



**AMPHASTAR PHARMACEUTICALS, INC.**

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November 23, 2004

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

**RE: Docket Number 2003P-0064: Comments in Response to Aventis' October 13, 2004 Submission (RC1)**

Dear Sir or Madam:

This document is submitted on behalf of Amphastar Pharmaceuticals, Inc., (“Amphastar”) in response to Aventis Pharmaceuticals’ (“Aventis”) latest submission to the above-referenced docket in its ongoing attempt to delay approval of generic enoxaparin products. In March 2003, Amphastar submitted to FDA an abbreviated new drug application (“ANDA”) for enoxaparin sodium.

On February 19, 2003, Aventis, through its counsel filed the above referenced Citizen Petition requesting that the 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.” On February 12, 2004, Aventis filed a supplement to its Citizen Petition. On October 13, 2004, Aventis filed a response (“Aventis Response”) to three of the four comments that have been submitted in response to the Citizen Petition, including comments submitted to FDA by Amphastar in a letter dated May 13, 2004 (“Amphastar Comment”). Amphastar’s Comment was submitted to the docket on June 1, 2004.

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**I. Amphastar's Comment Explained that its Enoxaparin Sodium Product is the Same as Lovenox.**

Amphastar's Comment summarized and provided documentation of studies which taken together establish that Amphastar's proposed generic enoxaparin sodium product is the same as Aventis' Lovenox. These studies include comparisons of the products' physical and chemical properties including molecular weight, biochemical activity with respect to anti-factors Xa, IIa, and their ratio, characterization of enoxaparin sodium by UV spectrum, IR spectrum, proton NMR spectrum, C<sub>13</sub> NMR spectrum, HPLC-SAX chromatogram, and HPLC-SEC chromatogram, examination of disaccharide building blocks, direct analysis of certain sequences of saccharide contained in the major oligosaccharides found in enoxaparin sodium, and in vivo profile studies comparing anti-Xa and anti-IIa activity.

Amphastar's Comment also argued that Aventis' manufacturing process is not uniquely defined. In any event, there is no requirement that generic drugs have to use the same manufacturing process as the innovator. As described in an earlier comment submitted in response to the Aventis Citizen Petition, duplicating the innovator's manufacturing process is not required by law or regulations. It is not the standard for demonstrating "sameness."<sup>1</sup> The requirements that a generic applicant demonstrate sameness and describe its manufacturing process are two distinct requirements set forth in 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).<sup>2</sup>

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<sup>1</sup> Comments in Opposition to Aventis' Citizen Petition on Enoxaparin Sodium, submitted by Hyman, Phelps & McNamara, P.C. ("C1") at 8 (October 17, 2003).

<sup>2</sup> Id. at 8-9.

## II. Aventis' Arguments are Flawed.

The October 13, 2004 Aventis Response, among other things, criticizes Amphastar's enoxaparin data. Aventis' criticisms are in part irrelevant and in part based on an apparent misunderstanding of the underlying data. Indeed, the data supplied in the Amphastar Comment, taken together, establish that Amphastar's enoxaparin sodium is the same as Aventis's Lovenox, and support Amphastar's request that the Citizen Petition be denied without delay.

### A. Aventis' discussion of the importance of the 1,6 anhydro ring is moot as to Amphastar's product.

Aventis' Response discusses at length the importance of the 1, 6 anhydro ring structure and cites its experimental work with enoxaparin containing a greater or lesser percentage of the structure than is called for in the current product labeling.<sup>3</sup> This issue has no bearing on approval of Amphastar's product. Amphastar has submitted data in its ANDA that demonstrate the presence of the 1, 6 anhydro ring structure in the appropriate percentage of its enoxaparin sodium product.

### B. Aventis misunderstands or Incorrectly Compares Chromatograms

Aventis claims that Amphastar's chromatograms are not reliable.<sup>4</sup> This demonstrates a fundamental misunderstanding of the specific study objectives under which the chromatograms were prepared.

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<sup>3</sup> Aventis Response at 5-6.

<sup>4</sup> Id. at 9-12.

To investigate the composition of enoxaparin sodium, chromatograms are prepared at different levels of detail to achieve different objectives. First, to understand the overall composition (i.e., to get a global picture) various major subgroups such as the tetrasaccharides, hexasaccharides, and octasaccharides are separated. This may be termed, for convenience purposes, as the “Level-1 Detail” of a chromatogram study. Second, to separate as many individual components as possible into single peaks, a higher resolution chromatogram is prepared. This may be termed as the “Level-2 Detail” of a chromatogram study. Finally, to further study each individual peak identified in a Level-2 Detail study, more advanced technology such as mass spectroscopy may be used. This is termed the “Level-3 Detail” of a chromatogram study. Obviously, the Level-3 Detail provides more detailed information (such as mass spectrum) at each moment of the chromatogram of a Level-2 Detail study.

Study of complicated systems at various levels is a very common philosophy used in scientific investigation. For example, a human body study may be performed at several levels of detail: Level-1, Global information such as height and body weight; Level-2, organ system information to study brain, heart, lung, etc; Level-3, cell information, cell nuclei etc; and Level-4, molecular level, etc.

In reaching its flawed conclusion that Amphastar’s chromatograms are unreliable, Aventis compared a Level-1 chromatogram prepared by Amphastar to a higher resolution Level-2 chromatogram of its own.<sup>5</sup> Amphastar provided much more detailed studies (Level-3) in Amphastar’s Comments.<sup>6</sup> Aventis fails to explain why it did not compare like chromatograms.

A comparison between studies performed at different levels of detail is meaningless.

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<sup>5</sup> Aventis Response at 9-10, figures 2 and 3.

<sup>6</sup> Amphastar Comment at 6-9.

In addition, Aventis compared Amphastar's chromatogram of enoxaparin disaccharide building blocks (Figure 4) to its own chromatogram of a similar study of Lovenox (Figure 5).<sup>7</sup> In comparing these chromatograms, Aventis concluded that Amphastar's chromatogram lacked clarity. In fact, this comparison is misleading too. Figure 4 (Amphastar) shows the complete chromatogram whereas Figure 5 (Aventis) shows only the bottom portion of the chromatogram. The main peak in Figure 5 appears to have been truncated and the bottom portion enlarged. The difference between a complete chromatogram and an enlarged truncated chromatogram would be evident to a chemist experienced in chromatography. It is definitely misleading to compare two chromatograms at different scales.

It is unclear why Aventis chose to challenge Amphastar in this way.

Aventis's criticisms of Amphastar's data are flawed. The data submitted in the Amphastar Comment establish that Amphastar's enoxaparin sodium is the same as Lovenox.

**C. Dimethyl Formamide ("DMF").**

As Aventis notes, Appendix 2 of Amphastar's Comment compared three lots of Amphastar's enoxaparin active pharmaceutical ingredient ("API") to that of three lots of Lovenox per the specifications set forth in the European Pharmacopoeia. Since Lovenox API is not available, laboratory lots of API were prepared from Lovenox finished product. It is obvious the API prepared from Lovenox lot number 1446 was contaminated with DMF to a detectable level (the contaminated level is about one tenth of the allowed amount per specification) during the lyophilization process. We have no

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<sup>7</sup> Aventis Response at 11-12.

reason to believe, however, that this would call into question the other specifications that were tested in that lot or the others.

**D. Aventis does not understand that some comparisons must use finished products, and some must use API**

Aventis complains that in conducting its comparative analyses Amphastar “picks and chooses” its batches. The two sets of batch numbers challenged by Aventis differ because one set is for finished product (112002C, 112002D and 111802A) and the other (EO093002, EO100202 and EO101402) is for API. Depending upon the comparison item being tested, API or finished product was used as appropriate. For example, color of solution etc. must be compared with finished product; Nitrogen amount (by weight) or NMR etc. must be compared with API.

As is required in pharmaceutical manufacturing, the batch numbers for finished product and API are different. Aventis ignores this differentiation and attempts to compare materials at different points in the overall manufacturing process.

Therefore Aventis’ claim that Amphastar “picks and chooses” its batches are misleading.

**E. Amphastar compared the pH of the finished product.**

Aventis argues that Amphastar’s pH measurements must be incorrect because pH should be tested on a 1% solution for the API and on a 10% solution for the finished product and the measurements are the same in both Appendices 2 and 3 of Amphastar’s May 13 2004 comment.<sup>8</sup> The Appendix-2 cited by Aventis is only a portion of an

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<sup>8</sup> Aventis Response at 15.

Amphastar report that compares the API of Amphastar and Lovenox. However, due to the limited amount of API for Lovenox, the listed pH values were for Lovenox finished product as explained in the text of the report.

In summary, Aventis' criticisms of Amphastar's data are flawed. The data submitted in the Amphastar Comment establish that Amphastar's enoxaparin sodium is the same as Lovenox. Therefore, for the reasons cited above as well as those cited in our earlier May 13, 2004 submission, Amphastar respectfully requests that Citizen Petition 2003P-0064 be denied without delay.

Respectfully,

A handwritten signature in black ink, appearing to read "Stephen A. Campbell". The signature is fluid and cursive, with a large initial "S" and "C".

Stephen A. Campbell, Esq.  
Senior VP, Regulatory Affairs