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Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, on behalf of Aventis Pharmaceuticals Inc. ("Aventis"), a subsidiary of Aventis SA, submits this petition under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355 (b) and (j)) and 21 C.F.R. § 10.30, to request that the Commissioner of Food and Drugs withhold approval of any abbreviated new drug application ("ANDA") for a generic version of Lovenox® (enoxaparin sodium injection) ("enoxaparin") until the conditions set forth in this petition are satisfied. Aventis is the manufacturer and distributor of enoxaparin, a low molecular weight heparin.

I. Actions Requested

1. Until such time as enoxaparin has been fully characterized, Aventis requests that FDA refrain from approving any ANDA citing Lovenox®as the reference listed drug unless the manufacturing process used to create the generic product is determined to be equivalent to Aventis' manufacturing process for enoxaparin, or the application is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials.

2. Aventis also requests that FDA refrain from approving any ANDA citing Lovenox®as the reference listed drug unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15% and 25% of its polysaccharide chains.

II. Brief Statement of Grounds

Section 505(j)(2)(A)(ii)(I) of the FDCA (21 U.S.C. § 355(j)(2)(A)(ii)(I)) provides that, with regards to drugs containing only one active ingredient, any person

filing an abbreviated application for the approval of a new drug must show, among other things, that the new drug has the "same" active ingredient as the approved pioneer drug.[1] Section 505(j)(2)(C)(ii) of the Act requires that a person wishing to submit an ANDA for a new drug which contains a different active ingredient than that of the reference drug may do so only upon petition to FDA. FDA must deny such application if the drug "may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application."[2] For the reasons set forth below, a generic product cannot achieve the "same" active ingredient as enoxaparin unless it utilizes Aventis' manufacturing process, or an equivalent. Unless it does so, FDA must require that the generic demonstrate equivalent safety and effectiveness with enoxaparin through clinical trials.

Enoxaparin is a low molecular weight heparin ("LMWH"). Like all LMWHs, enoxaparin comes from unfractionated heparin source material ("unfractionated heparin").[3] Unfractionated heparin is a highly complex collection of molecules composed of linear polysaccharide (glycosaminoglycan) chains of varying chemical structure. During heparin biosynthesis, these chains occupy different positions on the core protein and, thus, represent glycoforms.[4] To manufacture LMWH, the larger unfractionated heparin chains are broken down into smaller chains through varying processes of chemical or enzymatic depolymerization. Each LMWH manufacturer utilizes a distinct process of depolymerization. This results in LMWHs with distinct chemical structures and, therefore, differing pharmacological activity and approved indications for clinical use.[5] For enoxaparin, Aventis employs a specific, tightly controlled, validated process of chemical depolymerization.

Part III of this petition sets forth a full statement of grounds. Part III(A) begins by providing the necessary background framework for understanding the process of creating enoxaparin from unfractionated heparin. To that end, section III(A)(1) provides an introduction to LMWHs and section III(A)(2) discusses the origins and chemical structure of source unfractionated heparin. Sections III(A)(3), (4), and (5) provide a detailed description of LMWHs discussing, in turn, how they are manufactured from unfractionated heparin, the important ways in which they are

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[1] 21 U.S.C. § 355(j)(2)(A)(ii)(I).

[2] 21 U.S.C.§ 355(j)(2)(C)(ii).

[3] Most LMWHs come from porcine intestinal source heparin. Enoxaparin comes exclusively from porcine intestinal source heparin. *See* Declaration of Christian Viskov, Ph.D. (hereinafter, "Viskov Declaration").

[4] Declaration of Robert J. Linhardt, Ph.D. (hereinafter "Linhardt Declaration").

[5] *See* Linhardt RJ, et al. Production and chemical processing of low molecular weight heparins. *Seminars in Thrombosis and Hemostasis* 1999; 25(3 Supp.): 5-16.

differentiated from one another, and the advantages of LMWH over unfractionated heparin. Part III(A) concludes in section III(A)(6) by outlining Aventis' unique process for manufacturing enoxaparin.

Aventis' manufacturing process creates a highly complex collection of macromolecules with a chemical structure that is unique among currently approved LMWHs. This structure is marked by distinct polysaccharide sequences and structural modifications (or "fingerprints") that are highly sensitive to Aventis' process (detailed in Part III(B)). The recognition of these fingerprints has only become possible due to recent advances in the field of analytical technology.

Through a series of preclinical tests, discussed in detail below, Aventis has discovered that one of these fingerprints, the 1,6 anhydro ring structure, makes several important contributions to enoxaparin's overall pharmacological effect. Many of these contributions likely bear clinical significance. In addition, testing of the other fingerprints that Aventis has identified may lead to further findings of therapeutic significance.

In addition to the structural fingerprints Aventis has already discovered, approximately 30% of the polysaccharide chains comprising enoxaparin have yet to be directly analyzed (without the benefit of complete enzymatic digestion of the sample) because of limitations on current analytical technology. As this technology continues to improve, investigation of the unexplored portions of enoxaparin may yield additional unique and process-dependent structural modifications with pharmacological activity. Many of these may also have clinical significance. A generic product must contain those modifications (known or undiscovered) in order to be considered the "same" as enoxaparin. It cannot claim to have the same pharmacological activity as enoxaparin simply because it has the same molecular weight, anti-Xa activity, and/or anti-Xa/anti-IIa ratio. Both published scientific articles and Aventis' own testing on the 1,6 anhydro ring structure demonstrate that these traditional LMWH markers cannot completely characterize overall pharmacological activity of LMWHs like enoxaparin.

Part III(B) of this petition therefore discusses enoxaparin's structural identity at length and provides support for Aventis' findings of pharmacological relevance. Section III(B)(1) begins by demonstrating how Aventis' manufacturing process results in distinctive chemical structures for enoxaparin. Section III(B)(2) outlines Aventis' ongoing efforts to characterize enoxaparin and discusses the distinctive structural fingerprints it has found to date. Section III(B)(3) examines the pharmacological activity of those structural fingerprints. Because Aventis has thus far been able to study only the 1,6 anhydro ring structure, this section focuses on that structure's pharmacological activity and its implications for enoxaparin's safety and efficacy, as demonstrated by preclinical testing.

Section III(B)(4) then discusses the limitations on Aventis' ability to characterize enoxaparin and identifies the large portion of the complex collection of

macromolecules that is as yet unexplored. Next, section III(B)(5) demonstrates that traditional markers such as average molecular weight, anti-Xa activity, and anti-Xa/anti-IIa ratio are insufficient indicators of an LMWH's overall pharmacological activity. Finally, sections III(B)(6) and (7) discuss relevant legal precedents, distinguishing enoxaparin from the *Serono* case (Pergonal) and establishing a similarity with the case of conjugated estrogens (Premarin).

Part IV of this petition concludes that in order to demonstrate sameness, a generic enoxaparin must utilize Aventis' manufacturing process, or an equivalent. In light of the fact that enoxaparin is indicated for treatment and management of several life-threatening indications, it is of critical importance that a generic product contain all of those modifications that may bear clinical significance. Because enoxaparin is not fully characterized, utilizing Aventis' process (or an acceptable equivalent) is the only way to ensure that the generic product will contain all of the pharmacologically active components (both known and yet to be discovered) of enoxaparin. Absent that, FDA cannot consider the generic to have the "same" active ingredient as enoxaparin and must therefore require a demonstration of equivalent safety and effectiveness through clinical testing.

III. Complete Statement of Grounds

A. Background

1. Introduction of LMWHs

The first LMWH, enoxaparin, was approved by the FDA and introduced into the United States in 1993. There are currently three LMWHs approved for use in the United States. Fragmin® (dalteparin sodium injection) and Innohep® (tinzaparin sodium injection) were approved in 1994 and 2000, respectively. Normiflo® (ardeparin sodium) was approved in 1997, but withdrawn at the manufacturer's request in 2002.

LMWHs are approved in the United States for some or all of the following indications: prophylaxis and treatment of deep vein thrombosis ("DVT") during certain surgical procedures, inpatient and outpatient treatment of DVT, and prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction. Each currently approved LMWH has a different set of approved clinical indications. Additionally, in the United States, enoxaparin is currently the only LMWH approved for use in patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

In many cases, these are life-threatening conditions. DVT and pulmonary embolism (collectively known as venous thrombo-embolism or "VTE"), in particular, remain significant causes of morbidity and mortality. Approximately

600,000 patients per year are hospitalized for DVT in North America.[6] In the United States, approximately 250,000 patients are hospitalized with VTE each year.[7] Symptomatic pulmonary embolism is directly or indirectly responsible for up to 200,000 annual patient fatalities.[8] The mortality rate for PE has been reported as high as 17.5%.[9]

2. Unfractionated Heparin

Enoxaparin, as with typical LMWHs, is prepared from porcine intestinal heparin source material. Heparin, commonly called "unfractionated heparin" since the invention of LMWHs, was first discovered in dog liver in 1916 by Jay Maclean. Although unfractionated heparin can be found in virtually all mammalian species, in the United States and Europe it is primarily extracted from porcine intestinal tissue. It is used as an anticoagulant in both humans and animals.[10]

Heparin is biosynthesized in mast cells and certain other types of granulated cells as a proteoglycan. It is composed of a core protein with a number of linear polysaccharide chains extending from the protein. Each chain, comprising a certain number of disaccharide subunits, has a reducing end and a non-reducing end. Some of the disaccharides contain sulfo groups, while others do not. Proteoglycan heparin has an average molecular weight of approximately 10^6 daltons ("Da."). On extraction from mammalian tissues, the average molecular weight of unfractionated heparin is reduced through the action of endogenous tissue proteases and glycosidases to approximately 10^4 Da.[11]

Unfractionated heparin acts as an anticoagulant by binding with antithrombin III ("ATIII"), a plasma protein synthesized in the liver and other endothelial cells. Heparin's interaction with ATIII is mediated by a specific pentasaccharide sequence that is distributed across approximately one-third of the heparin chains. ATIII inactivates serine proteases, most notably factor IIa (thrombin) and factor Xa, within the coagulation cascade.[12] On its own, ATIII is a slow inhibitor.

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[6] Turpie AGG. Management of venous thromboembolism: optimization by clinical trials. *Haemostasis* 1996; 26(4 Suppl):220 at 221.

[7] Goldhaber SZ. Pulmonary embolism. *N. Engl. J. Med.* 1998; 339(2):93.

[8] Dalen JE, Albert JS. Natural History of Pulmonary Embolism. *Prog. Cardiovasc. Dis.* 1975; 17:259.

[9] Goldhaber, *supra* note 7, at 93.

[10] *See* Linhardt Declaration.

[11] *See* Capila I, Linhardt RJ. Heparin-protein interactions. *Angewandte Chemie Int. Ed.*. 2002; 41:390-412.

[12] *See* Weitz JI. Low-molecular-weight heparins. *N Engl. J. Med.* 1997; 337:688.

It allows the serine proteases to generate significant amounts of thrombin and fibrin before inactivation. When bound to heparin at these pentasaccharide sequences, however, the reaction becomes almost instantaneous, thus preventing virtually all thrombin and fibrin formation. This interrupts the coagulation cascade at the common pathway.[13]

Unfractionated heparin can bind with ATIII to inactivate factor Xa or factor IIa. Only chains containing both the specific pentasaccharide sequence and having 18 saccharides or more, however, are capable of inactivating factor IIa.[14] Because unfractionated heparin is composed of nearly equal amounts of longer and shorter chains, unfractionated heparin has an anti-Xa/anti-IIa ratio of approximately 1.[15]

Unfractionated heparins were available in the United States prior to the enactment of the Federal Food, Drug, and Cosmetic Act of 1938.

3. LMWHs

Unfractionated heparin polysaccharide chains range in length and molecular weight with an average molecular weight of approximately 15,000 Da. To create LMWH from source heparin, the longer heparanic polysaccharide chains must be broken down into shorter chains of lower molecular weight. This is done by either chemical or enzymatic depolymerization. The result is an average molecular weight for LMWH polysaccharide chains of approximately 5,000 Da.[16]

LMWHs, like unfractionated heparin, inhibit coagulation by binding to ATIII at particular pentasaccharide sequences distributed along some of the polysaccharide chains. Whereas the ATIII binding pentasaccharide sequence appears on approximately 30% of unfractionated heparin chains, it is present in only 15-25% of LMWH chains. The particular process used to depolymerize unfractionated heparin determines how many ATIII binding sites are preserved intact on the LMWH polysaccharide chains. With current analytical technology, it is very difficult to accurately assess the presence of all ATIII binding sites.[17]

LMWH polysaccharide chains are generally shorter than unfractionated heparin chains. Most LMWH chains have less than the 18 saccharide units required to

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[13] Aguilar D, Goldhaber SZ. Clinical uses of low-molecular-weight heparins. *Chest* 1999; 115:1418.

[14] *See* Weitz, *supra* note 12, at 688-92.

[15] *See id.*

[16] *See* Linhardt Declaration.

[17] *See id.*

inactivate factor IIa. As a result, they have a greater activity in the inactivation of factor Xa, and less of an effect on factor IIa (thrombin).[18] In contrast to unfractionated heparin, LMWHs have anti-Xa/anti-IIa ratios ranging from 4:1 to 2:1.[19]

4. Differentiation Among LMWHs

LMWHs are differentiated by the various depolymerization processes used to make them. As a result, LMWHs are more heterogeneous than is unfractionated heparin. Each different process causes unique and highly complex structural modifications to the polysaccharide chains. These modifications include differences in chain lengths and chain sequences, as well as structural fingerprints. Consequently, the different LMWHs each have distinctive pharmacological profiles and different approved clinical indications.

For example, Fragmin® (dalteparin sodium injection) is produced through nitrous acid-based controlled depolymerization. This results in a number of distinct chemical modifications including termination of dalteparin's reducing ends with a process-derived anhydromannose residue.[20] Similarly, tinzaparin and enoxaparin demonstrate significant differences in activated partial thromboplastin time ("aPTT"). Four hours after the injection of a curative dose of tinzaparin, the aPTT is usually prolonged by 2 to 3 times, whereas a comparable dose of enoxaparin prolongs aPTT only 1.2 to 1.5 times.[21] This is so despite the fact that enoxaparin has a higher circulating anti-Xa activity.[22]

FDA recognized early on the fact that the varying depolymerization processes used to create LMWHs create chemically distinct drug products. Thus, in 1993, FDA issued an alert to physicians stressing that the various LMWHs may not be used interchangeably.[23] This warning is also found in the approved prescribing information for all currently available LMWHs.

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[18] *See* Weitz, *supra* note 12, at 688-90.

[19] Hirsh J, Raschke R, et al. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1995; 108 (4 suppl): 258S at 267S.

[20] Linhardt RJ, et al. Oligosaccharide mapping of low molecular weight heparins: Structure and activity differences. *J. Med. Chem.* 1990; 33:1639-45.

[21] *See* Boneu B. Low molecular weight heparins: Are they superior to unfractionated heparins to prevent and to treat Deep Vein Thrombosis? *Thrombosis Research* 2000; 100:v113 at V115.

[22] *See id.*

[23] *See* Nightingale SL. Appropriate use of low-molecular-weight heparins (LMWHs). *JAMA* 1993;270(14):1672. *But see* Prandoni P & Nenci GG. Low molecular weight (continued...)

5. Important Differences Between Unfractionated Heparin and LMWHs Require Different Generic Approval Processes

As yet, there are no generic LMWHs in either the United States or Europe. In many ways, due to their complex structures and sensitivity to the particular manufacturing process used, LMWHs more clearly resemble biologics than small molecule drugs. Aventis questions, therefore, whether the generic drug approval model (i.e., the ANDA process) is appropriate for these complex macromolecule collections even though they have officially fallen under CDER's jurisdiction.

LMWH demonstrates a number of important differences from unfractionated heparin that highlight the need for greater precision in the approval process for generics. LMWHs have low clearance, weak binding to endothelial cells, weak neutralization by protein binding, dose-independent clearance, and better bioavailability relative to unfractionated heparain, resulting in better predictability of anticoagulant activity. This greater anticoagulant predictability promotes enhanced bioavailability for LMWHs.[24] Thus, whereas unfractionated heparin must generally be administered in a hospital with plasma monitoring and dose titration, neither monitoring nor titration is required for LMWHs. In addition, LMWHs are currently administered subcutaneously, without the need for an intravenous (IV) bolus. Thus, depending on the indication, LMWHs can be given on an outpatient basis or self-administered.[25]

Second, LMWHs have plasma half-lives ranging from two to four times that of unfractionated heparin.[26] This is because unfractionated heparin has a high binding affinity to macrophages and endothelium, resulting in faster hepatic clearance. LMWHs, by contrast, do not have such a high affinity to macrophages and endothelium. As a result, they exhibit slower hepatic clearance and a longer plasma half-life. This enhanced half-life, plus LMWH's greater bioavailability allows them to be dosed once or twice daily. By contrast, unfractionated heparin dosing must be continually adjusted on an inpatient basis.[27]

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heparins: are they interchangeable? Yes/No. *J. Thromb. Haemost.* 2003; 1:10-13 (citing debate on interchangeability of LMWHs).

[24] *See* Weitz, *supra* note 12, at 688-90.

[25] *See* Lovenox® Product Labeling.

[26] *See* Weitz, *supra* note 12, at 690.

[27] *See* Hirsh J, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy and safety. *Chest* 2001; 119:64S.

Third, the mixture of polysaccharide chains in unfractionated heparin is associated with variability in its observed clinical effects. This variability may be ascribed to multiple factors such as:

- Absorption: "The absorption of heparin following subcutaneous administration is reported to vary from patient to patient, and from day to day in the same patient."[28]

- Mode of action: binding to various proteins;

- Underlying disease: e.g., unfractionated heparin may have a shorter half-life in patients with pulmonary embolism necessitating a higher dose and other adjustments;

- Intrinsic patient characteristics[29]; and

- Differences in characteristics of commercially available unfractionated heparin.[30]

Consequently, despite the existence of USP criteria for unfractionated heparin, appropriate use in a clinical setting requires frequent monitoring and individualized dosing. Additionally, intravenous administration is employed for critical illness such as the treatment of DVT and pulmonary embolism, and treatment of myocardial infarction, to ensure complete bioavailability. Further, the intravenous infusion is individually titrated based upon frequent measurements of aPTT times. Doses are routinely adjusted based on unfractionated heparin dosing nomograms.[31]

This is in contrast to LMWHs where, for some clinical indications, the same dose can be given to different patients and administered subcutaneously, even in an outpatient setting. Further, unlike the aPTT, which can be used to monitor and titrate unfractionated heparin in a clinical setting, routine monitoring of enoxaparin is not

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[28] Nicolaides AN, et al. Subcutaneous heparin, plasma heparin levels and postoperative wound haematoma. *Br. J. Surg.* 1984; 71:62 at 63.

[29] Simon TL, et al. Heparin pharmacokinetics: increased requirements in pulmonary embolism. *Br. J. Haematol.* 1978; 39:111; Hirsh J, et al. Heparin kinetics in venous thrombosis and pulmonary embolism. *Circulation* 1976; 53:691.

[30] Mulloy B, et al. Characterization of unfractionated heparin: comparison of materials from the last 50 years. *Thromb. Haemost.* 2000; 84(6):1052; Hurst RE, et al. Heterogeneity in the composition of commercial heparins: comparison of anticoagulant activities and biochemical compositions of anionic density-fractionated heparins. *Thromb. Res.* 1982; 25(3):255-65.

[31] *See* Hirsh J, *supra* note 27.

established in a clinical setting. As a result, for the reasons cited above, it is more important for the physician and the patient to be able to rely upon the known clinical parameters established for the LMWHs as a result of clinical trials than it is for unfractionated heparin, which can be titrated in a hospital setting. In light of the life-threatening conditions for which they are indicated, it is therefore critical that a generic LMWH be rigorously scrutinized for identity to insure that it shares all of the reference LMWH's pharmacological activity.

6. Enoxaparin

Enoxaparin is a widely prescribed low molecular weight heparin in the United States. It is indicated for the prophylaxis of DVT during abdominal surgery, hip replacement surgery, knee replacement surgery, and in patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness. It is also indicated for prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin. Enoxaparin is the first LMWH indicated for inpatient treatment of acute DVT (with or without pulmonary embolism), and outpatient treatment of acute DVT (without pulmonary embolism) (in both cases, when administered in conjunction with warfarin sodium).

To manufacture enoxaparin from unfractionated heparin, Aventis uses a depolymerization process of β-elimination of uronic benzylic esters by alkaline media. The reaction takes place under certain specified and tightly controlled parameters for temperature, reaction duration, and base concentration. The process results in smaller polysaccharide chains averaging a molecular weight of 4,500 Da. (approximately one-third the average molecular weight of unfractionated heparin).[32]

B. Until Enoxaparin is Fully Characterized, FDA Should not Approve any ANDA Based Upon Enoxaparin Unless it is Determined to have been Manufactured in Accordance with Aventis' Manufacturing Process or an Equivalent Process, or the Product Demonstrates Equivalent Safety and Effectiveness Through Clinical Studies

1. Aventis' Manufacturing Process Creates Distinct Chemical Structures for Enoxaparin

As discussed above, Aventis utilizes a process of β-elimination of uronic benzylic esters to manufacture enoxaparin. This process creates a distinct drug product

[32] *See* Viskov Declaration.

with a unique chemical structure that is sensitive to specified temperature, base concentration, and duration factors in the reaction.[33]

Each LMWH's manufacturing process results in particular structural characteristics of its polysaccharide chains.[34] The Aventis process results in polysaccharide chains for enoxaparin ranging from two saccharides to oligomers containing 32 saccharides. As stated in its product labeling, in enoxaparin, not more than 20 percent of the polysaccharide chains have a molecular mass of less than 2,000 Da., at least 68 percent have a molecular mass between 2,000 and 8,000 Da., and no more than 18% have a molecular mass higher than 8,000 Da.[35] Different LMWHs, manufactured through different depolymerization processes will have different ranges.[36]

Aventis' process also results in particular saccharide sequences within each given chain. This includes the distribution of specific structures, like the ATIII binding pentasaccharides, as well as the type and arrangement of saccharides within a given chain. Different processes will result in different permutations for each LMWH.[37]

Finally, Aventis' manufacturing process creates specific process-dependent structural modifications to enoxaparin's chemical structure. Using improved analytical technology, Aventis has been able to discover several such modifications, or "fingerprints" of enoxaparin on the polysaccharide chains with average molecular weight of less than 3,600 Da.[38] This portion of enoxaparin's polysaccharide structure accounts for approximately 70-80% of the drug product. The remaining polysaccharide chains (those with molecular weight above 3,600 Da.) have yet to be fully characterized due to limitations on current analytical technology.[39]

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[33] Since the initial development of enoxaparin in 1981, the steps of the manufacturing process have remained unchanged. Clinical supplies used in a few of the initial clinical studies, however, were made from batches where some of the conditions (e.g., time and temperature) were modified. Aventis conducted pivotal clinical trials on batches with and without those modifications. All of those pivotal trials were included in enoxaparin's NDA and formed the basis for enoxaparin's approval by FDA.

[34] *See* Linhardt Declaration.

[35] *See* Lovenox® product labeling.

[36] *See* Linhardt Declaration.

[37] *See id.*

[38] This represents polysaccharide chains ranging from disaccharides to dodecasaccharides.

[39] *See* Viskov Declaration.

2. Aventis has Identified Structural Fingerprints in Enoxaparin's Chemical Structures Which May Possess Pharmacological Activity

Through its ongoing analysis of the polysaccharide chain fragments with molecular weight below 3,600 Da., Aventis has thus far discovered the following important structural fingerprints of enoxaparin that may contribute to its pharmacological activity:

Oligosaccharides with Odd Numbered Saccharide Units

The polysaccharide chains that characterize enoxaparin are composed almost entirely of even numbers of saccharide units. A typical LMWH, for example, will have polysaccharide chains of two, four, six, eight, ten, twelve, etc. saccharide units in length.[40] Enoxaparin, however, contains odd numbered polysaccharide chains in addition to even numbered chains. Hence enoxaparin has chains of two, three, four, five, six, seven, eight, nine, etc. saccharide unit length up to oligomers containing 32 saccharides.[41]

The presence in enoxaparin of odd numbered oligosaccharides is distinctive and is the result of Aventis' manufacturing process. In unfractionated heparin, uronic acids alternate with glucosamine residues resulting in the formation of chains with even numbers of saccharides. During Aventis' manufacturing process, however, the oligosaccharide chains undergo alkaline hydrolysis. We believe that the glucosamine moieties are removed from the oligosaccharide at its reducing end, resulting in formation of oligosaccharides with odd numbers of saccharide units.[42]

Galacturonic Acid Moieties

Aventis' process also results in the formation of galacturonic acid moieties in the polysaccharide sequences. The moieties appear to be the result of both a side reaction from heparin processing in alkaline media, and desulfation of 2-0 sulfo iduronic moieties.[43]

Epimerization of Reducing Ends

In enoxaparin, all reducing ends are epimerized in a mixture of 70% glucosamine and 30% mannosamine. Equilibrium is dependent on the solvent nature

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[40] *See* Linhardt Declaration

[41] *See* Viskov Declaration

[42] *See id.*

[43] *See id.*

and the strength of the base. The reaction quickly reaches a thermodynamic steady state, and is caused by the acidic α-position of the hemiacetal.[44]

1,6 Anhydro Ring Structure

Aventis' manufacturing process results in the formation of a 1,6 anhydro ring (bicyclic) structure at the reducing end of all oligosaccharides bearing 6-O-sulfo groups on the glucosamine moiety. Aventis scientists discovered the chain using new and improved analytical techniques during a structural investigation of enoxaparin.[45] Formation of the 1,6 anhydro ring occurs during the β-elimination depolymerization process. The cyclization probably takes place by intramolecular nucleophilic substitution. In the enoxaparin process, the yield of 1,6 anhydro ring is 15-25% (i.e. 15-25% of the polysaccharide chains in enoxaparin possess the 1,6 anhydro ring structural feature).[46] The 1,6 anhydro ring characterizes enoxaparin.

Unlike the other structural fingerprints of enoxaparin, Aventis has had the opportunity to study the 1,6 anhydro ring structure through preclinical testing (described in more detail below). As a result, Aventis has learned that formation of the 1,6 anhydro ring is sensitive to Aventis' process conditions. If one of these conditions is modified, a change in the presence, or at least the frequency, of the 1,6 anhydro ring structure may occur.[47]

3. Pharmacological Activity and Implications for Clinical Safety and Effectiveness of Enoxaparin's Structural Fingerprints

Due to advances in analytical technology, Aventis has discovered the above-described structural fingerprints. Aventis has performed multiple tests on the 1,6 anhydro ring but has not yet assessed the pharmacological activity of the other fingerprints. Many of these fingerprints, however, represent significant structural modifications and will likely prove to be pharmacologically and clinically active.

For example, as discussed above, Aventis' manufacturing process results in particular polysaccharide chain sequences as well as particular saccharide sequences within each given chain. A generic product that did not utilize Aventis' process or an equivalent, would almost certainly have a different polysaccharide permutation. Aventis believes that these differences between enoxaparin and such a generic product would cause the two drugs to demonstrate dissimilar pharmacokinetics and potentially dissimilar clinical activities. This is because different chain length/sequence

[44] *See id.*

[45] *See id.*

[46] *See id.*

[47] *See id.*

permutations lead to time dependent variation in anti-Xa/anti-IIa circulating activity. This has been clearly recognized for heparins where the higher-molecular-weight species are cleared from the circulation more rapidly than the lower-molecular-weight species. This differential clearance results in accumulation *in vivo* of the lower-molecular-weight species, which have a lower ratio of anti-IIa to anti-Xa activity.[48] Hence, even though enoxaparin and such a generic may have the same anti-Xa/anti-IIa ratio as measured before injection, differences in polysaccharide length/sequence permutations would likely lead to varying rates of absorption and elimination and, thus, different circulating anti-Xa/anti-IIa ratios.[49]

A real world example can be found in a comparison of enoxaparin and nadroparin, an LMWH available in Canada. The two drugs have a similar molecular weight distribution and anti-Xa/anti-IIa ratio. Nevertheless, nadroparin has a significantly longer Tmax and a significantly higher Cl/f for anti-Xa activity. Further, despite demonstrating an equivalent anti-Xa/anti-IIa activity before injection, the two drugs diverge after injection to demonstrate different *in vivo* ratios.[50]

Unlike enoxaparin's other structural fingerprints, Aventis has been able to conduct preclinical testing on the 1,6 anhydro ring structure. By duplicating Aventis' manufacturing process except for a discrete change in certain parameters, Aventis scientists constructed two LMWHs similar to enoxaparin in molecular weight, anti-Xa activity, and anti-Xa/anti-IIa ratio, but with dissimilar 1,6 anhydro ring content. The first of these alternative LMWHs contained the 1,6 anhydro ring structure in only minimal amounts ("< 7% 1,6 anhydro LMWH").[51] The second contained the ring but at a higher concentration than is present in enoxaparin ("40-50% 1,6 anhydro LMWH).[52]

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[48] *See* Hirsch J, *supra* note 27.

[49] This is, in part, a function of the fact that anti-IIa activity is absorbed more slowly and eliminated more quickly than anti-Xa activity. *See* Sanderink G-J, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. *Clin Pharmacol. Ther.* 2002; 72:308.

[50] Stiekema JCJ, et al. A cross-over comparison of the anti-clotting effects of three low molecular weight heparins and glycosaminoglycuronan. *Br. J. Clin. Pharmacology* 1993; 36: 51-56; Collignon F, et al. Comparison of the pharmacokinetic profiles of three low molecular mass heparins - dalteparin, enoxaparin, and nadroparin - administered subcutaneously in healthy volunteers (doses for prevention of thromboembolism). *Thromb. Haemost.* 1995; 73:630-40.

[51] This compound contained the 1,6 anhydro ring at less than 7% concentration, and is referred to as the "Type I, Batch No. DIA2844" compound in the Study Reports, attached hereto as Appendix A.

[52] This compound contained the 1,6 anhydro ring at between 40% and 50% concentration, and is referred to as the "Type II, Batch No. DIA2648" compound in the Study Reports, attached hereto as Appendix A.

Enoxaparin contains the 1,6 anhydro ring structure at 15-25% frequency. All three of these LMWHs had similar anti-Xa level, molecular weight, and anti-Xa/anti-IIa activity.[53] Aventis then compared various aspects of their pharmacological activity in order to gauge the pharmacological relevance of the 1,6 anhydro ring structure.

As expected, the 1,6 anhydro ring structure at 15-25% frequency demonstrated pharmacological activity. We believe that the bicyclic acetal's presence protects the oligosaccharides to which it is attached from exposure to chemical function and conditions including oxidation reaction and enzymatic cleavage.[54] These factors produce a number of pharmacological effects that likely bear clinical significance. As discussed below, both the < 7% 1,6 anhydro LMWH as well as the 40-50% 1,6 anhydro LMWH demonstrated appreciable differences in activity.

Inflammation

Aventis' testing revealed that the 1-6 anhydro ring at 15-25% frequency makes an important contribution to enoxaparin's anti-inflammatory properties. Inflammation is recognized as a major component of myocardial ischemia. Inflammation within vulnerable coronary plaques may cause unstable angina by promoting rupture and erosion.[55] Previous studies have already established that heparin inhibits induction of inducible nitrite oxide synthase by cytokines in endothelial cells by modulation of inducible nitrite oxide mRNA.[56] Nitrite oxide is a reactive oxygen species strongly implicated in the pathophysiology of ischemia.[57] Aventis compared enoxaparin (15-25% 1,6 anhydro ring content) with the <7% 1,6 anhydro LMWH and the 40-50% 1,6 anhydro LMWH in an animal model. Nitrite/Nitrate (markers of inflammatory response) production and accumulation in blood was induced in mice by administering E. coli lipopolysaccharide ("LPS").[58] Details of this study are attached hereto in Petitet, Appendix A.

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[53] *See* Viskov Declaration.

[54] *See id.*

[55] Buffon A, et al. Widespread coronary inflammation in unstable angina. *N. Engl. J. Med.* 2002; 347(1):5.

[56] Bonmanne, et al. Heparin inhibits induction of nitrite oxide synthase by cytokines in rat brain microvascular endothelial cells. *Neuroscience Letters* 1998; 253:95; Upchurch GR. High dose heparin decreases nitrite oxide production by cultured bovine endothelial cells. *Circulation* 1997; 95:2115.

[57] Chester AH, et al. Low basal and stimulated release of nitric oxide in atherosclerotic epicardial coronary arteries. *Lancet* 1990; 336:897-900.

[58] *See* Petitet, Appendix A.

Aventis found that enoxaparin (15-25% anhydro) produced an appreciably greater anti-inflammatory effect than either the < 7% or 40-50% 1,6 anhydro LMWHs. Enoxaparin demonstrated an appreciable reduction in LPS-induced nitrite/nitrate plasmatic increase, thus giving enoxaparin an ID50 of 0.18 mg/Kg. The < 7% 1,6 anhydro LMWH demonstrated an ID50 of 0.60 mg/Kg., meaning that it requires a dose more than three times higher than enoxaparin to produce the same anti-inflammatory effect. The 40-50% 1,6 anhydro LMWH also demonstrated a reduced anti-inflammatory effect as compared to enoxaparin. It demonstrated an ID50 of 0.46 mg/Kg, meaning it requires a dose twice as high as enoxaparin to produce the same anti-inflammatory effect.[59] Thus the presence of the 1,6 anhydro ring structure in enoxaparin at 15-25% concentration makes notable contributions to enoxaparin's anti-inflammatory properties.

There is ample reason to believe that the 1,6 anhydro ring's anti-inflammatory properties will bear clinical significance in humans. In addition to it being a component in myocardial ischemia and a cause of tissue damage, inflammation is an important factor in the treatment of UA/non-STEMI.[60] Multiple sources confirm that inflammation plays an important role in the development of atherosclerosis.[61] There is extensive evidence that the acute coronary syndrome, which is the characteristic of unstable angina and non-ST myocardial infarction, is also associated with an inflammatory response.[62] Only enoxaparin has been demonstrated to have clear superiority to unfractionated heparin treatment for this condition.[63]

Smooth Muscle Cell Proliferation

The 1,6 anhydro ring also contributes to enoxaparin's inhibition of smooth muscle cell proliferation. Smooth muscle cell proliferation is at least a partial cause of vascular pathologies such as atherosclerosis, hypertension, and restenosis

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[59] *See id.*

[60] *See* Roque M, et al. Pathophysiology of unstable angina. *Thromb. Res.* 1999; 95:v5-v14.

[61] *See, e.g.*, Ross R. Atherosclerosis: an inflammatory disease. *N. Engl. J. Med.* 1999; 340:115-26.

[62] *See* Libby P. Molecular basis of the acute coronary syndromes. *Circulation.* 1995; 91:2844-50.

[63] *See* Cohen M, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N. Engl. J. Med.* 1997; 337(7):447.

following angioplasty.[64] Artery enlargement is a reaction to increased blood flow and/or the formation of an atherosclerotic plaque. Both of these events are involved in unstable angina and non-Q-wave myocardial infarction. Aventis conducted an *in vitro* study on smooth muscle cell proliferation isolated from explants of human internal mammary artery samples. Details of this study are attached hereto in Dilley & Little, Appendix A.

Aventis found that the 1,6 anhydro ring structure increases enoxaparin's inhibitory action on smooth muscle cell proliferation. Both the < 7% 1,6 anhydro LMWH and the 40-50% 1,6 anhydro LMWH exhibited distinctive inhibitory properties. Both compounds demonstrated low inhibitory capacity at low concentrations. The 40-50% 1,6 anhydro LMWH, however, was a more potent inhibitor of smooth muscle cell proliferation at higher concentrations than the < 7% 1,6 anhydro LMWH. Relative to enoxaparin, the < 7% 1,6 anydro LMWH had, on average, about 35% less inhibitory capacity than enoxaparin.[65] These results suggest that the 1,6 anhydro ring is necessary for dose dependent inhibition of human smooth muscle cell growth. Again, this has potential therapeutic significance. Abnormal levels of proliferation of arterial smooth muscle cells are key mechanisms in the pathogenesis of major vascular diseases including atherosclerosis, hypertension, and restenosis following angioplasty.[66] Atherosclerosis and restenosis are significant contributory factors in the occurrence of unstable angina and non-Q-wave myocardial infarction.[67]

Angiogenesis

Enoxaparin potentiates the aFGF induced human endothelial cell proliferation, necessary for stimulation of angiogenesis. There is a current need for angiogenesis stimulating drugs for alleviating and ameliorating diseases characterized by microvascular insufficiency such as ischemic heart disease.[68] Formation of new capillaries by endothelial cells is highly important in coronary disease where hypoxic myocardium needs formation of new vessels to limit ischemic injury. In this regard, the ability of human growth factor, FGF, to induce neoangiogenesis in the ischemic myocardium has been demonstrated in animals and in patients with coronary heart

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[64] Pickering JG, et al. Proliferative activity in peripheral and coronary atherosclerotic plaque among patients undergoing percutaneous revascularization. *J. Clin. Invest.* 1993; 91:1469-80.

[65] *See* Dilley & Little, Appendix A.

[66] *See* Pickering, *supra* note 64.

[67] Theroux P & Fuster V. Acute coronary syndromes: Unstable angina and non-Q-wave myocardial infarction. *Circulation* 1998; 97:1195-1206.

[68] *See* Isner JM. Angiogenesis for revascularization of ischemic tissues. *European Heart J.* 1997; 18:1.

disease.[69] FGF plays a crucial role in this phenomena, but needs protection against degradation and damage. Heparins (including LMWHs) stabilize an active conformation of FGF that becomes less sensitive to acid or heat denaturation and more favorable to interaction with specific cellular receptors. In its preclinical testing, Aventis has found that the 1,6 anhydro ring optimizes enoxaparin's interaction with FGF.

Aventis tested enoxaparin and the alternative LMWHs on a BHK-21 cell line (baby hamster kidney cells). Cell proliferation was then quantified by use of radioactive thymidine incorporation. Aventis tested the three LMWHs in multiple doses ranging from 0 to 200 mcg. The different formulations exhibited differing levels of BHK cell proliferation stimulation, demonstrating that the 1,6 anhydro ring (and the specific concentration thereof), influences enoxaparin's interaction with FGF, which plays a crucial role in angiogenesis.[70] Details of this study are attached hereto in von Specht, Appendix A.

Pharmacokinetics

In an animal study conducted by Aventis, the three studied LMWHs demonstrated statistically significant differences in plasma anti-Xa activity. The < 7% 1,6 anhydro LMWH showed a statistically significant increase in plasma anti-Xa activity and anti-IIa activity as compared to enoxaparin. The 40-50% 1,6 anhydro LMWH demonstrated a decreased plasma anti-Xa activity and anti-IIa activity.[71] Details of this study are attached hereto in "DMPK Report," Appendix A. This study clearly demonstrated that systematic reductions in the amounts of 1,6 anhydro ring results in corresponding systematic increases in the anti-Xa activity and clearly establishes the relevance of the 1,6 anhydro ring to *in vivo* anti-Xa levels.

Safety Profile

As discussed above, the presence of the 1,6 anhydro ring at 15-25% frequency causes enoxaparin to have a certain plasma anti-Xa activity. High anti-Xa activity may be associated with an increased risk of bleeding in certain patient populations.[72] Thus a generic product that failed to follow Aventis' manufacturing

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[69] Schumacher B, et al. Induction of neoangiogenesis in ischemic myocardium by human growth factors: First clinical results of a new treatment of coronary heart disease. *Circulation* 1998; 97:645.

[70] *See* von Specht, Appendix A.

[71] *See* DMPK Report, Appendix A.

[72] *See* Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. *J. Am. Coll. Cardiol.* 1997; 29: 1474-1482.

process or an acceptable equivalent, and thus did not contain the 1,6 anhydro ring, may pose an increased threat of hemorrhagic complications in patients.

Effect on Coagulation and Thrombosis

Aventis' tests showed no statistically significant differences between enoxaparin and the two alternative LMWHs in activated partial thromboplastin time, prothrombin time, thrombin generation, anti-Xa activity, anti-IIa activity, or thromboelastography. Details of this study are attached hereto in Laux, Appendix A.

4. Large Portions of Enoxaparin Remain Uncharacterized

Limitations on current analytical technology have prevented Aventis from exploring large portions of enoxaparin. Enoxaparin is composed of literally millions of oligosaccharides. In this complex collection of macromolecules, we find polysaccharide chains ranking from disaccharides to oligomers with 32 saccharide units. Aventis so far has not been able to isolate those polysaccharide chain fragments of molecular weight above 3,600 Da. (i.e., oligomers containing from 13 to 32 saccharide units).[73] This completely unexplored (by direct analysis) portion of the enoxaparin represents approximately 20% to 30% of the drug product (molar).[74]

Thus, as much as 30% of enoxaparin remains incompletely characterized.[75] Further, Aventis' process almost certainly creates distinctive and pharmacologically active chemical structures in those chains above 3,600 Da. Because Aventis has found distinctive fingerprints with pharmacological activity (and likely therapeutic significance) in polysaccharide chains weighing less than 3,600 Da., distinctive fingerprints with pharmacological relevance presumably exist in those chains above 3,600 Da.

5. In Order to Duplicate Enoxaparin's Pharmacological Activity, a Generic Manufacturer Must Use the Aventis Manufacturing Process or an Equivalent Process

A generic product cannot duplicate enoxaparin's pharmacological activity by duplicating only enoxaparin's molecular weight or anti-Xa/anti-IIa activity.

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[73] *See* Viskov Declaration.

[74] *See id.*

[75] This does not imply that Aventis has fully characterized all of those chains below 3,600 Da. even though the technology exists to do so. Aventis has not yet had the opportunity to explore all of the chains under 3,600 Da. What exploration Aventis has done, however, has already yielded a considerable number of distinct structural fingerprints. *See* Viskov Declaration.

First, these markers are not sufficient indicators of the overall pharmacological effect of an LMWH.[76] Numerous studies have been conducted, for example, to assess the utility of anti-factor Xa monitoring in the treatment of DVT. None of these studies, however, have demonstrated a link between activity of anti-factor Xa and the effectiveness of the treatment of DVT by LMWH.[77]

Indeed, the exact mechanism by which LMWHs produce their anti-coagulant effects remains unsettled. It is widely acknowledged that a specific pentasaccharide sequence binding to ATIII plays a critical role in LMWH anti-coagulation activity. Some experts have argued, however, that tissue-factor-pathway inhibitor, or other factors may also contribute to the inhibition of factor Xa.[78] Even the relative importance of inhibition of factor Xa versus factor IIa remains unclear.[79]

Second, as discussed in detail above, Aventis scientists have been able to construct two LMWHs that are similar to enoxaparin in molecular weight and anti-Xa/anti-IIa ratio but differ from enoxaparin in the content of certain relevant structural features. This is demonstrated by the comparative testing Aventis did, described above, between enoxaparin, the < 7% 1,6 anhydro LMWH, and the 40-50% 1,6 anhydro LMWH. Both the < 7% and 40-50% 1,6 anhydro LMWHs were identical to enoxaparin in anti-Xa/anti-IIa ratio and molecular weight but did not contain the 1,6 anhydro ring in the proper proportion. As a result, both of these alternative LMWHs exhibited different pharmacological activity than enoxaparin in several respects. Several of these differences are quite likely to have clinical significance despite all three LMWHs having the same traditional markers.

Finally, as described above, a large portion of enoxaparin remains uncharacterized. It is impossible, at this time, to know what additional structural modifications with likely clinical significance are present in those unexplored portions of the complex collection of macromolecules. Simply duplicating enoxaparin's anti-Xa/anti-IIa ratio and molecular weight will not insure that those features in the unexplored portion of the product are duplicated.

As a result, until enoxaparin becomes fully characterized, the only way for a generic to insure that it contains all of the therapeutically significant structural features of enoxaparin (both known and yet to be discovered) is to duplicate Aventis'

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[76] Greaves M. Limitations of the Laboratory Monitoring of Heparin Therapy. *Thromb. Haemost* 2002; 87:163.

[77] *See* Rosenbloom D, Ginsberg JS. Arguments against monitoring levels of anti-factor Xa in conjunction with low-molecular-weight heparin therapy. *Can. J. Hosp. Pharm.* 2002; 55:15; Greaves, *supra* note 77, at 163.

[78] *See* Weitz, *supra* note 12, at 688.

[79] *See id.*

manufacturing process or utilize an equivalent. If it does not do so, it cannot claim to have the "same" active ingredient as enoxaparin. In such a case, the section 505(j)(2)(A)(ii)(II) of the FDCA prohibits FDA from approving such a generic product unless it establishes equivalent safety and effectiveness through clinical trials.

6. Distinguishable from Cases Where no Likely Clinical Significance Is Found

The case of enoxaparin is distinguishable from previous cases where FDA has determined that variances in active ingredient chemical structure between a pioneer drug and a generic are insufficient to deter FDA from making a finding of "sameness." For example, in December 1992, Serono Laboratories, Inc. submitted a citizen petition to FDA regarding generic competitors for Pergonal. Pergonal is a menotropin, derived from the urine of post-menopausal women, for treatment of infertility. The drug contains two active ingredients, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[80]

In 1990 Lederle Parenterals, Inc. submitted an ANDA for Repronex, a generic form of Pergonal. Repronex contained LSH, but in a different isoform than that found in Pergonal. Serono argued in its 1992 citizen petition that because of this difference in isoforms, Repronex did not contain the "same" active ingredient as Pergonal. It thus argued that FDA should not approve Repronex's ANDA.[81]

Although it recognized the difference in isoforms, FDA rejected Serono's argument. It reasoned that the isoform variation "was not 'clinically significant for the product's intended uses' and therefore did not preclude a 'sameness' finding for purposes of 21 U.S.C. § 355(j)."[82] After Serono sued FDA in federal district court, the D.C. Circuit held that FDA was entitled to deference in its interpretation of the meaning of the word "same" in the statute.[83]

Unlike the isoform variation at issue in *Serono*, our preclinical tests show that the presence of the 1,6 anhydro ring on 15-25% of enoxaparin's polysaccharide chains may well have clinical significance for enoxaparin's intended uses. This is because the 1,6 anhydro ring represents a chemical modification of the polysaccharide chains on which it appears, not just a variation in three dimensional structure. Changes to the anti-inflammatory properties and plasma anti-Xa activities from the approved enoxaparin could be unsafe in patients being treated for life-threatening conditions such as DVT, pulmonary embolism, and coronary artery diseases such as unstable angina and

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[80] *See Serono Labs., Inc.* v. *Shalala*, 158 F.3d 1313 (D.C.Cir. 1998).

[81] *See id.*

[82] *Id.*

[83] *See id.*

certain types of myocardial infarction. The 1,6 anhydro ring structure also contributes to enoxaparin's effects on smooth muscle cell proliferation and angiogenesis. Changes to these properties from the approved enoxaparin are also likely to have clinically significant consequences, as discussed above. Thus, our position with regards to enoxaparin is consistent with FDA's own definition of "sameness" as set forth in its response to Serono's citizen petition.

Also, as discussed above, the presence of the 1,6 anhydro ring has an effect on enoxaparin's anti-Xa level.[84] Higher anti-Xa levels may be associated with increased bleeding in patients with specific conditions such as renal impairment, which results in a decreased clearance and consequently higher Xa levels. Thus, absence of the 1,6 anhydro ring in a generic may cause it to have higher anti-Xa levels and a resulting increased risk of hemorrhagic complications. Aventis has not, however, run tests comparing the incidence of bleeding under administration of enoxaparin, the < 7% 1,6 anhydro and the 40-50% 1,6 anhydro.[85]

Finally, in *Serono*, Pergonal was fully characterized at the time that Repronex submitted its ANDA. Thus, FDA was in a position to assess all of the possible structural differences between the two products for clinically significant variances. By contrast, large portions of enoxaparin remain uncharacterized and may contain clinically significant structural fingerprints. Thus, unless a generic enoxaparin is manufactured in accordance with Aventis' product, FDA will have no reliable way to insure that the generic's active ingredient is the same as enoxaparin.

7. Similarity to the Premarin Case

The case of enoxaparin is highly analogous to the situation involving Premarin in the late 1980s/early 1990s. There, Wyeth-Ayerst claimed that Premarin, a conjugated estrogen product, could not be adequately characterized, and therefore could not be duplicated by a generic. Derived from pregnant mare's urine, it was well known that Premarin contained a variety of different estrogenic compounds including the two thought to be most responsible for the drug's therapeutic effect, estrone and equilin. It was thought, however, that estrogen mixtures could be identified simply through reference to its total estrogenic potency, thereby obviating any need to characterize all of its component estrogens.

> Little data were available when the first monographs were published on the detailed composition of Premarin or the pharmacologic activity of its components. The scientific belief at the time was that all estrogens were similar in

[84] *See* DMPK Report, Appendix A.

[85] Recognizing these risks, Aventis has filed a supplemental NDA with FDA.

> their pharmacologic actions on the body and, therefore, the pharmacologic activity of an estrogen preparation could be described in terms of its total estrogenic potency. The effects of different estrogens in a mixture were believed to be additive and the identity of any particular estrogen contributing to the estrogenic potency was not considered crucial.[86]

New discoveries regarding the therapeutic activity of certain component estrogens, however, led FDA to conclude in 1997 that Premarin must be characterized before synthetic generic Premarin's could be approved. In particular, it was discovered that the estrogen compound delta (8,9) dehydroestrone sulfate (DHES) generated a significant concentration of a potentially active metabolite despite the fact that DHES made up only 5% of the total mixture. FDA found this fact "[h]ighly illustrative of the need for further characterization of Premarin."[87]

As a result of these findings, FDA determined that Premarin was not adequately characterized and, therefore, it was impossible to define its active ingredients. FDA reasoned that no synthetic generic Premarin could claim to have the "same" active ingredients as did Premarin until Premarin's active ingredients were defined. As a result, FDA declared that it would not approve any ANDA for synthetic generic Premarin until such time as Premarin became adequately characterized.[88] FDA noted, however, that it would approve generic Premarin products that were made, like Premarin, from pregnant mare's urine. By using the same source material, FDA could be assured that the generic contained the same active ingredients as Premarin.

In the case of enoxaparin, Aventis anticipates that generic products will be manufactured from natural unfractionated heparin source material. Unlike conjugated estrogens, however, the composition of enoxaparin is not solely a factor of the source material used. The chemical structure of enoxaparin, like all LMWHs, is highly dependent upon the precise manufacturing process employed. As has been discussed in detail above, Aventis' manufacturing process results in distinctive structural components some of which, like the 1,6 anhydro ring, make a significant contribution to enoxaparin's overall therapeutic activity.

The discovery of the pharmacological contributions of the 1,6 anhydro ring, for example, is highly analogous to the discovery of the contributions of DHES in Premarin. In Premarin, DHES represented the prospect that estrogenic components

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[86] *FDA Backgrounder on Conjugated Estrogens*, November 20, 2002, *available at* http://www.fda.gov/cder/news/cebackground.htm.

[87] *See id.*

[88] *See id.*

may exist in pregnant marc's urine that had significant therapeutic activity, but may not be present in a synthetic generic Premarin. Similarly, the 1,6 anhydro ring represents the fact that Aventis' manufacturing process creates biologically relevant structures that do not exist in the natural source material. These include structures that have been discovered (the 1,6 ring) as well as structures that have not yet been identified (i.e. those found in tetradecasaccharide to 32 oligomers). Because Aventis uses a tightly controlled process, it is able to insure that all of these significant structural modifications (both known and unknown) are consistently present in enoxaparin. Truly, with enoxaparin, the process makes the product.

We recognize that there are several generic heparin products currently on the market. The use of porcine intestinal heparin source material to create LMWH does not, in and of itself, create an obstacle to approval of generic LMWHs. The obstacle and, thus, the similarity to the Premarin case, arises from the fact that creation of LMWHs and, particularly, enoxaparin, is highly process dependent. Because Premarin was, at the time, insufficiently characterized, one could not be sure that all of its components would be present in a synthetic version of the drug. Similarly, because enoxaparin is insufficiently characterized, one cannot be sure that a generic product will contain all of enoxaparin's clinically significant structures unless it is manufactured in accordance with Aventis' process. This is so even if the generic product comes from the same unfractionated heparin source material.

IV. Conclusion

As a result of the above, there are only three ways that a generic can meet the statutory requirement of "sameness" necessary for approval of a generic product. First, a generic can wait until enoxaparin becomes fully characterized. At that point, FDA and the generic drug industry will be able to identify all of the pharmacologically active and potentially clinically significant structural modifications (and their frequency) in enoxaparin. The generic company can then insure that all of those components are in its product.

Second, while enoxaparin remains only partially characterized, a generic wishing to insure that those necessary components are in a generic product must duplicate Aventis' manufacturing process for enoxaparin or have an acceptable equivalent. Enoxaparin's structural modifications are caused by Aventis' manufacturing process and are sensitive to factors such as time, temperature, and base concentration. By following that process, or an equivalent, the generic and FDA can know that even the as yet undiscovered modifications are present in the generic product.

If a generic manufacturer does not follow Aventis' process, however, FDA will not be able to make the required finding of "sameness." FDA will have no way of knowing whether the clinically significant structural modifications caused by Aventis' manufacturing process are present in the product. As a result, the only remaining way for FDA to approve the generic product, consistent with the Act, is to

require that the product demonstrate equivalent safety and effectiveness through clinical trials.

V. Required Material

A. Environmental Impact

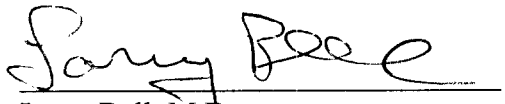
The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31(a).

B. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

C. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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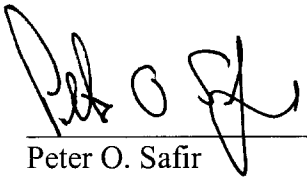
Respectfully submitted,



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Attachments

Appendix A