



JUL 23 2010

Péter O. Safir
Scott L. Cunningham
Covington & Burling
1201 Pennsylvania Ave., N.W.
Washington, D.C. 20004-2401

Re: Docket No. FDA-2003-P-0273

Dear Mr. Safir and Mr. Cunningham:

This letter responds to your citizen petition submitted on behalf of Aventis Pharmaceuticals, Inc. (Aventis) on February 19, 2003 (Petition),¹ requesting that the Food and Drug Administration (FDA or the Agency) withhold approval of any abbreviated new drug application (ANDA) for a generic² version of Lovenox (enoxaparin sodium injection) (hereafter, "generic enoxaparin") unless certain conditions are met. Specifically, you make the following requests:

- That until enoxaparin has been fully characterized, we not approve any ANDA citing Lovenox as the reference listed drug (RLD) unless the manufacturing process used to create the generic drug product is determined to be equivalent to Aventis's manufacturing process for enoxaparin or the application is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials.
- That we not approve any ANDA citing Lovenox as the RLD unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15 percent and 25 percent of its poly(oligo)saccharide chains.³

We have carefully reviewed your petition and the supplements submitted by you on behalf of Aventis and its successors in interest on February 12, 2004 (Supplement No. 1), September 26, 2005 (Supplement No. 2), September 14, 2006 (Supplement No. 3), and June 29, 2007 (Supplement No. 4), as well as the comments submitted by you (dated September 1, 2004, October 13, 2004, March 17, 2005, March 16, 2006, August 25, 2006, March 2, 2007, March 15, 2007, and

¹ This citizen petition was originally assigned docket number 2003P-0064/CP1. The number was changed to FDA-2003-P-0273 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

² The term "generic" refers to a drug product for which approval is sought under an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act).

³ A monosaccharide is a simple sugar (carbohydrate) that cannot be decomposed by hydrolysis to obtain smaller molecules of carbohydrate. A saccharide chain contains a series of monosaccharides linked by glycosidic bonds. A polysaccharide is a saccharide chain composed of many monosaccharides joined by glycosidic bonds. An oligosaccharide is a saccharide chain containing a small number of monosaccharides linked by glycosidic bonds. The terms polysaccharide and oligosaccharide are sometimes used interchangeably.

April 14, 2009). We have also reviewed the comments submitted by Amphastar Pharmaceuticals, Inc. (Amphastar) (dated May 13, 2004, November 23, 2004, July 18, 2005, October 6, 2005, and October 7, 2005), Hyman, Phelps & McNamara, P.C. (dated October 17, 2003, and August 4, 2004), Teva Pharmaceuticals USA Inc. (dated August 20, 2004), and other commenters. We have also extensively reviewed relevant scientific evidence and information.

For the reasons stated below, your petition is granted in part with respect to your request that generic enoxaparin contain the 1,6 anhydro ring structure at the reducing ends of between 15 percent and 25 percent of its poly(oligo)saccharide, but denied in all other respects.⁴

OVERVIEW

To obtain ANDA approval, an applicant must submit sufficient information to show that its generic drug product is bioequivalent to and has the same active ingredient(s), route of administration, dosage form, strength, previously approved conditions of use, and (with certain exceptions) labeling as the RLD. The underlying premise of the ANDA approval requirements is that the generic drug product and the RLD can be substituted for each other with the full expectation that they will have the same clinical effect and safety profile.⁵

The primary issue raised by the petition and related comments is whether an ANDA applicant for enoxaparin can demonstrate that its product has the same active ingredient (i.e., enoxaparin sodium or "enoxaparin") as that of the RLD (i.e., Aventis's Lovenox). The crux of your petition and related supplements is that we should not approve an ANDA for enoxaparin unless the ANDA applicant: (1) completely characterizes enoxaparin by isolating, purifying, and sequencing each of its unique polysaccharide chains and determining their relative abundance, which you state is currently impossible, (2) uses Aventis's or the equivalent manufacturing process, or (3) conducts clinical trials to demonstrate the equivalent safety and effectiveness of the product.

We do not find it necessary for an ANDA applicant seeking approval of generic enoxaparin to submit the information you request. Nonetheless, we recognize that the approval of ANDAs for enoxaparin raises complicated scientific and regulatory issues, which we have carefully considered. Lovenox, a naturally sourced drug product, has some degree of batch-to-batch variability,

⁴ As discussed in section VI, you do not clarify in your petition and supplements what you mean by your request that an ANDA applicant for enoxaparin use a manufacturing process equivalent to Aventis's manufacturing process. To manufacture enoxaparin, an ANDA applicant generally (1) would depolymerize heparin by chemical (alkaline) β -elimination and (2) would adjust process conditions such that they result in manufacturing the same active ingredient as Lovenox's enoxaparin. To manufacture enoxaparin, the process conditions could (but do not necessarily need to) be the same as those used for Lovenox's enoxaparin. Insofar as an equivalent manufacturing process for enoxaparin could be interpreted only to be one in which every step of the manufacturing process, including process conditions, are identical to those of Aventis's manufacturing process for Lovenox, your request is denied.

⁵ FDA classifies as therapeutically equivalent, and thus substitutable, those products that are (1) approved as safe and effective, (2) pharmaceutically equivalent (which means, in part, drug products in identical dosage forms that contain identical amounts of the identical active ingredient; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency (21 CFR 320.1(c)), (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with Current Good Manufacturing Practice regulations. See Orange Book, 30th Ed., at iv. The terms "therapeutically equivalent" and "substitutable" are used interchangeably in this response.

and the active ingredient has not been fully characterized. Based on our evaluation of all the relevant data and other current relevant scientific information, our experience and expertise, Agency precedent, and applicable law, we find that enoxaparin has been adequately characterized for the purposes of approving naturally sourced generic enoxaparin; and we conclude that an ANDA applicant for enoxaparin can demonstrate active ingredient sameness by meeting five criteria,⁶ each of which captures different aspects of the active ingredient's "sameness."

In very general terms, the five criteria involve (1) the physical and chemical characteristics of enoxaparin, (2) the nature of the source material and the method used to break up the polysaccharide chains into smaller fragments, (3) the nature and arrangement of components that constitute enoxaparin, (4) certain laboratory measurements of anticoagulant activity, and (5) certain aspects of the drug's effect in humans. The equivalence evaluation for these criteria generally is based upon qualitative and/or quantitative comparisons of the generic drug product's enoxaparin to multiple batches of Lovenox's enoxaparin and takes into consideration the batch-to-batch variability and sampling of Lovenox, and analytical test variability. The equivalence evaluation demonstrates that the molecular diversity⁷ of the generic drug product's enoxaparin and Lovenox's enoxaparin is equivalent, including with respect to the 1,6 anhydro ring structure at the reducing ends of between 15 percent and 25 percent of its poly(oligo)saccharides. Equivalent molecular diversity demonstrates sameness for enoxaparin.⁸ These five criteria together comprise a robust test that provides overlapping evidence by which an ANDA applicant for enoxaparin can demonstrate active ingredient sameness for enoxaparin within the meaning of the Act and FDA regulations.

This approach to determining active ingredient sameness for enoxaparin has been considered extensively by various components of the Agency's Center for Drug Evaluation and Research (CDER), including the Office of Pharmaceutical Science (including the Office of Generic Drugs, the Office of New Drug Quality Assessment, and the Office of Biotechnology Products), and the Office of New Drugs (including the Division of Gastrointestinal and Coagulation Drug Products and the Division of Medical Imaging/Hematology Products).⁹ We made this decision after carefully considering the petition (including supplements and comments), other correspondence, relevant scientific publications regarding characterizations of LMWHs, ANDAs for enoxaparin, and other relevant information. As with all complex scientific issues, it is possible that with improvement in the understanding of the biological and clinical properties of enoxaparin and/or advances in the analytical technologies that might be used to characterize enoxaparin, other approaches might emerge to establish the sameness of enoxaparin.

⁶ The terms "criteria" and "criterion," as used in this response, refer to a particular demonstration or showing of a specific aspect of active ingredient sameness.

⁷ See footnote 25.

⁸ As discussed in section I.B, it is well established that certain activities (anti-Xa activity and anti-IIa activity) explain, in significant part, the pharmacological activity for low molecular weight heparins (LMWHs) (including enoxaparin). Other mechanisms of action also may be important for the pharmacological activity of LMWHs (including enoxaparin). The five criteria ensure that generic enoxaparin will have the same active ingredient components as those of Lovenox's enoxaparin (within the context of its variability) even though the contribution of each component has not been fully elucidated. Therefore, pharmacological activity of the active ingredient of the generic enoxaparin and that of Lovenox can be expected to be the same.

⁹ As a result of CDER's reorganization, responsibility for reviewing the NDA for Lovenox was transferred from CDER's Division of Gastrointestinal and Coagulation Drug Products to the Division of Medical Imaging/Hematology Products.

In addition to the issues raised in your petition, we have also considered issues related to immunogenicity. It is important that ANDA applicants assess the potential of the generic product to generate a greater immune response as compared to the RLD, Lovenox.

This response contains seven sections. Section I contains relevant background information. Section II describes the statutory and regulatory framework for active ingredient sameness. Section III discusses the five criteria that provide sufficient information to enable us to conclude active ingredient sameness for enoxaparin. Section IV explains that our decision on enoxaparin sameness is consistent with previous ANDA approval decisions. Section V summarizes the relevant case law, which supports our decision. Section VI addresses specific arguments and information in your petition and related comments and explains why those arguments and information do not preclude a finding of active ingredient sameness for enoxaparin. Finally, section VII summarizes our conclusion.

DISCUSSION

I. BACKGROUND

A. Lovenox

FDA approved Aventis's new drug application (NDA) for Lovenox (enoxaparin sodium injection, NDA 20-164) on March 29, 1993.¹⁰ Lovenox is indicated for:

- Prophylaxis of deep vein thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness
- Inpatient treatment of acute DVT with or without pulmonary embolism
- Outpatient treatment of acute DVT without pulmonary embolism

¹⁰ Upon approval of Lovenox, Aventis received 5 years of marketing exclusivity and other patent listing and certification benefits described in section 505 of the Act. Aventis subsequently received 3 years of marketing exclusivity for conducting necessary clinical studies in support of Lovenox labeling related to ST-segment elevation myocardial infarction (STEMI). This exclusivity expired on May 16, 2010. As a result of patent certifications submitted by ANDA applicants under section 505(j)(2)(A)(vii) of the Act and notice of those certifications, Aventis filed a lawsuit against those ANDA applicants for infringement of patents submitted by Aventis to FDA as required under section 505(b) and (c). After a trial, the district court found that U.S. Patent No. 5,389,618 (the '618 patent) and its replacement, U.S. Reissue Patent No. 38,743 (the '743 patent) were unenforceable on the grounds that Aventis committed inequitable conduct before the United States Patent and Trademark Office (PTO) in failing to disclose material information to the PTO. See *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 475 F. Supp. 2d 970 (C.D. Cal. Feb. 8, 2007). The United States Court of Appeals for the Federal Circuit affirmed that determination. See *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 525 F.3d 1334 (Fed. Cir. May 14, 2008). The Supreme Court denied the petition for certiorari. See *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc., et al.* 129 S.Ct. 2053 (April 27, 2009). ANDAs referencing Lovenox were submitted to FDA before the passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173) (MMA). Therefore, 180-day exclusivity for drug products referencing Lovenox is governed by section 505(j)(5)(B)(iv) of the Act as in effect before passage of the MMA. See Section 1102(b)(1) of the MMA. In accordance with the applicable exclusivity provisions, any 180-day exclusivity for these products was triggered on October 2, 2008, when the Federal Circuit issued the Mandate with respect to its May 14, 2008 decision affirming the district court's finding that the '618 and '743 patents are unenforceable due to inequitable conduct. The 180-day period expired on March 31, 2009.

- Prophylaxis of ischemic complications of unstable angina and non-Qwave myocardial infarction [MI]
- Treatment of acute ST-segment elevation myocardial infarction [STEMI] managed medically or with subsequent percutaneous coronary intervention [PCI].¹¹

Lovenox contains the active ingredient enoxaparin sodium and is part of a relatively new class of anticoagulants called LMWHs. Enoxaparin is composed of a diverse mixture of many oligosaccharide chains.¹²

B. Regulatory History of Heparin and Low Molecular Weight Heparins Such as Lovenox

LMWHs (such as enoxaparin) are manufactured by depolymerizing heparin sodium (heparin) polysaccharide chains into correspondingly shorter oligosaccharide chains.¹³ Accordingly, it is helpful to briefly discuss the regulatory history of heparin before discussing that of LMWHs.

Heparin, as an anticoagulant, has been on the market since 1939. It was the first widely used anticoagulant and continues to be widely used in the United States. Heparin is prepared by processes involving extraction from animal tissues (i.e., porcine intestinal mucosa or bovine lungs).¹⁴ Concerns over the potential risks posed by bovine spongiform encephalopathy (BSE) have made porcine tissue the principal source of heparin. Heparin products currently used in the United States are of porcine origin. Heparin is biosynthesized in the pig gut, rather than through chemical synthesis of the active ingredient, and its manufacturing process entails (1) purification of the heparin to separate it from other tissue components and (2) clearance or inactivation of potential pathogenic organisms.

Heparin is generally administered intravenously and remains one of the anticoagulants of choice when a rapid anticoagulant effect is needed. The anticoagulant effects of heparin can be monitored by widely available laboratory tests, and an antidote is readily available to quickly reverse the drug's anticoagulant effects. The approved heparin labeling includes general indications and dosage and administration instructions that reflect the need for frequent monitoring.¹⁵ Because of the long-standing and widespread clinical use of heparin, its risk-benefit profile is well known. The drug is known to be associated with serious risks, including heparin-induced thrombocytopenia (HIT), which is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. Because patients vary widely in their response to heparin, heparin therapy is generally restricted to hospital and other settings where its dose can be adjusted on a closely monitored patient. Currently, there are eleven approved NDAs and six

¹¹ Product Labeling for Lovenox (enoxaparin sodium injection), NDA 20-164; Revised December 23, 2009.

¹² See footnote 3.

¹³ Depolymerization refers to the breaking up (or cleavage) of polysaccharide chains into smaller oligosaccharide fragments by chemical or enzymatic means. Because LMWH chains are shorter than the parent heparin chains, we generally use in this response the term "oligosaccharides" in connection with LMWHs and the term "polysaccharides" in connection with heparin.

¹⁴ Mulloy, B., Gray E., Barrowcliffe, T.W. (2000), "Characterization of Unfractionated Heparin: Comparison of Materials From the Last 50 Years," *Thromb Haemost* 84:1052-1056.

¹⁵ See, e.g., Product Labeling for Heparin Sodium Injection USP, NDA 17-037; Revised December 2007. (Carton and Immediate Container Labels for Heparin Sodium Injection USP, NDA 17-037; Revised October 2009).

approved ANDAs for heparin sodium injection, which are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).¹⁶

LMWHs, as noted above, are manufactured through depolymerization of heparin.¹⁷ Both heparin and LMWHs act as anticoagulants by inactivating both factor Xa and factor IIa in the coagulation cascade.^{18, 19} Other mechanisms may also account for the anticoagulant activity of these drugs. For example, heparin and LMWHs are known to promote the release of tissue factor pathway inhibitor (TFPI), which prevents the progression of the coagulation cascade.²⁰ In comparison to heparin, LMWHs possess a longer half-life, a more predictable anticoagulant response, and reduced side effects of fatal adverse reactions related to thrombocytopenia. Accordingly, LMWHs do not require frequent laboratory monitoring of coagulation parameters and are used in a wider range of treatment settings, including outpatient settings.

To date we have approved four NDAs for LMWHs: Lovenox (enoxaparin sodium) (NDA 20-164), Fragmin (dalteparin sodium) (NDA 20-287), Normiflo (ardeparin sodium) (NDA 20-227) (withdrawn in 2001 at the request of the manufacturer),²¹ and Innohep (tinzaparin sodium) (NDA 20-484). The active ingredients in these NDA-LMWH products are derived from different modes of depolymerization²² yielding drug products containing active ingredients with different distributions of oligosaccharide sequences and different chemical modifications at the terminal ends of these oligosaccharide chains.²³ These NDA-LMWH products are regarded as containing different active ingredients, and thus are not substitutable. Today, more than 15 years after the

¹⁶ The approved generic heparin products are not expected to pose any safety or effectiveness risks beyond those already associated with their respective RLDs. The recent severe anaphylactoid reactions reported following intravenous heparin administration were not attributed to the heparin active ingredient in approved products, but rather to the presence of over-sulfated chondroitin sulfate (OSCS), a synthetic contaminant introduced into the heparin active ingredient. See Kishimoto, T.K. et al. (2008), "Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System," *New England Journal Medicine* 358: 2457-2467; Guerrini, M. et al. (2008), "Oversulfated Chondroitin Sulfate is a Contaminant in Heparin Associated Clinical Events," *Nature Biotechnology* 26: 669-675. As a result of this contamination, the *U.S. Pharmacopeia* (USP) has revised its monograph for Heparin Sodium USP to incorporate, among other things, a nuclear magnetic resonance (NMR) and a high performance liquid chromatography (HPLC) test as part of the standard of identity for heparin sodium (October 1, 2009). These NMR and HPLC chromatographic tests are also used to detect the presence of the OSCS contaminant. FDA expects all approved NDAs and ANDAs for Heparin Sodium Injection USP to comply with the updated USP standard to detect the presence of OSCS.

¹⁷ Linhardt, R.J., Gunay, N.S. (1999), "Production and Chemical Processing of Low Molecular Weight Heparin," *Semin Thromb Hemost* 25 S3:5-16.

¹⁸ Factor Xa is a protein factor in the coagulation cascade that activates prothrombin (factor II) into thrombin (factor IIa). Thrombin is a factor in the coagulation cascade that converts fibrinogen to fibrin monomers, which eventually self-associate and are cross-linked during clot formation (blood coagulation).

¹⁹ Lin, R., Hu, Z. (2000), "Hematologic Disorders," in Melmon and Merrelli's *Clinical Pharmacology*, Carruthers, S.G. et al., eds., 4th ed., New York: McGraw Hill, 737-797.

²⁰ Hirsh, J., Warkentin, T.E., Shaughnessy, S.G., Anand, S.S., Halperin, J.L., Raschke, R., Granger, C., Ohman, E.M., Dalen, J.E. (2001), "Heparin and Low-Molecular Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety," *Chest* 119:64S-94S.

²¹ 67 FR 6264 (February 11, 2002).

²² We use in this response the term "depolymerization mode(s)" or "mode(s) of depolymerization" to refer to the chemical (or enzymatic) means by which heparin is cleaved into LMWH.

²³ The terminal ends are the ends of a heparin or LMWH saccharide chain. Each chain contains a "reducing" and "non-reducing" end.

first NDA approval of a LMWH product (i.e., Lovenox), FDA is approving the first ANDA for a LMWH product (i.e., an ANDA for enoxaparin).²⁴

C. Molecular Diversity²⁵ of LMWH

Knowledge of the molecular diversity of heparin is important for understanding the molecular diversity of LMWH. Heparin is a mixture of linear polysaccharides that are variable in length, consisting of disaccharide²⁶ repeating units composed of glucosamine and uronic acid (either iduronic or glucuronic acid) with the following linkage sequence: [(1→4) α-D-glucosaminyl – (1→4) β-D-hexuronosyl]_n (Figure 1). Thus, as explained more fully below, the molecular diversity of heparin comes from (1) the polydispersity²⁷ of chain length and (2) the diversity of disaccharide units and the corresponding distribution of disaccharide unit sequences in the polysaccharide chains.²⁸

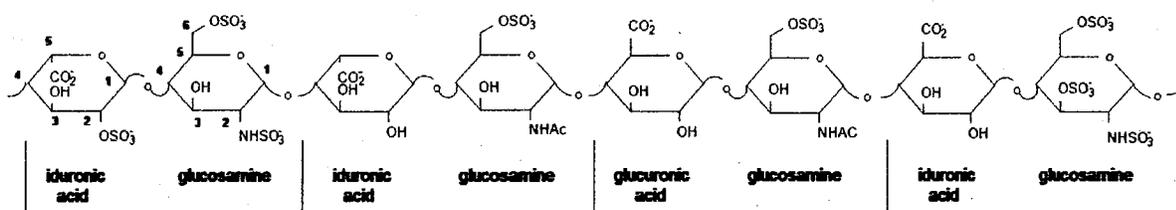


Figure 1. Representative polysaccharide in heparin showing four disaccharide units. These repeating units are composed of glucosamine and a uronic acid (either iduronic or glucuronic acid) with the linkage sequence: [(1→4) α-D-glucosaminyl – (1→4) β-D-hexuronosyl]_n.

The first dimension of the molecular diversity of heparin is the polydisperse chain length of polysaccharides. These polysaccharides have molecular weights ranging from 5,000 to 40,000 daltons (Da) and an average molecular weight of ~15,000 Da. The polydispersity of heparin, characterized by a ratio of weight average to number average molecular weight (M_w/M_n), varies between approximately 1.1 and 1.6.²⁹

The second dimension of heparin's molecular diversity derives from the diversity of disaccharide units and the corresponding distribution of disaccharide unit sequences in the polysaccharide chains. The diversity of disaccharide units (constituent building blocks of polysaccharide chains) arises not only from the possibility of two different uronic acid components (iduronic or glucuronic acid), but also from differential modification at four possible positions of the disaccharide unit. For example, the second carbon (C2) of the uronic acid and C3 and C6 of the

²⁴ We approved Sandoz Inc.'s (Sandoz) ANDA (77-857) for enoxaparin. The agency has determined that Sandoz's ANDA meets all the requirements for ANDA approval, including those for active ingredient sameness.

²⁵ The term "molecular diversity" refers to the heterogeneity of oligosaccharides and is used throughout this response for brevity.

²⁶ A disaccharide is a carbohydrate composed of two monosaccharides.

²⁷ Polydispersity is a measure of the distribution of molecular weights in a given polymer, and is defined as weight average molecular weight divided by the number average molecular weight. As polymer chains approach uniform chain length, polydispersity approaches unity.

²⁸ Capila, I., Linhardt, R.J. (2002), "Heparin-Protein Interactions," *Angew Chem Int Ed* 41:391-412.

²⁹ Linhardt, R.J. (2003), "Heparin: Structure and Activity," *J Med Chem* 46:1-14.

glucosamine can be O-sulfated. In addition, C2 of the glucosamine can be N-acetylated or N-sulfated.³⁰ The molecular diversity of heparin originates from the biosynthetic pathway of heparin biosynthesis.³¹

Heparin can be depolymerized into LMWHs which have approximately one-third the molecular weight of the parent heparin. The reduced average molecular weights of LMWHs vary between 3000 and 7000 Da, and the polydispersity ranges from 1.1 to 1.5.³² Because these LMWHs are obtained from the diverse mixture of polysaccharides that comprise heparin, the molecular diversity associated with these LMWHs also derives, like heparin, from the polydispersity of chain lengths, the diversity of disaccharide units, and the corresponding distribution of disaccharide unit sequences in the oligosaccharide chains.

Unlike heparin, LMWHs may have unique chemical modifications (or “fingerprints”) at the non-reducing and reducing ends (or terminal ends) of the oligosaccharide chains, which provide an additional, third dimension of molecular diversity not present in heparin. These unique chemical fingerprints at the terminal ends of the chains are a result of the mode of depolymerization used to manufacture the LMWH.³³ For instance, enoxaparin sodium is derived by esterification³⁴ of heparin derived from porcine intestinal mucosa to the corresponding heparin benzyl ester. The intermediate heparin benzyl ester undergoes alkaline β -elimination cleavage.³⁵ This results in selective cleavage between the uronic and glucosamine residues and fragmentation of heparin polysaccharides into smaller oligosaccharide fragments, with the majority of the components having a 4,5 delta ($\Delta^{4,5}$)-uronate structure at the non-reducing end of the chain.³⁶ On the other hand, in the case of dalteparin, depolymerization of heparin polysaccharides through deaminative cleavage using nitrous acid results in oligosaccharide fragments with a 2,5-anhydro-D-mannitol structure at the reducing end of the chain.³⁷ Because of differing depolymerization modes, the four approved LMWHs (enoxaparin, tinzaparin, dalteparin, and ardeparin) differ in their terminal ends as well as their distribution of disaccharide unit sequences in the oligosaccharide chains.³⁸

³⁰ To illustrate, in Figure 1 above, in the first disaccharide unit, C2 of iduronic acid is O-sulfated and C2 and C6 of glucosamine are N-sulfated and O-sulfated, respectively; in the second disaccharide unit, iduronic acid is not modified, and C2 and C6 of glucosamine are N-acetylated and O-sulfated, respectively.

³¹ Capila, I. et al. 2002.

³² Linhardt 2003.

³³ Linhardt 1999; European Pharmacopeia (EP), 5th ed., 2006, Enoxaparin Sodium, at 3493-3494; EP, Dalteparin Sodium, at 3925-3926; EP, Tinzaparin Sodium, at 2586; Fragmin (dalteparin sodium) injection package insert; Lovenox (enoxaparin sodium) injection package insert; Innohep (tinzaparin sodium) injection package insert; Debie, R. (February 14, 1995), “Mixtures of Particular LMW Heparinic Polysaccharides for the Prophylaxis/Treatment of Acute Thrombotic Events,” U.S. Patent No. 5,389,618 (February 14, 1995).

³⁴ Esterification, in this instance, is a process that modifies the carboxylate of the uronic acid structures into the corresponding benzyl ester.

³⁵ Specifically, the approved product labeling for Lovenox states that “enoxaparin sodium is obtained by alkaline [i.e., chemical] depolymerization of heparin benzyl ester derived from porcine intestinal mucosa.”

³⁶ Linhardt 1999; EP at 3493-3494; Lovenox injection package insert; Debie 1995.

³⁷ Linhardt 1999.

³⁸ As noted, we use in this response the term “depolymerization mode(s)” or “mode(s) of depolymerization” to refer to the chemical (or enzymatic) means by which heparin is cleaved into LMWH; however, we do not use the term to refer to the specific process conditions (operating parameters such as temperature, pH and depolymerization time) used to depolymerize heparin into LMWH. For example, the depolymerization mode used to manufacture enoxaparin is “cleavage by alkaline β -elimination of the benzyl ester derivative of heparin,” whereas for dalteparin it is “nitrous acid depolymerization of heparin.”

In sum, the molecular diversity of LMWHs comes from (1) the polydispersity of chain length, (2) the diversity of the disaccharide units and corresponding distribution of disaccharide unit sequences in the oligosaccharide chains, and (3) the diversity of modified terminal end disaccharide units in the oligosaccharide chains.

II. THE AGENCY HAS BROAD DISCRETION UNDER THE ACT AND FDA REGULATIONS TO DETERMINE SAMENESS OF ACTIVE INGREDIENTS

A. Summary of Legal Framework for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the ANDA approval process. To obtain approval, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the drug product. Instead, an ANDA applicant relies on the Agency's previous finding that the RLD is safe and effective. To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that the generic drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the Act).³⁹ In addition, an ANDA must contain sufficient information to show that the generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain exceptions) labeling as the RLD (sections 505(j)(2)(A) and (j)(4) of the Act). The Agency must approve the ANDA unless, among other things, the ANDA applicant has provided insufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the Act).

The premise underlying the Hatch-Waxman Amendments is that drug products that are (1) approved as safe and effective, (2) pharmaceutically equivalent,⁴⁰ (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with Current Good Manufacturing Practice regulations are therapeutically equivalent and can be substituted for each other with the "full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed [RLD] product."⁴¹

B. Summary of Statutory and Regulatory Provisions on Active Ingredient Sameness

Section 505(j)(2)(A)(ii)(I) of the Act states that, for a single active ingredient drug product, an ANDA must contain information to show that the active ingredient⁴² of the generic drug product

³⁹ Under the Act, "[a] drug shall be considered to be bioequivalent to a listed drug if . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." See section 505(j)(8)(B)(i); see also implementing regulations at 21 CFR part 320.

⁴⁰ See 21 CFR 320.1(c) (pharmaceutical equivalents means, in part, drug products in identical dosage forms that contain identical amounts of the identical active ingredient and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency).

⁴¹ See footnote 5.

⁴² FDA regulations (at 21 CFR 210.3(b)(7)) provide that "[a]ctive ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention

is the “same” as that of the listed drug. Under section 505(j)(4)(C)(i) of the Act, we must approve an ANDA referencing a listed drug that has only one active ingredient unless the ANDA contains insufficient information to show that the active ingredient is the same as that of the listed drug.

These statutory provisions do not describe the type or amount of information that an ANDA applicant must submit to demonstrate that the active ingredient in the generic drug product is the same as the active ingredient in the RLD, nor do these provisions describe the type or amount of information on which we may rely in determining whether the ANDA applicant has provided sufficient information to show that the active ingredient is the same. Accordingly, Congress recognized that we must have broad discretion with respect to the information we may consider in making a finding on the “sameness” of an active ingredient.⁴³

Parallel FDA regulations implementing these statutory provisions (i.e., sections 505(j)(2)(A)(ii) and (j)(4)(C)) can be found at 21 CFR 314.94(a)(5)(i) and 314.127(a)(3). FDA regulations also provide that an ANDA is suitable for consideration and approval if the generic drug product is the same as the RLD (21 CFR 314.92(a)(1)). Specifically, § 314.92(a)(1) states that the term “same as” means, among other things, “identical in active ingredient(s).” In the preamble to the final rule implementing title I of the Hatch-Waxman Amendments, we specifically rejected the suggestion that we adopt a requirement that active ingredients “exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics and solid state forms of the drug have not been altered.”⁴⁴ Instead, we adopted a more flexible approach, stating that we would “consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity.”⁴⁵ We further stated that, in most cases, the standards for identity are described in the USP, although we might prescribe “additional standards that are material to the ingredient’s sameness.”⁴⁶ In the case of enoxaparin, there is a USP monograph,⁴⁷ and there are additional standards that are material to enoxaparin’s sameness.

As FDA’s regulations and preamble reflect, and as you acknowledge (Petition at 21), we have broad discretion in determining whether an ANDA applicant has submitted sufficient information upon which we can reasonably conclude that the generic drug product’s active ingredient is, as a matter of law, the “same” as that of the RLD.

of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.” FDA regulations (at 21 CFR 314.3(b)) also provide that “*drug substance* means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use[d] in the synthesis of such ingredient.”

⁴³ See generally *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998); see also discussion in section V of this response.

⁴⁴ See 57 FR 17950 at 17958-59 (April 28, 1992).

⁴⁵ *Id.* at 17959.

⁴⁶ *Id.*

⁴⁷ See USP 32-NF 27 monograph for enoxaparin sodium (official on December 1, 2009).

III. **GENERIC ENOXAPARIN CAN CONTAIN THE SAME ACTIVE INGREDIENT (ENOXAPARIN) AS LOVENOX WITHIN THE MEANING OF THE ACT AND FDA REGULATIONS**

As discussed above, an ANDA applicant for generic enoxaparin must provide sufficient information to show that the generic drug product contains the “same” active ingredient (enoxaparin) as Lovenox. We have concluded, based on our evaluation of current data and other current relevant scientific information and our scientific experience and expertise, that the following five criteria (or standards for identity) together provide sufficient information to conclude that generic enoxaparin has the “same” active ingredient as Lovenox:⁴⁸

1. Equivalence of physicochemical properties
2. Equivalence of heparin source material and mode of depolymerization
3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
4. Equivalence in biological and biochemical assays
5. Equivalence of in vivo pharmacodynamic profile

These five criteria take into account the inherent molecular diversity associated with Lovenox’s enoxaparin and address (1) the polydispersity of chain length, (2) the diversity of the disaccharide units and corresponding distribution of disaccharide unit sequences in the oligosaccharide chains, and (3) the diversity of modified terminal end disaccharide units in the oligosaccharide chains. Lovenox has some degree of batch-to-batch variability, which you acknowledge is expected in any product derived from living organisms.⁴⁹ The equivalence evaluation for these criteria generally is based upon qualitative and/or quantitative comparisons of the generic drug product’s enoxaparin to multiple batches of Lovenox’s enoxaparin and takes into consideration the batch-to-batch variability and sampling of Lovenox, and analytical test variability. The equivalence evaluation for the above five criteria demonstrates that the molecular diversity of the generic drug product’s enoxaparin and Lovenox’s enoxaparin will be equivalent. Equivalent molecular diversity demonstrates sameness for enoxaparin.⁵⁰ Collectively, the five criteria are designed to provide overlapping evidence upon which we can conclude that the generic drug product’s enoxaparin is the same as Lovenox’s enoxaparin.

We provide below an explanation of why each of these five criteria is important to establish sameness of enoxaparin.

A. **Criterion 1: Equivalence of Physicochemical Properties**

The first criterion for demonstrating sameness of enoxaparin is equivalence of physicochemical properties, such as molecular weight distribution and overall chemical composition. Equivalence

⁴⁸ By virtue of satisfying the five criteria described in this section, the standards for identity described in the USP for enoxaparin and additional standards material to the ingredient’s sameness are met.

⁴⁹ Aventis October 13, 2004, Comments at 20 (acknowledging that, “[o]f course, it should be noted that some degree of variation is expected in any product derived from living organisms”).

⁵⁰ See footnote 8.

in these properties provides, for the most part, information on the broad characteristics of enoxaparin and is thus an important element in establishing active ingredient sameness.

As stated in section I.C of this response, one element of enoxaparin's molecular diversity is the polydispersity of the oligosaccharide chain lengths. Therefore, it is important that the generic drug product's enoxaparin has a distribution of oligosaccharide chain lengths equivalent to that of Lovenox's enoxaparin.

The molecular weight distribution determination, which is generally performed using size exclusion chromatography, provides information on the relative abundance of oligosaccharides of different molecular weights that comprise enoxaparin. Testing using size exclusion chromatography constitutes an important element for demonstrating equivalency of the oligosaccharide chain lengths, including their distribution and proportion. Due to the inherent low resolution of conventional size exclusion chromatography, it is also important to conduct a complementary analysis termed "chain mapping." Chain mapping involves using methodologies, such as CTA-SAX (cetyltrimethylammonium coated strong anion exchange) chromatography,⁵¹ MALDI-MS (matrix-assisted laser desorption ionization mass spectrometry), GPC-ESI-MS (gel permeation chromatograph - electrospray ionization mass spectroscopy), or RPIP-ESI-MS (reverse phase ion pair - electrospray ionization mass spectroscopy)⁵² to provide a high resolution fingerprint profile of oligosaccharide chain lengths. Demonstrating equivalence of the molecular weight distribution using both conventional size exclusion chromatography and complementary high resolution chain mapping helps to ensure that the extent and the pattern of depolymerization of heparin in the generic drug product's enoxaparin is equivalent to that of Lovenox's enoxaparin.

In addition to these analyses, it is also important to demonstrate equivalence of the overall chemical composition of the generic drug product's enoxaparin and Lovenox's enoxaparin. This type of analysis captures broad aspects of the aggregate mixture of oligosaccharides that comprise enoxaparin. For example, nuclear magnetic resonance (NMR) spectroscopy can be used to provide "spectroscopic fingerprints" of several of enoxaparin's characteristic structures, such as the epimerization state of the uronic acid structure (i.e., iduronic versus glucuronic acid), and the ratio of sulfated and non-sulfated $\Delta^{4,5}$ -uronate structures at the non-reducing end of the oligosaccharide chains.⁵³ Equivalency of ultraviolet (UV) specific absorbance can also be used to demonstrate the presence of unique functional groups such as the $\Delta^{4,5}$ -uronate structure known to be present in enoxaparin.⁵⁴ Other criteria for showing physicochemical equivalence can also be used that capture broad characteristics of enoxaparin, including, among other things, certain tests and acceptance criteria described in the USP monograph for enoxaparin (e.g., equivalent

⁵¹ Mourier, P.A.J., Viskov, C. (2004), "Chromatographic Analysis and Sequencing Approach of Heparin Oligosaccharides Using Cetyltrimethylammonium Dynamically Coated Stationary Phases," *Analytical Biochemistry* 332:299-313.

⁵² Thanawiroon, C., Rice, K.G., Toida, T., Linhardt, R.J. (2004), "Liquid Chromatography/Mass Spectrometry Sequencing Approach for Highly Sulfated Heparin Derived Oligosaccharides," *The Journal of Biological Chemistry*, 279: 2608-2615.

⁵³ Chuang, W., Christ, M.D., Rabenstein, D.L. (2001), "Determination of the Primary Structures of Heparin- and Heparin Sulfate-Derived Oligosaccharides Using Band Selective Homonuclear-Decoupled Two Dimensional ¹H NMR Experiments," *Anal. Chem.* 73:2310-2316.

⁵⁴ See USP 32-NF 27 (official on December 1, 2009).

¹³C NMR spectra, quantitative determinations for sodium content, and ratio of sulfate/carboxylate).

In sum, equivalence of physicochemical properties provides, for the most part, information on broad characteristics of enoxaparin, such as evidence of distribution of oligosaccharide chain lengths equivalent to that of Lovenox's enoxaparin and is an important element for demonstrating enoxaparin sameness. This criterion alone does not provide sufficient information (on the composition and sequence of enoxaparin oligosaccharide chains) upon which we can conclude enoxaparin sameness. Satisfaction of this criterion together with the remaining four criteria, however, would demonstrate that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides sufficient information to conclude active ingredient (enoxaparin) sameness.

B. Criterion 2: Equivalence of Heparin Source Material and Mode of Depolymerization

The second criterion for demonstrating the sameness of enoxaparin is equivalence of heparin source material (i.e., heparin that is derived from porcine intestinal mucosa and that meets USP monograph standards for Heparin Sodium USP) and mode of depolymerization (i.e., cleavage by alkaline β -elimination of the benzyl ester derivative of heparin). The importance of this criterion is best illustrated by considering how heparin source material and mode of depolymerization relate to the three important dimensions of enoxaparin's molecular diversity: (1) the polydispersity of chain lengths, (2) the diversity of disaccharide units and corresponding distribution of sequences of disaccharide units in the oligosaccharide chains, and (3) the diversity of modified terminal end disaccharide units in the oligosaccharide chains (see section I.C). Physicochemical properties provide information on the polydispersity of chain lengths as previously described in Criterion 1 (see section III.A), and once Criterion 1 has been met for a generic drug product's enoxaparin, the other two dimensions of molecular diversity and consequently equivalence can be addressed by the following two-part framework.

First, based on a fundamental understanding of cleavage chemistry, there is essentially no rearrangement of the sequences of "natural" disaccharide building blocks in heparin during the cleavage reaction of the parent heparin polysaccharide chains into enoxaparin oligosaccharide chains. The resultant distribution of sequences of disaccharide units in enoxaparin is essentially both a function of the (1) sequences found "naturally" in heparin and (2) site(s) where the cleavage reaction occurs in the parent heparin chains. Second, the new chemical structures introduced at the terminal ends of the cleaved oligosaccharide chains of enoxaparin are a result of the cleavage reaction by which the heparin polysaccharide chains are depolymerized to the enoxaparin oligosaccharide chains (Figure 2). This two-part framework is described in more detail below.

Part 1 of framework

If an ANDA applicant for enoxaparin shows that it uses the equivalent heparin source material and mode of depolymerization as that used for Lovenox's enoxaparin, then we can conclude that

the resultant distribution of sequences between the two enoxaparin active ingredients will be at least similar.

With respect to the heparin source material, the molecular diversity of natural disaccharide building block sequences within heparin results from its biosynthetic pathway. Thus, equivalent heparin source material, for the purposes of manufacturing enoxaparin, will be expected to have at least a similar distribution of natural disaccharide building block sequences (within the context of its variability). Furthermore, if the equivalent mode of depolymerization is used, we can expect the chemical selectivity of cleavage of the parent heparin polysaccharide chains for the generic drug product's enoxaparin and Lovenox's enoxaparin to be at least similar.⁵⁵ However, the chemical selectivity depends on both the cleavage chemistry (mode of depolymerization) and the process conditions (operating parameters such as temperature, pH, depolymerization time) used in the depolymerization process.⁵⁶ For the chemical selectivity to be equivalent, such process conditions would need to be appropriately adjusted.

Part 2 of framework

The depolymerization process essentially determines the structural identities of the modified disaccharide units at the terminal ends of the oligosaccharide chains that arise from the cleavage reaction.⁵⁷ Therefore, if the mode of depolymerization used to cleave heparin chains is equiva-

⁵⁵ Chemical selectivity refers to, among other things, the biases of the cleavage patterns or site(s) of cleavage of heparin polysaccharide chains. The chemical selectivity of the mode of depolymerization determines the resultant sequences of cleaved oligosaccharides. To illustrate, a single heparin polysaccharide chain with a sequence of ABCDEDA may be depolymerized through a process having a chemical selectivity with a bias to cleave adjacent to the C disaccharide unit, and this results in two oligosaccharide fragments, AB and CDEDA. However, the single heparin polysaccharide chain with the same sequence ABCDEDA may be depolymerized through a process having a different chemical selectivity with a bias to cleave adjacent to the D disaccharide unit, and this results in three oligosaccharide fragments, ABC, DE, and DA. Although there is no rearrangement of the sequences during the cleavage of the heparin polysaccharide chain, the chemical selectivity of depolymerization affects the final distribution of resultant oligosaccharide sequences. As a result, if a given heparin material is depolymerized by two different manufacturers with processes having the equivalent chemical selectivity, we can reasonably expect that the resultant oligosaccharides will have the equivalent distribution of sequences. Conversely, if a given heparin material is depolymerized by two different manufacturers with processes having different chemical selectivity, we can reasonably expect that the resultant oligosaccharides will have different distributions of sequences.

⁵⁶ For example, enoxaparin and tinzaparin are derived from heparin material isolated from porcine intestinal mucosa, but are manufactured by different modes of depolymerization (i.e., chemical (alkaline) versus enzymatic β -elimination, respectively). These differing modes of depolymerization have vastly different chemical selectivities of heparin polysaccharide chain cleavage. In the mode of depolymerization by enzymatic β -elimination, cleavage takes place **exclusively** in heparin polysaccharide chains at sites where the disaccharide unit has the 2-O-sulfo-uronic acid structure, whereas in the mode of depolymerization by chemical (alkaline) β -elimination, cleavage occurs without preference for the presence or absence of a 2-O-sulfo group in the iduronic acid structure. See Linhardt, R.J., Gunay, N.S. (1999), "Production and Chemical Processing of Low Molecular Weight Heparin," *Semin Thromb Hemost* 25 S3:10. If an ANDA applicant chooses a depolymerization mode of alkaline β -elimination of the heparin benzyl ester that is equivalent to that used for Lovenox's enoxaparin, then we can reasonably expect the chemical selectivity of the depolymerization process to be at least similar to that used for Lovenox's enoxaparin (i.e., relative cleavage at the 2-O-sulfo-uronic acid structures versus unsulfated iduronic acid structures would be at least similar).

⁵⁷ For example, dalteparin is depolymerized by deaminative cleavage using nitrous acid. This mode of depolymerization has the effect of introducing a modified disaccharide unit having a 2,5-anhydro-D-mannitol structure at the reducing end of the oligosaccharide chains where cleavage occurs. On the other hand, enoxaparin is depolymerized by alkaline (chemical) β -elimination of the benzyl ester of heparin. This mode of depolymerization has the effect of

lent for the generic drug product's enoxaparin and Lovenox's enoxaparin, then we can expect the modified disaccharide units at the terminal end of the oligosaccharides to be at least similar.

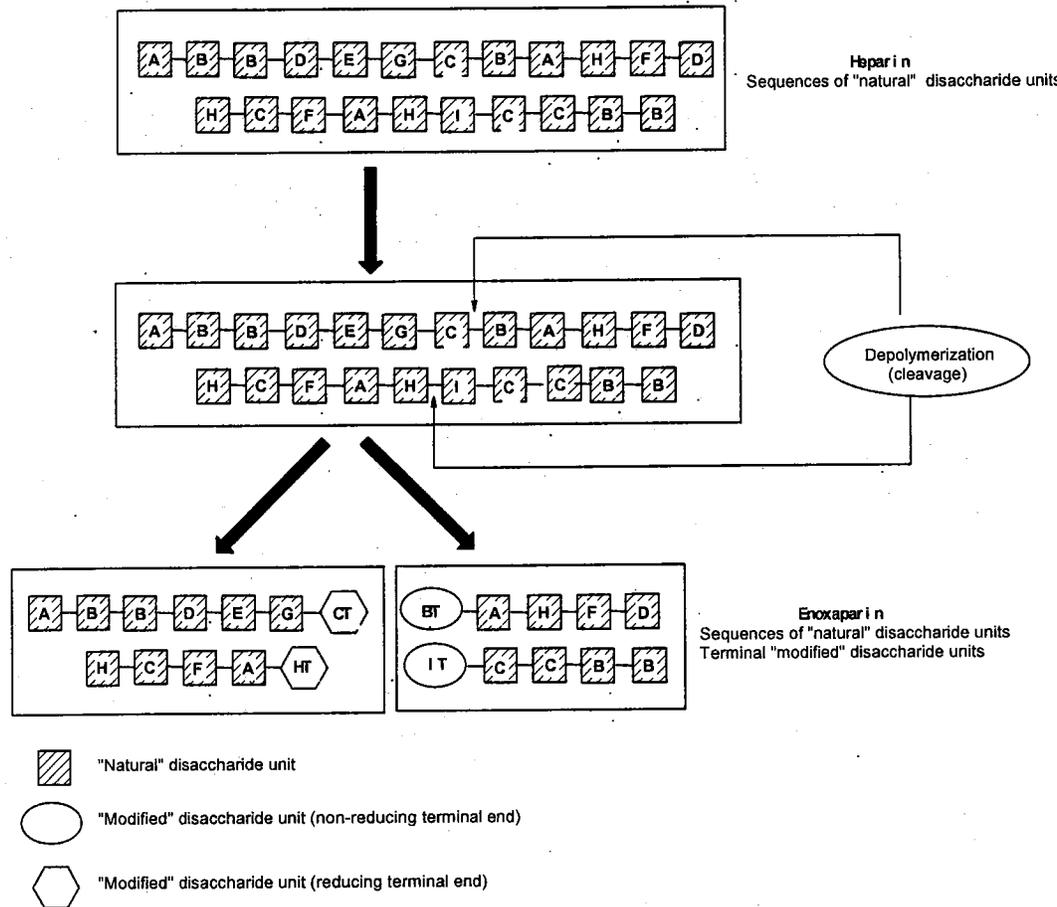


Figure 2. Enoxaparin consists of a distribution of sequences of "natural" disaccharide building blocks that derive from heparin "natural" disaccharide building block sequences. Enoxaparin also contains structurally modified terminal end disaccharide building blocks that arise from cleavage (depolymerization) of the heparin oligosaccharides.

In sum, we can reasonably conclude (provided there is equivalence of physicochemical properties) that if the ANDA applicant for enoxaparin shows that it uses the equivalent heparin source material and equivalent mode of depolymerization as that used for Lovenox's enoxaparin, then the resultant mixture of oligosaccharides will be *at least similar* with respect to both (1) the distribution of "natural" sequences of disaccharide units in the oligosaccharide chains and (2) diversity of the modified disaccharide building blocks at the terminal ends of the oligosaccharide chains. This provides important information for demonstration of enoxaparin sameness, but it is not sufficient by itself to conclude enoxaparin sameness. Satisfaction of the remaining three criteria in addition to the previous two criteria, however, would be sufficient to demonstrate that

introducing a modified disaccharide unit having a $\Delta^{4,5}$ -uronate structure at the nonreducing end of the chain where cleavage occurs. Therefore, the mode of depolymerization used to cleave heparin polysaccharide chains essentially determines the types of structures (or chemical functionality) of the modified disaccharide units present at the terminal ends of the oligosaccharide chains in LMWHs.

the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides sufficient information to conclude that the generic drug product's enoxaparin and Lovenox's enoxaparin are the *same*.

C. Criterion 3: Equivalence in Disaccharide Building Blocks, Fragment Mapping, and Sequence of Oligosaccharide Species

The third criterion for demonstrating the sameness of enoxaparin is equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species. If this third criterion is met in addition to Criteria 1 and 2, then collectively the information provides substantial supporting evidence that the distribution of sequences of disaccharide units in the oligosaccharide chains and the structures of the modified disaccharide units at the terminal ends of the oligosaccharide chains of the generic drug product's enoxaparin are equivalent to those in Lovenox's enoxaparin.

1. Equivalence in disaccharide building blocks

Equivalence in disaccharide building blocks is established by demonstrating equivalence in the composition (identity and quantitative levels) of disaccharide units (and other small oligosaccharide units)⁵⁸ which are the constituent building blocks of the oligosaccharide chains in enoxaparin.

Compositional analysis of these disaccharide building blocks can be achieved by exhaustive digestion of enoxaparin with purified heparin digesting enzymes (heparinases I, II, III) and nitrous acid, among other means, to yield the constituent disaccharide building blocks comprising enoxaparin. These individual disaccharide building blocks can then be separated and quantified by a variety of approaches, including capillary electrophoresis (CE),⁵⁹ reverse phase high performance liquid chromatography (RP-HPLC),⁶⁰ and strong anion exchange high performance liquid chromatography (SAX-HPLC).⁶¹ Identification of these disaccharide building block units can be achieved using several techniques including comparison to structurally assigned disaccharide units in the literature,⁶² spectroscopic approaches such as mass

⁵⁸ When we refer to the term disaccharide units in this section, the term also encompasses other small oligosaccharide units. Other small oligosaccharide units that are generated from this type of compositional analysis arise due to the fact that while compositional analysis yields primarily disaccharide building block units, it can also yield (in some instances) other small oligosaccharide units, such as trisaccharide units (which derive from enoxaparin oligosaccharides having an odd number of saccharide units) and tetrasaccharide units (which derive from the inherent resistance of some tetrasaccharide units to further cleave into disaccharide units).

⁵⁹ Sundarem, M., Qi, Y., Shriver, Z., Liu, D., Zhao, G., Venkataraman, G., Langer, R., Sasisekharan, R. (2003), "Rational Design of Low-Molecular Weight Heparins with Improved In Vivo Activity," *Proc Natl Acad Sci USA*, 100 651-656.

⁶⁰ Toyoda, H., Yamamoto, H., Ogino, N., Toida, T., Imanari, T. (1999), "Rapid and Sensitive Analysis in Heparin and Heparin Sulfate of Reversed-Phase Ion-Pair Chromatography on a 2 mm Porous Silica Gel Column," *J. Chromatography*, A 830 197-201.

⁶¹ Mourier P., Viskov C., (June 2, 2005), "Method for Determining Specific Groups Constituting Heparins or Low Molecular Weight Heparins," *US Patent Application Publication US2005/0119477 A1*.

⁶² Mourier 2005.

spectroscopy⁶³ and NMR spectroscopy,⁶⁴ and chemical approaches such as analysis with modifying reagents⁶⁵ (e.g., sodium borohydride, nitrous acid) or modifying enzymes (e.g., 2-O-sulphatase, 6-O-sulphatase, $\Delta^{4,5}$ -glycuronidase).^{66, 67} These analyses can be used to identify the structures of the disaccharide building block units including the sulfation and acetylation substitution patterns at specific disaccharide hydroxyl or amino groups. They can also be used to identify whether the disaccharide possesses, among other structures, a glucosamine, mannosamine, 1,6 anhydro ring,⁶⁸ or galacturonic acid structure.

Such analysis can be used to determine the composition of “natural” disaccharide units⁶⁹ that comprise the oligosaccharide chains. It can also be used to determine the composition of modified disaccharide units at the terminal ends of the oligosaccharide chains.^{70, 71} When a generic drug product’s enoxaparin has been shown to have the same composition of disaccharide units found in Lovenox’s enoxaparin, we can conclude that the generic drug product’s enoxaparin uses the same “natural” disaccharide units to assemble the distribution of sequences (of disaccharide units) of oligosaccharide chains as Lovenox’s enoxaparin. Moreover, from such information we can also conclude that the generic drug product’s enoxaparin has the same composition of modified disaccharide building blocks at the terminal ends of the oligosaccharide chains as Lovenox’s enoxaparin. This latter point is significant, as explained below.

Information derived from the analysis of the modified disaccharide building block units at the non-reducing and reducing ends of oligosaccharide chains in enoxaparin is of particular significance because, as stated in section III.B, the depolymerization process essentially determines the structural identity of the modified disaccharide units at the terminal ends of the oligosaccharide chains. Moreover, the quantitative levels of these modified disaccharide units at the terminal ends of the oligosaccharide chains are quite sensitive to variations in the process conditions (or operating parameters) – such as pH, temperature, and depolymerization time – that are used in the given mode of depolymerization (i.e., cleavage by alkaline β -elimination of the benzyl ester

⁶³ Saad, O.M., Leary, J.A. (2003), “Compositional Analysis and Quantification of Heparin and Heparin Sulfate by Electrospray Ionization Ion Trap Mass Spectrometry,” *Anal. Chem* 75, 2985-2995.

⁶⁴ Mourier 2005.

⁶⁵ Mourier 2005.

⁶⁶ Stringer, S.E., Balbant, S.K., Pye, D.A., Gallagher, J.T. (2003), “Heparin Sequencing,” *Glycobiology* 13(2) 97-103.

⁶⁷ Myette, J.R., Shriver, Z., Ksiltepe, T., McLean, M.W., Venkataraman, G., Sasisekharan, R. (2002), “Molecular Cloning of the Heparin/Heparin Sulfate Δ 4,5 Unsaturated Glycuronidase From *Flavobacterium Heparinum*, Its Recombinant Expression in *Escherichia Coli*, and Biochemical Determination of Its Unique Substrate Specificity,” *Biochemistry*, 41. 7424-7434.

⁶⁸ Equivalence in disaccharide building blocks together with equivalence in molecular weight distribution shows that generic enoxaparin contains the 1,6 anhydro ring structure at the reducing ends of between 15 percent and 25 percent of its poly(oligo)saccharide chains.

⁶⁹ These “natural” disaccharide units comprising enoxaparin essentially derive from the disaccharide units that comprise the heparin source material (from porcine intestinal mucosa) used in the manufacture of enoxaparin. Please refer to the discussion in section III.B.

⁷⁰ Compositional analysis can also be use to identify and quantify the modified disaccharide units that may be present in the middle of the oligosaccharide chains (as opposed to the terminal ends), such as those disaccharides containing (among others) the galacturonic acid structure.

⁷¹ This is performed in conjunction with the determination of the ratio of sulfated and nonsulfated $\Delta^{4,5}$ -uronate structures in the nonreducing end of the oligosaccharide chains by, for example, NMR spectroscopy, as discussed in section III.A.

derivative of heparin). For example, as you acknowledge in your petition (at 13), the content of the 1,6 anhydro ring structure at the reducing ends of the oligosaccharide chains in Lovenox's enoxaparin is quite sensitive to the process conditions that are used to cleave the benzyl ester of heparin by alkaline β -elimination. Therefore, an ANDA applicant would generally be expected not only to use a mode of depolymerization equivalent to that used in the manufacture of Lovenox's enoxaparin, but would also be expected to make appropriate adjustments in process conditions to manufacture enoxaparin that has the same composition of these modified disaccharide building block units as Lovenox's enoxaparin.

When an ANDA applicant makes appropriate adjustments in the depolymerization process conditions to manufacture a generic drug product containing enoxaparin with the same composition of modified disaccharide building block units as Lovenox's enoxaparin, the fact that the modified building blocks are the same provides evidence that the adjusted process conditions have a chemical selectivity of cleavage that is equivalent to the chemical selectivity of the depolymerization process used to manufacture Lovenox's enoxaparin. Thus, the analysis of these modified terminal disaccharide building block units serves as a sensitive surrogate marker of the underlying chemistry and, therefore, the chemical selectivity of depolymerization that is used in producing enoxaparin.

Further, our review of relevant scientific information provides confirmation of the discriminatory power of disaccharide building block unit compositional analysis to detect subtle differences in the molecular diversity of the oligosaccharides comprising enoxaparin.⁷² Therefore, such equivalence of disaccharide building block compositional analysis provides important evidence that the generic drug product's enoxaparin is the "same" as Lovenox's enoxaparin.

2. *Equivalence in fragment mapping*

As discussed above, equivalence in the composition of disaccharide building block units in conjunction with Criteria 1 and 2 described in sections III.A and III.B provides important evidence for determining whether the generic drug product's enoxaparin is the "same" as Lovenox's enoxaparin. However, it is important to conduct additional analyses to confirm that the distribution of sequences of disaccharide building block units in the oligosaccharide chains of the generic drug product's enoxaparin is the same as that of Lovenox's enoxaparin. This additional evidence of "sameness" of the distribution of sequences of disaccharide building block units in the oligosaccharide chains can be obtained by fragment mapping as explained below.

⁷² This conclusion regarding the discriminatory power of disaccharide building block unit compositional analysis is based on, among other things, data submitted by an ANDA applicant on development batches of drug product containing "enoxaparin-like material." The development batches of enoxaparin-like material were manufactured using the equivalent heparin source material and mode of depolymerization as were used for the ANDA registration batches, but they were manufactured under different process conditions. The enoxaparin-like material demonstrated important characteristics of Lovenox's enoxaparin based on compliance with then-proposed USP standards for enoxaparin, including molecular weight distribution, anti-Xa activity, anti-IIa activity, and anti-Xa/anti-IIa ratio. (The USP 32 NF 27 monograph for enoxaparin became official on 12/01/09.) Although the enoxaparin-like material was similar to Lovenox's enoxaparin, differences in the molecular diversity of oligosaccharides were readily identified based upon discernable differences in the quantitative levels of disaccharide building blocks units (particularly in the modified disaccharide building block units) relative to those present in Lovenox's enoxaparin.

Fragment mapping involves only a partial digestion of enoxaparin with heparinase enzymes (e.g., heparinase I, among other enzymes) into oligosaccharides (as opposed to a full digestion into disaccharide building blocks), followed by analysis of these oligosaccharide fragments using methods such as RPLC-HPLC or SAX-HPLC (among others).^{73, 74} Analogous to a tryptic map for proteins, the fragment map of partially digested enoxaparin oligosaccharides represents a signature of recurring oligosaccharide sequences unique to enoxaparin, and thus provides global information on sequences of oligosaccharides within the enoxaparin structure. When a generic drug product's enoxaparin has been shown to have the same oligosaccharide fragment mapping profile as Lovenox's enoxaparin, this information provides significant evidence that the generic drug product's enoxaparin possesses the same recurring global oligosaccharide sequence segments as those in Lovenox's enoxaparin.

In addition, fragment mapping provides important information regarding both the sequence structure of oligosaccharides present in the heparin source material and information related to the chemical selectivity of the depolymerization process used in producing enoxaparin from heparin. This is because, as noted in section III.B, the distribution of sequences of disaccharide units in enoxaparin is both a function of the sequences present in the heparin source material and the site(s) where the cleavage occurs in the parent heparin chains. Development data from an ANDA applicant for enoxaparin also show that the profiles of recurring global oligosaccharide sequence segments, as assessed by their oligosaccharide fragment mapping profiles, are quite sensitive to variations in the process conditions, which, as discussed, can affect the chemical selectivity of cleavage of the heparin source material.

Further, our review of relevant scientific information provides confirmation of the discriminatory power of oligosaccharide fragment mapping to detect subtle differences in the molecular diversity of oligosaccharides comprising enoxaparin.⁷⁵ Therefore, equivalence of fragment mapping provides further corroborative evidence that the generic drug product's enoxaparin is the "same" as Lovenox's enoxaparin.

3. *Equivalence in sequence of oligosaccharide species*

As discussed above, equivalence in disaccharide building block units and equivalence of fragment mapping, in conjunction with Criteria 1 and 2 described in sections III.A and III.B, provides important evidence for determining whether the generic drug product's enoxaparin is the "same" as Lovenox's enoxaparin. Additional information confirms through direct sequencing of oligosaccharides that the distribution of sequences of disaccharide building block units in the oligosaccharide chains of the generic drug product's enoxaparin is the same as that of Lovenox's enoxaparin.

⁷³ Linhardt, R.J., Rice, K.O., Kim, Y.S., Lohse, D.L., Wang, H.M., Loganathan, D. (1988), "Mapping and Quantification of the Major Oligosaccharide Components of Heparin," *Biochem. J.* 254 781-787.

⁷⁴ Chuang, W.L., McAllister, H., Rabenstein, D.L. (2001) "Chromatographic Methods for Product-Profile Analysis and Isolation of Oligosaccharides Produced by Heparinase-Catalyzed Depolymerization of Heparin," *Journal of Chromatography, A* 932 65-74.

⁷⁵ Maddineni, J., Walenga, J.M., Jeske, W.P., Hoppensteadt, D.A., Fareed, J., Wahi, R., Bick, R.L. (2006), "Product Individuality of Commercially Available Low-Molecular-Weight Heparins and their Generic Versions: Therapeutic Implications, Clinical and Applied," *Thrombosis/Hemostasis* 12:267-276.

Recent advances in structural analysis of carbohydrates have made possible the direct sequencing of oligosaccharide chains from enoxaparin. For example, this can be done through property-encoded nomenclature (PEN) in conjunction with MALDI-MS,^{76,77} by iterative chemical and enzymatic digestion of fluorescent tagged oligosaccharides in conjunction with analysis by polyacrylamide gel electrophoresis,⁷⁸ or by enzymatic digestion in conjunction with NMR spectroscopy.⁷⁹ When a comparable subset of oligosaccharides from both a generic drug product's enoxaparin and Lovenox's enoxaparin is isolated and shown to possess the same sequence, this information provides further corroborative evidence that the generic drug product's enoxaparin possesses the same distribution of oligosaccharide sequences as Lovenox's enoxaparin.

Data from an ANDA applicant also show that the resultant sequenced oligosaccharides in enoxaparin are quite sensitive to variation in the process conditions used, which, as discussed, can affect the chemical selectivity of cleavage of the heparin source material.⁸⁰ This is particularly true for the subset of shorter chain oligosaccharides, which, by virtue of being the result of the most cleavage reactions of the heparin oligosaccharide chains, are those oligosaccharides whose sequence identities are most dependent on the chemical selectivity of depolymerization that is used to produce enoxaparin from heparin.⁸¹

As noted in section III.B, the distribution of sequences of disaccharide units in enoxaparin is a function of the (1) sequences found "naturally" in heparin and (2) site(s) where the cleavage reaction occurs in the parent heparin chains. If there is equivalence in physicochemical properties, heparin source material, and mode of depolymerization together with this sensitive marker of equivalent chemical selectivity (i.e., based upon data showing equivalence of disaccharide compositional analysis, fragment mapping, and sequences of short chain oligosaccharides), this information provides evidence that the manufacturing process for generic enoxaparin will cleave the heparin polysaccharide chains at sites equivalent to those for Lovenox's enoxaparin.

⁷⁶ Venkataraman, G., Shriver Z., Raman, R., Sasisekharan, R. (1999), "Sequencing Complex Polysaccharides," *Science* 286:537-542.

⁷⁷ Shriver, Z., Raman, R., Venkataraman, G., Turnbull, K.J., Toida, T., Linhardt, R., Bieman, K., Sasikharan, R. (2000), "Sequencing of 3-O Sulfate Containing Heparin Decasaccharides with Partial Antithrombin III Binding Site," *Proc. Natl. Acad. Sci. USA* 97:10359-10364.

⁷⁸ Turnbull, J.E., Hopwood, J.J., Gallagher, J.T. (1999), "A Strategy for Rapid Sequencing of Heparin Sulfate and Heparin Saccharides," *Proc. Natl. Acad. Sci. USA* 96:2698-2703.

⁷⁹ Yamada, S., Sakamoto, K., Tsuda, H., Yoshida, K., Sugiura, M., Sugahara, K. (1999), "Structural Studies of Octasaccharides Derived from the Low-Sulfated Repeating Disaccharide Region and Octasaccharide Serine," *Biochemistry* 38 838-847.

⁸⁰ This conclusion is based on, among other things, data submitted by an ANDA applicant on development batches of drug product containing "enoxaparin-like material" as described in footnote 72. Although the enoxaparin-like material in development was similar to Lovenox's enoxaparin based upon the then-proposed USP standards for enoxaparin, including molecular weight distribution, anti-Xa activity, anti-IIa activity, and anti-Xa/anti-IIa ratio, discernable differences in the sequences of short oligosaccharides were identified. This information demonstrates that the sequences of short oligosaccharides are quite sensitive to variations in the process conditions (or operating parameters) used during depolymerization.

⁸¹ If this condition is met (in conjunction with the other criteria for sameness), we can reasonably conclude that the sequences of higher order oligosaccharide chains in the generic drug product's enoxaparin will be the same as those in Lovenox's enoxaparin. This is because the sequences of higher order oligosaccharide chains have sequence identities that are less dependent on the chemical selectivity of the cleavage process because they result from fewer cleavage reactions.

Therefore, we would expect the active ingredient in the generic enoxaparin to be the same as Lovenox's enoxaparin with respect to the distribution of sequences of disaccharide units in the oligosaccharide chains.

Further, consistent with these conclusions, our review of relevant scientific information provides confirmation of the discriminatory power of oligosaccharide sequencing to detect subtle differences in the molecular diversity of enoxaparin.⁸² Therefore, equivalence of oligosaccharide sequences provides further corroborative evidence that the generic drug product's enoxaparin is the "same" as Lovenox's enoxaparin.

In sum, when the first two criteria described in sections III.A and III.B are met, the third criterion – equivalence of disaccharide building blocks, fragment mapping, and sequencing of oligosaccharide species – provides crucial evidence towards demonstrating that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides important information to help conclude that the generic drug product's enoxaparin is the same as Lovenox's enoxaparin.

D. Criterion 4: Equivalence in Biological and Biochemical Assays

The fourth criterion for establishing sameness of enoxaparin is equivalence of in vitro biological and biochemical assay results. Although the first three criteria together provide crucial evidence of equivalent molecular diversity, this fourth criterion provides additional important evidence of active ingredient sameness based on the biological and biochemical properties of enoxaparin.

To meet the criterion of equivalence of biological assays, it is important to demonstrate that the generic drug product's enoxaparin is equivalent to Lovenox's enoxaparin with respect to in vitro biological assays for relevant markers of anticoagulant activity, such as measurements based on (among other things) aPTT (activated partial thromboplastin time) and Heptest prolongation time.

To meet the criterion of equivalence of biochemical assays, it is important to demonstrate that the generic drug product's enoxaparin is equivalent to Lovenox's enoxaparin with respect to measurements of factor Xa inhibition (anti-Xa) and factor IIa inhibition (anti-IIa). This biochemical inhibitory effect on factor IIa and factor Xa in the coagulation cascade accounts for the most thoroughly understood pharmacological basis by which heparins and LMWHs (including enoxaparin) function as anticoagulants.

The molecular basis for factor Xa inhibition (anti-Xa) is mediated by an AT-III binding pentasaccharide sequence motif that is present in heparin and LMWHs. This particular protein binding motif, which is present in approximately 30 percent of heparin polysaccharide chains and 15 to 25 percent of LMWH oligosaccharide chains, has a high affinity for AT-III, an

⁸² This conclusion regarding the discriminatory power of oligosaccharide sequencing is based on, among other things, data submitted by an ANDA applicant on so-called "generic enoxaparins" marketed in other foreign countries. Although the enoxaparin-like material was similar to Lovenox's enoxaparin, including molecular weight distribution, anti-Xa activity, anti-IIa activity, and anti-Xa/anti-IIa ratio, differences in the molecular diversity of oligosaccharides were readily identified based upon discernable differences in the subset of shorter oligosaccharide sequences relative to those present in Lovenox's enoxaparin.

endogenous serpin inhibitor. Binding of this pentasaccharide sequence motif to AT-III results in an activated AT-III-polysaccharide complex that inhibits the proteolytic activity of factor Xa in the coagulation cascade. Similarly, the molecular basis for factor IIa inhibition (anti-IIa) is mediated by this particular AT-III binding pentasaccharide sequence. However, in this instance, the AT-III-polysaccharide complex will inhibit factor IIa only if the AT-III binding pentasaccharide sequence is present in a polysaccharide chain at least 18 saccharide units in length.⁸³ Because a large proportion of heparin polysaccharide chains are longer than 18 saccharide units, this results in heparin having an anti-Xa/anti-IIa ratio of approximately 1. By contrast, because LMWHs (including enoxaparin) are derived through controlled cleavage of heparin polysaccharide chains, most LMWH oligosaccharide chains have less than 18 saccharide units, and this results in LMWHs having anti-Xa/anti-IIa ratios that are greater than 1. Differences in anti-Xa and anti-IIa activities among the various approved LMWHs (which are readily measured using standard amidolytic chromogenic assays)⁸⁴ can be used to differentiate enoxaparin from other LMWH products marketed in the United States. Accordingly, a demonstration of equivalence in anti-Xa activity, anti-IIa activity, and anti-Xa/anti-IIa ratio between the generic drug product's enoxaparin and Lovenox's enoxaparin provides important evidence of equivalence of biochemical characteristics – which, at a minimum, is responsible for an important and well-established mechanism of action that explains, in significant part, the pharmacological activity for LMWHs (including enoxaparin).

In sum, equivalence in biological and biochemical assay results provides important evidence of enoxaparin sameness. This criterion by itself is not sufficient to conclude enoxaparin sameness. Satisfaction of the first four criteria together with the remaining criterion described below, however, would be sufficient to demonstrate sameness of enoxaparin.

E. Criterion 5: Equivalence of In Vivo Pharmacodynamic Profile

The fifth criterion for establishing sameness of enoxaparin is equivalence of in vivo pharmacodynamic profile. The comparison of in vivo pharmacodynamic profiles is based upon measurements of in vivo anti-Xa and anti-IIa profiles. It is well established that the different LMWH products approved in the United States have different pharmacodynamic profiles based on their in vivo anti-Xa and anti-IIa profiles.⁸⁵ These differing pharmacodynamic profiles might be due in part to differences in anti-Xa/anti-IIa ratio⁸⁶ or molecular weight distribution of oligosaccharide chains,⁸⁷ among other reasons.⁸⁸ Therefore, it is important that an ANDA

⁸³ Hirsh J., Warkentin T.E., Shaughnessy S.G., Anand S.S., Halperin J.L., Raschke R., Granger C., Ohman E.M., Dalen J.E. (2001), "Heparin and Low-Molecular Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety," *Chest* 119 64S-94S.

⁸⁴ See USP 32-NF 27 (official on December 1, 2009).

⁸⁵ Erickson, B.I., Soderberg, K., Widlund, L., Wandeli, B., Tengborn, L., Risberg, B. (1995), "A Comparative Study of Three Low-Molecular Weight Heparins (LMWH) and Unfractionated Heparin (UH) in Healthy Volunteers," *Thrombosis and Haemostasis* 73, 398-401.

⁸⁶ Administration of products with differing anti-Xa/anti-IIa ratios would result in differences in in vivo pharmacodynamic profiles, as these are assessed based on the in vivo profiles of anti-Xa and anti-IIa activities.

⁸⁷ This phenomenon derives from the fact that higher molecular weight poly(oligo)saccharide species are cleared from the circulation more rapidly than the lower molecular weight poly(oligo)saccharide species. This in vivo accumulation of lower molecular weight poly(oligo)saccharide chains (which tend to have lower anti-IIa activity) may result in differences in circulating anti-Xa/anti-IIa ratios. See Hirsh, J., Warkentin, T.E., Shaughnessy, S.G., Anand, S.S., Halperin, J.L., Raschke, R., Granger, C., Ohman, E.M., Dalen, J.E. (2001), "Heparin and Low-

applicant meet this fifth criterion to provide important evidence of active ingredient sameness.

In sum, we conclude, based on our scientific experience and expertise and current relevant scientific evidence, that if an ANDA applicant meets each of the five criteria described in section III, this robust showing enables us to conclude that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides sufficient information to conclude that the generic drug product's enoxaparin is the same as Lovenox's enoxaparin.

As with all complex scientific issues, it is possible that, with improvement in the understanding of the biological and clinical properties of enoxaparin and/or advances in the analytical technologies that might be used to characterize enoxaparin, other approaches might emerge to establish the sameness of enoxaparin. Currently, however, the five sameness criteria specified above constitute adequate standards for identity for establishing enoxaparin sameness.

IV. OUR APPROACH TO DETERMINING SAMENESS OF ENOXAPARIN IS CONSISTENT WITH AGENCY PRECEDENT

Our approach to determining the sameness of enoxaparin is consistent with our previous ANDA approval decisions for other generic drug products containing active ingredients that are heterogeneous polysaccharides. Specifically, our conclusions of active ingredient sameness for generic heparin and hetastarch are based on the relevant scientific information and our knowledge of those active ingredients. As discussed below, to demonstrate active ingredient sameness the Act does not require ANDA applicants to (1) completely characterize all the different polysaccharides of enoxaparin by isolating, purifying, and sequencing each of its unique polysaccharide chains and determining their relative abundance, (2) use the same manufacturing process as that used for the RLD, or (3) conduct clinical studies to demonstrate equivalent safety and effectiveness.

A. Our Approach to Determining Active Ingredient Sameness for Enoxaparin is Consistent with Our Determination of Active Ingredient Sameness for Heparin

As previously noted, there are currently six approved ANDAs for heparin sodium injection, which are listed in the Orange Book. These approved generic heparin products are considered therapeutically equivalent to (and substitutable with) their respective RLDs, and two of them have been marketed for decades. The criteria for establishing active ingredient sameness were

Molecular Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety," *Chest* 119 64S-94S.

⁸⁸ For example, enoxaparin (derived by chemical β -elimination cleavage) and nadroparin (derived from deaminative cleavage) have similar molecular weight distributions and ratio of anti-Xa/anti-IIa activities, but have different pharmacodynamic profiles (see, e.g., EP 5th. Ed. (2007) (5.6) Nadroparin Calcium, at 2075-2077; Collignon, F., Fryman, A., Caplain, H., Ozoux, M.L., Roux, Y.L., Bouthier, J., Thebault, J.J. (1995), "Comparison of the Pharmacokinetic Profiles of the Three Low Molecular Mass Heparins — Dalteparin, Enoxaparin, and Nadroparin — Administered Subcutaneously in Healthy Volunteers (Doses for Prevention of Thromboembolism)," *Thrombosis and Haemostasis*, 73(4) 630-640; Stiekema, J.C.J., van Griensven, J.M.T., Dinther, T.G.V., Cohen, A.F. (1993), "A Cross-Over Comparison of the Anti-Clotting of Three Low Molecular Weight Heparins and Glycosaminoglycuronan," *British Journal of Clinical Pharmacology*, 36 51-56).

based on the USP monograph for heparin sodium in place at the time of ANDA approval.⁸⁹ As a general matter, to demonstrate active ingredient sameness for heparin, ANDA applicants showed that the generic drug product's active ingredient (heparin) (1) was isolated from the same animal tissue source as that of the RLD (e.g., porcine intestinal mucosa) and (2) had appropriate potency based on in vitro coagulation and anti-factor Xa activities.

Despite the relative simplicity of these criteria for demonstrating sameness, there has been no evidence of significant risks related to safety or effectiveness with the approved generic heparin products beyond those already associated with their respective RLDs. Particularly with respect to safety, the recent severe anaphylactoid reactions reported following intravenous heparin administration were not attributed to the heparin active ingredient, but to the presence of OSCS, a synthetic contaminant introduced into the heparin active ingredient.⁹⁰ Thus, based on relevant scientific information and our knowledge of heparin at the time of ANDA approval, the criteria provided sufficient information to conclude that the generic drug product's heparin was the same as the RLD's heparin.

Compared to heparin, enoxaparin has greater molecular diversity in its oligosaccharides because of the additional depolymerization step in the manufacturing process. We conclude, based on relevant scientific data and information and our scientific experience and expertise, that ANDA applicants for enoxaparin can demonstrate active ingredient sameness to Lovenox's enoxaparin by meeting the five criteria described in section III, and these criteria take into account the additional degree of molecular diversity for enoxaparin. We conclude that such a showing demonstrates that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides sufficient information to conclude that the generic drug product's enoxaparin is the same as Lovenox's enoxaparin. As with heparin, we conclude that it is not necessary to completely characterize all the different polysaccharide sequences, nor is it necessary to use the same manufacturing process as that used for the RLD or to conduct clinical trials to demonstrate equivalent safety or effectiveness.

B. Our Approach to Determining Active Ingredient Sameness for Enoxaparin is Consistent with Our Determination of Active Ingredient Sameness for Hetastarch

Hetastarch (hydroxyethyl starch) is widely used as a plasma expander and in many ways is chemically analogous to enoxaparin. Hetastarch is a mixture of polysaccharides derived through chemical modification (hydroxyethylation with ethylene oxide) and chemical cleavage (acid-catalyzed depolymerization) of highly heterogeneous amylopectin polysaccharides (a plant-derived natural product).⁹¹ Like enoxaparin, hetastarch consists of a distribution of polysaccharides that differ in length as well as in composition and sequence of repeating units (chemically

⁸⁹ USP has revised its monograph (October 1, 2009) for Heparin Sodium USP to incorporate as part of the standard for identification applicable tests and acceptance criteria based upon (1) NMR, (2) HPLC chromatography, (3) anti-factor Xa to anti-factor IIa ratio, and (4) presence for sodium. The USP monograph has also included quality tests and limits for assay, inorganic, organic impurities, residual solvents, pH, bacterial endotoxins, sterility and loss on drying. FDA expects all approved NDAs and ANDAs for Heparin Sodium Injection USP to comply with the updated USP standards.

⁹⁰ See footnote 16.

⁹¹ Ferber, H.P., Nitsch, E., Forster, H. (1985), "Studies on Hydroxyethyl Starch Part II," *Arzneim-Forsch/Drug Res.* 35 (I) 3 615-622.

heterogeneous modified monosaccharide units). On the other hand, unlike enoxaparin, which is composed of linear chain oligosaccharides, hetastarch polysaccharides possess chain branching. Therefore, the polysaccharide chains in hetastarch differ not only in their sequence of modified monosaccharide units but also in chain branching.

We have approved four ANDAs for hetastarch, which are listed in the Orange Book. To demonstrate active ingredient sameness for hetastarch, ANDA applicants: (1) demonstrated equivalence of physicochemical properties, including molecular weight distribution of polysaccharide chains and overall chemical composition (e.g., extent of hydroxyethylation) and (2) used the equivalent source material as the RLD (i.e., amylopectin polysaccharides derived from plants), as well as an equivalent mode of chemical modification (i.e., hydroxyethylation with ethylene oxide) and depolymerization (acid-catalyzed depolymerization).⁹² When comparing the molecular weight distributions, we took into account the lot-to-lot variation of the RLD, noting that hetastarch is "extremely polydisperse."⁹³ Based on relevant scientific information and our knowledge of hetastarch, these criteria provided sufficient information to conclude that the generic drug product's hetastarch was the same as the RLD's hetastarch.

To demonstrate enoxaparin sameness, ANDA applicants meet not only criteria analogous to those for determining sameness for hetastarch (including equivalence of physicochemical properties, equivalence of source material, and mode of depolymerization), but also additional criteria (i.e., equivalence of disaccharide building block units, sequence of oligosaccharide species, fragment mapping, in vitro biochemical and biological assays, and in vivo pharmacodynamic parameters). As with hetastarch, we conclude that it is not necessary to completely characterize all of the different polysaccharide sequences, nor is it necessary to use the same manufacturing process as that used for the RLD or to conduct clinical trials to demonstrate equivalent safety or effectiveness.

In sum, our active ingredient sameness conclusion for enoxaparin is consistent with those for other generic drug products containing active ingredients that are heterogeneous polysaccharide mixtures. Our conclusion for enoxaparin (like those for heparin and hetastarch) is based on relevant scientific information and our knowledge of the active ingredient.

V. OUR APPROACH TO DETERMINING ACTIVE INGREDIENT SAMENESS COMPORTS WITH CASE LAW

The U.S. Court of Appeals for the District of Columbia's decision in *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998), supports our approach to determining sameness of enoxaparin. In *Serono*, the Court of Appeals squarely addressed the issue of active ingredient sameness within the meaning of the Act and FDA regulations.

⁹² Letter dated July 25, 1996, to Richard J. Meader, McGaw, Inc., from Kathryn C. Zoon and Janet Woodcock, FDA, in response to Citizen Petition No. 96P-0024/CP1, at 2-3. This citizen petition was originally assigned docket number 96P-0024/CP1. The number was changed to FDA-1996-P-0001 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

⁹³ Id.

Serono involved a legal challenge to our approval of a generic version of Pergonal, a menotropins product used to treat infertility. This product contains two active ingredients: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As the court noted, we concluded that to be the same, the generic drug product's active ingredients and Pergonal's active ingredients were expected to have the same primary structure, potency, and degree of batch-to-batch uniformity. One of the active ingredients included natural variations known as microheterogeneity. We maintained that an isoform variation in the active ingredient of the generic drug product did not preclude a finding of active ingredient "sameness" for purposes of ANDA approval. We noted in documents cited by the court that "complete chemical identification of all the carbohydrate variants in a protein product often is not possible or feasible."⁹⁴ We stated "[i]ndeed, it usually is not even possible to 'assure by chemical analysis that different batches' of the same product 'are identical at the level of the carbohydrate side chains' – including different batches of Pergonal itself."⁹⁵

The D.C. Circuit upheld as reasonable the Agency's interpretation of the "sameness" statutory requirement, as well as the Agency's interpretation of the word "identical" in 21 CFR 314.92(a)(1).⁹⁶ The court concluded that the statute does not unambiguously require the term "same as" to be defined as "complete chemical identity," noting that the statute says nothing at all about the type of information an applicant must submit to demonstrate "sameness" nor about the type of information upon which the FDA may rely.⁹⁷ The court characterized the sameness provision as a "broad grant of discretion" to the Agency with respect to the information it may consider and noted that the phrase "must be read in the context of the kind of drug at issue."⁹⁸

Our decision here, as in *Serono*, takes into account the "kind of drug at issue" and is based on current scientific information and our knowledge of enoxaparin. Lovenox's enoxaparin is naturally sourced and has batch-to-batch variability. As discussed at length, we have determined, based on relevant scientific data and information and our scientific experience and expertise, that demonstration of active ingredient sameness for enoxaparin does not call for, nor does the Act require, the ANDA applicant to establish sameness by meeting the requests set forth in your petition regarding complete characterization of enoxaparin, manufacturing processes, or clinical trials. We have concluded that if an ANDA applicant meets the five criteria (or standards for identity) described in section III of this response, this evidence demonstrates that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides sufficient information to conclude that the generic drug product's enoxaparin is the same as Lovenox's enoxaparin.

⁹⁴ 158 F.3d at 1318.

⁹⁵ Id.

⁹⁶ Id. at 1321.

⁹⁷ Id. at 1319.

⁹⁸ Id. You also acknowledge that "the Act does not define what 'information' must be shown to establish sameness. Just what 'information' an ANDA must contain, therefore, depends on the nature of the active ingredient." (Aventis Comments dated October 13, 2004, p. 26.)

VI. SPECIFIC RESPONSES AND COMMENTS ON PETITION, SUPPLEMENTS, AND RELATED COMMENTS

We have explained at length the basis for our decision on enoxaparin sameness. We address below the arguments you raise in the Petition, the Supplements, and related comments.⁹⁹

You assert that to demonstrate active ingredient sameness, the ANDA applicant must (1) completely characterize all the different polysaccharides of enoxaparin by isolating, purifying, and sequencing each of its unique polysaccharide chains and determining their relative abundance, (2) use Aventis's or an Aventis-equivalent manufacturing process, or (3) conduct clinical trials to demonstrate equivalent safety and effectiveness. As summarized below, we have thoroughly considered your arguments, and we reject them.

A. To Demonstrate Active Ingredient Sameness, ANDA Applicants for Enoxaparin Do Not Need to Completely Characterize All the Different Polysaccharide Sequences

You claim that the only method by which an ANDA applicant could ensure its product would have the same biological and clinical effects as enoxaparin (other than use of an Aventis-equivalent manufacturing process or clinical trials to establish safety and effectiveness) is to characterize and compare all of the different polysaccharide sequences and their relative amounts (Supplement No. 3 at 2-3). You state that approximately 30 percent of the polysaccharide chains comprising enoxaparin have yet to be directly analyzed (without the benefit of complete enzymatic digestion of the sample) because of the limitations on current analytical technology (Petition at 3). You note that sequencing of polysaccharides is difficult, laborious, and time-consuming, and you comment on the need to assure purity of samples (Supplement No. 3 at 9-11). You state that Aventis has not been able to isolate those polysaccharide chain fragments of molecular weight above 3,600 Da and that this portion remains unexplored by direct analysis (Viskov Declaration, at 4).¹⁰⁰ You state that as technology continues to improve, investigation of the unexplored portions of enoxaparin may yield additional unique and process-dependent structural modifications with pharmacological activity (Petition at 3). You also state that a "generic product must contain those modifications (known or undiscovered) to be considered the 'same' as enoxaparin" (Petition at 3). You state that an ANDA applicant 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 (Petition at 3-4, 20).

⁹⁹ You take issue with the analytical techniques and data submitted by an ANDA applicant in its May 13, 2004, letter to Lester M. Crawford, D.V.M., Ph.D., then Acting Commissioner, FDA, that was subsequently forwarded to the docket by cover letter dated June 1, 2004 (Aventis Comments dated October 13, 2004, and March 17, 2005, and Supplement No. 2). FDA, as the Agency charged with reviewing ANDAs, considers the data and information submitted in ANDAs before reaching any approval decisions. Accordingly, it is unnecessary to respond to your assertions and judgments about the data and information submitted by any particular ANDA applicant to the citizen petition docket in this regard. Further, we are not generally permitted to disclose from ANDAs confidential commercial or trade secret information.

¹⁰⁰ We note that Aventis has not sought to fully characterize enoxaparin even for those chains for which the technology exists (Viskov Declaration at 4, noting "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").

Based on current relevant scientific data and information and our scientific experience and expertise, we conclude that it is not necessary to completely characterize all the different polysaccharide sequences of enoxaparin. Our finding of sameness for enoxaparin is not based solely on the equivalence in molecular weight, anti-Xa activity, and/or anti-Xa/anti-IIa ratio. We conclude that the five criteria described in section III provide sufficient information to demonstrate active ingredient sameness. Such a showing demonstrates that molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides sufficient information to conclude that the generic drug product's enoxaparin is the same as Lovenox's enoxaparin. As discussed at length in sections III, IV, and V, this conclusion is supported by relevant scientific evidence, Agency precedent (e.g., heparin and hetastarch), and law.

B. ANDA Applicants for Enoxaparin Do Not Need to Demonstrate That They Use the Same Manufacturing Process as Aventis

We first address below your general claim regarding the need for using Aventis's manufacturing process or the equivalent, and then we turn to your specific assertions and the information you submitted.

1. Your general claim

You state that until enoxaparin has been fully characterized, we should refrain from approving any ANDAs citing Lovenox as the RLD unless, among other things, the manufacturing process used to create the generic drug product is deemed to be equivalent to Aventis's manufacturing process for enoxaparin (Petition at 1, 10). You state that Aventis uses a process of β -elimination of uronic benzylic esters to manufacture enoxaparin and that the process creates a distinct drug product with a unique chemical structure that is sensitive to specified temperature, base concentration, and duration factors in the reaction (Petition at 10-11). In particular, you state that different LMWHs manufactured through different depolymerization processes will have different ranges of oligosaccharide chains having a given molecular mass (Petition at 11). You claim that Aventis's process results in particular saccharide sequences, which include distribution of specific structures as well as the type and arrangement of saccharides within a given chain (Petition at 11). You also assert that the manufacturing process creates specific process-dependent structural modifications (e.g., fingerprints) to enoxaparin's chemical structure (Petition at 11). You claim that use of a manufacturing process that differs from that for Lovenox would likely result in a drug with a different oligosaccharide permutation, different pharmacokinetics, and potentially dissimilar clinical activities. In particular, you claim that differences in oligosaccharide length and sequence permutations would likely lead to varying rates of absorption and elimination and different circulating anti-Xa/anti-IIa ratios (Petition at 13-14).¹⁰¹ You maintain that until enoxaparin becomes fully characterized, the only way to ensure that generic enoxaparin contains all the therapeutically significant structural features of

¹⁰¹ In addition to our response to your arguments in the text of this response, we note that any such differences that you claim may affect the rates of absorption and elimination or different circulating anti-Xa/anti-IIa ratios are further ruled out by the active ingredient sameness criterion on equivalence of in vivo pharmacodynamic profiles, as explained in section III.E of this response.

enoxaparin (both known and yet to be discovered) is to duplicate Aventis's manufacturing process or use an equivalent process (Petition at 20-21).

As discussed at length above, the Act and implementing regulations require the ANDA applicant as a condition of approval to provide sufficient information to demonstrate that the active ingredient in the generic drug product is the same as that of the RLD. We conclude that the five criteria described in section III of this response provide sufficient information to establish active ingredient sameness for enoxaparin. One of the five criteria involves using the equivalent heparin source material (i.e., heparin that is derived from porcine intestinal mucosa and that meets USP monograph standards for Heparin Sodium USP) and the equivalent mode of depolymerization (i.e., cleavage by alkaline β -elimination of the benzyl ester derivative of heparin) as that used for Lovenox's enoxaparin.¹⁰² In addition to meeting these criteria, the ANDA applicant would likely have to make appropriate adjustments to the operating conditions of the depolymerization process to meet the other criteria described in section III. An ANDA applicant would not need to know Aventis's exact manufacturing process parameters and conditions (e.g., depolymerization time, pH, and temperature) to manufacture the same active ingredient as Lovenox's enoxaparin.¹⁰³ There is no requirement that an ANDA applicant achieve active ingredient "sameness" for enoxaparin by using the same manufacturing process as that used for the RLD. You have not provided any information to show that an ANDA applicant's manufacturing process would be incapable of producing the same active ingredient as Lovenox's enoxaparin within the meaning of the Act and regulations.

Although you ask in your petition that ANDA applicants for enoxaparin use an Aventis-equivalent manufacturing process, it is unclear to what processes you are referring.¹⁰⁴ The Act and implementing regulations require an ANDA applicant, as a condition of approval, to ensure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are *adequate* to assure and preserve the identity, strength, quality, and purity of the drug.¹⁰⁵ The two requirements – that an ANDA applicant demonstrate active ingredient

¹⁰² Lovenox's enoxaparin is derived by benzyl esterification of the free carboxylate (uronic acid residue) of heparin, which is obtained from porcine intestinal mucosa. This benzylated ester of heparin is treated under alkaline conditions to induce β -elimination, which results in polysaccharide chain cleavage. Likewise, we expect the ANDA applicant to use heparin derived from porcine intestinal mucosa and to depolymerize this source material through cleavage by alkaline (chemical) β -elimination of the benzyl ester derivative of heparin.

¹⁰³ As a general matter, manufacturing information is considered confidential commercial and/or trade secret information, which cannot be disclosed by the Agency.

¹⁰⁴ You note that since the initial development of enoxaparin in 1981, the steps of the Lovenox manufacturing process have remained unchanged (Petition at 11). On the other hand, you state that between March 1996 and April 2004, you submitted 24 CMC supplements, sixteen of which were drug product related and the remaining eight of which were not solely drug product related (Aventis October 13, 2004, Response to Comment at 20-22).

¹⁰⁵ See section 505(j)(4)(A) of the Act, and 21 CFR §§ 314.127(a)(1) and 314.94(a)(9)(i) (referencing 314.50(d)(1)). The ANDA applicant submits the same type of information on chemistry, manufacturing, and controls as NDA applicants, including the following: "A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and

sameness and submit designated information on the manufacturing process – are independent statutory and regulatory requirements and are addressed in two different sections of the statute and regulations. Neither the Act nor FDA regulations require that an ANDA applicant use the *same* methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the *RLD* to assure and preserve the identity, strength, quality, and purity of the *generic drug*.¹⁰⁶ As discussed elsewhere, once we conclude that an ANDA for enoxaparin meets the requirements for ANDA approval, the generic enoxaparin and Lovenox can be substituted with the full expectation that generic enoxaparin will produce the same clinical effect and safety profile as Lovenox.

2. *Your specific assertions*

a. The 1,6 anhydro ring structure

You specifically request that we not approve generic enoxaparin unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15 to 25 percent of its oligosaccharide chains (Petition at 1). You state that Aventis's manufacturing process results in formation of the 1,6 anhydro ring during the β -elimination depolymerization process, and the formation or frequency of the 1,6 anhydro ring is sensitive to Aventis's process conditions (Petition at 13). You state that unlike enoxaparin's other structural fingerprints, you have conducted preclinical tests on the 1,6 anhydro ring structure which lead you to conclude that this structure has pharmacological activity at the 15 to 25 percent frequency and might have an effect on inflammation, smooth muscle cell proliferation, angiogenesis (potentiation of acidic fibroblast growth factor (aFGF)-induced endothelial cell proliferation), coagulation and thrombosis, pharmacokinetics, and safety profile (Petition at 14-19). You state that Aventis's 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 (i.e., <7 percent 1,6 anhydro LMWH and 40 to 50 percent 1,6 anhydro LMWH) (Petition at 14). You state that Aventis compared these two alternative LMWHs with enoxaparin to assess various aspects of pharmacological activity and gauge the pharmacological relevance of the 1,6 anhydro ring structure (Petition at 15).

As discussed in section III, if an ANDA applicant for enoxaparin meets the five criteria, this robust showing demonstrates that the molecular diversity of the generic drug product's enoxaparin and the Lovenox's enoxaparin will be equivalent, including with respect to the 1,6 anhydro ring structure.¹⁰⁷ This will also result in meeting the standards for identity described in the USP monograph for enoxaparin sodium, which states that "[a]bout 20 percent of the materials contain

analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph."

¹⁰⁶ We need not decide whether for a different active ingredient (i.e., an active ingredient other than enoxaparin) the same methods, facilities, and controls used for the manufacturing, processing, and packing as those used for the RLD would be needed to assure and preserve the identity, strength, quality, and purity of the generic drug; here, we conclude that this is not the case for enoxaparin.

¹⁰⁷ Recognition of these fingerprints, as you also acknowledge (Petition at 3), is possible due to recent advances in the field of analytical technology (see also section III.C).

a 1,6 anhydro derivative on the reducing end of the chain, the range being between 15 and 25 percent.”¹⁰⁸

We also note that you have not provided adequate information for us to conclude that the 1,6 anhydro ring structure is clinically significant, as you claim. In considering your arguments, we have reviewed all of the articles and information submitted with your petition and supplements. You refer to in vitro and preclinical studies to support your claims regarding the purported contributions of the 1,6 anhydro ring structure at a frequency of 15 to 25 percent. Given the quantum of articles and reports submitted, it is not possible to address each one in this response, nor do we find it necessary. Nonetheless, we provide below some examples to convey the nature of the materials submitted.

Inflammation

Some of the data you submitted on their face do not fully support the conclusions you attempt to draw regarding the purported effect of the 1,6 anhydro ring structure on inflammation. For example, you refer to the Petitet report to support your claims regarding the purported contributions of the 1,6 anhydro ring structure to the anti-inflammatory activity of enoxaparin (Petition, Appendix A). Although the report includes data on the inflammatory properties of enoxaparin, <7 percent 1,6 anhydro LMWH, 40 to 50 percent 1,6 anhydro LMWH, and other saccharide fragments, the conclusion drawn by the author relates only to the anti-inflammatory properties of enoxaparin, and not to contributions of the 1,6 anhydro ring structure to the anti-inflammatory activity of enoxaparin (Petitet report at iv). Additionally, you cite another study that used CD54 expression to account for enoxaparin’s anti-inflammatory effects, but enoxaparin’s effect on CD54 expression was found not to be dependent on the 1,6 anhydro group content (Supplement No. 4 at 4).

Smooth muscle proliferation

Some of your statements on the purported effect of the 1,6 anhydro ring structure on smooth muscle proliferation are merely speculative. For example, you state that “a product claiming to be enoxaparin that lacked the 1,6 anhydro ring structure (or had it in a different concentration) could have a different effect on inhibition of SMC [smooth muscle cell] proliferation” (Supplement No. 1 at 10) (emphasis added). Further, some of the data you submitted on their face do not fully support the conclusions you attempt to draw with respect to smooth muscle proliferation. For example, while the Dilley & Little authors (Petition, Appendix A) reported that both the < 7 percent 1,6 anhydro LMWH and the 40 to 50 percent 1,6 anhydro LMWH exhibited distinctive inhibitory properties of smooth muscle cell proliferation (Dilley & Little at 7), the same authors also indicated that variability was an issue in these experiments. These authors indicated that in these experiments it was difficult to determine whether there was a consistent dose-response relationship and suggested that more extensive analysis of these compounds may provide more accurate data (Dilley & Little at 9).

¹⁰⁸ See USP 32-NF 27 monograph for enoxaparin sodium (official on December 1, 2009).

Angiogenesis

Some of your statements regarding the purported effect of the 1,6 anhydro ring structure on angiogenesis are also speculative. For example, you state that “a product that claimed to be enoxaparin but lacked the 1,6 anhydro ring structure (or had it in a different concentration than is found in enoxaparin) could have a different effect on stimulation of angiogenesis than does enoxaparin” (Supplement No. 1 at 10) (emphasis added). Further, some of the data you submitted on their face do not fully support the conclusions you attempt to draw with respect to angiogenesis. For example, while the report from von Specht (Petition, Appendix A) indicates that the < 7 percent 1,6 anhydro LMWH is significantly more active than the 40 to 50 percent 1,6 anhydro LMWH when assayed through BHK cell line (baby hamster kidney cells) (von Specht at 10), the same author indicates that because of the high standard deviations obtained in cell culture assays, they were unable to calculate a rank order of the LMWHs tested. Moreover, the same author’s test results (using the chorion allantois membrane (CAM) assay (at 8 µg of LMWH dose) to assess angiogenesis) suggest that the 40 to 50 percent 1,6 anhydro LMWH (as opposed to the < 7 percent 1,6 anhydro LMWH) was more active (von Specht at 10), which appears to contradict the results obtained from the BHK cell test.

Coagulation and thrombosis

Again, some of your statements regarding the effect of the 1,6 anhydro ring structure and bleeding profiles are merely speculative. For example, you state that the “presence of the 1,6 anhydro ring structure appears to change the anti-coagulant potency and antithrombic effect of enoxaparin, which may . . . lead to different bleeding profiles in patients” (Supplement No. 1 at 8) (emphasis added). In addition, some of the data you submitted are on their face inconsistent with the conclusions you attempt to draw with respect to coagulation and thrombosis. For example, you concede that your tests did not show a statistically significant difference between enoxaparin (containing the 1,6 anhydro ring at 15 to 25 percent frequency) and the two alternative LMWHs (containing other frequencies of the 1,6 anhydro ring structure) with respect to activated partial thromboplastin time, prothrombin time, thrombin generation, anti-Xa activity, anti-IIa activity, or thromboelastography (Petition at 19). In another study that examined the capacity of enoxaparin and its components to attenuate tissue factor (TF) expression and subsequent activation of coagulation on the cell surface, you found that the 1,6 anhydro group was not an important determinant of enoxaparin’s activity in this assay (Supplement No. 4 at 7).

You also claim that a recent study demonstrates that TFPI inhibition reversal is another process-dependent biological property of enoxaparin that may have clinical significance (Supplement No. 2 at 3-4). Specifically, you state that the study demonstrates that both polysaccharide chain length and 1,6 anhydro ring structure concentration affect enoxaparin’s reversal of TFPI inhibition (Supplement No. 2 at 4). You state that TFPI release plays a major role in neutralization of the TF/factor VIIa complex initiating coronary thrombosis after artery injury or plaque rupture (Supplement No. 2 at 2-5). Therefore, you state that if an ANDA applicant does not use an Aventis-equivalent manufacturing process, the enoxaparin “might” exhibit a different anti-thrombotic profile than enoxaparin (Supplement No. 2 at 5). We note that your conclusions are not based on relevant data, but instead are hypothetical outcomes. As the authors noted,

“[f]urther studies are needed to define the role and mechanisms of 1,6 anhydro in endothelial TFPI under various conditions” (Supplement No. 2, Exhibit A).

Pharmacokinetics

Your claim regarding the purported contributions of the 1,6 anhydro ring structure at a frequency of 15 to 25 percent with respect to enoxaparin pharmacokinetics (in vivo pharmacodynamic profiles) is based upon studies in beagle dogs, as opposed to studies in humans. We further note that even these pharmacokinetic (in vivo pharmacodynamic profiles) data on their face do not support the conclusions you attempt to draw. For example, you state that <7 percent 1,6 anhydro LMWH showed a statistically significant increase in plasma anti-Xa activity and anti-IIa activity compared to enoxaparin (Petition at 18, Appendix A; Report DMPK/FRA/2003-0029 (DMPK Report), pp. 20-25). In your report, you state that for the <7 percent 1,6 anhydro LMWH after one subcutaneous administration in dogs, there were statistically significant differences in certain parameters compared to enoxaparin (DMPK Report, pp. 20). However, you also state that other anti-Xa and anti-IIa pharmacokinetic parameters were not statistically significant. Further, you state that after administration of the 40 to 50 percent 1,6 anhydro ring LMWH, no statistically significant differences between the pharmacokinetics of that compound and enoxaparin were observed (DMPK Report at 25).

Safety profile

Some of the data you submitted are on their face inconsistent with the conclusions you attempt to draw with respect to safety profile. For example, heparin-induced thrombocytopenia (HIT) is a potentially fatal complication of heparin therapy; however your in vitro studies showed that the 1,6 anhydro ring structure does not modify enoxaparin's HIT cross-reactivity (Supplement No. 1 at 11). We also note that your statements on the purported effect of the 1,6 anhydro ring structure and safety profile are merely speculative. For example, you state that “a generic product that ... did not contain the 1,6 anhydro ring may pose an increased threat of hemorrhagic complications in patients” (Petition at 19) (emphasis added).

Although you speculate that the studies submitted “likely bear clinical significance” (Petition at 3), you have not provided any clinical studies to support your claim. Accordingly, you have not provided sufficient evidence upon which we can reasonably conclude that the 1,6 anhydro ring structure at the 15 to 25 percent frequency has the pharmacological activity or clinical significance in humans that you claim.¹⁰⁹

¹⁰⁹ While you submitted information on the 1,6 anhydro structure to support labeling changes for Lovenox (NDA 20-164/S-055 at 3), the review division concluded that additional studies would be needed to “establish the clinical importance of this chemical characteristic.” See Kathie M. Robie-Suh, M.D., Ph.D., Medical Team Leader, Review 20-164/S-055 dated July 22, 2004.

(http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/020164_S055_Lovenox_Approval_Package.pdf)

b. AT-III binding oligosaccharides¹¹⁰

You assert that LMWHs inhibit coagulation by binding to AT-III, a plasma protein synthesized in the liver and other cells (Supplement No. 1 at 3). You state that LMWH interaction with AT-III is mediated by a specific pentasaccharide sequence that is distributed across 15 to 25 percent of LMWH polysaccharide chains (Supplement No. 1 at 3). You state that you discovered that process-dependent variations in saccharide sequence within a given oligosaccharide affect the oligosaccharide's affinity for AT-III (Supplement No. 1 at 4). You state that the differences in the disaccharide sequences occur depending upon where the unfractionated heparin is cleaved during the manufacturing process, and Aventis's process results in three main process-dependent octasaccharide sequences (Supplement No. 1 at 5). You state that Aventis conducted in vitro experiments to measure the AT-III affinity and the anti-Xa activity of its three octasaccharide sequences (Supplement No. 1 at 5). You state that these findings show that different octasaccharides in enoxaparin do not have identical in vitro anti-Xa activity and there can be considerable variation in affinity for AT-III (Supplement No. 1 at 6-7). You maintain that a recent study shows that these process-dependent AT-III binding sites are found not only in enoxaparin's octasaccharide fractions, but in all of the drug's oligosaccharide fractions (Supplement No. 2 at 7-8). You claim that sequence variations might cause differences in the half-lives of the anti-Xa activity, leading to different profiles of bleeding safety and antithrombotic effectiveness (Supplement No. 1 at 4-7).

You state that the AT-III binding affinity of what you refer to as the "classical" AT-III binding sequence in enoxaparin is influenced by the nature of the particular saccharide units flanking that sequence, and that the use of a surrogate for the classical AT-III binding sequence such as the one you reference cannot adequately predict AT-III binding activity (Supplement No. 3 at 3-6).¹¹¹ You also claim that some polysaccharides have AT-III binding affinity even though they lack the classical AT-III sequence (Supplement No. 3 at 7-9). You state that any differences could influence antithrombotic activity (Supplement No. 3 at 8). You state that these apparent findings underscore the need to characterize all the oligosaccharides in enoxaparin (Supplement No. 3 at 6 and 7). You also discuss Dr. Boudier's findings that non-ionic interactions are important in the binding of octasaccharide D with AT-III. You indicate this demonstrates that "small changes in sugar structures flanking the classical AT-III binding sequence can have large effects on AT-III binding" (Supplement No. 4 at 10).

You cite in vitro studies to support your claims regarding the possible contributions of what you refer to as process-dependent sequences flanking the AT-III binding sites. Many of your statements regarding process-dependent AT-III binding oligosaccharides are merely speculative. For example, you refer to a recent study that you claim demonstrates that enoxaparin has a process-dependent inhibitory effect on factor VIIa generation, which you state is linked to arterial thrombogenesis (Supplement No. 2 at 5-7). You state that the study demonstrates that

¹¹⁰ The terms "process-dependent AT-III binding oligosaccharides" and "process-dependent sequences flanking the AT-III binding oligosaccharides" are used interchangeably for purposes of this response.

¹¹¹ You state that researchers collaborating with one ANDA applicant have published this method for detecting this purported surrogate for AT-III binding activity (Supplement No. 3 at 6). We note that we would not consider a generic drug product's enoxaparin to be the same as Lovenox's enoxaparin based solely upon the surrogate you describe. As discussed at length, we consider the generic drug product's enoxaparin to be the same as Lovenox's enoxaparin if the five criteria described in section III are met.

the concentration of AT-III binding sites within enoxaparin influences factor VIIa generation inhibition (Supplement No. 2 at 6). You state that enoxaparin's inhibition of factor VIIa generation represents another biological property of enoxaparin with "possible" clinical significance (Supplement No. 2 at 6). You speculate that a generic enoxaparin that did not use an equivalent manufacturing process "might" contain a different distribution and structure of AT-III binding sites, and this in turn "could" lead to a different effect on inhibition of factor VIIa, and such a product "might" exhibit a different effect on arterial thrombosis which "could" have clinical consequences (Supplement No. 2 at 5-7). Even the study authors propose four areas of future study that would be needed for a "complete description and comparison of the oligosaccharides effect on the blood coagulation process" (Supplement No. 2, Appendix B). Further, Dr. Boudier in his studies of octasaccharide D acknowledges that both the small size of these products and their high affinity for AT-III "may" confer a substantial specificity (especially product D), a key advantage in pharmacology (Supplement No. 4, Appendix F).

We conclude that you have not provided sufficient information upon which we can conclude that what you refer to as process-dependent AT-III binding oligosaccharides are clinically significant. Although you speculate as to the clinical significance of your studies, you have not provided any clinical studies to support your claim. Without data from clinical studies, we cannot reasonably conclude that what you refer to as the process-dependent AT-III binding oligosaccharides and "nonclassical" AT-III binding sequences you reference are pharmacologically and clinically active in humans.

Based on the available scientific evidence, we conclude that in conjunction with showing conformance to the other criteria described in section III, performing a sequence analysis on a subset of oligosaccharides in enoxaparin (having sequences that are sensitive to variations of process conditions used during depolymerization) and demonstrating that this subset of oligosaccharides has sequence(s) equivalent to a comparable subset of oligosaccharides in Lovenox's enoxaparin provides sufficient evidence that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent, including the process-dependent AT-III binding oligosaccharides and "nonclassical" AT-III binding sequences that you describe.¹¹² Equivalent molecular diversity demonstrates sameness for enoxaparin.

c. Other structural fingerprints

In your petition, you state that you have identified several other structural fingerprints in enoxaparin that you claim "may contribute to its pharmacological activity" (Petition at 12). You state that these include oligosaccharides with odd-numbered saccharide units, galacturonic acid moieties, and epimerized reducing ends in a mixture of 70 percent glucosamine and 30 percent mannosamine (Petition at 12). You concede that Aventis "has not yet assessed the pharmacological activity of the[se] other fingerprints" (Petition at 13). You nonetheless speculate that

¹¹² As discussed in section III, the ANDA applicant can ensure that the depolymerization process conditions used in the manufacture of the generic drug product's enoxaparin have a chemical selectivity of cleavage that is equivalent to the chemical selectivity of the depolymerization process used to manufacture Lovenox's enoxaparin. Thus, the ANDA applicant can ensure that the site(s) where the unfractionated heparin is cleaved will be equivalent between the generic drug product's enoxaparin and Lovenox's enoxaparin. We can expect the generic drug product's enoxaparin to be equivalent to Lovenox's enoxaparin with respect to what you refer to as process-dependent AT-III binding oligosaccharides.

“[m]any of these fingerprints . . . represent significant structural modifications and will likely prove to be pharmacologically and clinically active” (Petition at 13).

We have concluded that you have not submitted any data to show that these other structural modifications are pharmacologically or clinically active. Therefore, your statements are conclusory and speculative and do not support your claims. As stated above, if an ANDA applicant meets the five criteria described in section III of this response, this robust showing demonstrates that the molecular diversity of the generic drug product’s enoxaparin and Lovenox’s enoxaparin will be equivalent — including with respect to the odd-numbered saccharide units, galacturonic acid moieties, and epimerized reducing ends having a mixture of glucosamine and mannosamine structures. Equivalent molecular diversity demonstrates sameness for enoxaparin.

C. ANDA Applicants Are Not Required to Submit Clinical Trials to Establish the Safety and Effectiveness of Enoxaparin

Absent full characterization or use of Aventis’s or an equivalent manufacturing process for enoxaparin, you state that we cannot consider the generic drug product to have the “same” active ingredient as enoxaparin and, therefore, we must require a demonstration of equivalent safety and effectiveness through clinical testing. In such cases, you state that section 505(j)(2)(A)(ii)(II) of the Act prohibits FDA from approving the ANDA unless the applicant establishes the safety and effectiveness of its enoxaparin product through clinical trials (Petition at 1, 21).¹¹³

Your claim is without merit. Section 505(j)(2)(A)(ii)(I) of the Act provides that an ANDA applicant must submit “information to show that the active ingredient of the new drug is the same as that of the listed drug.”¹¹⁴ The Act also provides that we must approve an ANDA unless, among other things, it includes “insufficient” information to show active ingredient sameness.¹¹⁵ Section 505(j)(2)(A)(ii) of the Act does not, as you claim, prohibit us from approving an ANDA that does not include clinical trials to demonstrate the safety and effectiveness of the enoxaparin product. This section of the Act does not include any language specifying the type of information needed to demonstrate active ingredient sameness, and we find clinical studies to demonstrate safety and effectiveness are not necessary here. The requirement you propose would be contrary to one of the principal purposes of the ANDA statutory approval provisions, which is “to encourage competition by decreasing the time and expense of bringing

¹¹³ You also assert that enoxaparin is similar to a biologic (Petition at 8). You question whether the generic drug approval model is appropriate (Petition at 8). Lovenox is not a biological product licensed under section 351 of the Public Health Service Act (PHS); rather, Lovenox is approved under section 505 of the Act. Although it is not a foregone conclusion that a showing of active ingredient sameness can be made for all drugs approved under section 505 of the Act, we conclude that active ingredient sameness can be demonstrated for enoxaparin. FDA can address your arguments regarding the specific characteristics of enoxaparin without wholesale rejection of the statutory process applicable to ANDA applications under section 505 of the Act. As with certain other naturally sourced products, like heparin and hetastarch, approval of ANDAs for enoxaparin under section 505(j) of the Act is appropriate.

¹¹⁴ You specifically refer to section 505(j)(2)(A)(ii)(II) of the Act, which pertains to drugs containing more than one active ingredient. Elsewhere in your petition you refer to section 505(j)(2)(A)(ii)(I) of the Act, which pertains to single active ingredient drugs. Enoxaparin sodium injection is a single active ingredient drug.

¹¹⁵ See section 505(j)(4)(C)(i) of the Act.

generic drugs to market, and thereby to provide the public with low cost drugs.”¹¹⁶ Further, the conduct of duplicative studies raises ethical concerns because it could subject humans and animals to medically or scientifically unjustified testing.

As discussed and as you acknowledge (Aventis October 13, 2004, Comments at 26), we have considerable discretion to determine what type of information is sufficient to demonstrate active ingredient sameness for ANDA approval. Based on our scientific experience and expertise and relevant scientific information, we have determined that ANDA applicants can provide sufficient information to demonstrate the sameness of enoxaparin by showing that the generic drug product’s enoxaparin meets the five criteria (or standards for identity) discussed in section III of this response. Submission of ANDAs under section 505(j) of the Act is an appropriate pathway for approval of generic enoxaparin.

D. Contrary to Your Assertions, Approval of an ANDA for Enoxaparin Is Consistent With FDA Precedent

1. Pergonal

You state that the case of enoxaparin is distinguishable from previous cases in which we have concluded that a proposed generic drug was the same as the RLD despite differences in active ingredient chemical structure (Petition at 21). Specifically, you state that we approved an ANDA for a generic version of Pergonal (with active ingredients FSH and LH), even though the generic version had a different isoform of FSH than Pergonal (Petition at 21). You state that we concluded the isoform variation was not clinically significant for the product’s intended uses and, therefore, it did not preclude a sameness finding (Petition at 21). You recognize that in *Serono*, the Court of Appeals held that we are entitled to deference in our interpretation of the meaning of “same as” in the statute (Petition at 21). However, you claim that, unlike the isoform variation at issue in *Serono*, preclinical tests show that the 1,6 anhydro ring structure at a frequency of 15 to 25 percent in enoxaparin “may well” have clinical significance (Petition at 21). You also state that, unlike Pergonal’s active ingredient at the time of ANDA submission, Lovenox is not fully characterized (Petition at 22). Therefore, you claim that we cannot ensure that a generic drug product’s enoxaparin is the same as Lovenox’s enoxaparin unless the product is manufactured using a process equivalent to the Lovenox process (Petition at 22).

Your discussion of the approval of Pergonal does not support your arguments with respect to Lovenox. Consistent with *Serono*, our finding of active ingredient sameness is based on relevant scientific information and is specific to each active ingredient. Although enoxaparin and menotropins (FSH and LH) are heterogeneous mixtures of molecular entities, the active ingredients have different origins and are composed of entirely different molecular structures. Enoxaparin is a heterogeneous mixture of oligosaccharides produced through alkaline depolymerization of the benzyl ester of heparin derived from porcine intestinal mucosa, whereas Pergonal’s menotropins are a mixture of protein isoforms of FSH and LH derived from the urine of post-menopausal women.

¹¹⁶ See 54 FR 28872 at 28874 (July 10, 1989).

For Pergonal, we expected the active ingredient in the generic version to have the same primary structure (assured by using the same natural source material), potency, and degree of batch-to-batch uniformity as the innovator's active ingredient. We concluded that any differences in isoform variation between the generic drug product's active ingredient and Pergonal's active ingredient were not clinically significant. For enoxaparin, we have concluded that the five criteria described in section III (which result in satisfaction of the USP monograph for enoxaparin sodium, as well as additional standards that are material to enoxaparin's sameness) are sufficient to demonstrate enoxaparin sameness. Although you have not provided adequate data to demonstrate that the 1,6 anhydro ring structure or other structures have pharmacological activity or clinical significance in humans as discussed in section VI, our five criteria approach for enoxaparin sameness demonstrates that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent, including with respect to the 1,6 anhydro ring structure. Equivalent molecular diversity provides sufficient information to conclude that the generic drug product's enoxaparin is the same as Lovenox's enoxaparin.

Based on relevant scientific evidence (and the vastly differing structures of the molecular entities that comprise enoxaparin and menotropins (FSH and LH)), it is reasonable and appropriate for the Agency to take into account their respective molecular diversity and form conclusions and approaches specific to each active ingredient.

2. *Premarin*

You state that the case of enoxaparin is highly analogous to that of Premarin, a conjugated estrogen product for which the innovator claimed the active ingredient had not been adequately characterized and, therefore, could not be duplicated by ANDA applicants (Petition at 22). You note that in 1997, FDA concluded that Premarin must be characterized before synthetic generic Premarins could be approved (Petition at 23). You also acknowledge that FDA stated that it would approve a generic version of Premarin that was made using the same source material (pregnant mare's urine) as that of Premarin (Petition at 24). You state that unlike conjugated estrogens, the composition of enoxaparin is not solely a factor of the source material used, but is also highly dependent on the manufacturing process (Petition at 23). You allege that for enoxaparin, the process makes the product (Petition at 24). You also claim that the discovery of the pharmacological contributions of the 1,6 anhydro ring to enoxaparin's activity is analogous to the discovery of the contributions of Δ (8,9) dehydroestrone sulfate (DHES) in Premarin (Petition at 23). You state that the 1,6 anhydro ring in enoxaparin shows that Aventis's manufacturing process creates biologically relevant structures that do not exist in the natural source material (Petition at 24). You maintain that Aventis ensures that all significant structural modifications are consistently present in Lovenox through use of its tightly controlled manufacturing process (Petition at 24).

The parallels you attempt to draw between enoxaparin and Premarin are misplaced. Our finding of active ingredient sameness is based on relevant scientific information and is specific to each active ingredient. Although both enoxaparin and conjugated estrogens are heterogeneous mixtures of molecular entities, these products are derived from different origins and are composed of entirely different molecular structures. Enoxaparin is a heterogeneous mixture of oligosaccharides produced through alkaline depolymerization of the benzyl ester of heparin

derived from porcine intestinal mucosa, whereas Premarin's conjugated estrogens are a mixture of steroids derived from pregnant mare's urine.

For Premarin, we determined that we could not make a finding of active ingredient sameness for *synthetic* versions of Premarin because the Premarin active ingredient had not been adequately characterized.¹¹⁷ As you also acknowledge (Petition at 23), our conclusion for Premarin did not preclude a finding of sameness for a generic drug product's active ingredient if the active ingredient was derived from the same natural source material as the RLD.¹¹⁸ Our conclusions regarding active ingredient sameness for both synthetic and naturally derived Premarin were based on relevant scientific information available at the time and our knowledge of the active ingredient.

For enoxaparin, we have concluded based on relevant scientific evidence that there is sufficient information to assess whether generic enoxaparin contains the same active ingredient as Lovenox. Specifically, we conclude that the five criteria described in section III are sufficient to conclude enoxaparin sameness. As described in section III, these criteria – including the use of equivalent heparin source material – are designed to take into account the molecular diversity of enoxaparin. As described in sections III and VI.B.2.a, we can expect that the generic drug product's enoxaparin would contain the 1,6 anhydro ring structure at a frequency of 15 to 25 percent.¹¹⁹ Based on the available relevant scientific evidence (and the differing structures of the molecular entities that comprise enoxaparin and conjugated estrogens), it is reasonable and appropriate for the Agency to take into account their respective molecular diversity and form conclusions and approaches specific to each active ingredient.

3. *Hyaluronidase*

You state that our comments in response to a citizen petition submitted by ISTA Pharmaceuticals, Inc. (ISTA) concerning marketing exclusivity for its naturally sourced hyaluronidase product, Vitrase, support denial of approval of generic enoxaparin (Aventis March 16, 2006, Comments at 3). You note that in the citizen petition, ISTA requested that we reverse our decision to grant a 5-year period of marketing exclusivity for Vitrase and instead grant a 3-year

¹¹⁷ 62 FR 42562 at 42564-42572 (August 7, 1997). We concluded at that time that there was insufficient information to show that the active ingredients of the *synthetic* conjugated estrogen tablets were the same as the active ingredients in the reference listed drug (derived from natural source material — pregnant mare's urine). We could not determine which constituents in the product were responsible for making clinically meaningful contributions to its therapeutic effects. Among other things, we noted that (1) the contribution of the two most abundant estrogens, sodium equilin sulfate and sodium estrone sulfate, to the overall estrogenic potency of Premarin was not well understood; and (2) although the available evidence indicated that sodium Δ 8,9-dehydroestrone sulfate (DHES) was active and contributed to the estrogenic potency, the clinical significance of that contribution had not been determined.

¹¹⁸ Memorandum to Douglas L. Sporn, Director, Office of Generic Drugs from Director, CDER, Subject: Approvability of a Synthetic Version of Premarin, May 5, 1997.
<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm168836.htm>.

¹¹⁹ We also note that your comparison of the 1,6 anhydro ring structure in enoxaparin to the DHES in Premarin is somewhat misplaced because, as stated above, you have not provided any clinical data on the potential significance of the 1,6 anhydro ring structure (whereas there were clinical data regarding DHES and its contribution to Premarin).

exclusivity period (Aventis March 16, 2006, Comments at 2). You also note that in a letter to ISTA dated October 25, 2005, we denied ISTA's request.¹²⁰

You maintain that in rejecting ISTA's request, we relied heavily on the fact that hyaluronidase is not fully characterized (Aventis March 16, 2006, Comments at 2). You also note that our response to ISTA stated that because hyaluronidase was not fully characterized, we did not know whether hyaluronidase products contained any previously approved active moieties. You further state that because enoxaparin, like hyaluronidase, is not fully characterized, there is no way for us to determine whether the active ingredient specified in an ANDA for enoxaparin is the same as the active ingredient in Lovenox.¹²¹

Our hyaluronidase decision focused primarily on the appropriate application of certain exclusivity provisions (including the phrase "previously approved active moiety") to applications for hyaluronidase submitted under section 505(b)(2) of the Act. As you note, we stated in our response to the ISTA petition that "[g]enerally, if the Agency has insufficient information to know whether a product contains a previously approved active moiety, the applicant would be required to submit an NDA containing substantial clinical safety and efficacy data."¹²² We concluded that we had "no information showing that any hyaluronidase products have been adequately characterized to enable the Agency to determine whether they contain a previously approved active moiety."¹²³ We also referred to hyaluronidase as an unusual circumstance and ultimately concluded that it was appropriate to grant 5 years of exclusivity to the applications at issue. Although the hyaluronidase decision you reference focused primarily on the question of exclusivity, we stated in a footnote that "FDA currently would also be unlikely to consider these products [at issue] to have the same active ingredient for purposes of approving an application under section 505(j) of the Act."¹²⁴

Nonetheless, the parallels you attempt to draw between enoxaparin and hyaluronidase are misplaced and not relevant. While both enoxaparin and hyaluronidase are heterogeneous mixtures of molecular entities, these two active ingredients are derived from different origins and are composed of entirely different molecular structures. Enoxaparin consists of a heterogeneous mixture of oligosaccharides produced through alkaline depolymerization of the benzyl ester of heparin derived from porcine intestinal mucosa, whereas hyaluronidase is a mixture of glycosylated protein isoforms (isoenzymes) that is derived from either naturally sourced tissue – ovine tissue (Vitrase) or bovine tissue (Amphadase, Hydase) – or through recombinant means (Hyl-enex).

¹²⁰ Letter to Marvin J. Garrett, Vice President, ISTA Pharmaceuticals, Inc., from Steven K. Galson, FDA, Docket No. 2005P-0134/CP1, October 25, 2005 (Response to ISTA). (The docket number for this citizen petition was changed to FDA-2005-P-0005 as a result of FDA's transition to its new docketing system.)

¹²¹ In a previous comment, you stated that "Aventis has never argued that FDA may not approve a generic Enoxaparin product until Enoxaparin is fully characterized." Aventis October 13, 2004, Comments at 28-29.

¹²² Response to ISTA at 9 (ISTA's petition concerned whether an active moiety had been previously approved for purposes of determining marketing exclusivity under 21 CFR 314.108 for an application submitted under 505(b)(2) of the Act, whereas your petition concerns the sameness of the active ingredient of a generic drug product under § 314.92(a)(1) for an ANDA submitted under section 505(j) of the Act).

¹²³ Response to ISTA at 5.

¹²⁴ Response to ISTA at 11.

For hyaluronidase, we noted that “the active ingredient in [hyaluronidase] has not yet been sufficiently characterized to permit the Agency to conclude that another hyaluronidase product has an identical active ingredient.”¹²⁵ At the time of the decision, we noted that we lacked sufficient information to conclude active ingredient sameness for hyaluronidase. In contrast, enoxaparin has been adequately characterized for naturally sourced generic enoxaparin and there is sufficient information for enoxaparin to conclude that the generic drug product’s active ingredient is the same as Lovenox’s enoxaparin. Based on the available relevant scientific evidence (and the differing structures of the molecular entities that comprise enoxaparin and hyaluronidase), it is reasonable and appropriate for us to take into account their respective molecular diversity and form conclusions and approaches specific to each active ingredient.

E. Current Approval Requirements for ANDAs for Enoxaparin are Scientifically Appropriate and Address the Safety Profile of Enoxaparin.

The North American Thrombosis Forum (NATF), for example, states that current guidelines for generic drug approval may not be applicable for the approval of therapeutic agents that are biologically based. In particular, NATF and other comments state that there is the potential for unanticipated adverse events or immune response, and that clinical testing is essential (February 22, 2010 and March 2, 2010, NATF Comments; May 26, 2010, Society of Hospital Medicine Comment; and May 28, 2010, Victor Tapson, Duke University Medical Center Comment).

It is important that ANDA applicants assess the potential of the generic product to generate a greater immune response as compared to the RLD, Lovenox.¹²⁶ In the case of enoxaparin, an immune response can be generated that may lead to a known adverse event, thrombocytopenia. There is evidence that the immune response resulting in thrombocytopenia is stimulated by the active ingredient. The pathogenesis of this response has been extensively investigated and involves a critical step of association of enoxaparin (or other LWMHs) oligosaccharides to platelet factor 4 (PF4) via a non-specific (sequence independent) electrostatic interaction primarily based on oligosaccharide chain length and charge density.¹²⁷ Therefore, a demonstration of equivalence of molecular diversity of the generic drug product’s enoxaparin to Lovenox’s enoxaparin is a strong indication that the generic enoxaparin would not differ from Lovenox with respect to its immunogenicity. Nonetheless, immune responses are very complex and even when they are stimulated by the active ingredient (as is the case with enoxaparin sodium), they may be influenced by impurities or other substances in the product that may modify the immune response to the active ingredient. Given the safety profile of Lovenox, we believe that, in addition to demonstrating sameness of the generic drug product’s enoxaparin to Lovenox’s enoxaparin, sponsors should submit a comparative assessment of their generic enoxaparin and

¹²⁵ Response to ISTA at 11.

¹²⁶ ANDA applicants are not only required to demonstrate active ingredient sameness, but also to assure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packaging of the drug are adequate to assure and preserve the identity, strength, quality and purity of the drug (see section II.A of this response).

¹²⁷ Greinacher, A. (1995), “Characterization of the Structural Requirements for a carbohydrate based anticoagulant with a reduced risk of inducing the immunological type of heparin-associated thrombocytopenia,” *Thrombosis and Haemostasis* 74:886-892; and Newman, P.M., Swanson, R.L., and Chong B.H. (1998), “Heparin-induced thrombocytopenia: IgG binding to PF4-heparin complexes in the fluid phase and cross-reactivity with low molecular weight heparin and heparinoid.” *Thrombosis and Haemostasis* 80:292-297.

Lovenox for potential impurities that may have an adverse impact with respect to immunogenicity. Based on review of available data, we have determined that it is possible, by satisfying the five criteria and (as a conservative measure) by conducting in vitro and in vivo assays to address impurities, to provide scientifically appropriate assurance that the risk of immunogenicity due to potential impurities in the generic enoxaparin will not be greater than that of Lovenox. In such cases, clinical testing to demonstrate safety and effectiveness is not necessary for enoxaparin sodium injection (see also sections VI.C. and VI.F.). We expect that a generic enoxaparin that meets the requirements for ANDA approval will be therapeutically equivalent to and can be substituted for Lovenox with the expectation that it will produce the same clinical effect and safety profile as Lovenox.

F. Although FDA Regularly Takes Note of the Actions of Other National or International Regulatory Authorities, Those Actions Do Not Constrain Our Decision-Making

You state that the European Committee for Medicinal Products for Human Use held its plenary meeting in June 2006 (Aventis August 25, 2006, Comment at 2). You also state that the meeting report reflects that the Co-coordination Group for Mutual Recognition and Decentralised Procedures has determined that LMWHs should be considered “biological medicinal products.” (Aventis August 25, 2006, Comments at 2). You state that this means that applicants for generic LMWHs in the European Community may not seek approval of their products as generic medicinal products (Aventis August 25, 2006, Comments at 2). Instead, a company seeking approval of a generic LMWH will need to seek approval as a “similar biological medicinal product,” which you state requires the submission of far more data than is submitted in an ANDA (Aventis August 25, 2006, Comments at 2). You also state that the European Medicines Agency’s (EMA’s) Committee for Medicinal Products for Human Use published a draft “Concept Paper on Similar Biological Medicinal Products Containing Low Molecular Weight Heparins – (Non) Clinical Issues” (the “Concept Paper”) (Aventis March 2, 2007, Comments at 2).¹²⁸ You also submitted the “EMA, Committee for Medicinal Products for Human Use (CHMP): Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing [LMWHs]” (EMA Guideline) (Aventis April 14, 2009, Comments at 1). The EMA Guideline recommends in vitro and in vivo pharmacodynamic studies, in vivo toxicological studies, and clinical studies (Aventis April 14, 2009, Comments, Attachment). The EMA Guideline also recommends methods for the detection and monitoring of HIT in the clinical trial.

¹²⁸ You state that according to the draft Concept Paper, the EMA indicates that the assessment of applications for LMWHs is difficult for several reasons including (1) the limited physicochemical characterization of the LMWHs due to the high complexity of the molecules and the limited knowledge about the qualitative and quantitative contribution to safety and efficacy of each fraction and (2) the fact that while the kinetics of LWMH are based upon pharmacodynamic measurements, there is no demonstrated quantitative correlation between pharmacodynamics and clinical efficacy (Aventis March 2, 2007, Comments at 2). You state that for these reasons, the EMA indicates that classical bioequivalence studies are not sufficient to establish therapeutic equivalence between LMWHs (Aventis March 2, 2007, Comments at 2). You state that, in light of these difficulties, the draft Concept Paper recommends drafting a guideline on the (non) clinical aspects of the development and assessment of similar biological products containing LMWHs (Aventis March 2, 2007, Comments at 2). You ask that we give the European decision consideration as we evaluate your petition (Aventis March 2, 2007, Comments at 3). The EMA requested public comment on the draft Concept Paper. We have considered the draft Concept Paper.

Although FDA regularly takes note of the actions of other national or international regulatory authorities, those actions do not constrain our decision-making. The European regulatory authority has different standards and procedures for the review and approval of drugs and biological products. Moreover, although we generally concur with the EMEA conclusion of possible limitations regarding (1) physicochemical characterization of LMWHs, (2) biological and biochemical assays, and (3) demonstration of comparable kinetics based upon the pharmacodynamic measurements, we would not draw a conclusion of active ingredient sameness for enoxaparin based solely upon equivalence of physicochemical properties (section III.A), equivalence of biological and biochemical assays (section III.D), and equivalence of in vivo pharmacodynamic profiles (section III.E).

Rather, we can draw a conclusion of active ingredient sameness based upon five criteria, two of which were not specifically considered by the EMEA Guideline, including equivalence of heparin source material and mode of depolymerization (section III.B) and equivalence of disaccharide building blocks, fragment mapping, and sequences of oligosaccharide species (section III.C). As explained earlier in this response, we have concluded, based on the current scientific evidence, that if an ANDA applicant meets the five specified criteria, this information enables us to conclude that a generic drug product's enoxaparin is the same active ingredient as Lovenox's enoxaparin. In such instances, an ANDA applicant would meet the requirement for active ingredient sameness under the Act and FDA regulations.

Further, we note that the EMEA Guideline has set forth guidelines for LMWH products that contain a *similar* (as opposed to the same) active ingredient as that contained in another already marketed LMWH product. Because the proposed product in Europe will contain an active ingredient that is *similar* (as opposed to the same), it may exhibit important differences from the active ingredient in the already marketed LMWH product. Accordingly, there might be uncertainties regarding the safety and effectiveness of the proposed similar product. Thus, sponsors under the EMEA framework are expected to provide clinical studies showing comparable effectiveness to the proposed similar LMWH product as well as clinical data showing comparable safety, including with respect to HIT.

This contrasts with the approach taken by FDA. In this petition response, the Agency has set forth the basis upon which we can conclude that a generic enoxaparin contains the **same** active ingredient as the RLD, Lovenox. Because an ANDA for generic enoxaparin must contain sufficient data demonstrating that the active ingredient is the **same** (as opposed to *similar* in the EMEA framework) as Lovenox's enoxaparin, and because the Agency will carefully evaluate impurities in the generic product, particularly with respect to their adjuvant effect on immunogenicity, there is no underlying scientific need for the ANDA sponsor to duplicate clinical studies to demonstrate safety (such as with respect to HIT) and effectiveness.

Furthermore, although the EMEA Guideline describes the need for clinical studies in order to demonstrate comparable effectiveness to the proposed similar LMWH, the Agency notes the five criteria described above in section III of this response are more sensitive to differences between two enoxaparin products than the clinical studies recommended in the EMEA Guideline. For example, a double blind clinical study showed that the rating of deep-vein thrombosis after

orthopedic surgery was equivalent for two LMWHs: enoxaparin and tinzaparin.¹²⁹ However, as discussed under section III.B of this response, despite such evidence of equivalence of clinical effectiveness, enoxaparin and tinzaparin would not be considered to have the same active ingredient, given that they are manufactured via different modes of depolymerization,¹³⁰ have different anti-IIa/anti-Xa ratios,¹³¹ have different proportions of sulfated and non-sulfated $\Delta^{4,5}$ -uronate structures at the non-reducing end of the oligosaccharide chains,¹³² and have different pharmacokinetics,¹³³ among other differing characteristics.

We considered whether we should expect ANDA applicants of generic enoxaparin to conduct any studies recommended in the EMEA's guideline other than the ones we are recommending in section III of this response. Based on our scientific experience and expertise, and relevant scientific information, we have determined that no other studies are needed for approval of a generic enoxaparin.

VII. CONCLUSION

For the reasons stated above, we conclude that the following five criteria are sufficient to demonstrate sameness of the enoxaparin active ingredient:

- Equivalence of physicochemical properties
- Equivalence of heparin source material and mode of depolymerization
- Equivalence in disaccharide building blocks, sequence of oligosaccharide species, and fragment mapping
- Equivalence in biochemical and biological assays
- Equivalence of in vivo pharmacodynamic profile

Meeting these specified active ingredient sameness criteria will ensure that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent, including with respect to the 1,6 anhydro ring structure. Equivalent molecular diversity demonstrates enoxaparin sameness. The Act and FDA regulations require ANDA applicants to demonstrate (among other things) that the generic drug product's active ingredient is the same as the RLD's active ingredient and to demonstrate that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure

¹²⁹ Planes, A. et al. (1999), "Prevention of Deep Vein Thrombosis after Hip Replacement: Comparison between Two Low-Molecular Heparins, Tinzaparin and Enoxaparin," *Thrombosis and Haemostasis* 81: 22-25.

¹³⁰ Whereas enoxaparin is manufactured by chemical alkaline β -elimination, tinzaparin is manufactured via enzymatic β -elimination.

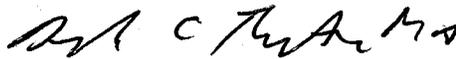
¹³¹ For tinzaparin anti-IIa/anti-Xa ratios varies between 1.5 and 2.5 (see footnote 33), and for enoxaparin this ratio varies between 3.3 and 5.3 (see footnote 54).

¹³² This is because in the mode of depolymerization by enzymatic β -elimination, cleavage takes place exclusively in heparin polysaccharide chains at sites where the disaccharide unit has the 2-O-sulfo-uronic acid structure, whereas in the mode of depolymerization by chemical (alkaline) β -elimination, cleavage occurs without preference for the presence or absence of a 2-O-sulfo group in the iduronic acid structure. See Linhardt, R.J., Gunay, N.S. (1999), "Production and Chemical Processing of Low Molecular Weight Heparin," *Semin Thromb Hemost* 25 S3:10.

¹³³ Eriksson, B.I. et.al., (1995), "A comparative study of three low-molecular weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers," *Thrombosis and Haemostasis* 73: 398-401.

and preserve its identity, strength, quality, and purity. You ask that an ANDA applicant use a manufacturing process equivalent to Aventis's manufacturing process. Insofar as an equivalent manufacturing process for enoxaparin could be interpreted only to be one in which every step of the manufacturing process, including process conditions, are identical to those of Aventis's manufacturing process for Lovenox, your request is denied. We also are denying your requests that we require an ANDA applicant to completely characterize enoxaparin by isolating, purifying, and sequencing each of its unique polysaccharide chains and determining their relative abundance or to conduct clinical trials to establish the safety and effectiveness of its product.

Sincerely,

A handwritten signature in black ink, appearing to read "D. C. Throckmorton".

Douglas Throckmorton, M.D.
Deputy Director
Center for Drug Evaluation and Research