTE prophylaxis can be described as "missed opportunities" (**Figure 3** on page 5).[7]

The figures that stand out are the 68% of patients for whom prophylaxis was inadequate and the 47.7% who did not receive prophylaxis. The data indicate, again, that physicians are not aware of risk for VTE and PE, or, if they are aware of risk, they are dealing with it inadequately. Reasons for omission or inadequacy of VTE prophylaxis may include lack of reliable data regarding risk in various patient populations.

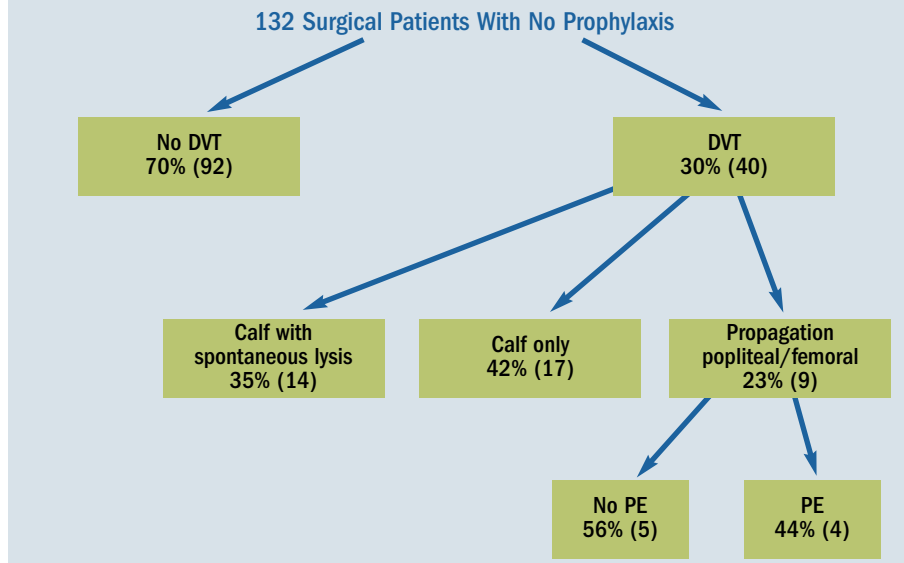
What can be done to increase physician awareness of risk for VTE? An approach that should be mandatory for all hospitals is screening for VTE risk in all patients, with daily reassessment of risk and prompt prophylaxis as indicated.[8,9]

What is the optimal prophylactic intervention? A number of studies looking at low-dose UH or LMWH as compared to no prophylaxis in medical patients showed that intervention after (1) no prophylaxis or (2) placebo resulted in significant (trials

Figure 1. Pulmonary Embolism Misdiagnosed as a "COPD Flare"

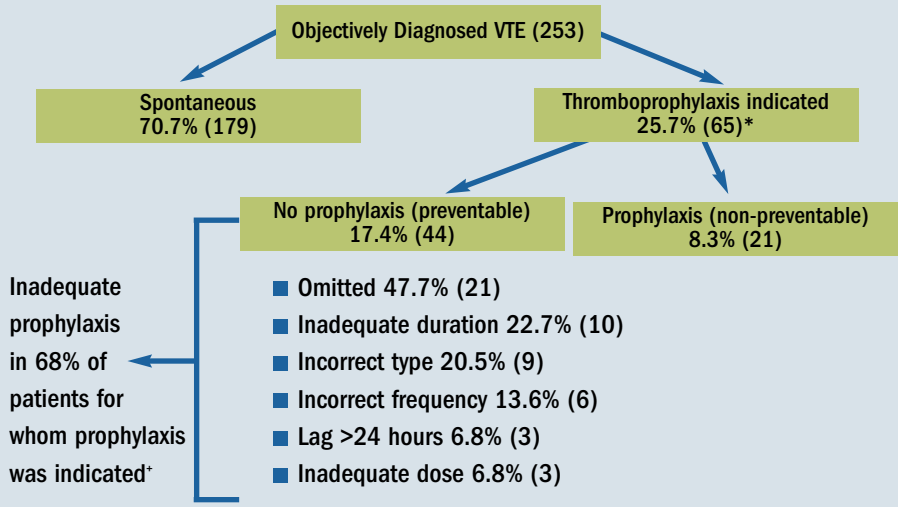
COPD=chronic obstructive pulmonary disease.
Courtesy of Victor F. Tapson, MD

Figure 2. Natural History of Deep Vein Thrombosis[4]



DVT=deep vein thrombosis; PE=pulmonary embolism.

Figure 3. Missed Opportunities in Venous Thromboembolism (VTE) Prevention[7]



*3.6% (9) ineligible for prophylaxis.
+Multiple causes in 7 patients.

Table 1. Cost of Deep Vein Thrombosis (DVT)[15]

			COST			
Complication	No.	LOS (d)	Day	Stay	Post	Total
None	1387	4.5	$ 820	$3486	$1616	$5102
Major bleed	287	8.6	$1460	$11,189	$5980	$17,168
Minor bleed	410	6.9	$1174	$7980	$4162	$12,142
PE	725	7.5	$1320	$9476	$5173	$14,649
Thrombocytopenia	143	6.6	$1378	$8679	$4790	$13,459
None of 4 above	27,321	5.7	$1020	$5561	$4223	$9784
All DVT	29,295	5.8	$1036	$5779	$4293	$10,072

LOS=length of stay; PE=pulmonary embolism.
Adapted from O'Brien JA, Caro JJ [15]

Table 2. FDA-Approved Indications for LMWH

FDA-Approved Indication	Enoxaparin (Lovenox®)	Dalteparin (Fragmin®)	Tinzaparin (Innohep®)
Abdominal surgery	■	■	
THR (during hospitalization)	■	■	
THR (extended prophylaxis)	■		
TKR	■		
Hip fracture surgery			
Medically ill prophylaxis	■	■	
Inpatient DVT +/- PE	■		■
Outpatient DVT	■	■	
Extended therapy (cancer)	■	■	
ACS	■	■	

FDA=US Food and Drug Administration; LMWH=low-molecular-weight heparin; THR=total hip replacement; TKR=total knee replacement; DVT=deep vein thrombosis; PE=pulmonary embolism; ACS=acute coronary syndrome.

summarized below) risk reduction with one exception—when the LMWH dose was too low (20 mg as compared to 40 mg).[8] Risk reduction was clearly dose-dependent. The PRIME[10] and PRINCE[11] trials found enoxaparin equally effective in preventing DVT as UH while resulting in a smaller incidence of bleeding and other adverse events. The MEDENOX[12] trial showed that enoxaparin prophylaxis at a 40-mg daily dose was superior to placebo in preventing DVT ($p<.001$), without increases in adverse events. The 40-mg dose was demonstrated to be superior to the 20-mg dose in DVT risk reduction. The PREVENT trial[13] looked at dalteparin, 5000 IU for 12 to 14 days, versus placebo for DVT prophylaxis in 2681 acutely ill hospitalized patients. Improvement was seen in the primary endpoints of sudden death, asymptomatic proximal DVT, and objectively verified symptomatic DVT or PE. No fatal PEs occurred in patients receiving dalteparin versus two in the patients receiving placebo.

Failure to initiate prophylaxis or to ensure adequate prophylaxis may result in VTE during or after hospitalization. Some patients who receive appropriate prophylaxis go on to develop VTE despite the prophylaxis, demonstrating that prophylaxis reduces, but does not eliminate risk.[14]

Risk reduction versus risk prevention raises the following question: Is VTE prophylaxis cost-effective? Anticoagulant drugs represent a cost to consider in the overall treatment of a hospitalized patient, and LMWH costs more than does UH. Does the cost of reducing risk for VTE and PE outweigh the cost of anticoagulant drugs? **Table 1** summarizes data for costs of DVT in hospitalized patients, including the cost of a major bleed that may be associated with DVT prophylaxis.[15]

Overall, prophylaxis does lower costs for the hospitalized patient, and the cost of VTE prophylaxis is cost-effective.[16]

Data thus demonstrate that, although LMWH is regarded as a "high risk" drug on the basis of its anticoagulant activity, it has a good profile for safety and effectiveness, and it is cost-effective in reducing risk for VTE and its sequelae in hospitalized patients.

As the currently available branded LMWH drugs begin to go off-patent, there will be movement to seek regulatory approval for LMWH drugs that would be called "generic" if they were chemical drugs. Each currently available branded LMWH drug has specific indications approved by the US Food and Drug Administration, as shown in **Table 2**.

The specific indications for each branded LMWH drug show prescribers that currently available LMWH drugs are not always interchangeable one-for-one. Substitution of one LMWH with another may have clinical consequences that put the patient at risk.

continued on page 10

Differentiation Among the Low-Molecular-Weight Heparins

Jawed Fareed, PhD

The four classes of antithrombotic drugs (heparins, vitamin K antagonists, direct thrombin inhibitors, factor Xa inhibitors) have different targets in the coagulation cascade (**Figure 1**). The heparins also have indirect effects or nonanticoagulant effects that may contribute to the antithrombotic effects—for example, downregulation of adhesion molecules and endothelin.

The complex molecular structure of the heparins accounts for these effects that are not fully understood in terms of their relative contributions, but ongoing research will eventually provide the necessary understanding.

There is some overlap in the targets of the antithrombotic drugs, and this has clinical value for individualizing therapy to the needs and characteristics of the patient.

The low-molecular-weight heparins (LMWHs) have a fairly broad spectrum of therapeutic usefulness. We describe LMWHs as a biologic product derived from unfractionated heparin (UH), which are obtained from mammalian tissue—usually pig intestines. UH is a molecule of 15 kDa in size with an anti-factor Xa/IIa activity of 1.0. The UH molecule is a complex mixture of oligosaccharide chains made up of sugar units.

LMWHs are produced by depolymerization of the long oligosaccharide chains of UH into smaller chains. The average weight of a LMWH is about 3.7 kDa, with anti-factor Xa/IIa activity of 2 to 8. The molecule characterized as an ultra-LMWH ranges between 1 and 3 kDa, and its anti-factor Xa/IIa activity is 10 to 50. A synthetic heparinoid, a laboratory-produced drug such as a pentasaccharide, weighs less than 2 kDa and has pure anti-factor Xa activity.

The LMWH products in our formularies are differentiated by more than their brand names and US Food and Drug Administration–indicated use. Each LMWH drug has been reduced in size by depolymerization of UH, but each has also been made by a unique, proprietary manufacturing process that affects specific structural features of the heparin macromolecule, as shown in **Table 1**.

Each of the LMWH agents can be characterized by specific molecular and structural differences.[1-4] The specific carbohydrate units and the sequence in which they appear in the molecule can mediate specific biologic properties that are unique to each agent. Structural differences in the LMWH molecules can relate to sulfate groups, acetyl groups, charge density, double-bond formation, formation of specific structures such as anhydromanno or anhydrogluco groupings, and the presence of 5-membered rings.

Each of the LMWH agents in use today is produced by a different manufacturing process—for example, chemical β-elimination (enoxaparin), enzymatic β-elimination (tinzaparin), nitrous acid depolymerization (dalteparin), and oxidative cleavage (ardeparin, parnaparin).

Some of the molecular components of LMWHs cannot be analyzed by direct analysis, and their functionality remains unknown. To what extent some of these unknowns may contribute to side effects such as immunogenicity remains to be discovered. Also, not yet fully explained is why 60% to 70% of LMWH molecules do not contribute to their anticoagulant actions.[1-6]

The differentiation of LMWH molecules based on chemical structure may be characterized as *primary*, relating to molecular structure; *secondary*, relating to the "chemical fingerprint," which differs with each depolymerization process; and *tertiary*, the "pharmacologic fingerprint" manifested in antithrombin III–binding sequences and biologic and pharmacologic effects that may be different in various populations.

Modification of molecular structure and the chemical/pharmacologic/clinical effects (using β-elimination as the example) are shown in **Figure 2**[5] and **Table 2** (J. Fareed, PhD, written communication) on page 7.

Variations are also seen in the antithrombin III and heparin cofactor II binding

Figure 1. Antithrombotic Drugs and Their Targets

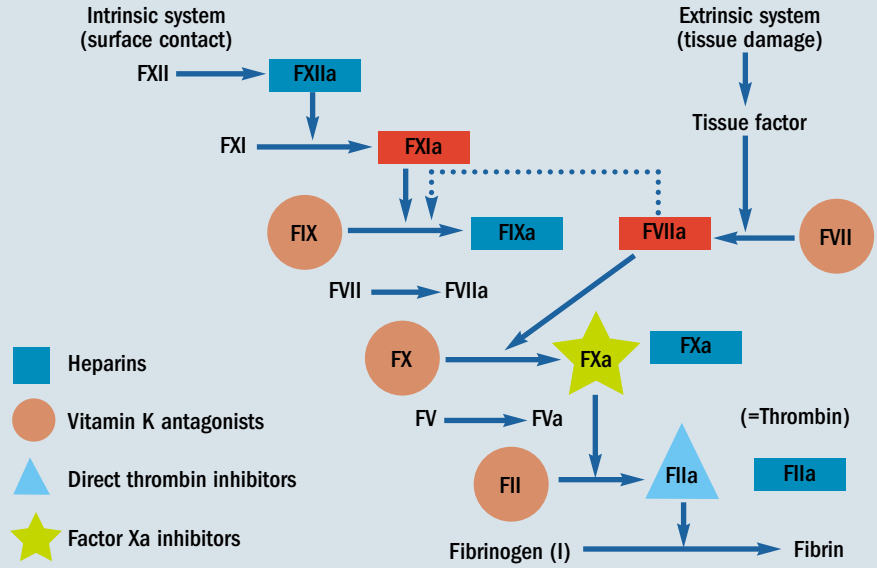


Table 1. LMWHs Can Be Differentiated by the Various Depolymerization Processes[5]

- Each LMWH manufacturer uses a distinct process of chemical or enzymatic depolymerization
  - Chemical β-elimination: enoxaparin, bemiparin
  - Enzymatic β-elimination: tinzaparin
  - Nitrous depolymerization: dalteparin, nadroparin, reviparin, certoparin
  - Oxidative cleavage: ardeparin, parnaparin
- The different depolymerization methods result in LMWHs with distinct chemical structures (length, chain sequences, structural fingerprints)
- Approximately 30% of the enoxaparin molecules cannot be characterized by direct analysis. There may be additional structural differences that would cause differentiation between LMWHs.

LMWHs=low-molecular-weight heparins.

of the various LMWH agents, and these agents can also be differentiated on this basis.[6,7]

Structural differences in LMWHs result in differentiating tertiary effects, which are shown in **Table 3**.

Manufacturers use anti-factor Xa and antithrombin activities to differentiate their LMWH products (**Table 4** on page 8).[8,9]

These data also have clinical significance[8,9] (eg, the plasma anti-Xa activity at approved doses for deep vein thrombosis prevention).[10,11]

The clinical differentiation of LMWH agents has not been compared on an agent-versus-agent basis. Comparisons are based on available data from individual studies (**Table 5**).

Renal failure is a condition that requires special consideration in the use of LMWHs. These agents are cleared primarily by renal excretion, with the result that the drugs have a prolonged biologic half-life in patients with renal failure. There are observed increases in anti-factor Xa activity in patients with diminished renal function. Renal insufficiency also increases risk for bleeding complications associated with therapeutic doses of LMWH. Unfortunately, there is no single creatinine cutoff level that correlates with increased risk for bleeding. However, at therapeutic doses, clearance of enoxaparin and nadroparin, but not tinzaparin, is linearly related to creatinine clearance—another indication that the differing pharmacokinetics of LMWHs may be especially important in renal failure.[12]

Data from studies, from clinical experience, and from manufacturers call attention to the fact that there are key differentiating factors between LMWH agents:

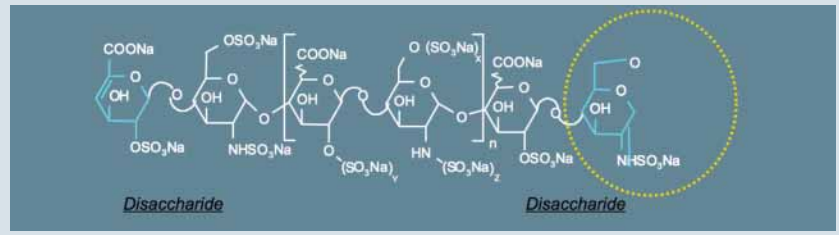
- LMWHs are similar in mean molecular weight, but compositional variations due to different manufacturing techniques give each agent a unique drug profile.
- Potency adjustments based solely on anti-factor Xa/IIa do not minimize variations between LMWH agents.
- Pharmacologic individuality based on the different chemical structures of LMWHs may be partly responsible for the clinical individuality of the agents in specific clinical indications.

Data clearly indicate that LMWHs are not interchangeable one-for-one. A number of US, European, and international regulatory bodies and medical societies have stated the following[13]:

- LMWHs cannot be used interchangeably, unit for unit, with heparin.
- No individual LMWH can be used interchangeably with another.
- The choice of LMWH should reflect the level of clinical evidence and the approval of regulatory authorities for that indication.

Figure 2. *Primary:* Structural Modification at the Cleavage Point[5]

- β-elimination (chemical or enzymatic): enoxaparin, bemiparin, tinzaparin



- Nitrous acid cleavage: dalteparin, nadroparin

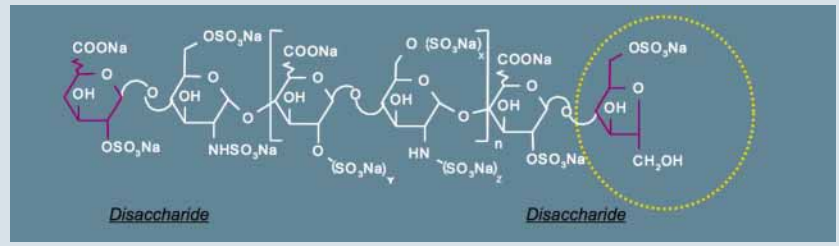


Table 2. *Secondary:* Depolymerization Modifies the Endogenous Backbone[5]

- Example: the β-elimination chemical fingerprints in the manufacturing of enoxaparin, bemiparin, tinzaparin

	Enoxaparin	Bemiparin	Tinzaparin
Condition	Chemical β-elimination: basic media	Chemical β-elimination: basic media	Enzymatic β-elimination: neutral media
Reaction	Depolymerization of heparin benzyl ester by base	Depolymerization of heparin benzethonium salt by CTA^+,OH^-	Depolymerization of heparin by heparinase I
Main side reactions	→1,6-anhydro ring, odd-numbered oligosaccharides →2-O desulfation →Epimerization in mannosamine	→2-O desulfation →Epimerization in mannosamine	No side reactions

- The 1,6-anhydro ring and odd-numbered oligosaccharides are both characteristic fingerprints of enoxaparin

Table 3. LMWH Tertiary Effects[5]

- Anticoagulant effects
  - Interaction with antithrombin (anti-factor Xa, anti-factor XIIa activities), heparin cofactor II, platelet factor 4
  - Inhibition of factor VIIa generation
  - Release of mediators from endothelial cells (tissue factor pathway inhibitor, tissue plasminogen activator, plasminogen activator inhibitor)
  - Modulation of activated protein C
- Antithrombotic effects
  - Cellular interaction
  - Downregulation and release of cellular adhesion molecules
- Anti-inflammatory effect
- Antiproliferative effects
- Immunologic effects
- Elimination half-life
- Renal clearance
- Safety
- Efficacy

LMWH=low-molecular-weight heparin.

Table 4. *Tertiary:* Anti-FXa and Antithrombin Activities of Various LMWHs[8,9]

LMWH	Anti-FXa (U/mg)	Antithrombin (U/mg)	Anti-FXa/ Anti-FIIa Ratio
Enoxaparin	100-110	25-30	3 to 4/1
Dalteparin	140-160	50-60	2 to 3/1
Nadroparin	90-100	25-30	3/1
Tinzaparin	90	50	2/1
Bemiparin	80-110	5-10	8/1
Heparin	160-180	160-180	1/1

FXa=factor Xa; LMWH=low-molecular-weight heparin; FIIa=factor IIa.

Table 5. Clinical Differentiation of LMWHs

Indication	Clinical Finding
DVT prophylaxis	Optimized dosages vary widely in terms of both gravimetric and anti-FXa U dosages
DVT treatment	Optimized dosages and dosing schedules are product specific
Acute coronary syndromes*	Individual products do not provide similar outcomes; only one product proven superior to UH
PCI	Individual products produce varying degrees of anticoagulation
Thrombotic stroke	Marked variations in clinical outcomes in terms of efficacy and bleeding
Combination therapy	Interactions with GP IIb/IIIa inhibitors and thrombolytics are influenced by the type of LMWH

LMWHs=low-molecular-weight heparins; DVT=deep vein thrombosis; UH=unfractionated heparin; PCI=percutaneous coronary intervention; GP=glycoprotein.
*Acute coronary syndrome=unstable angina and non-ST-elevation myocardial infarction

Looking to the question posed to this roundtable, we can ask, "What are the characteristics of a well-defined LMWH?"

Characteristics that we should like to see are:

- *Reproducibility* of pharmacologic activities beyond anti-factor Xa and anti-factor IIa activities despite (1) high complexity of molecular structure and (2) biologic origin or source material
- *Reliability* of clinical use in any clinical setting and studies (1) in sufficiently large patient populations and (2) special patient populations.

These are issues that will necessarily have to be considered if follow-on ("generic", "biosimilar") LMWHs are developed and regulatory approval is sought for them.[14,15] At least five companies have submitted applications to market biosimilar versions of enoxaparin and dalteparin in the United States.

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Safety of Biosimilar Compounds: Implications for Anticoagulants

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The Institute for Safe Medication Practices (ISMP) has identified medications with high risk in clinical practice. The list includes medications delivered by intravenous, intramuscular, and subcutaneous routes. Anticoagulants are on this list, including warfarin delivered orally and heparins or low-molecular-weight heparins (LMWHs) delivered intravenously or subcutaneously (**Table 1**).[1]

The MedWatch monitoring program of the US Food and Drug Administration (FDA) is a national inventory of information regarding medication safety. Analyses from national medical monitoring databases report information to pharmacy benefit managers in order to provide immediate action based on efficacy and safety analyses. Postmarketing information is collected for branded drugs, but postmarketing information is not required for generic products. The fact that data submission to MedWatch is voluntary limits the value of the program, as does the fact that reporting of an adverse event may be delayed. Other limitations of MedWatch include (1) its exhaustive review form that may militate against its use, (2) the definition of adverse events that may put pharmacists at odds with clinicians in identifying an adverse event, and (3) its dependence on the number of patients who have received the medication in a setting that can be monitored for safety.

Many opportunities for error resulting in safety issues are present in the manufacture, prescription, delivery, and monitoring of anticoagulants:

Manufacture

- Good manufacturing practices
- Quality assurance
- Processes for branded versus processes for generic products

Prescription

- Indications for use
- Patient characteristics (eg, weight, renal function)
- Interchangeability of drugs

Monitoring

- Accountability for agent use and delivery
- Identifying and reporting outcomes
- Efficacy and safety
- Appropriately trained allied professionals.

Other presenters in this roundtable have emphasized that the LMWH drugs currently in our formularies are not interchangeable. They have also emphasized the point that each LMWH drug has unique characteristics due to biologic origin and manufacturing process. Given that the currently available LMWHs are each unique products that are not interchangeable, the development and regulatory approval of follow-on ("generic," "biosimilar") LMWHs is likely to be very difficult.

Guidelines for the development of nomenclature for generic follow-on biologic agents and biopharmaceuticals have been issued by the International Proprietary Names arm of the World Health Organization. These guidelines state that (1) nomenclature must be based on analytical tools that prove that two chemical products produced by two different manufacturing processes are identical and (2) efficacy of the two products must be proven to be the same. The guidelines are meant to ensure the safety of prescription medications in prescribing, dispensing, and monitoring.[2,3]

For traditional generic chemical drugs, (1) similar efficacy is assumed, (2) safety is not monitored after product introduction, (3) interchangeability is assumed, (4) there are economic advantages in replacing the branded agent with the generic, and (5) agent use may be driven by physician preference and/or choice of pharmacy benefit managers.[2,3]

In the case of biologic agents such as LMWH, the starting material is derived from living cells, rendering it difficult to impossible to copy or duplicate. This can result in LMWHs that elicit significantly different immune responses from patients as a side effect. There is no scientific evidence to guarantee safety if biologic agents such as LMWH are interchanged. Molecular characterization is difficult, and mechanisms of action are unknown for the molecular structure that does not contribute to anticoagulation.

Table 1. Safety Assessment for Anticoagulants[1]

- Institute for Safe Medication Practices
  - Identification of high-risk medications
    - Anticoagulants: oral (warfarin)
    - Anticoagulants: IV and SC (UH and LMWH)
    - Chemotherapy
    - Epidurals
    - Insulin
    - Adrenergic agents (vasopressors)
    - Opioids
    - Total parenteral nutrition (TPN)
    - Dextrose (greater than 20%)
    - Hypertonic saline
    - Neuromuscular blockers

IV=intravenous; SC=subcutaneous; UH=unfractionated heparins; LMWH=low-molecular-weight heparin.

Immune responses to biopharmaceuticals can be classified on the basis of the origin of the immunogenic molecule—exogenous or endogenous. Exogenous proteins of nonhuman origin stimulate formation of neutralizing antibodies. The response is mediated by T cells, is very rapid, and occurs with the host's first encounter with the antigen. Endogenous proteins (of human origin) stimulate formation of binding antibodies. The response is mediated by B cells through breakdown of immune tolerance; the response develops slowly and disappears after the endogenous protein is no longer present (eg, therapeutic use of the endogenous protein is completed).[4,5]

Biopharmaceuticals that are not entirely soluble may be identified as viruses or viral-derived particles by the immune system, leading to B-cell activation via a signal to T cells that breaks B-cell tolerance.

Immunogenicity has clinical consequences, including the increased risk for severe allergic or anaphylactic reaction, reduced efficacy of the therapeutic agent, and autoimmunity in the patient.

We have routinely accepted the fact that overall efficacy is questionable for some agents that are standard in our formularies. A prime example is unfractionated heparin (UH)—a molecule with efficacy limited to 20% to 30% of the molecular structure, with unknown effects that may be associated with the major portion of the molecular structure.

How many of these "unknowns" are we prepared to accept for follow-on ("generic," "biosimilar") LMWH agents that will not be identical to the branded drugs? One such "unknown" is the capacity of a therapeutic molecule such as LMWH to initiate an immune reaction in a patient.

The stimulation of neutralizing antibodies is likely to have more impact on the safety and efficacy of follow-on LMWHs than is the stimulation of nonneutralizing antibodies. Neutralizing antibodies bind to the drug molecule and neutralize its clinical effect. Examples of neutralizing antibodies stimulated by biologics include[4]:

- Erythropoietin (immune-mediated pure red cell aplasia)
- Salmon calcitonin (neutralizing antibodies found in 40% to 70% of patients treated for longer than 4 months)
- Growth hormone (neutralizing antibodies reported in 3% to 16% of patients)
- Factor VIII (neutralizing antibodies reported in 35% of patients, loss of drug efficacy)

- Interferon-α and interleukin (neutralizing antibodies developed in 50% of patients).

Factors that influence immunogenicity include:

- Genetic background
- Type of protein given therapeutically
- The patient's disease
- Fragments and conjugates of the protein agents
- Route of administration
- Dose frequency (frequent administration, especially subcutaneously, is more likely to result in a reaction)
- Manufacturing process by which the drug is produced
- Handling and storage of the drug.

Managing immune response or preventing immune response in patients may be accomplished by:

- Discontinuing the drug, which may or may not be on option for an individual patient
- Substituting the drug with another protein, which may or may not be an option considering patient characteristics and interchangeability of agents
- Introduction of immune tolerance (eg, administering factor VIII with an immunosuppressive agent).

Recent Heparin-Related Safety Events in the United States

Three heparin-bacterial contamination incidents occurred recently in the United States. Two of the incidents involved the organism *Serratia marcescens*. The third was the presence in heparin of a contaminant that caused allergic response in a number of patients in the United States and other countries. The contaminant has recently been identified as oversulfated chondroitin sulfate (OSCS) and has been linked to the anaphylactoid reactions that have surfaced globally. In a recent review by Kishimoto and colleagues,[6] the group described the delicate balance of the chondroitin sulfate and how the compound is able to activate the contact system. The reaction results in the activation of the contact system (ie, kinin-kallikrein pathway) and bradykinin, a potent vasodilator. The activation of the complement system can also result in the generation of complement proteins, which have potential to cause anaphylaxis type reaction.[6]

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Background, Scope of the Problem, and Therapeutic Options

continued from page 5

Philip Marcus, MD, MPH, FCCP and Victor F. Tapson, MD, FCCP

In light of these caveats regarding currently available branded LMWH drugs, a number of questions will need to be addressed regarding development and regulatory approval of "generic" biosimilar LMWH drugs (**Table 3**).

Table 3. Questions to be Addressed

- Does the current drug approval process for "generic" compounds of biologics adequately protect patients?
- What should be the level of evidence required for consideration of a "generic" LMWH in patient practice?
- What measures and precautions need to be addressed to ensure the safe coordination of patient care if "generic" LMWHs become available?
- What measures should be endorsed and undertaken to ensure that health care professionals understand that "generic" LMWHs should not be considered identical to the parent compounds?
- How should the FDA statements against the interchangeability of branded LMWHs be interpreted and applied to "generic" products?

LMWH=low-molecular-weight heparin; FDA=US Food and Drug Administration.

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Regulatory Issues and Approval Pathways: Ensuring Patient Safety

Lilia Talarico, MD

In the United States, pharmaceutical drugs and biologic products are approved by the US Food and Drug Administration (FDA) under separate regulatory mechanisms:

- Chemical drugs are regulated and approved by the Center for Drug Evaluation and Research (CDER) under Section 505 of the Food, Drug, and Cosmetic Act (FD&C Act).
- Biologic products are regulated and licensed by the Center for Biologic Evaluation and Research (CBER) under Section 351 of the Public Health Service Act (PHS Act).

The distinction between these two regulatory mechanisms in terms of assignment of pharmaceutical products is not absolute because some biologic products, including hormones such as insulin, human growth hormone, menotropins, and hyaluronidase, have traditionally been regulated by CDER under the FD&C Act. Heparin and, subsequently, the low-molecular-weight heparins (LMWHs) have also been regulated by CDER.

In the late 1970s, with the development of biotechnology, more biologic products were developed. Products such as cytokines, immunomodulators, and blood products were regulated by CBER, whereas others such as recombinant proteins, monoclonal antibodies, and hormones were regulated as drugs by CDER. In 2003, certain protein products were transferred from CBER to CDER with no change to the applicable regulatory authority—that is, the biologic products that had been transferred to CDER continued to be regulated under Section 351 of the PHS Act.

The approval process for a specific indication of new pharmaceutical products, whether chemical drugs or biologics, is long and very expensive. The average time from application to approval is more than 10 years at a cost of several million dollars. With the escalating cost of medical care, the US Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act) to expedite the availability of less costly generic drugs and to stimulate the development of new therapies. The Act allows the FDA to approve abbreviated new drug applications for generic versions of an approved reference drug by relying on prior determination of efficacy and safety of the reference product. The abbreviated approval mechanism under Section 505(j) of the FD&C Act eliminates the need for expensive and duplicative clinical trials.[1]

The manufacturers of the generic products must provide complete chemistry, manufacturing and controls, and pharmacokinetic/pharmacodynamic data to demonstrate that their product is pharmaceutically equivalent to the branded products. Pharmaceutical equivalence requires that drug products contain identical amounts of active ingredients; bioequivalence indicates that the rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions. Most drug products approved under Section 505(j) are therapeutically equivalent to reference products—that is, they have the same clinical effect and safety profile when administered as indicated and can be substituted for the branded product.

There has been great reservation regarding the feasibility of generic biotechnology because of safety concerns and limitations of the technology needed to characterize, measure, and compare biologic products.

Section 505 of the FD&C Act contains a second abbreviated pathway of drug approval: Section 505(b)2, which allows an applicant for a product not identical to an approved branded product (thus, not qualifiable as generic) to reference efficacy and safety data from studies not conducted by or for the applicant and without right of reference.[2] The data can derive from published studies or from the FDA's findings of effectiveness and safety of the reference products. The 505(b)2 applicant must provide any additional preclinical or clinical data necessary to demonstrate the safety and effectiveness of the product. The Hatch-Waxman generic drug amendment has been very successful in expanding the availability of drugs at reduced cost without interfering with the development of new drugs.

Another effort by the FDA to stimulate medical product development is the Critical Path Initiative, designed to improve the development of new innovator drugs, devices, and biologics. The initiative has applications for the development of generic drugs as well by improving the efficiency of current methods for assessment of bioequivalence and biomarkers, and for developing methods to characterize complex drug substances and products.

During the past several years, there has been increasing interest from the pharmaceutical industry, government, and patients for the development of "generic" biologic products, based on continued advances in manufacturing and understanding of the physical structure of these products. The development of biogenerics or follow-on biologic products has not been as straightforward and well defined as that of chemical drugs. The concept of generic versus brand name implies "sameness" of the two products. However, when biologic compounds are developed as branded biologics go off-patent, they cannot meet the criteria applicable to generic drugs because of inherent structural differences between drugs and biologics and because of differences in the oversight and manner in which they are regulated. At present, the FDA prefers using the term "follow-on" to describe off-patent biologics that are intended to be sufficiently similar to an approved product to permit reliance on existing knowledge of the efficacy and safety of the approved branded product.

Unlike Section 505 of the FD&C Act, Section 351 of the PHS Act has no provision for abbreviated applications that would allow the licensing of follow-on products based on the agency's prior licensing of biologic reference products. Ultimately, the decision to proceed with a program applicable to follow-on biologics regulated under Section 351 of the PHS Act rests with Congress. The FDA has, however, the authority to act on relatively simple, small biologic molecules regulated by CDER under Section 505 of the FD&C Act as advances in technology have made it possible to assess with a high degree of confidence the similarity between the follow-on and certain branded products. Clear understanding of the mechanism of action, long history of use, and safety of the branded product also facilitates the approval of the follow-on product. For follow-on products such as the hyaluronic acid Hylenex®, the glucagon GlucoGen®, and the human growth hormone Omnitrope™,[3] it was possible to apply Section 505(b)2 of the FD&C Act, relying on earlier approval of the innovator product.

There has been great reservation regarding the feasibility of generic biotechnology because of safety concerns and limitations of the technology needed to char-

acterize, measure, and compare biologic products. However, the high cost of biotechnology medicine has raised the interest of industry in the development of biosimilar or follow-on biologics. The high cost of medical care has also prompted policy makers to promote legislation initiatives to establish new regulations for biologics. A bill titled Access to Life-Saving Medicine Act and two other bills have been introduced in the Senate; they would direct the FDA to establish a path to regulatory approval of follow-on biologics. The FDA has held meetings and workshops to address scientific and technical issues related to follow-on biologics.[4]

Most biologic and biotechnology-derived products are large, complex, heterogenous, and often not fully characterized molecules obtained from a variety of starting material and made in complex manufacturing processes. The product is strictly dependent on the starting material; even a small variation in starting material can have significant consequences for the product. Small changes in manufacturing introduced by design or by chance, unpredictable or undetectable by current analytic technology, can affect the efficacy and safety of the product in clinical use. A high degree of structural similarity and reliable performance are essential for follow-on products, which must be substantially similar in clinical effect to branded products, frequently indicated for serious conditions and rare diseases.[5]

A major concern for biologic follow-on products is safety, particularly the potential immunogenicity of these products. Biologic products, more so than chemical products, can trigger an immune response with serious clinical consequences. Immunogenicity may be caused by impurities, neoantigens, or downregulation of immune tolerance and may be influenced by structural properties of the molecule, glycosylation, route of administration, and duration of therapy. Immunogenicity can range from development of antibodies of no clinical significance to severe or even fatal allergic reactions. Immunogenicity can induce (1) most commonly, loss of therapeutic effect, (2) increased effect, as seen with human growth hormone, and (3) neutralization of native protein, as seen with erythropoietin and megakaryocyte/granulocyte growth factor. There are no laboratory tests to detect the immunogenic potential of a product.

Compounds that have stimulated interest for the development of follow-on products are represented by the LMWHs. Heparin and LMWH, although of biologic origin, have been regulated and approved under Section 505 of the FD&C Act. However, their complex structure and manufacturing process make their follow-on versions unsuitable for approval under Section 505 of the FD&C Act. Notably, LMWHs have been considered biologic products by the European Medicines Agency, and specific guidelines are being considered for the development and assessment of "biosimilar" LMWHs.

By US regulatory standards, each branded LMWH has been considered a distinct pharmacologic agent requiring product-specific clinical trials for the approval of each clinical indication. Three branded LMWH products are available in the United States—dalteparin, enoxaparin, and tinzaparin. Each has specific biochemical characteristics determined by a manufacturing process that may affect, in different ways, other cellular functions, such as release of tissue factor pathway inhibitor, modulation of the inflammatory process, angiogenesis, apoptosis and cancer growth, and regulation of cytokines, eicosanoids, and nitric oxide.

Heparin and, to a lesser degree, LMWHs can induce antibodies directed against the complex heparin/LMWH and endogenous platelet factor 4 with development of immune thrombocytopenia and, in severe cases, catastrophic thrombotic complications.

Currently, there are no US regulatory guidelines or consensus opinions on the acceptance of follow-on versions of the branded LMWHs. Challenges to the development of these products include:

- Absence of statutory framework for their approval
- Limited physicochemical characterization of the product due to the complexity of the molecule
- Limited knowledge regarding the quantitative and qualitative contribution of each fraction to efficacy and safety
- Uncertainty of pharmacodynamic markers as representative of clinical outcome
- Difficulty in duplicating manufacturing methods of branded products due to limitations of intellectual property protection
- Inadequacy of bioequivalence studies to establish therapeutic equivalence between LMWHs
- Need to assess each product on a one-for-one basis
- Requirement for clinical trials and risk management plans.

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Health Care System Issues and Implications for Other Drug Classes

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We know that many issues need to be addressed within the health care system regarding choice, cost, and use of drugs, including biologics. Whereas we know some of the issues and the questions that we must ask, we do not know them all, and it is likely that we do not know all of the relevant issues or the associated questions we should be asking, especially in regard to follow-on biologics.

In a 2001 paper, Merli et al[1] analyzed therapeutic interchange (TI) programs that some health care institutions adopt as part of a strategy to reduce health care costs. The rationale for TI programs is to reduce costs by establishing criteria for the interchange of therapeutically equivalent but chemically distinct drugs. The Merli paper's analysis was specifically of TI programs established for interchange of low-molecular-weight heparins (LMWHs). The authors concluded that differences between LMWH drugs made it inadvisable to establish TI programs for LMWHs.

Table 1 lists issues we understand regarding follow-on biologic agents such as the LMWHs.

As discussed by Dr. Talarico ("Regulatory Issues and Approval Pathways: Ensuring Patient Safety"), the transfer of jurisdiction for some drugs to the Center for Drug Evaluation and Research (CDER) has clinical implications currently and will likely have more as the US Food and Drug Administration (FDA) deals with questions regarding follow-on biologic agents. How the review and approval of applications for follow-on biologics will eventually be approached is a matter yet to be determined.

An example of issues and questions regarding follow-on biologics is illustrated by the approval of Omnitrope™, a somatotropin of recombinant DNA origin indicated for long-term treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone. The FDA does not describe Omnitrope™ as a generic biologic and does not describe it as therapeutically equivalent to (and interchangeable with) any other approved growth hormone product. The FDA's preferred characterization of Omnitrope™ is as a "follow-on protein product."

A "follow-on protein product" is described by the FDA as "a protein or peptide product intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Follow-on products may be produced through biotechnology or derived from natural sources."[2]

The approval of Omnitrope™ should not be taken as evidence of a new pathway for approval of follow-on versions of all protein products, the FDA points out. Rationale offered by the FDA for approval of Omnitrope™ includes[2]:

- Human growth hormone is well characterized; sugar molecules are not added to the product to increase its complexity and render it more difficult to compare molecular structure from one version of the protein to another using standard assay technique.
- Human growth hormone's mechanism of action is known and its human toxicity profile is well understood.

The FDA's statements regarding the rationale for approval of Omnitrope™ may be taken to indicate that criteria for approval of one class of follow-on biologic drugs do not necessarily apply to future approval of other classes of biologics.

What questions should we be asking regarding the characteristics of well-defined follow-on biologic drugs? We should be asking about:

- Reproducibility of pharmacologic activities beyond any existing surrogate markers despite (1) high complexity of molecular structure and (2) biologic origin
- Reliability of clinical use of reference or follow-on agent in any clinical setting, as demonstrated by (1) studies in sufficiently large populations and (2) studies in special patient populations.

We should also be asking:

- Are there risks to patients due to immunogenicity or other causes such as patient-specific responses?
- Are there nonclinical risks and ethical issues (eg, how accurate, comprehensive, and transparent is information given to the physician and/or patient)?
- Are cost issues and appropriateness of treatment issues compatible?

A recent illustration of cost-of-product versus safety/efficacy of treatment is the allergic reactions that occurred in some patients due to heparin derived from biologic sources in China. The China source reduces the cost of the product; we must question whether this cost reduction is related to the safety/efficacy problems with the product.

We know that small manufacturing changes in the production of a biologic can have clinical consequences. An example is a minor change in the formulation of an epoetin-α product resulting in the development of neutralizing antibodies both to the drug and to native erythropoietin in some patients.[3]

Another well-documented illustration of the clinical effects of drug substitution is a report by Witt et al[4] regarding the effects of substituting oral anticoagulants (generic for branded warfarin) in 2,299 patients. The data cover 90 days before the substitution and 90 days after substitution (**Table 2** on page 14).

- 72% had a 10% change in international

Table 1. Health Care System Issues and Indications for Other Drug Classes

- Cost or other advantages
  - Is there a cost advantage associated with therapeutic interchange?
- Pharmacologic equivalence
  - Are there follow-on agents pharmacologically equivalent to branded drugs and/or to one another?
- Supportive clinical evidence
  - Is there adequate evidence to support each indication?
  - Is there equivalent efficacy/safety within each indication?
  - Is there equivalent durability within each indication?
- Process support within the health care system
  - Thorough analysis
  - Education of prescribers, pharmacists, and nurses
  - Notification and documentation
- Outcomes monitoring
- Variance opportunity
  - Ability of physicians to prescribe medications as they believe appropriate and necessary

normalized ratio (INR) control after substitution.

- 13% had <50% variation in INR control after substitution.
- 83 patients died or discontinued warfarin during the period and were not included in analysis.

In another well-documented instance, the hospital formulary purchased a warfarin substitute rather than a generic version of warfarin, but failed to notify prescribers.[5] Change in prothrombin time of patients, factor Xa, and necessary changes in dosage were significant ($P<0.05$). Two patients required hospitalization for excessive anticoagulation. The estimated savings on a 1000-count bottle of drug was $1.50, whereas estimated cumulative charges of treatment was $14,175 (1988).

The cited examples stress the necessity for pharmacovigilance regarding both chemical drugs and biologics that includes[3]:

- Being aware that biosimilar products are not identical to their reference products, and that there may be unknown or untested safety issues
- Insisting on extensive testing of safety/efficacy risks—immunogenicity in particular for biologics such as LMWH—both preapproval and postapproval of a follow-on biologic
- Adopting postapproval mechanisms to facilitate detection of rare adverse events associated with each manufacturer's follow-on product
- Adopting distinct International Proprietary Names and trade names for each biologic follow-on product to prevent prescribing errors and facilitate reporting of adverse events and product tracking.

The question of "biosimilarity" and "bioequivalence" must be addressed with appropriate assays. The testing is of a different order than that required for chemical drugs. Many biopharmaceutical products are recombinant protein molecules synthesized in living cells.[6,7] Manufacturing processes are highly complex, are often proprietary, and may be impossible to duplicate for a follow-on biologic.[8] Different manufacturing processes may be associated with differences in molecular structure between reference and follow-on products as well as between follow-on products. These structural differences may have clinical implications for efficacy and safety.[9,10]

Manufacturers should provide information to all stakeholders, including patients, physicians, and pharmacists, regarding risks associated with switching from a branded product to a follow-on product.

We do not yet know the potential for cost savings as follow-on LMWH products become available. Development costs, including any mandated clinical trials, will be reflected in the price of a follow-on agent. The ability or inability to interchange LMWH agents will also be reflected in overall costs.

Regulatory bodies and current clinical guidelines from organizations such as the US Food and Drug Administration, the American College of Chest Physicians, the American College of Cardiology/American Heart Association, and an International Consensus Panel regard LMWH drugs as distinct and not interchangeable.[11-14] These known differences between branded products portend many difficulties as efforts are made to develop and gain regulatory approval for follow-on products that are equivalent to branded LMWH agents.

Table 2. Effects of Oral Anticoagulant Substitution[4]

Event	Before	After	*P* Value
Time in INR range, %	65.9	63.9	<0.0002
Patients with ≥1 dose change, %	37.5	40.5	<0.05
Total number of bleeding & TE	15	23	NS
Complication rate (per 100 patient years)	2.65	4.06	NS

INR=international normalized ratio; TE=thromboembolic events; NS=not significant.

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Conclusion

Currently available (branded) low-molecular-weight heparin (LMWH) agents will soon go off-patent. Follow-on ("generic," "biosimilar") LMWHs will be developed, and regulatory approval will be sought for them.

A number of applications for follow-on LMWH agents have been submitted to the US Food and Drug Administration (FDA) for review and approval. Similar applications have been made to the European Medicines Agency (EMEA). The FDA currently has no process in place for review and approval of applications for follow-on biologic agents such as LMWH. The FDA has stated that it prefers the term "follow-on" to describe biologic agents that would be called "generic" if they were chemical drugs. The term "biosimilar" is preferred by the EMEA.

Before review and approval of follow-on versions of LMWH agents is undertaken, a number of questions should be addressed and resolved:

- Currently available branded LMWH agents are regarded as noninterchangeable because of biologic origin, differing manufacturing processes, differing chemical and pharmacologic profiles, and immunogenic potential. Each agent has also been studied for specific indications.
- Before follow-on versions of chemical drugs are approved, the reference (branded) drug must be fully characterized, and the follow-on agents must show evidence of pharmacokinetic equivalence. It is assumed that equal clinical efficacy would then result. No such characterization exists for LMWH agents. However, full characterization of a reference LMWH agent should be required before a follow-on agent is approved if "biosimilarity" is to be required of the follow-on agent.
- Manufacturing processes for branded LMWH agents are proprietary and may not be made available to manufacturers of follow-on versions of a LMWH agent. However, reproducibility of the manufacturing process should be required before a follow-on agent is approved.
- Reliable analytic tests to assess safety and efficacy of follow-on LMWH agents should be widely available.
- Reliable bioassay technology should be available to compare chemical and pharmacologic characteristics of branded and follow-on agents and to compare such characteristics of follow-on agents.
- Characterization of the molecule of a follow-on LMWH agent should include assessment of its immunogenic potential.
- Review of an application for approval of a follow-on LMWH agent should include assessment of its reliability of clinical use in a specific clinical setting, as shown by studies of the reference and/or follow-on agent in sufficiently large patient populations and special patient populations.
- Manufacturers of follow-on LMWH agents should be required to provide all clinically relevant information about the agent and its studied indications to physicians, pharmacists, other health care providers, and patients.
- A monitoring system should be in place to identify and report all adverse events involving follow-on LMWH agents.
- Indications for use of follow-on LMWH agents should include information on noninterchangeability and safety and efficacy issues associated with interchangeability.