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Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: **Docket No. 2003P-0064/CP1**
Request That FDA Withhold Approval of Generic Versions of Lovenox®

Teva Pharmaceuticals USA Response to February 19, 2003 Citizen Petition and February 12, 2004 Supplement Submitted on Behalf of Aventis Pharmaceuticals

I. INTRODUCTION

Teva Pharmaceuticals USA Inc. (Teva) submits this response to the above-referenced citizen petition and the February 12, 2004 supplement thereto, submitted on behalf of Aventis Pharmaceuticals (Aventis). Aventis' citizen petition and supplement are yet another example of a brand drug company seeking to cast doubt on the approvability of generic versions of branded drug products, with the purpose of delaying generic competition, in this case for Aventis' lucrative Lovenox® (enoxaparin sodium) injection product. Aventis' petition specifically requests that FDA refrain from approving generic enoxaparin sodium injection products

- "until such time as enoxaparin has been fully characterized"; and
- "unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15% and 25% of its polysaccharide chains."

Aventis' Petition is based on unsupported speculation about the significance of certain new-found structural features of the active ingredient of Lovenox®, and the ability of generic enoxaparin products to adequately demonstrate "sameness" of the active ingredient in all relevant respects. Aventis thus essentially asks FDA to categorically stop all review of enoxaparin ANDAs until such time (which may never come) that Aventis believes enoxaparin has been "adequately" characterized. However, FDA has ample expertise, and the inherent authority, to continue its review of enoxaparin ANDAs, and to evaluate any

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relevant or significant chemistry issues within the ANDA review process. *See* 21 C.F.R. § 314.92(a) ("For determining the suitability of an abbreviated new drug application, the term "same as" means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use."). Upon such review, Teva is confident that the Agency will conclude that Teva's generic enoxaparin product meets all legal and scientific bases for approval. For the reasons set forth herein, Aventis' petition should be denied.

II. OVERVIEW

Aventis' Petition argues that because enoxaparin is allegedly not fully characterized, the Agency must refrain from approving any ANDA for enoxaparin sodium injection unless the generic product's manufacturing process is determined to be equivalent to Aventis' manufacturing process. Presumably, Aventis' definition of an "equivalent manufacturing process" is one that is protected by US Patents 4,692,435 and/or 5,389,618, in which case the true anti-competitive motivation for Aventis' speculative scientific arguments becomes abundantly clear. In any event, despite Aventis' "finding" that its manufacturing process results in a particular enoxaparin structure, Aventis has not demonstrated, nor is it the case, that alternative manufacturing processes cannot achieve enoxaparin that can be shown to be legally and clinically the "same" as Lovenox®. Thus, the principal fallacy of the Aventis Petition is that a generic product must be manufactured by the same process as the brand product in order to be eligible for ANDA approval. In reality, an ANDA may be submitted, and approved, even for a drug which is not "fully characterized," so long as FDA, in the course of its administrative review of the ANDA, concludes that the generic product meets all statutory approval criteria, including "sameness" of the active ingredient.

III. DISCUSSION

A. The Sameness Standard For ANDA Approvals

Aventis has conducted ongoing studies of enoxaparin in an effort to sow doubt and uncertainty about the chemical structure of enoxaparin and to allege various potential clinical differences that might arise from generic enoxaparin products produced by different processes than Lovenox®. Aventis puts the cart before the horse however, by seeking to gloss over the fundamental point that "sameness" of manufacturing processes is not a requirement for approval of a generic drug under an ANDA. *See* 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.94. Rather, Aventis argues that Lovenox® has certain chemical characteristics, and then speculates that such characteristics must be entirely dependent on its manufacturing process. The only support for this unproven assertion however, is the statement that "clinical supplies used in a few of the initial [Lovenox®] clinical studies...were made from batches where some of the conditions (e.g., time and temperature) were modified." Petition at 11, n. 33 (emphasis added). However, as Aventis concedes in its supplemental submission, "FDA must evaluate each drug independently, making a case-by-case determination regarding sameness," and "the Agency can base 'sameness' under the

FDCA on pharmacological identity, rather than absolute identity." Aventis Suppl. at 13, *citing Serono Labs v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998). Thus, Aventis' request that enoxaparin ANDAs must be approved only if they use the same manufacturing process as for Lovenox® is simply not a request that FDA is authorized to grant.

In addition, Aventis' "product by process" theory is contradicted by the known variability of Lovenox® itself. For example, Momenta Pharmaceuticals' International Patent Application WO 03/078960 A2 contains results of studies of the variability of Lovenox®'s disaccharide "building blocks," concluding that "the variation between batches of commercially available Lovenox® is substantial." The table below (from International Patent Application WO 03/078960 A2), presents the results of enzymatic depolymerization followed by capillary electrophoresis of three batches of Lovenox® and reflects that Aventis' manufacturing process is not in fact an answer to its arguments regarding structural variations of enoxaparin and the alleged potential clinical effects of such differences.

Excerpt from International Patent Application WO 03/078960 A2 presenting disaccharide variability data for three batches of Lovenox®

Saccharide	Enox. Batch 1	Enox. Batch 2	Enox. Batch 3	Variation (%)
p1	60.8	63.5	63.6	4
p2	7.0	7.2	8.3	17
p3	11.8	10.8	11.3	9
p4	2.5	2.1	2.0	23
p5	3.6	3.5	3.5	3
p6	1.8	2.0	1.8	11
p7	5.4	4.3	1.9	91
p8	6.6	5.8	6.4	13
p9	0.2	0.4	0.5	82
p10	0.3	0.4	0.7	86

Aventis' effort to create complexity and confusion as to the nature of enoxaparin are also inconsistent with the fact that enoxaparin is defined in both the European Pharmacopoeia (EP) and the British Pharmacopoeia (BP) as the sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerization of the benzyl ester derivative of heparin from porcine intestinal mucosa. Moreover, a proposed USP monograph has been published in the November-December 2003 *Pharmacopeial Forum* (pp. 1876-1882), and the proposed USP definition of enoxaparin sodium is identical in content to the EP and BP definition: "... the sodium salt of a depolymerized heparin. It is

obtained by alkaline depolymerization of heparin benzyl ester. The starting material, heparin, is obtained exclusively from porcine intestinal mucosa." Accordingly, any enoxaparin product meeting the requirements of the EP, BP, and forthcoming USP monographs will use the same source material (heparin obtained from porcine intestinal mucosa), and a comparable method of preparation (alkaline depolymerization of heparin benzyl ester).

The Pharmacopeial definitions of enoxaparin's manufacturing process are highly pertinent to discussion of Aventis' citizen petition, yet Aventis' attempted rebuttal of Hyman, Phelps' comment (Aventis Feb. 12, 2004 Supplement, p. 13) fails to adequately address the significance of the Pharmacopeial definitions of enoxaparin's manufacturing process. As a baseline regulatory matter, generic versions of drugs defined in the USP are presumptively approvable if they meet the USP standards for strength, quality, and purity, as measured by the tests and assay methods set forth in the USP. *See* 21 U.S.C. § 351(b) (defining "adulterated" drugs to include those that fail to meet compendial standards). Teva, the world's leading generic drug manufacturer, and the holder of hundreds of approved ANDAs, recognizes that compliance to compendial tests and specifications is not necessarily sufficient for approval of any ANDA, and that FDA may require additional tests and specifications beyond those mandated by the USP. However, as discussed below, Teva has conducted adequate and appropriate tests, and submitted the results of those tests to FDA via its ANDA, to demonstrate that its enoxaparin product is sufficiently the "same" as Lovenox® in all relevant respects to allow ANDA approval.

B. Aventis' "Structural Fingerprints" Arguments Do Not Preclude Approval of Teva's Enoxaparin Product

Not only is Aventis' alleged process dependency/structural fingerprints argument fallacious as a legal/regulatory matter, it is incorrect scientifically. Specifically, Aventis' February 19, 2003 petition lists oligosaccharides with odd numbered saccharide units, galactouronic acid moieties, and epimerization of reducing ends with 15% - 25% 1,6 anhydro ring structures as newly discovered structural fingerprints of enoxaparin, and suggests that this "fingerprint" is unachievable with any process other than Aventis'. This is incorrect. Teva's enoxaparin oligosaccharide profile has been compared to that of Aventis' Lovenox® using ion-pair HPLC- separation with TOF-MS methodology/detection. Results for polysaccharide chains with molecular mass less than 3,600 Da. indicate that both enoxaparin products show essentially the same variability. Moreover, the amino sugar composition of Teva's enoxaparin has been compared to that of Aventis' Lovenox® using HPLC methodology analysis of hydrolyzed enoxaparin preparations with post-column derivatization. Results show essentially identical amino sugar composition for both products, corresponding to 70% glucosamine and 30% mannosamine at the reducing ends.

In addition, the 1,6-anhydro ring structure content of the oligosaccharide chains reducing end was evaluated using SAX-HPLC analysis of partially depolymerized enoxaparin preparations. Results for several lots of Teva's enoxaparin and of Aventis'

Lovenox® were similar, and both products were within the 15% - 25% range. And, the presence of galactouronic acid moieties in Teva's enoxaparin has been confirmed by GC-MS analysis of samples subjected to methanolysis followed by derivatization. Finally, preliminary studies have shown that Teva's enoxaparin and Aventis' Lovenox® (after partial depolymerization) contain similar, small amounts of a trisaccharide component, an odd-numbered polysaccharide. Additional characterization studies are ongoing, and it is Teva's intention to submit these studies for Agency review as part of our pending ANDA for enoxaparin sodium injection.

Finally, Aventis uses an assortment of theoretical suppositions and *in vitro* data in support of their contention that generic enoxaparin products might exhibit different pharmacodynamic profiles, anti-inflammatory effects, inhibition of smooth muscle cell proliferation, and stimulation of angiogenesis. Teva agrees that ANDA applicants for generic enoxaparin sodium injection should perform a comparative pharmacodynamic study vs. the reference listed drug Lovenox®. It is Teva's intention to submit the PD study results for Agency review as part of our pending ANDA for enoxaparin sodium injection. Nothing in Aventis' petition provides a basis for FDA to refuse to review such data and approve Teva's ANDA if, as expected, the results of Teva's tests reveal sufficient sameness (but not necessarily exact chemical identicality) to Lovenox®.

C. The Lack Of "Full Characterization" Of Enoxaparin Does Not Bar Generic Approvals

Aventis' Petition relies heavily on the assertion that enoxaparin is not "fully characterized" and that therefore generic versions cannot be approved until such time as full characterization is achieved. Specifically, Aventis postulates that its failure to characterize approximately 20% to 30% of the components of their product should be cause for FDA to delay generic competition. This position is an obvious one for Aventis to take with respect to a complex product like enoxaparin that is derived from animal material, but it is also a position that has been considered and rejected by FDA when used by other brand companies seeking to thwart lower priced generic competition.

Specifically, in the case of FDA's approval of generic menotropins drug products, the key issue was whether a non-fully characterized brand product could be insulated from generic competition because it was not fully characterized. FDA and the courts ultimately and conclusively ruled that for products such as menotropins (and enoxaparin here), the lack of full characterization is not a barrier to ANDA approval. Rather, FDA and the courts held that absolute chemical identity is *not* required for generic approval, and indeed, that such a requirement would appear to be contrary to Congressional intent. *Serono Labs v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998). Contrary to Aventis' assertion, in response to the comments of Hyman Phelps, that Pergonal® is or was fully characterized, less than five percent of Pergonal® consists of the active FSH and LH, with uncharacterized urinary proteins (UUP) and the excipient lactose constituting the remainder. In approving generic menotropins, FDA concluded, among other things, that menotropins isoform variations were

of no clinical significance, that chemical analysis could not assure that two batches of Pergonal® were identical, and that the UUP were considered to be impurities rather than excipients.[1]

Aventis' February 12, 2004 Supplement introduces limited additional findings of questionable clinical significance. For example, Aventis' Supplement introduces a newly-discovered, sequence-dependent difference in ATIII binding affinity of enoxaparin octasaccharides, which Aventis speculates may have clinical significance based on a possible difference in half-life of their anti-Xa activity. Aventis further theorizes that this characteristic may also be applicable to all enoxaparin oligosaccharide types — a veritable "mother lode" of future Supplements to their Petition! The Aventis Supplement also discusses *in vitro* anticoagulation test results in which ≥ hexadecasaccharide fractions from enoxaparin with 15% to 25% 1,6 anhydro ring structure exhibited greater anticoagulant activity than did ≥ hexadecasaccharide fractions from LMWH with <7% 1,6 anhydro ring structure. However, this effect was shown only in one of the six enoxaparin / LMWH fractions studied. Finally, Aventis reports the results of *in vitro* studies with the same enoxaparin / LMWH fractions discussed above, assessing their interaction with acidic fibroblast growth factor (aFGF). The results showed no consistent pattern, and their potential clinical significance is doubtful. Neither is any clinical significance apparent for the *in vitro* smooth muscle cell proliferation studies reported in the February 12, 2004 Supplement.[2]

D. Aventis' Petition Is Nothing More Than An Anti-Competitive Strategy

Aventis' submissions reveal a clear and disturbing strategy — specifically, we anticipate that Aventis will continue to periodically submit new supplements introducing new allegedly relevant information, all of which Aventis will argue preclude FDA from approving enoxaparin ANDAs. Of course Aventis will never introduce evidence that will assist FDA and generic applicants in meeting Aventis' distorted and anti-competitive notion of what is required for generic approvals, but rather will simply continue to try to delay Agency action on the petition and on pending ANDAs. Aventis' delaying tactics are unscientific, unsupported by law or regulation, and should not be tolerated by the Agency.

[1] Teva agrees with the analysis of the Premarin scenario as presented in Hyman, Phelps & McNamara's October 17, 2003 comment in opposition to Aventis' petition. To the best of our knowledge and belief, current FDA policy would permit, and most assuredly *should* permit, approval of a generic equivalent to Premarin® which was derived from the same source material and chemically characterized consistent with the current state of the art. FDA's decision not to approve synthetic generic conjugated estrogens, containing five components found in the natural source product, has no relevance to enoxaparin.

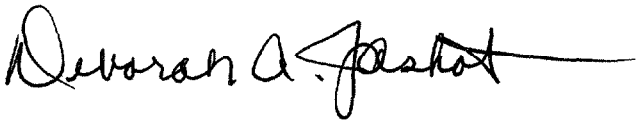
[2] With regard to Aventis' other allegations of potential clinical significance, we note that none of these alleged pharmacologic activities is discussed in Aventis' April, 2004 Lovenox® prescribing information. This is clearly similar to Wyeth's Premarin® situation, in which a frenzy of speculation regarding the alleged cancer protective effects of Wyeth's poorly bioavailable formulation and "mystery guest" component, delta 8,9 DHES, helped protect Wyeth's monopoly profits for several additional years (until further clinical studies demonstrated that Premarin® has *no* cancer protective effect).

The adverse effect of Aventis' Petition strategy on the public health is predictable and dramatic. According to FDA's June 12, 2003 White Paper, "Improving Access to Generic Drugs" initiative, "Encouraging rapid and fair access to generic medications is one of the FDA's major priorities. Americans need generic drugs more than ever..." The economic benefits of availability of generic equivalents to Lovenox® can be estimated by comparing the US price of the innovator product (where it has no substantial competition from any low molecular weight heparins) to its price in Europe (where other LMWH products compete with Lovenox®). For example, in France and Italy, six 40 mg syringes of Lovenox®/Clexane® are sold for approximately 40 Euros (approximately $48). By contrast, in the US, with essentially no competition, the Lovenox® Wholesale Acquisition Cost (reported by Price Probe effective April 2, 2004) was $22.76 per 40 mg syringe — nearly triple the cost of the same drug in Europe. American consumers deserve the cost savings associated with robust and fair generic competition, and Aventis' blatant and unjustified efforts to deny that competition for its own benefit should be rejected.

D. Conclusion

In conclusion, Aventis' petition raises only issues that should be addressed within the existing ANDA review process. All relevant chemistry data can be reviewed within the Office of Generic Drugs for ANDAs submitted under section 505(j) of the Food, Drug & Cosmetic Act. We respectfully request that the Agency deny the Aventis petition and review the "sameness" of generic enoxaparin products as part of the standard ANDA review, according to its current regulations.

Sincerely,



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