

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON
NEW YORK
SAN FRANCISCO
LONDON
BRUSSELS

110 32 117 2000

March 17, 2005

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: Docket Number 2003P-0064: Response to Amphastar
Pharmaceuticals, Inc. Comment of November 23, 2004 (C6)**

On November 23, 2004, Amphastar Pharmaceuticals, Inc. ("Amphastar") filed a second comment to the above-referenced docket (the "November 23rd Amphastar Comment").¹ The undersigned, on behalf of Aventis Pharmaceuticals, Inc., a subsidiary of sanofi-aventis, successor in interest to Aventis Pharmaceuticals, SA ("sanofi-aventis"), now submits these comments in response to certain matters raised in the November 23rd Amphastar Comment.

I. The November 23rd Amphastar Comment Does Not Resolve the Flaws in Amphastar's Chromatograms

On June 4, 2004, Amphastar submitted a comment to this docket containing several chromatograms of its proposed generic version of enoxaparin.² Amphastar provided these chromatograms in an effort to demonstrate that its proposed generic product is equivalent to sanofi-aventis' marketed product, Lovenox[®] (enoxaparin sodium) ("Enoxaparin"). On October 13, 2004, sanofi-aventis submitted a comment pointing out that Amphastar's chromatograms are (a) flawed, and (b) insufficient (even were they not flawed) to ensure that Amphastar's proposed generic is equivalent to Enoxaparin.³

¹ FDA docket number 2003P-0064/C6 (November 23, 2004).

² FDA docket number 2003P-0064/C2 (Filed by FDA to this docket on June 4, 2004).

³ FDA docket number 2003P-0064/RC1 (October 13, 2004).

2003P-0064

RC 2

Dockets Management Branch (HFA-305)
March 17, 2005
Page 2

In the November 23rd Amphastar Comment, Amphastar attempted to provide a response to sanofi-aventis' critiques. As discussed below, however, Amphastar's response fails to adequately address the issues sanofi-aventis raised regarding these test results.

A. Amphastar's Direct Analysis Chromatograms Provide Insufficient Detail for a Comparison of Amphastar's Product to Enoxaparin

In its submission of October 13, 2004, sanofi-aventis pointed out that Amphastar's direct analysis HPLC-SAX chromatogram (reprinted here as Figure 1) is poorly resolved and therefore cannot be used to establish equivalence between Amphastar's proposed generic product and Enoxaparin.⁴ To illustrate this point, sanofi-aventis provided its own direct analysis chromatogram (reprinted here as Figure 2) and pointed to distinct differences in resolution and clarity between the two.⁵

In its November 23rd Amphastar Comment, Amphastar responded that sanofi-aventis has simply misunderstood the "specific study objectives under which the chromatograms were prepared."⁶ Amphastar argued that different chromatograms are intended to provide different levels of detail depending upon the objectives of the chromatogram. For example, Amphastar asserted that so-called "Level-1" chromatograms contain less detail in order to provide a "global picture." Level-2 and Level-3 chromatograms contain greater detail, and are therefore used to accomplish different objectives.⁷ Amphastar concluded that sanofi-aventis unfairly "compared a Level-1 chromatogram prepared by Amphastar to a higher resolution Level-2 chromatogram of its own."⁸

This explanation, however, misses the point of sanofi-aventis' critique. To compare two complex products through chromatography, one must provide the highest level of resolution available in order to compare even the smaller peaks. Amphastar has presented the chromatogram in Figure 1 as evidence that its product is equivalent to Enoxaparin. Yet its resolution is sufficient only to provide a very general view of Amphastar's product.⁹ If

⁴ *See id.* at 9.

⁵ *See id.* at 10.

⁶ November 23rd Amphastar Comment, at 3

⁷ *See id.* at 4

⁸ *Id.*

⁹ Amphastar claims that its June 4, 2004 comment provided a more detailed "study" and questions why sanofi-aventis "did not compare like chromatograms." *See* November 23rd Amphastar Comment, at 4. Even a brief examination of Amphastar's June 4, 2004 comment, (continued...)

COVINGTON & BURLING

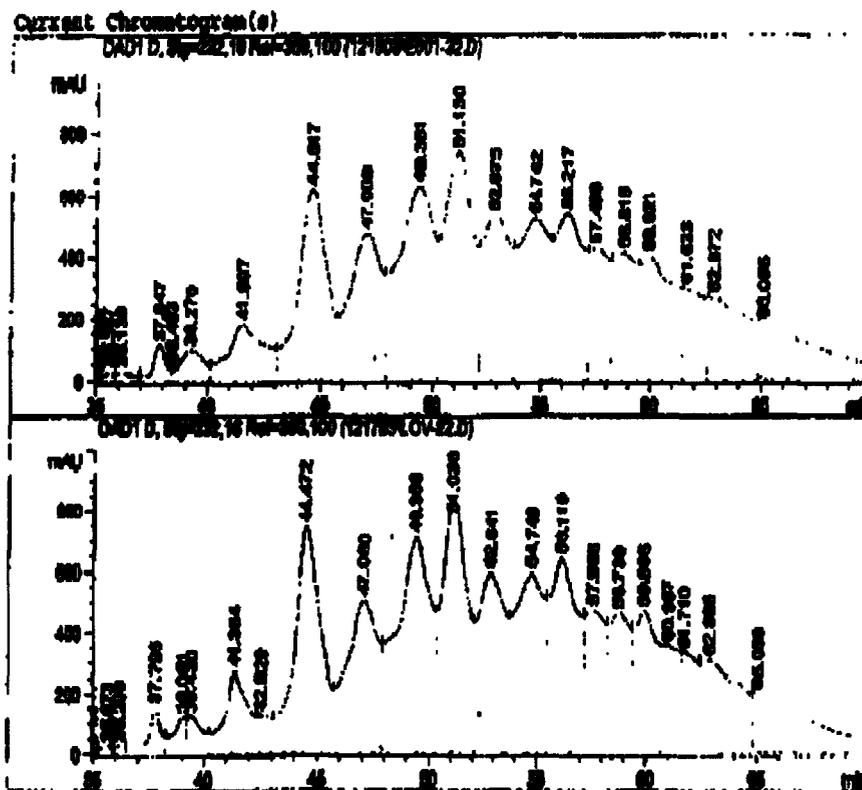
Dockets Management Branch (HFA-305)

March 17, 2005

Page 3

Amphastar wishes to compare its product to Enoxaparin, it would be better to employ state-of-the-art chromatographic resolution technology, such as CTA-SAX technology, as sanofi-aventis has done in Figure 2. Only then can the scientific community even begin to meaningfully compare the chromatograms and evaluate the differences.

Figure 1: Amphastar HPLC -SAX chromatography of LMWH batches (reprinted from Amphastar's June 4, 2004 Comment, Appendix 3, 2003P-0064/C2).

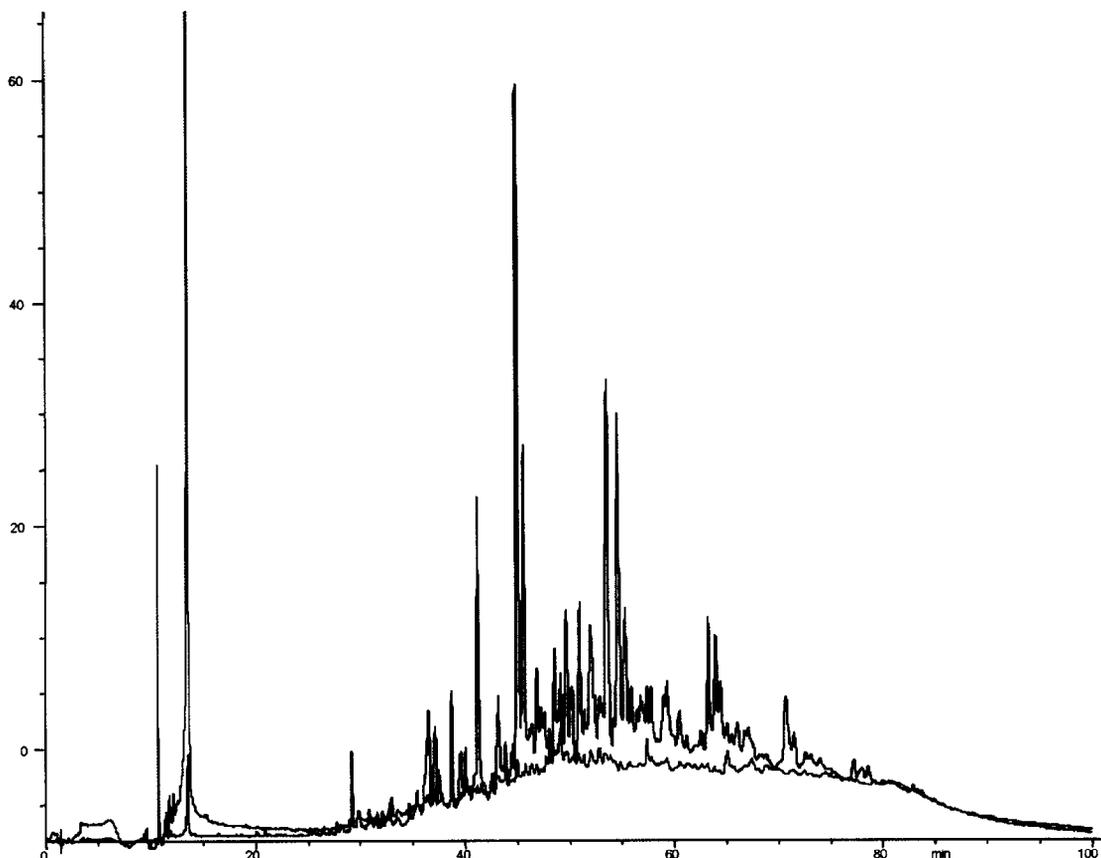


Dockets Management Branch (HFA-305)

March 17, 2005

Page 4

Figure 2: Experimental CTA-SAX chromatography of a Lovenox[®] batch (detection — 232nm ; — 202 – 245nm), prepared by sanofi-aventis.



B. Amphastar's Building Block Chromatograms Are Fatally Flawed

In addition to the direct analysis chromatogram in Figure 1, Amphastar's June 4, 2004 comment also provided a so-called "building blocks" chromatogram of its product after controlled heparinase pretreatment.¹⁰ As stated in sanofi-aventis' October 13, 2004 comment, however, this chromatogram (reprinted in Figure 3) is also flawed.

In this type of analysis, the most obvious examination technique is the exhaustive depolymerization of Enoxaparin by the mixture of heparinases (I, II, and III) that lead mainly to a mixture of disaccharides. However, some oligosaccharidic moieties (e.g. 3-O sulfated

¹⁰ FDA docket number 2003P-0064/C2, at Appendix 3, page 8 (Filed by FDA to this docket on June 4, 2004).

COVINGTON & BURLING

Dockets Management Branch (HFA-305)

March 17, 2005

Page 5

disaccharides and 1,6-anhydro groups) cannot be cleaved by heparinases and therefore remain as tri or tetrasaccharides. These resistant tri and tetrasaccharides comprise only a certain amount of the total Enoxaparin mixture.

In Amphastar's building blocks chromatogram, however, these resistant tri and tetrasaccharides make up too large a percentage of Amphastar's overall mixture. This can be seen in the number of peaks to the right of the main peak at about 30 minutes (the disaccharide containing three sulfate groups (Δ UA(2S)-GlcNS(6S)). At higher retention times (35 to 50 min) only tetrasaccharides can elute. Given the number of peaks in the 35-50 minute range in Amphastar's Figure 3 chromatogram, it is clear that Amphastar's product contains more tetrasaccharides than that found in Enoxaparin. Clearly, Amphastar's pretreatment process has not exhaustively digested the product. Thus, Amphastar's building blocks chromatogram cannot be used to compare Amphastar's proposed generic product to Enoxaparin.

Figure 3: Chromatograms of "LMWH disaccharide building blocks" (reprinted from Amphastar's June 4, 2004 Comment, Appendix 3, 2003P-0064/C2).



Dockets Management Branch (HFA-305)

March 17, 2005

Page 6

C. Amphastar's Critique of Sanofi-Aventis' Building Blocks Chromatogram Are Irrelevant

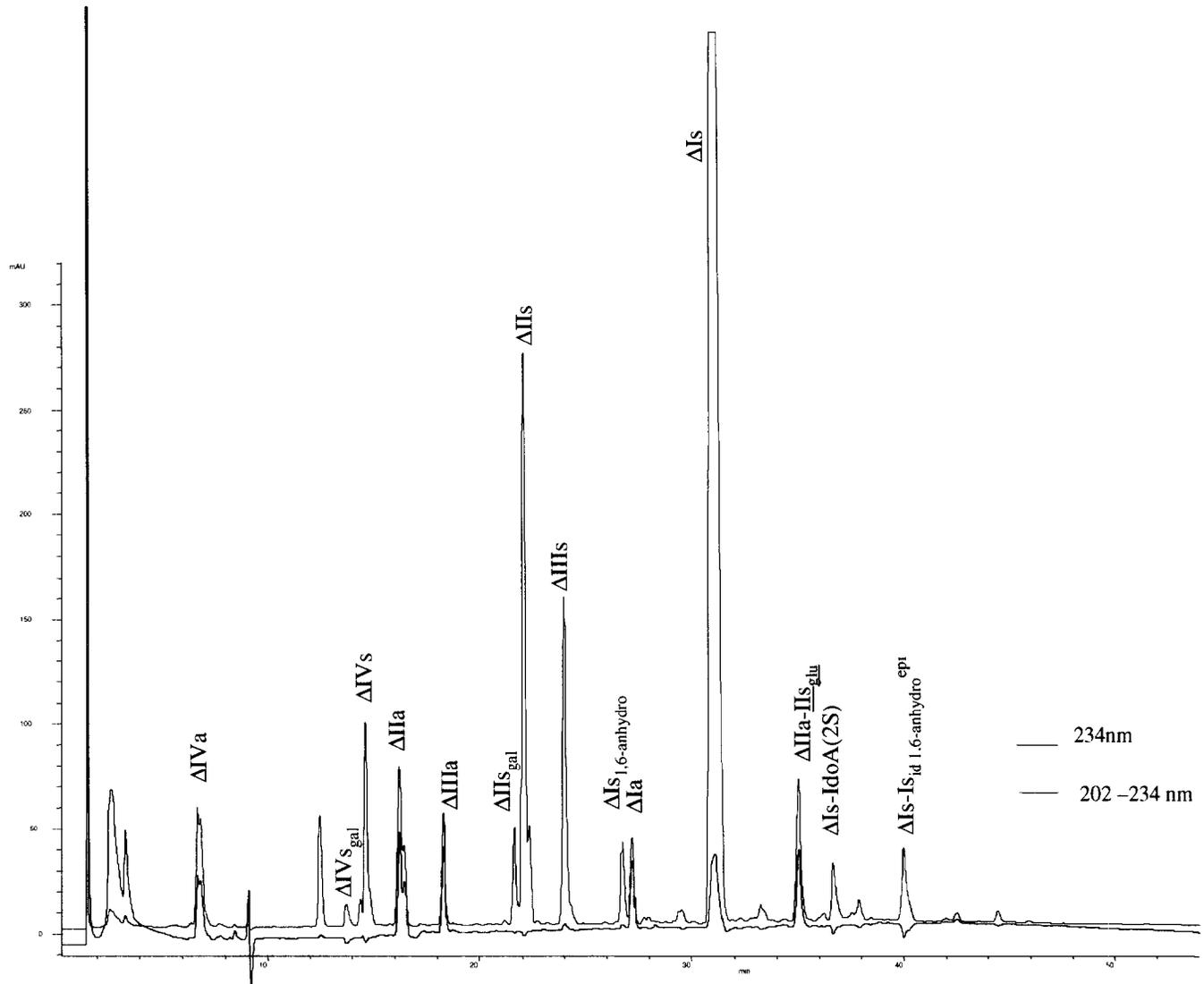
In its November 23rd Comment, Amphastar attempts to defend its flawed building blocks chromatogram (Figure 3) by attacking the comparison sanofi-aventis drew to its building blocks chromatogram (reprinted here in Figure 4). Amphastar argued that sanofi-aventis' Figure 4 chromatogram is truncated, providing only the bottom portion. Thus, it is misleading to compare it to Amphastar's complete chromatogram (Figure 3).¹¹

This argument ignores the fundamental point of chromatogram analysis. Cutting the higher part of a building blocks chromatogram, as sanofi-aventis has done in Figure 4, is the only way to amplify the chromatogram so as to focus on the most interesting part - namely the smaller peaks. These smaller peaks such as the di and tetrasaccharides bearing the 1,6-anhydro ring structure are the key elements that show Enoxaparin's product characteristics. Those smaller building blocks are also key to revealing the dramatic complexity of the heparinoid structure. For example, after exhaustive depolymerization, the 1,6-anhydro saccharides represent about three percent of the total chromatographic area. This means that the degree of precision of the chromatogram provides resolution at even lower than the one percent level. These saccharides that are observable in an amplified and highly resolved chromatogram are born by about 20 percent of the oligosaccharide chains in Enoxaparin and may have significant effect on their biological properties.

One need not run a chromatogram of Enoxaparin to know that the Δ UA(2S)-GlcNS(6S) disaccharide is the main building block of the product. Yet this is all that Amphastar has done with its chromatogram in Figure 3. It is a well known limitation of the disaccharide building blocks methodology that it only enables one to quantitate the disaccharide units from which the heparinoid is made. However, any information regarding how these building blocks are assembled in the polysaccharide chains is completely lost. Therefore, the only useful information gained by this methodology is to be found in the small characteristic peaks. This is precisely what sanofi-aventis has shown in its "truncated" building blocks chromatogram in Figure 4. For a meaningful comparison of chromatograms, Amphastar should have shown at least an expanded view of the key disaccharide building blocks to compare it accurately to the sanofi-aventis chromatogram. Because Amphastar didn't provide such comparison, its chromatograms are of little value in comparing its proposed generic product to Enoxaparin.

¹¹ November 23rd Amphastar Comment, at 5.

Figure 4: Chromatogram of an exhaustively depolymerized Lovenox® batch.¹²



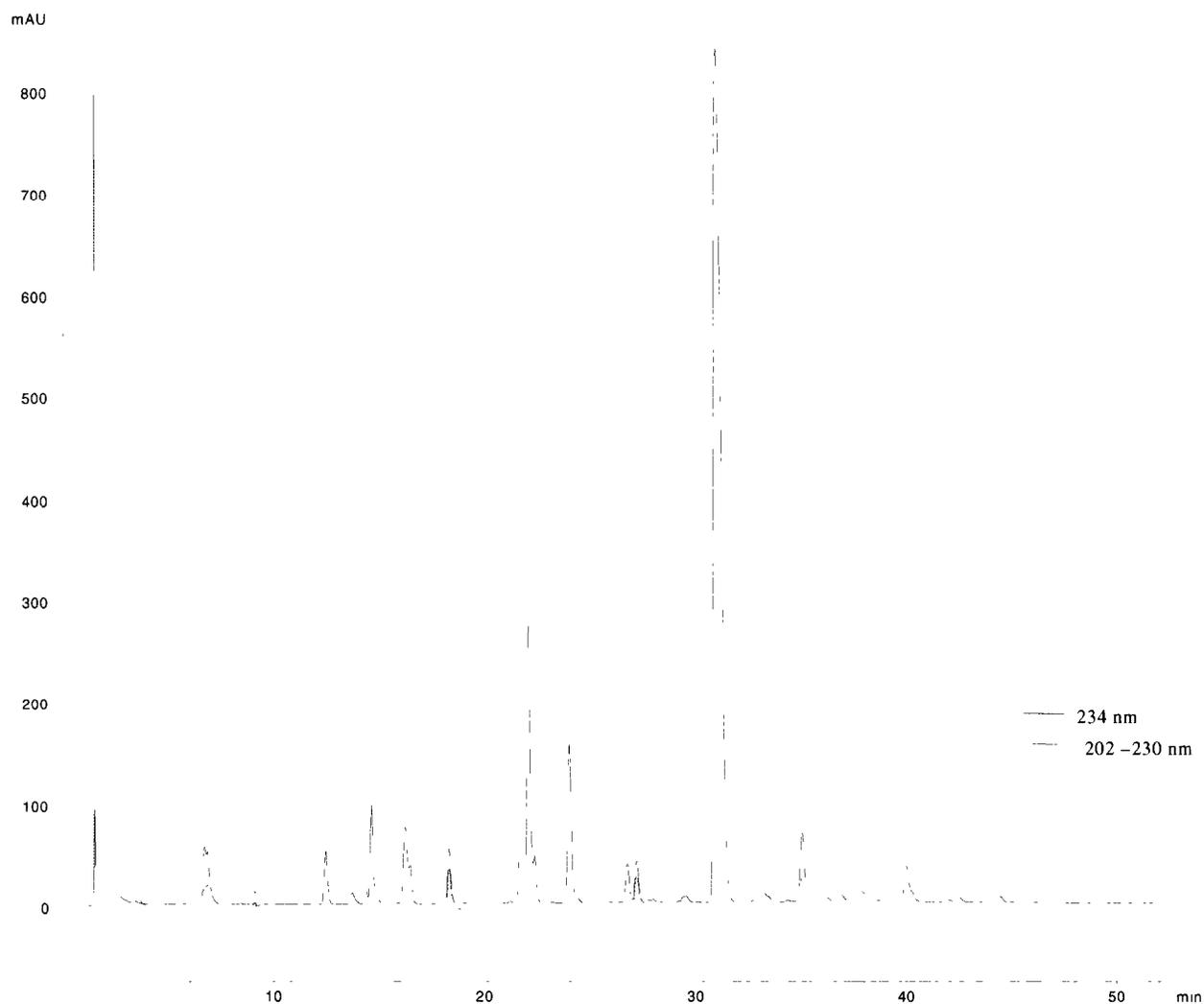
In order to fully-address Amphastar’s complaint, however, Figure 5 presents a “non-truncated” version of sanofi-aventis’ building blocks chromatogram. Even in this chromatogram at Amphastar’s suggested scale, sanofi-aventis’ building block peaks are far more highly resolved, thus providing meaningful information about Enoxaparin’s fingerprints. Even comparing Amphastar’s chromatogram in Figure 3 with sanofi-aventis’ chromatogram in Figure

¹² Figure excerpted from International Patent Application WO 2004/027087 A2.

Dockets Management Branch (HFA-305)
March 17, 2005
Page 8

5 makes clear that Amphastar's chromatograms are flawed, and incapable of rendering a useful comparison of products.

Figure 5: Full chromatogram of an exhaustively depolymerized Lovenox[®] batch



II. Amphastar Has Failed to Address the Principal Issue in Sanofi-Aventis' Critique

In addition to its critiques of Amphastar's chromatograms and other test results, sanofi-aventis' October 13, 2004 comment made a separate, more fundamental point. Even if Amphastar's data were reliable (which they are not), they still would not demonstrate that Amphastar's proposed generic is equivalent to Enoxaparin. As sanofi-aventis has pointed out

Dockets Management Branch (HFA-305)

March 17, 2005

Page 9

several times in this docket, and has been independently confirmed in peer-reviewed journals, the mechanisms by which Enoxaparin achieves its pharmacological effects are not yet fully-understood. Thus, simple physico-chemical comparisons, such as those conducted by Amphastar, cannot ensure that a generic product will have the same safety and effectiveness profile as Enoxaparin.

Nowhere in either of its comments does Amphastar address this most fundamental problem of generic Enoxaparin. As sanofi-aventis has explained previously, Enoxaparin is created by applying a specified and tightly-controlled manufacturing process to organic material (porcine intestinal heparin), rather than through synthesis of known and fully-characterized chemical compounds. Thus, Enoxaparin resembles a biologic product far more than it does a traditional drug product. Neither Amphastar (nor Teva or Hyman-Phelps for that matter) have made any attempt to define the types of data and/or testing that would be sufficient to assure that a proposed generic product would provide the same safety and effectiveness profiles as a process-dependent biologically-derived product like Enoxaparin. Instead, they have provided only limited data and declared that this demonstrates equivalence, because they say so.

Amphastar's chromatograms provide a good example. In its June 4, 2004 submission, Amphastar announced that its chromatograms and other test results "indicate that Amphastar's Enoxaparin Sodium is equivalent to Aventis' Lovenox."¹³ Amphastar provided no explanation, however, for how these simple physico-chemical studies confirm that its product will have the same safety and effectiveness profile as Enoxaparin. It did not, for example, explain how these studies ensure that the uncharacterized portions of Enoxaparin do not contain yet unidentified fingerprints with potential clinical significance. Nor did it explain how these tests sufficiently guarantee sameness in a complex, process-dependant biologically-derived product. Sanofi-aventis pointed out this shortcoming in its October 13, 2004 submission.¹⁴ Amphastar has simply chosen not to address it.

Another example of Amphastar's unwillingness to face the larger issues involved in generic Enoxaparin is its discussion of the 1,6-anhydro ring structure. In its November 23rd Amphastar Comment, Amphastar states that "[t]his 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."¹⁵ Once again, this fundamentally ignores the broader issues that the example of the 1,6-anhydro ring structure presents.

¹³ FDA docket number 2003P-0064/C6.

¹⁴ See FDA docket number 2003P-0064/RC1, at 4-9.

¹⁵ FDA docket number 2003P-0064/C6, at 3.

Dockets Management Branch (HFA-305)

March 17, 2005

Page 10

In its original Citizen Petition, as well as the Supplement, sanofi-aventis presented data on the contribution of the 1,6-anhydro ring structure for two equally important reasons. First, rigorous scientific testing has confirmed that the 1,6-anhydro ring structure makes important contributions to Enoxaparin's overall anti-coagulant and non-anticoagulant activity, and many of these contributions may have clinical significance.¹⁶ As a result, it is critical that any proposed generic version of Enoxaparin contain the 1,6-anhydro ring structure in the proper concentration.

The Citizen Petition and Supplement also make clear, however, that the 1,6-anhydro ring structure is simply one example of a process-dependent structural fingerprint with potential clinical significance. The 1,6-anhydro ring structure is formed as a result of sanofi-aventis' specific manufacturing process.¹⁷ This same process also creates additional structural fingerprints in Enoxaparin that may have clinical significance. Some of these have already been identified and are discussed in the Citizen Petition and Supplement.¹⁸ Some others, however, have not yet been identified and may even reside in those portions of the macromolecule that have not yet been characterized. Because these fingerprints are process-dependent, a manufacturing process that is not equivalent to sanofi-aventis' process may generate some of these fingerprints, but not all of them. This may have significant impact on the overall safety and effectiveness profile of the generic product.

As a result, it is not enough for Amphastar, or any other generic manufacturer, to state that its product is equivalent to Enoxaparin because it contains the 1,6-anhydro ring structure. Amphastar's manufacturing process may (or may not) result in the formation of the 1,6-anhydro ring structure. But this is no guarantee that the other Enoxaparin structural fingerprints with possible clinical significance such as the process dependant ATIII binding sites or other as yet unidentified fingerprints will be present. Amphastar must therefore go further to demonstrate that its product includes all of the structural fingerprints (identified or as yet unidentified) contained in Enoxaparin that may have clinical significance. It can do this only by using a manufacturing process that is equivalent to sanofi-aventis' process for Enoxaparin. Otherwise, it must provide clinical testing sufficient to show that its product's overall safety and effectiveness profile is equivalent to Enoxaparin's. Only then can it truly state that the issues raised by the 1,6-anhydro ring structure have "no bearing on approval of Amphastar's product."

¹⁶ See Sanofi-Aventis Citizen Petition, at 13-19 (2003P-0064/CP1); Sanofi-Aventis Citizen Petition Supplement, at 8-14 (2003P-0064/SUP1).

¹⁷ See *id.*

¹⁸ See *id.*

COVINGTON & BURLING

Dockets Management Branch (HFA-305)

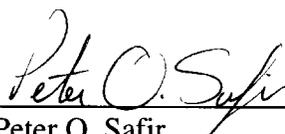
March 17, 2005

Page 11

III. Conclusion

For the reasons outlined herein, as well as in sanofi-aventis' Citizen Petition and other submissions to this docket, Amphastar has not demonstrated that its proposed generic product is equivalent to Enoxaparin, even if it contains the 1,6-anhydro ring structure.

Respectfully submitted,



Peter O. Safir

Scott L. Cunningham

By: SLC

Covington & Burling
1201 Pennsylvania Ave., N.W.
Washington, D.C. 20004-2401

Counsel to Aventis Pharmaceuticals, Inc.