

LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

JAMES R. PHELPS
PAUL M. HYMAN
ROBERT A. DORMER
STEPHEN H. MCNAMARA
ROGER C. THIES
THOMAS SCARLETT
JEFFREY N. GIBBS
BRIAN J. DONATO
FRANK J. SASINOWSKI
DIANE B. MCCOLL
A. WES SIEGNER, JR.
ALAN M. KIRSCHENBAUM
DOUGLAS B. FARQUHAR
JOHN A. GILBERT, JR.
JOHN R. FLEDER
MARC H. SHAPIRO
FRANCES K. WU
ROBERT T. ANGAROLA
(1945-1996)

700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D.C. 20005-5929
20775 04 703-8 2004
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

JENNIFER B. DAVIS
OF COUNSEL

DAVID B. CLISSOLD
CASSANDRA A. SOLTIS
JOSEPHINE M. TORRENTE
MICHELLE L. BUTLER
ANNE MARIE MURPHY
PAUL L. FERRARI
JEFFREY N. WASSERSTEIN
MICHAEL D. BERNSTEIN
LARRY K. HOUCK
DARA S. KATCHER*
KURT R. KARST
MOLLY C. ANDRESEN
SHAWN M. BROWN*

*NOT ADMITTED IN DC

DIRECT DIAL (202) 737-4282

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BY FACSIMILE/CONFIRMATION COPY BY FEDERAL EXPRESS

Division of Dockets Management
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 Supplement on Enoxaparin Sodium
Injection.**

Dear Sir or Madam:

On February 12, 2004, Aventis Pharmaceuticals (“Aventis”), through its counsel, filed the above-referenced citizen petition supplement (“Aventis Supplement”) to its original February 19, 2003 citizen petition (“Citizen Petition”), restating its request 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 name Lovenox®.

2003P-0064

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2603 MAIN STREET
SUITE 760
IRVINE, CALIFORNIA 92614
(949) 553-7400
FAX (949) 553-7433

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX (919) 313-4751

Specifically, the Aventis Citizen Petition and the Aventis Supplement request that:

1. FDA withhold approval of any ANDA for enoxaparin “[u]ntil 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 that
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.”¹

Aventis’s second request may no longer be at issue. FDA recently approved Aventis’s supplemental NDA, which revised the Lovenox labeling to include the 1,6 anhydro on the reducing end of 15 to 25% of the product’s polysaccharide chains.² A generic enoxaparin product would be required to conform to the updated labeling in order to obtain FDA approval. Still, to the extent that Aventis argues that a generic applicant must use the same manufacturing process as the innovator to obtain approval, Aventis’s reasoning is flawed. Indeed, provided that a generic manufacturer’s product conforms to the current labeling, it proves the point: the same manufacturing process is not required to produce a product that is the same as the innovator’s. Duplicating an innovator’s manufacturing process is not required by law and is not the standard for demonstrating sameness.

For all the reasons set forth in our comments filed on October 17, 2003 in response to Aventis’s original citizen petition (“HPM Comment”), FDA should deny Aventis’s first request, namely that FDA withhold approval an any enoxaparin ANDA until enoxaparin has been fully characterized, unless the manufacturing process is the same as that used by Aventis, or safety and effectiveness has been demonstrated through clinical trials. This request by Aventis should be denied because it ignores the regulatory scheme for the

¹ Citizen Petition at 1; Aventis Supplement at 2.

² See Approval letter for Aventis’s supplemental NDA, 20-164/S-055, which provided “additional characterization and new structural information on the active ingredient of the drug product, enoxaparin sodium” (July 23, 2004), and revised Lovenox labeling, available at <http://www.fda.gov/cder/foi/label/2004/20164s055/lbl.pdf>.

approval of generic products. FDA approval of such a request would be inconsistent with applicable precedent and against public policy.

I. Aventis's first request should be denied.

The Aventis Supplement does not include new data or information to cure the lack of scientific or regulatory justification for its request that the FDA bar approval of ANDAs that cite Lovenox® as the reference listed drug.

A. Aventis erroneously asserts that FDA should refuse to approve ANDAs citing Lovenox® as the reference listed drug until enoxaparin has been fully characterized.

Forcing generic applicants to wait for enoxaparin to be fully 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 discussed in our earlier comments, 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.³

³ Serono Lab. v. Shalala, 158 F.3d 1312, 1320 (D.C. Cir. 1998) (citations omitted).

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 new drug application (i.e., ANDA) procedure, while Title II provided for extended patent terms for approved new drugs.⁴ A primary objective of Congress was to ensure availability of affordable generic products for the benefit of consumers. 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.”⁵ It would be inconsistent with Congress’s intent and fundamentally unfair for FDA to hold the generic applicant to a higher standard than the innovator.

B. Duplicating the innovator’s manufacturing process is not required by law; it is not the standard for demonstrating “sameness.”

Aventis appears 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 “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. §§ 55(j)(2)(A)(ii)(I) (sameness) and 355(j)(2)(A)(vi) (description of the manufacturing process).⁶ There is no requirement that to achieve “sameness” the manufacturing process for the innovator and the generic be 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 or what parts of the manufacturing process Aventis would consider essential.

⁴ See 54 Fed. Reg. 28,872, 28,874 (Jul. 10, 1989).

⁵ Id. (emphasis added).

⁶ 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).

The delay Aventis proposes is not supported by scientific data. 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).”⁷ Likewise, Aventis has not demonstrated the clinical significance of its “newly discovered” so-called structural fingerprint – the structure of the antithrombin three (“ATIII”) binding sites – discussed in the Aventis Supplement. The Aventis Supplement further claims that the structure of these binding sites is dependent upon the manufacturing process.⁸ Once again, however, Aventis can only speculate as to the clinical significance, if any, of its discovery.⁹

Low molecular weight heparins (“LMWHs”) such as enoxaparin act by binding with ATIII, a plasma protein.¹⁰ According to the Aventis Supplement, in further studying the significance of the 1-6, anhydro ring, it discovered that different disaccharide sequences within an oligosaccharide in the enoxaparin chemical structure affect its affinity for ATIII.¹¹ Aventis states that the differences in the disaccharide sequences occur depending upon where the unfractionated heparin is cleaved during the manufacturing process, and that Aventis’s manufacturing process results in “three main process dependent octasaccharide sequences.”¹²

⁷ Serono Lab., 158 F.3d at 1317.

⁸ Aventis Supplement at 4.

⁹ Aventis merely hypothesizes that “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 . . . [and that] [t]hese sequence variations may cause differences in the half-lives of the anti-Xa activity, leading to different overall anti-coagulation profiles.” Id. (emphasis added).

¹⁰ Id. at 3.

¹¹ Id. at 4.

¹² Id. at 5.

Aventis conducted in vitro experiments to measure the ATIII affinity of its three octasaccharide sequences and the anti-Xa activity.¹³ Aventis speculates that “sequence variations may cause differences in the half-lives of the anti-Xa activity, leading to different overall anti-coagulation profiles.”¹⁴ Aventis concluded based on these experiments that “different octasaccharide variants in enoxaparin do not have identical in vitro anti-Xa activity and [that] there can be considerable variation in affinity for ATIII.”¹⁵

Aventis indicates that different binding sequences may demonstrate different binding potencies and ultimately may lead to different anti-coagulation profiles.¹⁶ But Aventis can only speculate as to whether this factor has any influence at all on the safety and effectiveness of enoxaparin.¹⁷

Aventis fails to establish any scientific basis for requiring a generic enoxaparin to demonstrate equivalence beyond traditional indicators such as average molecular weight, anti-X_a activity, and anti-X_a/anti-II_a ratio.

C. 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) in order to market a generic version of a drug. Aventis’s request is literally impossible. To require clinical studies of

¹³ Id. at 6.

¹⁴ Id. at 4.

¹⁵ Id. at 6-7.

¹⁶ Id. at 4.

¹⁷ Id. at 7.

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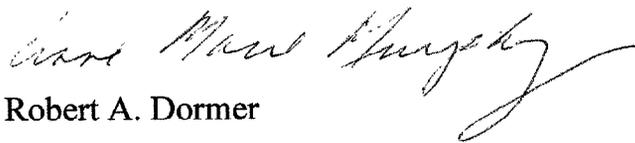
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safety and effectiveness for approval of an ANDA would mean that the application is no longer an ANDA.

To the extent that Aventis argues that a generic applicant must use the same manufacturing process to achieve sameness, its reasoning is flawed. As discussed in section I.B. above, duplicating an innovator's manufacturing process is not required by law and is not the standard for demonstrating sameness of a generic product.

For all the aforementioned reasons, the undersigned respectfully request that FDA deny Aventis's first request under the Citizen Petition.

Sincerely,



Robert A. Dormer

Anne Marie Murphy

RAD/AMM/vam