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CITIZEN PETITION SUPPLEMENT (03P-0064/CP1)

The undersigned, on behalf of Aventis Pharmaceuticals Inc. ("Aventis"), a subsidiary of Aventis SA, submits this Supplement to its Citizen Petition filed February 19, 2003 (03P-0064/CP1) (the "Citizen Petition"). The Citizen Petition requests that the Commissioner of Food and Drugs withhold approval of any abbreviated new drug application ("ANDA") for a generic version of Lovenox[®] (enoxaparin sodium injection) ("enoxaparin") until the conditions set forth in the Citizen Petition are satisfied. This Supplement is submitted under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355 (b) and (j)) and 21 C.F.R. § 10.30.

Following a background discussion in Part I, this Supplement provides the Agency with new discoveries in support of the Citizen Petition. Through continued testing of the complex enoxaparin macromolecular mixture, Aventis has recently discovered ATIII binding sequences that are highly dependent on Aventis' manufacturing process for enoxaparin. As will be explained in Part II below, these newly discovered sequences constitute an additional structural fingerprint of enoxaparin that may contribute to the ATIII dependent anti-thrombotic activity of enoxaparin.

In addition, through its continued testing, Aventis has discovered additional anti-coagulation and non-anti-coagulation contributions made to enoxaparin's overall pharmacological effect by the 1,6 anhydro ring structure (originally introduced in the Citizen Petition). Part III of this Supplement discusses those new discoveries in detail. Specifically, Aventis compared the pharmacological activity of six new enoxaparin oligosaccharide fractions containing the 1,6 anhydro ring

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structure in an amount between 15% to 25% to six oligosaccharide fractions containing only minimal concentrations of the 1,6 anhydro ring structure (< 7%).

Each of the new discoveries in Parts II and III supports the actions requested by Aventis in the Citizen Petition. In addition, Part IV briefly addresses a recent comment filed to this docket by Hyman, Phelps & McNamara, P.C. In particular, Part IV points out significant flaws in that comment's legal analysis.

I. Background

A. The Citizen Petition

Aventis filed the Citizen Petition on February 19, 2003. Aventis had found, through recent advances in analytical technology, that enoxaparin's chemical structure is marked by a 1,6 anhydro ring structure that is highly dependent on Aventis' manufacturing process. The Citizen Petition described preclinical tests demonstrating that the 1,6 anhydro ring structure makes several important contributions to enoxaparin's overall pharmacological effect. Many of these contributions likely bear relevant clinical significance.

The Citizen Petition noted that further testing may reveal additional contributions made by the 1,6 anhydro ring structure or contributions by the other structural fingerprints identified in enoxaparin. It also pointed out that about 30% of enoxaparin has not yet been fully characterized, leading to the possibility that additional structural fingerprints with pharmacological activity will be discovered in the future.

Because enoxaparin's structural fingerprints are process dependent, they might not be present, or present in the proper range of concentrations, in a generic product not employing a manufacturing process equivalent to Aventis' manufacturing process for enoxaparin. Such a product might exhibit different pharmacological activity than enoxaparin. As a result, Aventis filed the Citizen Petition with the following actions requested:

1. Until such time as enoxaparin has been fully characterized, Aventis requests that FDA refrain from approving any ANDA citing Lovenox[®] as the reference listed drug unless the manufacturing process used to create the generic product is determined to be equivalent to Aventis' manufacturing process for enoxaparin, or the application is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials.
2. Aventis also requests that FDA refrain from approving any ANDA citing Lovenox[®] as the reference listed drug unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15% and 25% of its polysaccharide chains.

As will be seen in Parts II and III, Aventis can now point to additional discoveries including (1) the process dependence of ATIII binding site distribution in enoxaparin oligosaccharide fractions, with a particular focus on ATIII binding compounds in the octasaccharide fractions, and (2) anti-coagulation and non-anti-coagulation contributions made by newly studied oligosaccharide fractions of enoxaparin containing the 1,6 anhydro ring structure in an amount between 15% to 25%. Each of these discoveries provides additional support for the two actions requested in the Citizen Petition.

B. Low Molecular Weight Heparins

As discussed in the Citizen Petition, enoxaparin is a low molecular weight heparin ("LMWH"). Like all LMWHs, enoxaparin comes from unfractionated heparin source material ("unfractionated heparin"). Unfractionated heparin is a highly complex collection of molecules composed of linear polysaccharide (glycosaminoglycan) chains of varying chemical structure on a central protein.¹

To manufacture LMWH, the larger unfractionated heparin chains are broken down into smaller chains through varying processes of chemical or enzymatic depolymerization. Each LMWH manufacturer uses a distinct depolymerization process. This results in LMWHs with distinct chemical structures and, therefore, differing pharmacological activity and approved indications for clinical use.² For enoxaparin, Aventis employs a specific, tightly controlled, validated process of chemical depolymerization.

Like unfractionated heparin, LMWHs inhibit coagulation by binding to antithrombin III ("ATIII" or "AT"), a plasma protein synthesized in the liver and other endothelial cells. LMWH interaction with ATIII is mediated by a specific pentasaccharide sequence that is distributed across approximately 15% to 25% of LMWH polysaccharide chains. ATIII inactivates serine proteases, most notably factor IIa (thrombin) and factor Xa, within the coagulation cascade.³

C. Enoxaparin

Enoxaparin is a widely prescribed LMWH in the United States. It is indicated for the prophylaxis of DVT during abdominal surgery, hip replacement surgery, knee replacement surgery, and in patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness. It is also

¹ See Citizen Petition, Declaration of Robert J. Linhardt, Ph.D.

² See Linhardt RJ, et al. Production and chemical processing of low molecular weight heparins. *Seminars in Thrombosis and Hemostasis* 1999; 25(3 Supp.):5-16.

³ See Weitz JI. Low-molecular-weight heparins. *N. Eng. J. Med.* 1997; 337:688.

indicated for prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin. Enoxaparin is the first LMWH indicated for inpatient treatment of acute DVT (with or without pulmonary embolism) and outpatient treatment of acute DVT (without pulmonary embolism) (in both cases, when administered in conjunction with warfarin sodium).

Aventis' manufacturing process for enoxaparin creates a highly complex collection of macromolecules with a chemical structure that is unique among currently approved LMWHs. This structure is marked by polysaccharide sequences and structural fingerprints that are highly sensitive to Aventis' manufacturing process.⁴ Limitations on current analytical technology, however, have prevented Aventis from completely characterizing this complex collection of macromolecules.

D. The 1,6 Anhydro Ring Structure

Finally, as described in the Citizen Petition, one of enoxaparin's distinct structural fingerprints is a 1,6 anhydro ring (bicyclic) structure found at the reducing end of all oligosaccharides bearing 6-O-sulfo groups on the glucosamine moiety. Formation of the 1,6 anhydro ring structure occurs because of Aventis' specific manufacturing process during β -elimination depolymerization. The 1,6 anhydro ring structure is found at the reducing ends of between 15% and 25% of enoxaparin's polysaccharide chains.⁵

II. Process Dependent ATIII Binding Oligosaccharides

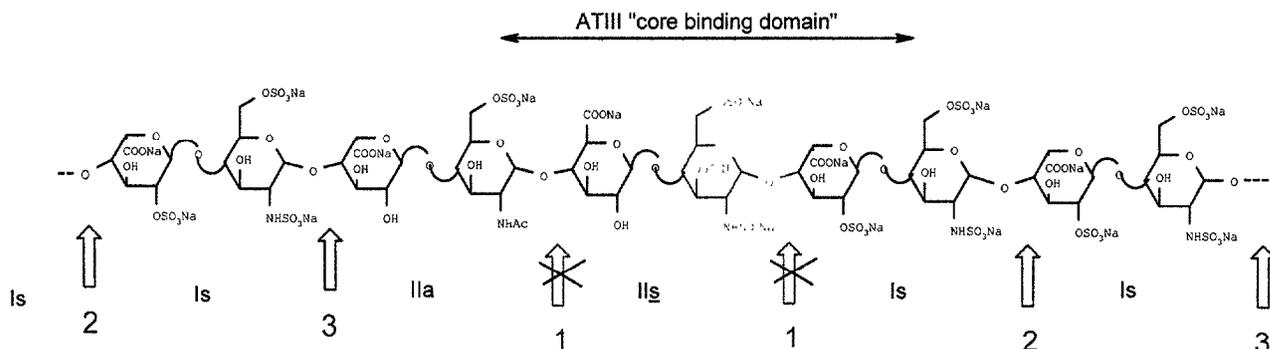
Aventis is submitting this Supplement to point out new discoveries regarding enoxaparin's distinct chemical structure. First, Aventis has learned that the structure of the ATIII binding sites in enoxaparin is process dependent, resulting in the discovery of yet another enoxaparin structural fingerprint. As part of its effort to further understand the contributions made by the 1,6 anhydro ring structure, Aventis studied oligosaccharides that have an affinity for ATIII. These studies demonstrate that process dependent variations in disaccharide sequence within a given oligosaccharide affect the oligosaccharide's affinity for ATIII. Thus, two oligosaccharides of the same chain length may demonstrate different ATIII binding potency, which is not necessarily correlated in the same way to the *in vitro* anti-Xa activity. These sequence variations may cause differences in the half-lives of the anti-Xa activity, leading to different overall anti-coagulation profiles.

To demonstrate the different sequence variations that can occur in a given oligosaccharide, the following diagram shows the positions at which the

⁴ Aventis' manufacturing process for enoxaparin is described in the Citizen Petition, Part III.A.6.

⁵ See Citizen Petition, Declaration of Christian Viskov, Ph.D.

antithrombin III domain of the unfractionated chain may be cleaved during a step of the manufacturing process called depolymerization:



To demonstrate the process dependency of the ATIII binding oligosaccharide, Aventis focused its analytical studies on the octasaccharide fraction of enoxaparin as a model representing the best compromise between structural simplicity and significant affinity for ATIII, as expressed by anti-Xa activity.⁶ In enoxaparin's octasaccharide fraction, there is no evidence that depolymerization occurs at the 1 position. Differences in the selectivity between positions 2 and 3 appear to be dependent on the strength of the base and steric hindrance. Thus, the temperature of the reaction will influence the ratio between the sequences resulting from cleavage either at the 2-2 or the 3-3 positions.⁷ Consequently, Aventis' manufacturing process creates the following three main process dependent octasaccharide sequences:

- Δ IIa-II β -Is-Is is the result of the position 3-3 cleavage of the macromolecule model
- Δ IIa-II β -Is-Is (1,6 anhydro) is the result of the position 3-3 cleavage, followed by 1,6 anhydro formation
- Δ Is-IIa-II β -Is: is the result of the position 2-2 cleavage⁸

The chemical structures of these oligosaccharide fractions were confirmed by NMR spectroscopy.⁹

⁶ This fraction was isolated by Gel Permeation Chromatography and is identical to the WSD 3093 Octasaccharides. See *infra* Table 2.

⁷ See Supplemental Declaration of Christian Viskov, Ph.D.

⁸ See Supplemental Declaration of Christian Viskov, Ph.D.

⁹ See Appendix A.

Aventis measured the affinity of these three octasaccharides toward ATIII, using a hexasaccharide and the synthetic pentasaccharide as reference compounds. The affinity of the octasaccharide to human ATIII was determined by measuring the increase of the fluorescence. The dissociation constant (Kd) was calculated from the slope and saturation point of the curve. The anti-Xa activity was assessed in buffer milieu. Results of this study (covering two separate sets of experiments) are summarized in Table 1 below. Details of the two experiments are attached hereto as Appendix B:

Table 1: Dissociation Constants and Anti-Xa Activity

<i>Compound</i>	<i>Dissociation Constant (Kd in nM) 1st series</i>	<i>Dissociation Constant (Kd in nM) 2nd series</i>	<i>Anti-Xa Activity% *</i>
Octa Δ I _{IIa} -II _S -Is-Is	34.1; SE = 58%	13; SE = 70%	133
Octa Δ I _{IIa} -II _S -Is-Is (1,6)	32.4; SE = 117%	18; SE = 30%	121
Octa Δ Is-II _a -II _S -Is	334.0; SE = 82%	120; SE = 18%**	113
Hexa Δ I _{IIa} -II _S -Is	62.8; SE = 63%	30; SE = 23%	124
Penta SR90107/ORG31540	19.0; SE = 57%	20; SE = 39%	100

SE: Standard Error

* The anti-Xa results were normalized on the pentasaccharide.

** Measurement repeated four times.

For the second set of experiments, the titration was continued far above the saturation point, which was an improvement resulting in lower standard errors in most cases. The reason for such standard errors is that the figures obtained by the curve fitting are very susceptible to small changes in the values of the points, especially for points in the region close to saturation. The improvement did not change the relative affinities of the compounds but rather improved precision in the measurement of the overall series.¹⁰

This study demonstrates that the Δ I_{IIa}-II_S-Is-Is octasaccharide and the Δ I_{IIa}-II_S-Is-Is (1,6 anhydro) octasaccharide have ATIII affinity similar to that of the pentasaccharide and anti-Xa activities of 133% and 121% of the pentasaccharide, respectively. The Δ Is-II_a-II_S-Is octasaccharide, however, behaved significantly differently. As seen in Table 1, despite a mean ATIII affinity approximately six to seventeen times lower than the pentasaccharide, its anti-Xa activity (113%) is still higher than the pentasaccharide. These findings demonstrate that the different

¹⁰ See Appendix B.

octasaccharide variants in enoxaparin do not have identical *in vitro* anti-Xa activity and there can be considerable variation in affinity for ATIII.

As discussed above, LMWHs act as anti-coagulants by binding with ATIII. The anti-coagulant effect in man is, moreover, likely a function of both the anti-Xa activity and the affinity for ATIII. Oligosaccharide fractions with a lower affinity for ATIII (due to sequence variations) may form weaker bonds with ATIII, resulting in different duration of the bond *in vivo*, and a different half-life of anti-Xa activity. This could result in anti-coagulant effects that differ significantly more than a superficial assessment of anti-Xa activity might suggest. Importantly, although Aventis has tested only octasaccharide fractions, which demonstrate varying ATIII affinities and differences in anti-Xa activity that do not correlate with the varying of ATIII affinities, this phenomenon is probably not limited to those fractions. Differences in the selection between the 2-2 and 3-3 positions demonstrated in the octasaccharide fraction likely create similar process dependent sequence variations in all of the oligosaccharide types (above the hexasaccharides) that comprise enoxaparin.¹¹

Because these sequence variations are process dependent, a product claiming to be enoxaparin that does not employ a manufacturing process equivalent to Aventis' process may not contain enoxaparin's oligosaccharide ensemble (the octasaccharides being one example) resulting in a different set of affinities for ATIII. Such a product might have an anti-Xa/anti-IIa ratio that is similar to enoxaparin, but would be expected to demonstrate a different profile of bleeding safety and antithrombotic effectiveness. As a result, the discoveries reported in this Part II add further strength to the arguments made in the Citizen Petition.

III. New Findings for the 1,6 Anhydro Ring Structure

Second, Aventis has discovered new anti-coagulation and non-anti-coagulation contributions made by the 1,6 anhydro ring structure. Since the submission of the Citizen Petition, Aventis has conducted further testing to evaluate the relevance of fractions containing the 1,6 anhydro ring structure. This additional testing has both confirmed previous findings and revealed further significant anti-coagulation and non-anti-coagulation contributions made by the 1,6 anhydro ring structure. These newly discovered contributions may also have clinical significance.

Specifically, through a series of assays, Aventis compared the pharmacological activity of six enoxaparin oligosaccharide fractions to six oligosaccharide fractions of the same length from an LMWH that was similar to enoxaparin in molecular weight, anti-Xa activity, and anti-Xa/anti-IIa ratio, but contained the 1,6 anhydro ring structure in only minimal (< 7%) amounts (the "< 7% 1,6 anhydro LMWH"). The six fractions from enoxaparin were labeled "WSD 3093."

¹¹ See Supplemental Declaration of Christian Viskov, Ph.D.

The six fractions from the < 7% 1,6 anhydro LMWH were labeled “DIA 2844.” The following table identifies each of the tested fractions (the “WSD/DIA Fractions”):

Table 2: Species Nomenclature

<i>Oligosaccharides (15-25% 1,6 anhydro)</i>	<i>Oligosaccharides (< 7% 1,6 anhydro)</i>
WSD 3093: Hexasaccharides	DIA 2844: Hexasaccharides
WSD 3093: Octasaccharides	DIA 2844: Octasaccharides
WSD 3093: Decasaccharides	DIA 2844: Decasaccharides
WSD 3093: Dodecasaccharides	DIA 2844: Dodecasaccharides
WSD 3093: < Hexadecasaccharides	DIA 2844: < Hexadecasaccharides
WSD 3093: ≥ Hexadecasaccharides	DIA 2844: ≥ Hexadecasaccharides

The results of these additional studies are summarized below.

A. Anti-coagulant Activity of Oligosaccharide Fractions

Aventis studied the WSD/DIA Fractions to evaluate their relative *in vitro* effect on coagulation. Three studies were performed (see Appendices C, D, and E)¹²:

- 1) Anti-Xa and anti-IIa activity in plasma and anti-coagulation activity in plasma were measured.
- 2) Thrombin generation was assessed using the Thrombogram-Thrombinoscope assay in platelet rich plasma.
- 3) Thromboelastography was performed on whole blood.

In all three studies, only the DIA ≥ hexadecasaccharide and WSD ≥ hexadecasaccharide fractions showed a difference in anti-coagulant activity, with the DIA fraction showing a greater anti-coagulant activity. These anti-coagulation results suggest additional important contributions of the 1,6 anhydro ring structure to enoxaparin’s pharmacological effect. The presence of the 1,6 anhydro ring structure appears to change the anti-coagulant potency and antithrombotic effect of enoxaparin, which may, among other things, lead to different bleeding profiles in patients. Thus, a product claiming to be enoxaparin that did not contain the 1,6 anhydro ring structure (or contained a different concentration of it) might exhibit a different anti-coagulant and

¹² The report by Reifert P & Gojowczyk G, et al., attached hereto as Appendix C refers to “non-anhydro counterparts” of the six tested enoxaparin (15-25% 1,6 anhydro) oligosaccharides. The report should refer to (and actually discusses testing of) oligosaccharides derived from the < 7% 1,6 anhydro LMWH.

antithrombotic profile than does enoxaparin, despite having a similar anti-Xa/anti-IIa ratio. This could be particularly significant for patients undergoing multiple antithrombotic therapies and/or percutaneous coronary intervention, because it is particularly important that enoxaparin be properly and precisely dosed in this population.

B. Fibroblast Growth Factor Differentiation

Acidic fibroblast growth factor ("aFGF") has been shown to induce neoangiogenesis in the ischemic myocardium in animals and patients with coronary heart disease.¹³ Neoangiogenesis would alleviate and ameliorate diseases characterized by microvascular insufficiency such as ischemic heart disease.¹⁴ Unfractionated heparin and LMWHs stabilize the active conformation of aFGF so that it becomes less sensitive to acid degradation or heat denaturation. The Citizen Petition cited studies demonstrating that the 1,6 anhydro ring structure influences enoxaparin's interaction with aFGF. These non-anti-coagulation studies further showed that if the concentration of the 1,6 anhydro ring structure is altered, then interaction with aFGF is affected.¹⁵

Since submitting the Citizen Petition, Aventis has conducted further non-anti-coagulation studies to assess the effect of the 1,6 anhydro ring structure on enoxaparin's interaction with aFGF. Aventis studied the WSD/DIA Fractions and individually assessed each oligosaccharide's interaction with aFGF using a BHK-21 cell line (baby hamster kidney cells). Cell proliferation was then quantified by use of radioactive thymidine incorporation. Details of this study are attached hereto as Appendix F.

Aventis found that the concentration of the 1,6 anhydro ring structure affects a given oligosaccharide's interaction with aFGF. At the lower chain lengths (6 - 10 saccharides), WSD (with 15-25% 1,6 anhydro ring structure) oligosaccharides tended to have a higher aFGF activity than DIA (with < 7% 1,6 anhydro ring structure) oligosaccharides of the same length. By contrast, for higher chain lengths, DIA oligosaccharides tended to have a higher aFGF activity than WSD oligosaccharides of the same length.¹⁶

¹³ Schumacher B, et al. Induction of neoangiogenesis in ischemic myocardium by human growth factors: First clinical results of a new treatment of coronary heart disease. *Circulation* 1998; 97:645.

¹⁴ See Isner JM. Angiogenesis for revascularization of ischemic tissues. *European Heart J.* 1997; 18:1.

¹⁵ Citizen Petition at III.B.3.

¹⁶ See Appendix F.

These non-anti-coagulation results confirm the studies discussed in the Citizen Petition. The presence of the 1,6 anhydro ring structure in enoxaparin oligosaccharides affects enoxaparin's interaction with aFGF. Thus, 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. This could impact patients with coronary disease where hypoxic myocardium needs formation of new vessels to limit ischemic injury.¹⁷

C. Smooth Muscle Cell Proliferation

Smooth muscle cell (SMC) proliferation is involved in coronary disease. It is responsible for coronary artery narrowing, which can reduce coronary blood flow and provoke myocardial ischemia. SMC proliferation is also involved in restenosis, which occurs after balloon induced coronary dilatation.¹⁸ So, inhibition of SMC proliferation may be beneficial for prevention or treatment of coronary diseases such as unstable angina or myocardial infarction, through improvement of coronary artery blood flow.

The Citizen Petition presented studies demonstrating that the 1,6 anhydro ring structure contributes to enoxaparin's inhibition of SMC proliferation.¹⁹ Since it submitted the Citizen Petition, Aventis has conducted further non-anti-coagulation studies on the effect of the 1,6 anhydro ring structure. Aventis compared the WSD/DIA Fractions in an *in vitro* study on smooth muscle cell proliferation isolated from explants of human internal mammary artery samples. Details of this study are attached hereto as Appendix G.

This new study shows that oligosaccharide WSD Fractions (containing the 1,6 anhydro ring structure in a 15-25% concentration) have a greater inhibitory effect on SMC than do DIA Fractions of equal length (with < 7% of the 1,6 anhydro ring structure). For example, in chains with less than 16 saccharide units, the WSD oligosaccharides have a five to six times greater inhibitory effect than do DIA oligosaccharides of the same length.²⁰ In light of these findings, 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 proliferation.

¹⁷ See Schumacher, *supra* note 13.

¹⁸ See Pickering JG, et al. Proliferative activity in peripheral and coronary atherosclerotic plaque among patients undergoing percutaneous revascularization. *J. Clin. Invest.* 1993; 91:1469-80.

¹⁹ Citizen Petition at III.B.3.

²⁰ See Appendix G.

D. Additional Studies

Aventis studied *in vitro* the effect of the WSD/DIA Fractions on heparin-induced thrombocytopenia (“HIT”), a potentially fatal complication of heparin therapy occurring in 1% to 5% of patients. In this non-coagulation study, summarized in Appendix H, Aventis found that the 1,6 anhydro ring structure does not modify enoxaparin’s HIT cross-reactivity. This suggests that the 1,6 anhydro structure in a concentration of 15-25% does not increase the risk of HIT.

Aventis has also found that *in vitro* the 1,6 anhydro ring structure has no relation to enoxaparin’s positive effect on P-selectin mediated platelets/neutrophils interaction. Details of this study are attached hereto as Appendix I.

IV. The Hyman Comment

On October 17, 2003, Hyman, Phelps & McNamara, P.C. submitted a comment (03P-0064/C1) (the “Hyman Comment”) urging FDA to deny the Citizen Petition. While the arguments made in the Hyman Comment are adequately addressed in the Citizen Petition, two arguments in particular are plainly erroneous and warrant further discussion. The first of these involves the scope and applicability of the case of *Serono Labs. v. Shalala*.²¹ The second involves the use of European pharmacopeial standards of identity for enoxaparin.

A. *Serono Labs. v. Shalala*

The Hyman Comment argues that *Serono* compels FDA to deny the Citizen Petition. We disagree. The Hyman Comment incorrectly reasons that *Serono* creates a rigid standard for evaluating the “sameness” requirement as applied to a generic copy of an innovator drug. It then wrongly argues that, under the circumstances presented by enoxaparin, *Serono* requires FDA to find that the sameness requirement can be met by a generic without using a manufacturing process that is equivalent to Aventis’ manufacturing process for enoxaparin.

Serono involved a citizen petition, submitted by Serono Laboratories, Inc., regarding generic competitors for Pergonal. Pergonal is a menotropin, with two active ingredients, follicle-stimulating hormone (“FSH”) and luteinizing hormone (“LH”).²² In 1990, Lederle Parenterals, Inc. submitted an ANDA for Repronex, a generic form of Pergonal. Repronex contained FSH, but in a different isoform than that found in Pergonal. Serono argued in its 1992 citizen petition that, because of this

²¹ 158 F.3d 1313 (D.C. Cir. 1998).

²² *Id.*

difference in isoforms, Repronex did not contain the “same” active ingredient as Pergonal and that FDA should not approve Repronex’ ANDA.²³

The chemical structure of FSH roughly consists of two components: (1) a protein backbone with a specific amino acid sequence and (2) carbohydrate side chains. FDA determined that the protein backbones and the amino acid sequences of the generic product were identical to the referenced drug. There were, however, natural variations in the carbohydrate chains due to a phenomenon known as “microheterogeneity.” The FDA found that this isoform variation “was not ‘clinically significant for the product’s intended uses’ and therefore did not preclude a ‘sameness’ finding for purposes of 21 U.S.C. § 355(j).”²⁴ After Serono sued FDA in federal district court, the United States Court of Appeals for the District of Columbia held that FDA was entitled to deference in its interpretation of the meaning of the word “same” in the statute. The Hyman Comment concludes that the D.C. Circuit’s holding in *Serono* compels the FDA to deny Aventis’ Citizen Petition.

The Hyman Comment fundamentally misunderstands the D.C. Circuit’s holding in *Serono*, as well as FDA’s underlying determination, in several respects. First, with Pergonal, FDA’s determination regarding isoform variations in the carbohydrate side chains hinged on FDA’s conclusion that these variations “demonstrated no differences in safety and efficacy” and were therefore not clinically significant for Pergonal’s intended use.²⁵ Had FDA concluded that the isoform variations were significant, FDA could not have approved the generic product based only on the same protein backbone. Essentially, FDA determined that “sameness” does not require that the active ingredient in the generic be absolutely identical to that of the pioneer. It is sufficient that the two active ingredients be identical in all important respects. Thus, FDA drew a distinction between “absolute” identity and “pharmacological” identity. The Citizen Petition and this Supplement point out that any product that claims to be enoxaparin that does not contain enoxaparin’s structural fingerprints will likely not be pharmacologically identical to enoxaparin.

Second, the court’s deference to FDA’s determination does not create a judicial standard for evaluating sameness. As stated in *Serono*, the statute must be read in the context of the drug or category of drug at issue.²⁶ Pergonal and enoxaparin are very different products. Pergonal has defined and characterized active ingredients; enoxaparin has not yet been fully characterized. Pergonal has natural variations due to microheterogeneity; enoxaparin’s 1,6 anhydro ring structure and other fingerprints are

²³ *Id.*

²⁴ *Id.* at 1317.

²⁵ *Id.* at 1320.

²⁶ *Id.* at 1319.

present as a result of Aventis' manufacturing process. Isoform variations in generic Pergonal had no effect on the drug's safety and effectiveness profile; enoxaparin's fingerprints have *in vitro* significance and may have clinical significance. Pergonal is used to treat infertility; enoxaparin is used to treat life-threatening conditions associated with thrombosis where the appropriate effective amount of the product is crucial to patient safety.

The court's holding in *Serono* does not alter the fact that FDA must evaluate each drug independently, making a case-by-case determination regarding sameness. The court held only that (a) the Agency can base "sameness" under the FDCA on pharmacological identity, rather than absolute identity, and (b) FDA's scientific judgments regarding pharmacological identity are entitled to a degree of deference from the courts. The Court of Appeals reversed the District Court because it felt that the District Court had not afforded the Agency's scientific judgments sufficient deference.

Unlike the isoform variations at issue in *Serono*, Aventis' Citizen Petition and this Supplement demonstrate that variations in enoxaparin's polysaccharide chains can result in differences in pharmacological effects that have *in vitro* significance and may have clinical significance. As a result, FDA should not approve a generic enoxaparin without assuring that enoxaparin's structural fingerprints (both discovered and undiscovered) are present in the generic.²⁷ As pointed out in the Citizen Petition, because these fingerprints are dependent upon the manufacturing process employed to create enoxaparin, FDA can assure sameness only by (a) requiring that any generic use a manufacturing process that is equivalent to Aventis' manufacturing process for enoxaparin or (b) providing proof of equivalent safety and effectiveness as demonstrated through clinical trials. The court's decision in *Serono* does not require a different result.

B. Pharmacopeial Standards

The Hyman Comment points out that Aventis has, in the past, analyzed its enoxaparin product for various factors contained in European pharmacopeial standards, such as molecular weight, anti-Xa activity, and free sulfates. It claims that Aventis has not, traditionally, evaluated enoxaparin according the presence of the 1,6

²⁷ The Hyman Comment also attempts to distinguish enoxaparin from the Premarin situation (Hyman Comment p.10), by claiming that Premarin was a mixture of active drugs while enoxaparin contains only one active ingredient. This misses the point of the Citizen Petition, which is that enoxaparin is not fully defined and is a complex collection of polysaccharide macromolecules composed of a number of polysaccharides that may each contribute to the global effect of enoxaparin. The complex collection of polysaccharide macromolecules taken as a whole, is, therefore, the active ingredient of enoxaparin. Hence, the Premarin example is both relevant and applicable.

anhydro ring structure or other structural fingerprints identified in the Citizen Petition. The Hyman Comment argues, therefore, that a generic should not be required to establish the presence of these fingerprints if Aventis itself does not. The Hyman Comment suggests that to do so would be to hold generic manufacturers “to a higher standard” than the Agency holds the pioneer.

This argument represents a fundamental misunderstanding of the Citizen Petition. As discussed at length in that document, Aventis does assure the presence of both the 1,6 anhydro ring structure and all of the other fingerprints identified in the Citizen Petition and Supplement. These fingerprints are dependent on, and are a function of, Aventis’ specific manufacturing process for enoxaparin. Aventis assures that the 1,6 anhydro ring structure and the remaining fingerprints are present at the appropriate levels in enoxaparin by maintaining a specific, tightly controlled, validated process of chemical depolymerization. Therefore, far from asking that generics be held to a higher standard, the Citizen Petition asks only that FDA hold generics to the same standard as Aventis, by requiring generic manufacturers to employ an equivalent manufacturing process.

Although Aventis’ manufacturing process may create some *de minimus* batch-to-batch variation in enoxaparin’s polysaccharide side chains, this variation results only in slight changes in the concentration of certain structural fingerprints, not changes in the presence or absence of these fingerprints.²⁸ For example, batch-to-batch variation in enoxaparin results in a concentration range for the 1,6 anhydro ring structure of 15-25%. Batch-to-batch variation in the pioneer drug, however, does not preclude FDA from finding that a generic is not the same as the pioneer. In the case of the menotropins, for example, FDA stated that the generic could be considered the same as the pioneer only “as long as ... the degree of batch-to-batch variation in isoforms is no different than that in Pergonal itself.”²⁹ Unlike the case of the menotropins, failure to use a manufacturing process equivalent to Aventis’ process could result in variations in the structure or composition of the generic that are different or greater than enoxaparin’s batch-to-batch variations.

Additionally, the mere existence of a European Pharmacopeia or British Pharmacopeia – or any other compendia standard – should not dictate that a regulatory agency must approve a request for market authorization based solely on that monograph. Even the *Serono* case states that, in some cases, the FDA may prescribe additional standards that are material to the product’s sameness.³⁰ Certainly, for the reasons stated in the initial Citizen Petition and herein, this case requires additional standards.

²⁸ See Supplemental Declaration of Christian Viskov, Ph.D.

²⁹ *Serono*, 158 F.3d at 1319.

³⁰ *Id.* at 1322, n.3 (quoting 57 Fed. Reg. 17950, 17959).

V. Conclusion

The Citizen Petition and this Supplement demonstrate that the 1,6 anhydro ring structure makes significant anti-coagulation and non-anti-coagulation contributions to enoxaparin's pharmacological effect that may have clinical significance. In addition, this Supplement has identified a new fingerprint, the process dependent ATIII binding sites in enoxaparin oligosaccharides, as exemplified by the octasaccharide fractions. These process dependent variations may affect enoxaparin's overall anti-coagulation profile. Far from the irrelevant differences presented by the isoforms in Pergonal, modification of these fingerprints in a product claiming to be enoxaparin could result in negative outcomes for patients with life-threatening conditions.

The Citizen Petition pointed out that further study of the complex macromolecule could reveal additional structural fingerprints that make significant contributions to enoxaparin's pharmacological activity. This Supplement provides such additional structural fingerprints and strengthens the Citizen Petition's request for the following actions:

1. Until such time as enoxaparin has been fully characterized, Aventis requests that FDA refrain from approving any ANDA citing Lovenox[®] as the reference listed drug unless the manufacturing process used to create the generic product is determined to be equivalent to Aventis' manufacturing process for enoxaparin, or the application is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials.
2. Aventis also requests that FDA refrain from approving any ANDA citing Lovenox[®] as the reference listed drug unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15% and 25% of its polysaccharide chains.

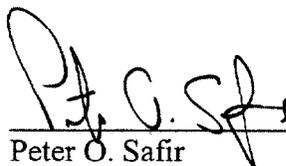
CERTIFICATION

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



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Respectfully submitted,



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Attachments