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October 17, 2003

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

RE: Docket No. 03P-0064 – Comments in Opposition to Aventis Pharmaceuticals Citizen Petition on Enoxaparin Sodium Injection.

Dear Sir or Madam:

On February 19, 2003, Aventis Pharmaceuticals ("Aventis"), through its counsel, filed the above-referenced citizen petition requesting that the Food and Drug Administration ("FDA") "withhold approval of any abbreviated new drug application ("ANDA")" for enoxaparin sodium ("enoxaparin"). Aventis markets this product under the trade name Lovenox.®

Specifically, the Aventis citizen petition requests that:

1. FDA withhold approval of any ANDA for enoxaparin "until such time as enoxaparin has been fully characterized," unless the manufacturing process used is equivalent to Aventis's manufacturing process or safety and effectiveness has been demonstrated through clinical trials; and

03P-0064 C 1

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2. FDA withhold approval of any ANDA for enoxaparin unless the generic product "contains a 1,6 anhydro ring structure at the reducing ends of between 15% and 25% of its polysaccharide chains."

According to data appended to the citizen petition, Aventis has relied on existing scientific compendial specifications – the same specifications on which a generic applicant would rely – to test its own enoxaparin active pharmaceutical ingredients (API). Now, on the eve of generic competition, Aventis argues that FDA should require more of a generic applicant, including that the generic applicant demonstrate its product contains Aventis's newly discovered structural "fingerprint" – the 1,6 anhydro ring. Aventis makes this argument despite the fact that it sets forth no more than speculation as to the clinical significance of the 1,6 anhydro ring. For these reasons, as set forth more fully below, the citizen petition should be denied.

I. Aventis sets forth no valid scientific or regulatory justification for its request that the FDA bar approval of ANDAs that cite Lovenox as the reference listed drug.

Neither science nor the applicable regulatory scheme supports the notion that FDA should withhold approval of generic enoxaparins. To do so would be inconsistent with precedent and against public policy.

A. Enoxaparin has been defined and is adequately characterized by compendia.

The FDA accepts and approves ANDAs for "[d]rug products that are the same as" the reference listed, i.e., innovator drug.[1] A drug product is the same as a listed drug if it contains the same active ingredient, and is the same with regard to dosage form, strength and route of administration.[2] Aventis argues that enoxaparin is not fully chemically characterized and that therefore a generic enoxaparin applicant will be unable to demonstrate sameness unless it uses the innovator's manufacturing process.[3] This is a flawed premise because enoxaparin, like most

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1 21 C.F.R. § 314.92(a)(1).

2 Id.

3 Aventis Citizen Petition at 20-21.

drugs, has been adequately defined and characterized and its specifications have been published in the European Pharmacopoeia ("EP")[4] and the British Pharmacopoeia ("BP").[5]

In fact, appended to the Aventis citizen petition is documentation that Aventis releases its own enoxaparin active pharmaceutical ingredient ("API") according to the EP specifications.[6] It is well settled that the FDA will not hold generic applicants to a higher standard than the innovator.[7] Thus, a generic manufacturer should be able to rely on these specifications to demonstrate sameness just as Aventis relies on these specifications for batch release.

We have reviewed publicly-available documents related to FDA's approval of Lovenox (i.e., the summary basis of approval or the "Lovenox SBA").[8] According to the Lovenox SBA, each lot of enoxaparin was analyzed for average molecular weight, anti-factor Xa activity, anticoagulant activity, free sulfates, pH, sterility, and pyrogens. These analyses are consistent with the specifications set forth in the EP and BP. Both the EP and BP include monographs, which define enoxaparin as the sodium salt of a low molecular weight heparin ("LMWH") that is obtained by alkaline depolymerization of the benzyl ester derivative of heparin from porcine intestinal mucosa.

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4 European Pharmacopoeia, Fourth Edition, 2002:1097 and 2002:0333.

5 British Pharmacopoeia 2000, Vol. I, at 609 (Dec. 1, 2000).

6 For example, Aventis released 659 grams of enoxaparin API, batch number WSD 3093 (0106699) in April 2001 based on the EP specifications. Aventis DMPK Report 2003-0029, at 50 (Feb. 14, 2003). This report is appended to the Aventis Citizen Petition at Exhibit E. The BP specifications for enoxaparin are the same.

7 See Serono Lab. v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998) ("FDA observed that Serono controls the batch-to-batch uniformity of Pergonal by using USP rat potency tests, and that Ferring does the same for Repronex. The agency concluded that 'it would be unreasonable to hold the generic menotropins product to a higher standard of uniformity than the standard used for Pergonal.'") (emphasis added) (citations omitted).

8 New Drug Application ("NDA") 20-164 (Mar. 29, 1993).

Even if we were to assume for the sake of argument that enoxaparin is not completely chemically characterized at this time, this would not preclude FDA from approving generic versions. Lack of complete chemical characterization of the innovator does not bar generics. Various products that are derived from natural sources, including proteins, lipids, phospholipids, and oligosaccharides "cannot be fully characterized chemically."[9] Refusing to approve generic drugs based on the innovator's failure to completely characterize its product would be inconsistent with Congress's intent in enacting the Hatch-Waxman Amendments:

> [I]f Congress had intended to exclude entire categories of drugs from the scope of the Hatch-Waxman Amendments, . . . there would be some mention of that fact in the statute or legislative history. Instead, both are wholly silent on the subject. We thus conclude that the statute does not unambiguously require the term "same as" to be defined as complete chemical identity.[10]

Aventis also raises the issue of variability of chemical structure, for example with regard to the 1,6 anyhdro ring.[11] As in the case of incomplete chemical characterization, variability of the chemical structure of an innovator drug does not preclude the FDA from approving generic versions.[12]

The FDA's analysis and actions with regard to generic menotropins were upheld by the court and are directly on point. In deciding to approve generic menotropins products, the FDA concluded that some variability of chemical structure was acceptable. Like enoxaparin, menotropins products are derived from a natural source, the urine of post-menopausal women. Menotropins contain two active ingredients, follicle-stimulating hormone ("FSH") and luteinizing hormone ("LH"). These injectable products are used to treat infertility.

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9 Id. at 1320.

10 Id. (citation omitted.)

11 Aventis Citizen Petition at 20.

12 Serono Lab., 158 F.3d at 1318.

Ferring's ANDA for a generic menotropin was approved by FDA in January, 1997. Serono, manufacturer of the innovator product (Pergonal), sued arguing that the active ingredient in the generic was not the same as the reference listed drug because of different FSH isoforms. The appellate court deferred to FDA's interpretation that FSH in the generic product was the same as that of the innovator, despite variation in chemical structure.[13] "In light of the fact that 'most glycoprotein products will have microheterogeneity,' the FDA determined that the relevant 'question is how much variation should be permitted.'"[14]

The chemical structure of FSH consists of a protein backbone and carbohydrate side chains. FDA concluded that the active ingredient in the generic was the "same as" that of the innovator because the protein backbones were identical, and despite variability in the structure of the carbohydrate side chains.[15] FDA noted that most glycoprotein products would have such variability, and that the question was how much variability the agency would permit.[16] FDA determined that generic menotropins products' FSH must have the same primary structure (i.e., protein backbone) as the reference listed drug, but that differences in the carbohydrate side chains (isoforms) are acceptable, provided the degree of batch-to-batch variation in the generic is similar to variation in the reference listed drug.[17] FDA approved generic menotropins despite variability in the carbohydrate side chain of FSH.

In the case of menotropins, FDA said that to be considered to have the same active ingredients as the reference listed drug, the generic product must have the same primary structure (which was assured by using the same natural source), the same potency, and the same batch-to-batch uniformity as measured via rat potency tests as specified in the U.S. Pharmacopeia ("USP").[18] Similarly, FDA should approve generic enoxaparin. Although

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13 See id. at 1313.

14 Id. at 1318 (citation omitted).

15 Id. at 1318 (citing Letter from J. Woodcock to Serono, June 17, 1997).

16 Id.

17 Id.

18 See Serono Lab., 158 F.3d at 1318 (citations omitted).

specifications for enoxaparin have not yet been set forth by the USP, other scientific compendia, i.e., EP and BP, have done so. Nothing precludes FDA from relying on other valid scientific standards: "FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia (USP)."[19]

B. Enoxaparin's lack of interchangeability with unfractionated heparin (UH) and other low molecular weight heparins (LMWHs) is irrelevant.

Aventis correctly states that enoxaparin is not interchangeable with other LMWHs or UH, but then makes the incorrect argument that the differences among the products mean that a "different generic approval process" should be required.[20] This underlying premise of Aventis's argument is false because generic enoxaparin would only be interchangeable with, or the same as, enoxaparin (Lovenox), not other LMWHs or UH.

Enoxaparin has a particular range of molecular weight (MW), average MW, and ratio of anti-factor X_a versus anti-factor II_a. These specifications are different for enoxaparin as compared to other LMWHs.[21] Generic enoxaparins will meet the same specifications, i.e., be the same as or interchangeable with, Lovenox, not with other LMWHs or UH.[22] Thus, this lack of interchangeability is irrelevant to FDA's approval of generic enoxaparin.

C. Aventis erroneously asserts that generic applicants can only satisfy the "sameness" requirement in one of three ways.

Aventis claims that in order to satisfy the sameness requirement, a generic applicant must do one of three things: 1) wait until enoxaparin becomes fully characterized; 2)

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19 57 Fed. Reg. 17,950, 17,959 (Apr. 28, 1992) (emphasis added).

20 Aventis Citizen Petition at 8.

21 See Appendices I and II.

22 Like Lovenox, a generic enoxaparin product's label would bear the same warning as other LMWHs regarding its lack of interchangeability with other heparins. See Aventis Citizen Petition at 7.

duplicate Aventis's manufacturing process; 3) demonstrate safety and effectiveness through clinical trials.

1. Forcing generic applicants to wait for enoxaparin to be further characterized chemically is inconsistent with legal precedent and legislative history, against public policy, and unnecessary.

Many products that are derived from natural sources are not fully chemically characterized. That does not mean that FDA cannot approve generic versions. Forcing generic applicants to wait for enoxaparin to become fully characterized chemically is not required by the statute or FDA's regulations and is scientifically unwarranted.

As explained in Section I-A of this document, FDA's actions with regard to menotropins are instructive in that FDA recognized that lack of complete characterization of the innovator is not a bar to the approval of generics.

> [I]f absolute chemical identity were required, not only menotropins but other categories of protein products would be excluded from the ANDA process as well . . . . Yet it seems likely – although by no means certain – that if Congress had intended to exclude entire categories of drugs from the scope of the Hatch-Waxman Amendments, which were passed to 'facilitat[e] the approval of generic copies of drugs,' there would be some mention of that fact in the statute or legislative history. Instead, both are wholly silent on the subject. We thus conclude that the statute does not unambiguously require the term 'same as' to be defined as complete chemical identity.[23]

Delaying availability of generic enoxaparin would be against public policy and inconsistent with legislative intent. In enacting the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Waxman-Hatch" amendments), Congress had two purposes. Title I provided for approval of generic versions of approved drugs through the abbreviated (i.e., ANDA) procedure, while Title II extended patent terms for approved new

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[23] Serono Lab., 158 F.3d at 1320 (citations omitted).

drugs.[24] A primary objective of Congress was to ensure availability of affordable generic products for the benefit of the public. Congress "intended to encourage competition by decreasing the time and expense of bringing generic drugs to market, and thereby to provide the public with low cost drugs."[25]

In addition, if the FDA were to delay approval of generic enoxaparin, there would be no incentive for the pioneer ever to further characterize its drug. It would be fundamentally unfair for FDA to hold the generic applicant to a higher standard than the innovator.

Moreover, the delay Aventis proposes is simply not necessary. In its assessment of menotropins, FDA acknowledged that there were variations in chemical structure, but concluded that they were 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)."[26] Aventis merely speculates as to any such clinical significance.[27]

2. Duplicating the innovator's manufacturing process is not required by law; it is not the standard for demonstrating "sameness."

Aventis attempts to equate the requirement that a generic be "the same as" the reference listed drug to its premise that the manufacturing process must be the same. This is not the standard set forth by law. The requirements that a generic applicant demonstrate

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24 See 54 Fed. Reg. 28,872, 28,874 (Jul. 10, 1989).

25 Id. (emphasis added).

26 Serono Lab., 158 F.3d at 1317.

27 For example, based on animal studies, Aventis states that the 1,6 anhydro ring structure makes several contributions to enoxaparin's pharmacological effect and that "[m]any of these contributions likely bear clinical significance." Aventis Citizen Petition at 3 (emphasis added). "There is ample reason to believe that the 1,6 anhydro ring's anti-inflammatory properties will bear clinical significance in humans." Id. at 16. "[T]he presence of the 1,6 anhydro ring on 15-25% of enoxaparin's polysaccharide chains may well have clinical significance for enoxaparin's intended uses." Id. at 21. No clinical data are cited to prove such differences are meaningful.

"sameness" and describe its manufacturing process are two separate and distinct requirements, which are addressed at two different sections of the statute: 21 U.S.C. §§ 355(j)(2)(A)(ii)(I) (sameness) and 355(j)(2)(A)(vi) (description of the manufacturing process).[28] There is no requirement that to achieve "sameness" the manufacturing process for the innovator and the generic be exactly the same.

Assuming for the sake of argument that FDA were to conclude that a generic applicant should duplicate Aventis's manufacturing process, Aventis has not identified the differences in the manufacturing process that would be unacceptable. Aventis asserts that "[a] generic product cannot duplicate enoxaparin's pharmacological activity by duplicating only enoxaparin's molecular weight or anti-X_a/anti-II_a activity."[29] Yet, according to the Lovenox SBA: "Each lot of enoxaparin is analyzed for molecular weight average and distribution, anti-X_a activity, anticoagulant activity free sulfates, pH, and it is checked for sterility and pyrogens."[30] Aventis fails to make the case for requiring FDA to require more of a generic applicant.

3. Requiring generic applicants to demonstrate safety and effectiveness through clinical trials is inconsistent with the regulatory scheme.

Aventis's suggestion that generic enoxaparin applicants be required to conduct full clinical trials to demonstrate safety and effectiveness simply ignores the regulatory scheme for approval of generic drugs. Aventis is asking that FDA require more than FDA may legally require in an ANDA. See 21 U.S.C. § 355(j)(2)(A) ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)."). To grant Aventis's request would mean that generic applicants would be required to submit full reports (i.e., a new drug application (NDA)) in order to market a generic version of a drug. Aventis's request is literally impossible. To require clinical studies of safety and effectiveness for approval of an ANDA would mean that the application is no longer an ANDA.

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28 For parenteral products, such as enoxaparin, FDA typically waives the requirement to submit in-vivo bioequivalence data. 21 C.F.R. § 320.22(b)(1).

29 Aventis Citizen Petition at 19-20.

30 See Lovenox SBA, Medical Officer's Review, at 4.

D. Contrary to Aventis's claims, FDA's treatment of Premarin is distinguishable.

In the 1990s, FDA concluded that synthetic generic forms of Premarin could not be approved at that time. Aventis claims that enoxaparin is analogous to Premarin. In fact, the two drugs are different and the reasons for not approving generics for Premarin are distinguishable. Premarin includes multiple ingredients that are potentially active.[31] Conversely, enoxaparin contains one active ingredient, which Aventis argues has variation in its chemical structure. Thus, enoxaparin is more like menotropins, for which FDA found approval of generic forms appropriate. Moreover, with regard to Premarin, FDA concluded it would not approve synthetic generic versions.[32] FDA did not conclude that it would not accept ANDAs for generic versions of Premarin where the active ingredients were derived from natural sources. In fact, Barr submitted an ANDA for a generic Premarin product on June 30, 2003.[33] Generic enoxaparin will be derived from the same natural sources as the innovator product.

E. Aventis argues that enoxaparin is similar to a biologic.

Enoxaparin is not a biological product; it is a drug subject to approval under the Food, Drug and Cosmetic Act. Assuming for the sake of argument that enoxaparin is in some respect comparable to a biologic, the bar to FDA approval of generic biologics is due to a lack of clear statutory authority. Biological products are subject to licensure under the Public Health Service Act, which contains nothing comparable to section 505(j) – the

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31 FDA statement on Generic Premarin (May 5, 1997), available at http://www.fda.gov/bbs/topics/news/new00565.html.

32 Id. ("Based on currently available data, there is at this time no way to assure that synthetic generic forms of Premarin have the same active ingredients as the brand-name drug.") (emphasis added).

33 The Pink Sheet (Oct. 13, 2003). The status of Barr's ANDA is unclear due to litigation between Wyeth and Natural Biologics, supplier of the raw material. A recent court decision permanently enjoined Natural Biologics from developing equine-derived estrogens, leaving Barr without a supplier for its raw material. See id. See also FDA's list of Paragraph IV Patent Certifications as of September 2, 2003, available at http://www.fda.gov/cder/ogd/ppiv.htm (indicating that an ANDA referencing Premarin has been received by the Office of Generic Drugs).

section of the FDCA that provides for submission of abbreviated applications for generic drug products. Congress may have to act to allow FDA to approve generic versions of biological products, but that is irrelevant to approval of generic enoxaparin.

For the reasons set forth above, Aventis presents no scientific or regulatory justification for FDA to bar approval of generic enoxaparin. Aventis's first request should be denied.

II. Request #2 should likewise be denied because Aventis's own data demonstrate that versions of enoxaparin with varying amounts of the 1,6 anhydro ring fail existing compendial specifications or are likely to fail internal limits.

Aventis asserts that FDA should not approve any ANDA unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15% and 25% of its polysaccharide chains.[34] But Aventis's own data undermine this argument. Aventis's data, which is appended to the citizen petition, demonstrate that enoxaparin products with varying amounts of the 1,6 anhydro ring can be identified by existing compendial specifications.

Aventis indicates that it has identified "structural fingerprints" in enoxaparin's chemical composition, which may be responsible for pharmacological activity, including:

1. Oligosaccharides with odd numbered saccharide units;
2. Galactuturonic acid moieties;
3. Epimerization of reducing ends; and
4. 1,6-Anhydro ring structure.

Aventis provides no quantitative analytical data or preclinical testing results for "fingerprints" one through three above.[35] Therefore, there is no scientific or regulatory basis to support that these characteristics have any influence whatsoever on the efficacy or safety of enoxaparin.

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[34] Aventis Citizen Petition at 1.

[35] Aventis Citizen Petition at 12-13.

With regard to the fourth so-called fingerprint, the 1,6-anhydro ring structure, Aventis states:

> Unlike enoxaparin's other structural fingerprints, Aventis has been able to conduct preclinical testing on the 1,6-anhydro ring structure. By duplicating Aventis' manufacturing process except for a discrete change in certain parameters, Aventis' scientists constructed two LMWHs similar to enoxaparin in molecular weight, anti-X_a activity, and anti-X_a/anti-II_a ratio, but with dissimilar 1,6 anhydro ring content. The first of these alternative LMWHs contained the 1,6 anhydro ring structure in only minimal amounts ("<7% 1,6 anhydro LMWH"). The second contained the ring but at a higher concentration than is present in Enoxaparin ("40-50% 1,6 anhydro LMWH). Enoxaparin contains the 1,6 anhydro ring structure at 15-25% frequency. All three of these LMWHs had similar anti-X_a level, molecular weight, and anti-X_a/anti-II_a activity.[36]

Based on these findings with regard to the "three LMWHs,"[37] Aventis requests that the percentage of 1,6 anhydro ring be an additional specification for generic enoxaparin.[38] Yet, as far as we know from our review of publicly available documents, Aventis's own specifications do not include a range for the 1,6 anhydro ring. According to the Lovenox SBA, each lot of enoxaparin is analyzed for molecular weight average and distribution, anti-factor X_a activity, anticoagulant activity, free sulfates, pH, sterility, and pyrogens.[39]

Adding a specification for the 1,6 anhydro ring is not necessary. Aventis's data on the average molecular weight, loss on drying, anti-factor X_a, and anti-factor X_a/II_a ratio – all of which are EP specifications – for "the three LMWHs," are summarized in the table

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36 Aventis Citizen Petition at 14-15.

37 Tracking the language of the citizen petition, the terms, "<7% 1,6 anhydro LMWH," "40 to 50% 1,6 anhydro LMWH," and "three LMWHs," will be used throughout this document only for the purpose of convenience. As explained herein, the "three LMWHs" are bioequivalent.

38 Aventis Citizen Petition at 1.

39 Lovenox SBA, Medical Officer's Review, at 4.

below. The data that appear in the table below were set forth by Aventis in its citizen petition.

Testing Item	EP Specification	Enoxaparin	<7% 1,6 anhydro ring	40-50% 1,6 anhydro ring	Reference*
Aventis' Batch No.	—	WDS3093	DIA2844	DIA2648	Page 14-15
Average MW	3500-5500 Dalton	4350	4300	4100	ibid
Loss on Drying	≤10%	7.4	9.2	**14.2**	ibid
Anti-factor X_a	90-125 U/mg	105	92.4	**81.4**	Page 50-52
Anti-X_a/II_a Ratio	3.3 to 5.3	4.3	4.3	4.4	ibid

* All cited page numbers correspond to the Aventis DMPK Report 2003-0029.

Based on the above summary:

(a) The "40-50% Anhydro" failed specifications for both anti-X_a and loss on drying; and
(b) The "<7% Anhydro" barely passed the EP specification for both anti-factor X_a and loss on drying. The quality control system of a cGMP compliant pharmaceutical company would identify the above test results for anti-X_a and loss on drying as requiring further investigation. That is, even if the values fall within the regulatory (i.e., EP) specifications they will fail internal alert limits. Consistent with applicable regulatory guidance, manufacturers set tighter in-house limits at the time of release in order to ensure that the product will remain within the regulatory acceptance criteria throughout its shelf life.[40]

The testing methods for EP specifications, such as anti-factor X_a and loss on drying etc., are well-developed and easily validated. These EP specifications are thorough enough to adequately characterize enoxaparin's molecular structure.

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40 65 Fed. Reg. 83,041, 83043 (Dec. 29, 2000) (publishing the International Conference on Harmonization; Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances).

Thus, all three of the Aventis "constructed" LMWHs (enoxaparin, "40-50% Anhydro", and "<7% Anhydro"), can be distinguished by the EP specification. The EP specification is adequate to characterize enoxaparin.

Both the LMWH with <7% anhydro ring and the LMWH with 40 to 50 % anhydro ring were identified by existing compedial specifications. In addition, Aventis has not demonstrated any clinical significance related to the variation. Therefore, Aventis has set forth no valid regulatory or scientific basis to specify that a generic enoxaparin drug product must contain a 1,6 anhydro ring structure on between 15% and 25% of its polysaccharide chains. Aventis's second request should be denied.

For all the aforementioned reasons, the undersigned respectfully requests that FDA deny the Aventis Citizen Petition.

Sincerely,

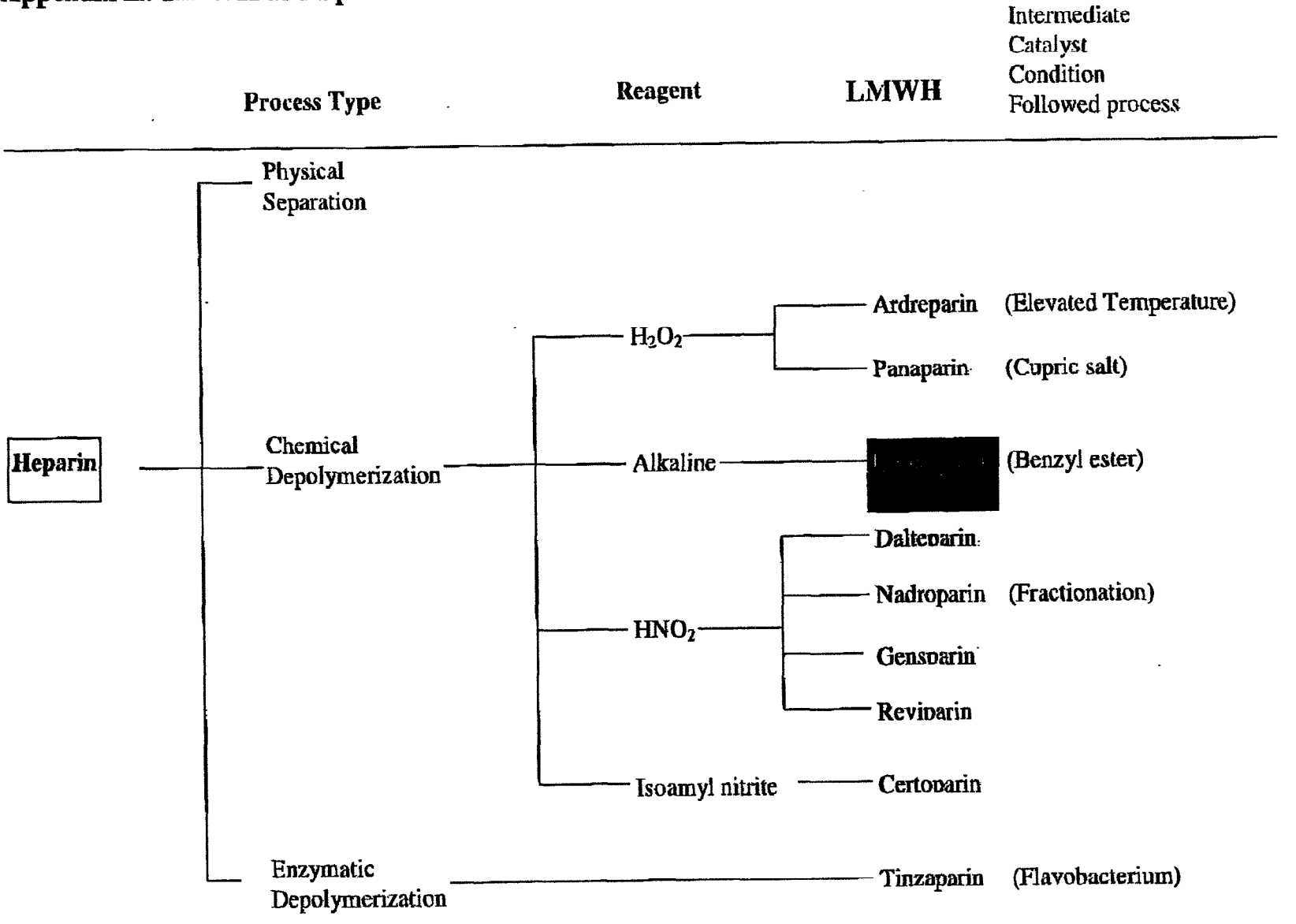
Robert A. Dormer

Anne Marie Murphy

Appendix I: Summary of Low Molecular Weight Heparin

Type of LMWH	Heparin Source	Depolymerization Process	Range of Ave. MW, dalton	Ave. MW, dalton	Anti-X_a, IU/mg	Ratio of X_a/II_a
Ardreparin	Porcine Intestinal Mucosa	Oxidative depolymerization with hydrogen peroxide at elevated temperature		6500	120±25	2
Certoparin	Porcine Intestinal Mucosa	Isoamyl nitrite depolymerization	4200-6200		80-120	1.5-2.5
Dalteparin	Porcine Intestinal Mucosa	Nitrous acid depolymerization	5600-6400	6400	110-210	1.9-3.2
Enoxaparin	Porcine Intestinal Mucosa	Alkaline depolymerization of benzyl ester derivative of heparin	3500-5500	4500	90-125	3.3-3.5
Nadroparin	Porcine Intestinal Mucosa	Nitrous acid depolymerization followed by fractionation to eliminate selectively most of the chains with MW < 2000	3600-5000	4300	95-130	2.5-4.0
Panaparin	Bovine or Porcine Intestinal Mucosa	Radical-catalysed depolymerization with hydrogen peroxide and cupric salt	4000-6000	5000	75-110	1.5-3.0
Reviparin	Porcine Intestinal Mucosa	Nitrous acid depolymerization		3900	130	>3
Tinzaparin	Porcine Intestinal Mucosa	Controlled enzymatic depolymerization of heparin using heparinase from Flavobacterium heparinum	5500-7500	6500	70-120	1.5-2.5

Appendix II: LMWH and Specified Process



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FACSIMILE TRANSMITTAL SHEET

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