

Aventis



September 1, 2004

BY HAND DELIVERY

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

Re: Comment to Citizen Petition (03P-0064)

Ladies and Gentlemen:

On May 13, 2004, Amphastar Pharmaceuticals, Inc. sent a letter to Acting Commissioner Lester Crawford regarding its ANDA for generic enoxaparin sodium injection. On June 4, 2004, FDA filed that letter to the above-referenced docket as Comment 2. This letter advises FDA that Aventis is currently in the process of developing a detailed response to Amphastar's submission.

Amphastar's Comment presents results of additional testing by Amphastar, comparing its proposed generic product to Aventis' innovator product, Lovenox[®]. Based on the results of these new studies, Amphastar urges FDA to determine that Amphastar's generic enoxaparin sodium product is equivalent to Lovenox[®].

These new studies, however, fail to establish that Amphastar's generic product will have the same safety and effectiveness profile as enoxaparin. In a Citizen Petition filed on February 19, 2003 (03P-0064/CP1), and a Supplement filed on February 13, 2004, Aventis identified several important structural modifications (or "fingerprints") that are distinct to enoxaparin and are a product of Aventis' particular manufacturing process. The Petition and Supplement show that these fingerprints make important contributions to enoxaparin's overall pharmacological effect, and likely bear clinical significance. FDA appears to agree, as it recently approved Aventis' sNDA making one of these fingerprints (the 1,6 anhydro ring structure) a necessary component of any product claiming to be enoxaparin.

Amphastar's submission of June 4 does not demonstrate that Amphastar's product contains the 1,6 anhydro ring structure, or the other currently identified important structural fingerprints of enoxaparin. Nor does it establish that, despite the absence of these fingerprints,

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its product will nevertheless exhibit the same safety and effectiveness profile as enoxaparin. Unless Amphastar conducts clinical testing or demonstrates that its manufacturing process is equivalent to Aventis', it will not be able to ensure that the important differences in pharmacological activity caused by these known fingerprints will be present in its generic product.

In addition, Amphastar's recent submission appears to ignore one of the central points of the Citizen Petition and Supplement. Because enoxaparin is not yet fully characterized, there are likely additional, as yet undiscovered, fingerprints created by Aventis' manufacturing process. It is reasonable to assume, therefore, that as enoxaparin becomes more characterized additional fingerprints will be discovered that also make important contributions to enoxaparin. Despite the data that Amphastar provided in its June 4 submission, Amphastar cannot ensure that its product will contain these as yet undiscovered fingerprints unless Amphastar uses a manufacturing process that is equivalent to Aventis'. Aventis strongly believes that approval of a generic enoxaparin product without supporting clinical testing or proof of an equivalent manufacturing process may jeopardize patients safety.

We are therefore in the process of preparing a detailed response to Amphastar's Comment of June 4. Recently (August 9, 2004), however, Hyman Phelps filed an additional comment to the Lovenox[®] docket (03P-0064/C3). We are in the process of reviewing this comment with counsel. Because of the presence of this new comment, we now plan to respond to both C2 and C3 at the same time, in a single document, rather than filing separate comments to address them individually.

Should you have any questions, please feel free to contact our regulatory counsel, Peter Safir and Scott Cunningham at 202-662-6000. Thank you.

Respectfully submitted



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