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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 Amphastar Pharmaceuticals, Inc. (C2), Hyman, Phelps (C3), and Teva Pharmaceuticals USA (C4)

Since Aventis filed its Citizen Petition on February 19, 2003¹, there have been four comments filed to the above-referenced docket. Aventis responded to the first comment in a Citizen Petition Supplement dated February 12, 2004.² Therefore, the undersigned, on behalf of Aventis Pharmaceuticals Inc., a subsidiary of Aventis SA, submits this response addressing the last three comments.

Comment Two

On June 4, 2004, FDA filed a letter from Amphastar Pharmaceuticals, Inc. to the above-referenced docket as Comment Two (the "Amphastar Comment").³
The Amphastar Comment:

1. provides the results of various tests Amphastar has conducted on its proposed generic enoxaparin sodium product, which it claims renders its

¹ FDA docket number 2003P-0064/CP1 (February 19, 2003) (the "Citizen Petition").

² FDA docket number 2003P-0064/SUP1 (February 12, 2004) (the Citizen Petition Supplement").

³ FDA docket number 2003P-0064/C2 (June 4, 2004).

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product equivalent to the reference listed drug, Aventis' Lovenox[®] (enoxaparin sodium) ("Enoxaparin"); and

2. disputes that Aventis' manufacturing process is uniquely defined and highly sensitive by alleging that Aventis has made multiple changes to its manufacturing process from March 1996 to April 2004.

Comment Three

On August 4, 2004, Hyman, Phelps & McNamara, P.C. filed Comment Three to the same docket (the "Hyman Comment").⁴ The Hyman Comment argues that:

1. FDA should approve ANDAs citing Lovenox[®] as the reference listed drug even though Enoxaparin has not been fully characterized;
2. duplicating an innovator's manufacturing process is not required by law; it is not the standard for demonstrating "sameness"; and
3. requiring ANDA applicants to demonstrate safety and effectiveness through clinical trials is inconsistent with the regulatory scheme.

Comment Four

On August 31, 2004, Teva Pharmaceuticals USA filed Comment Four expressing its views (the "Teva Comment").⁵ Some of Teva's arguments overlap with the Hyman Comment. Additionally, the Teva Comment presents results of tests provided in a third party's patent application allegedly assessing batch-to-batch variability of Enoxaparin.

For the reasons described herein, Aventis disagrees with the arguments in the Amphastar, Hyman, and Teva Comments. Not only are the scientific data presented by these comments flawed and unreliable, they also fail to establish the points that they are intended to support. In addition, the comments regarding purported changes in Aventis' manufacturing process for Enoxaparin are factually inaccurate. Finally, the legal arguments in the comments reveal fundamental misunderstandings of

⁴ FDA docket number 2003P-0064/C3 (August 4, 2004). This is the second comment that Hyman, Phelps has filed to this docket. Aventis responded to Hyman, Phelps' original comment (Comment 1) in its Citizen Petition Supplement of February 12, 2004.

⁵ FDA docket number 2003P-0064/C4 (August 31, 2004).

both the Citizen Petition and the statutory and regulatory scheme for approval of generic drugs.

I. The Comparative Analyses Provided by Amphastar Do Not Establish Similarity Between Its Proposed Generic Product and Enoxaparin

The Amphastar Comment presents data regarding tests Amphastar has run comparing Enoxaparin to its proposed generic product. The results of these tests, presented in Appendices 2 and 3 of the Amphastar Comment (the “Amphastar Data”) include:

- Equivalence comparison of physical properties and chemical properties
- Equivalence comparison of molecular weight, average, and distribution
- Equivalence comparison of biochemical activity, anti-factors Xa, IIa, and their ratio
- Characterization of Enoxaparin Sodium by UV spectrum, IR spectrum, proton NMR spectrum, C13 NMR spectrum, HPLC-SAX chromatogram, and HPLC-SEC chromatogram
- Examination of disaccharide building blocks
- Direct analysis of some of the sequences of saccharide contained in the major oligosaccharides found in Enoxaparin Sodium
- *In vivo* profile studies comparing the Anti-Xa and Anti-IIa⁶

Amphastar then claims that these studies “indicate that Amphastar’s Enoxaparin Sodium is equivalent to Aventis’ Lovenox.”⁷ We disagree.

Amphastar’s analysis suffers from two significant flaws. First, assuming that the Amphastar Data are valid and reliable, they do not demonstrate that

⁶ Amphastar Comment, at 2.

⁷ *Id.*

Amphastar's proposed generic is equivalent to Enoxaparin. As has been pointed out in Aventis' Citizen Petition and Supplement, as well as in peer-reviewed scientific 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. Second, Amphastar's testing methods suffer from several analytical flaws. These flaws render the data unreliable in establishing equivalence between the two products.

A. Amphastar's Comparisons Do Not Establish Equivalence

Amphastar's claim of equivalence ignores several important facts about Enoxaparin. First, the mechanisms of action through which Enoxaparin provides its anticoagulant effect are not fully understood. Attained anti-Xa levels are not the sole measure of anti-thrombotic effectiveness.⁸ In a recent study on the impact on the heterogeneity in low molecular weight heparins (LMWHs), Dr. Jawad Fareed evaluated eight low molecular weight heparins and unfractionated heparin in a rabbit model of jugular vein thrombosis. At equally effective doses, the range of anti-Xa levels varied by 3-fold.⁹ Thus, factors other than anti-Xa levels must contribute to anti-thrombotic effectiveness, a clinically relevant measure. Various studies have suggested, for example, that in addition to anti-Xa/IIa activity, endogenous release of a Kunitz-type inhibitor, Tissue Factor Pathway Inhibitor (TFPI), may contribute to Enoxaparin's anti-thrombotic properties.¹⁰

Second, the Citizen Petition and Supplement have also identified many non-anticoagulant effects of Enoxaparin. Enoxaparin exhibits an anti-ischemic effect

⁸ In fact, *in vitro* anti-Xa activity is only a rudimentary indicator of possible *in vivo* antithrombotic activity. See, e.g., HP Henny, et al. A randomized blind study comparing standard heparin and a new low molecular weight heparinoid in cardiopulmonary bypass surgery in dogs. *J. Lab. Clin. Med.* 1985; 106(2):187-196, 193 (noting that even though there was a measurable anti-Xa activity for a LMWH *in vitro*, it remained to be seen whether that activity reflected the *in vivo* antithrombotic activity that was evaluated).

⁹ J Fareed & D Hoppensteadt, et al. Heterogeneity in low molecular weight heparins. Impact on the therapeutic profile. *Current Pharm. Design* 2004; 10:983-999, 990.

¹⁰ See GT Gerotziafas, A Zafiroopoulos, et al. Inhibition of factor VIIa generation and prothrombin activation by treatment with enoxaparin in patients with unstable angina. *British J. of Haematol.* 2003; 120:611-617. See also, Fareed, *supra* note 9, at 986.

by reducing the infarct size in ischemic myocardium in dogs, and exhibits anti-inflammatory action by inhibiting P-Selectin mediated interaction between neutrophils and platelets. It also exhibits pro-angiogenic action through potentiation of Fibroblast Growth Factor induced endothelial cell proliferation, and exhibits hyperplasia inhibition through inhibition of smooth muscle cell proliferation.¹¹

As pointed out in the Citizen Petition and Supplement, these anticoagulant and non-anticoagulant properties of Enoxaparin are intimately linked with its method of manufacture. Thus, simple physico-chemical comparisons such as those presented by Amphastar are necessary but insufficient measures of equivalence between Enoxaparin and a proposed generic. Such tests may fail to account for factors other than anti-Xa/IIa activity that contribute to Enoxaparin's anticoagulant effect, and may also fail to account for non-anticoagulant properties of Enoxaparin.

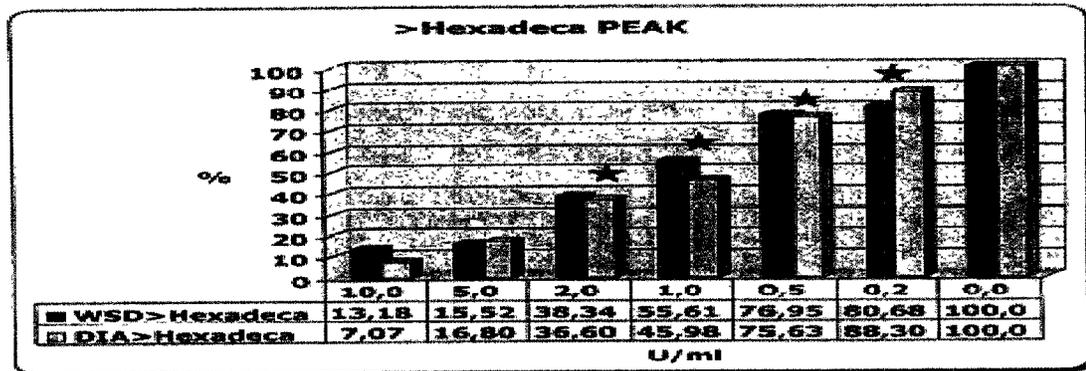
The inability of tests such as Amphastar's to measure equivalence is illustrated by differences observed in a comparison of Enoxaparin and two of its analogues, as detailed in Aventis' Citizen Petition and Supplement. Both of the tested analogues (< 7% 1,6 anhydro and 40-50% 1,6 anhydro) were similar to Enoxaparin in molecular weight, anti-Xa activity, and anti-Xa/anti-IIa ratio. Yet the analogues and their subfractions showed significant differences from Enoxaparin and its subfractions in both anticoagulant and non-anticoagulant properties.¹²

These differences may be particularly significant at higher concentrations, leading to increased safety problems, particularly in vulnerable patient populations like the elderly, the renally-impaired, and those with low body weight. For example, the analogues and their subfractions showed differences in thrombin formation (Figure 1) and peak Factor-Xa levels (Table 1) compared to Enoxaparin and its subfractions.

¹¹ See Aventis Citizen Petition, at 13-19; Aventis Citizen Petition Supplement, at 8-14.

¹² See *id.*

Figure 1¹³



* = p < 0,05

Table 1¹⁴

Comparison of plasma anti-Xa and anti-IIa pharmacokinetic parameters of compound with <7% of 1, 6 anhydro (test item no.1) versus enoxaparin

Plasma Anti-Xa activity					
	Amax IU/mL	tmax h	AUC _{0-t} (t=24h) IU.h/mL	AUC _{0-∞} IU.h/mL	t _{1/2} H
Enoxaparin <7% 1, 6 anhydro (Test item no. 1) % of change ^{\$}	0.934 1.02 + 9%	2 - 3 2 - 3	8.04 8.55 + 6%	8.53 9.03 + 6%	5.45 5.35 - 2%
	p = 0.0105 (S)	(NS)	(NS)	(NS)	(NS)
Plasma Anti-IIa activity					
	Amax IU/mL	tmax h	AUC _{0-t} (t=6h) IU.h/mL	AUC _{0-∞} IU.h/mL	t _{1/2} H
Enoxaparin <7% 1, 6 anhydro (Test item no. 1) % of change ^{\$}	0.153 0.163 + 7%	2 - 4 2 - 4	0.621 0.673 + 8%	0.907 0.945 + 4%	2.83 2.64 - 7%
	(NS)	(NS)	p = 0.0306 (S)	(NS)	(NS)

NS- not significant (P ≥ 0.05); S: significant (0.01 ≤ P < 0.05); \$ The % of changes correspond to [100x ((^{test item no.1} / Enoxaparin-1))].

With anti-Factor Xa levels in particular, this difference was noted at the peak concentrations around 1 IU/mL. This concentration is clinically observed in patients treated for acute coronary syndromes, those patients who are more likely to have an increased risk of bleeding because of increasing early use of invasive procedures, and those who are also taking concomitant medications that increase the risk of bleeding,

¹³ See Aventis Citizen Petition Supplement, at Appendix E.

¹⁴ See Aventis Citizen Petition, at Appendix A (DMPK Report).

e.g. NSAIDs, aspirin, and clopidogrel.¹⁵ The clinical implication of these data is that the risk of bleeding between Enoxaparin and a generic product may be dependent on the concentration achieved. This risk may be more apparent in the sickest patients, i.e. those with acute coronary syndromes who because of co-morbid conditions and medications may be at more risk for bleeding.

In this context, it is crucial to understand that Enoxaparin is indicated for treatment of life-threatening conditions (deep vein thrombosis and acute coronary syndrome). Therefore its manufacture, clinical activity, and chemical composition deserve higher scrutiny and rigor. FDA must take particular care to ensure that any proposed generic bears the same safety and effectiveness profile as Enoxaparin. For the reasons discussed above, this simply cannot be done through simple physico-chemical comparisons.¹⁶ Rather, equivalence can be ensured only by requiring an equivalent manufacturing process or requiring clinical testing.

Both the Amphastar and Teva Comments claim that this central argument of Aventis' Citizen Petition is simply an attempt by Aventis to use "endless delay tactics in order to keep [its] drug 'Evergreen.'"¹⁷ Aventis is not alone, however, in arguing that differences in the manufacturing process used to create a generic version of Enoxaparin could create significant differences in the drug product's pharmacological activity. For example, in his study of LMWHs, Dr. Fareed points out that "it is important to realize that differences in the manufacturing of these products lead to pharmacological differences in these drugs."¹⁸ Thus, regarding companies currently seeking approval of generic Enoxaparin, Dr. Fareed concludes:

[N]one of these companies have the required expertise to control the manufacture of enoxaparin or characterize it. Moreover, the current FDA guidelines for the acceptance of generic versions of branded drugs may not be adequate to address the fine micro-chemical and biochemical

¹⁵ See, e.g., C Macie & L Forbes, et al. Dosing practices and risk factors for bleeding in patients receiving Enoxaparin for the treatment of an acute coronary syndrome. *Chest* 2004; 125(5):1616-1621.

¹⁶ This is particularly true in the case of the Amphastar Data because, as described in subpart B, below, several of Amphastar's comparative analyses are flawed and unreliable.

¹⁷ Amphastar Comment, at 2.

¹⁸ Fareed, *supra* note 9, at 995 (emphasis added).

details for individual low molecular weight heparins. . . . Enoxaparin per se is more complex than other LMWHs due to the presence of anhydro-mano groups and non-dialyzable ether form of benzo residues. The pharmacokinetic behavior of this drug is also quite different than other LMWHs. A generic equivalent form, therefore, must exhibit all these properties. . . . [I]f any of the generic versions of enoxaparin are cleared by the agency merely based on the molecular profiles and anti-Xa activity, major clinical problems may be encountered. It should be emphasized that the regulatory agency should not clear any generic version of branded drug (sic) unless the consensus of expertise on the chemical characterization and bio-equivalence for these critical drugs are reached.¹⁹

Similarly, in their review of the scientific literature on the approved uses of LMWHs, Professors McCart and Kayser note that:

[t]here is general agreement that LMWHs are chemically and physically distinct agents. In addition, it is not known what LMWH properties explain their safety and efficacy. Based on our review, it cannot be assumed that LMWHs are equally safe and effective for any indication unless they have been appropriately studied. Only individual studies can provide the needed treatment information.²⁰

Far from being an attempt to “evergreen,” therefore, Aventis’ arguments raise legitimate scientific and patient safety concerns, which appear to be shared by the scientific community.

¹⁹ *Id.* at 997.

²⁰ GM McCart & SR Kayser. Therapeutic Equivalency of Low-molecular Weight Heparins. *The Annals of Pharmacotherapy* 2002; 36(June):1042-57, 1054.

B. Amphastar's Data Is Flawed, and Therefore Unreliable

The Amphastar Data also suffer from various analytical flaws. These flaws render the Amphastar Data unreliable and unusable for any effort to establish equivalence between Enoxaparin and Amphastar's proposed generic product.

1. Amphastar's Chromatograms Are Unreliable

Figure 2 reprints Amphastar's chromatograms of its proposed product and Enoxaparin, as found in Appendix 3 of the Amphastar Comment. These chromatograms have poor resolution and lack precision on the structure of the oligosaccharides constituting the analyzed LMWHs. Because of this lack of clarity or precision, it is difficult to draw either qualitative or quantitative conclusions regarding a comparison of the two products. Figure 3 shows an experimental chromatogram prepared by Aventis, using advanced techniques. In contrast to Amphastar's chromatogram of Figure 2, Aventis' experimental chromatogram of Figure 3 is more clearly resolved and presents more clearly identifiable individual peaks.

Figure 2: Reprint of HPLC –SAX chromatography of Amphastar enoxaparin and Aventis Lovenox batches from the Amphastar Comment

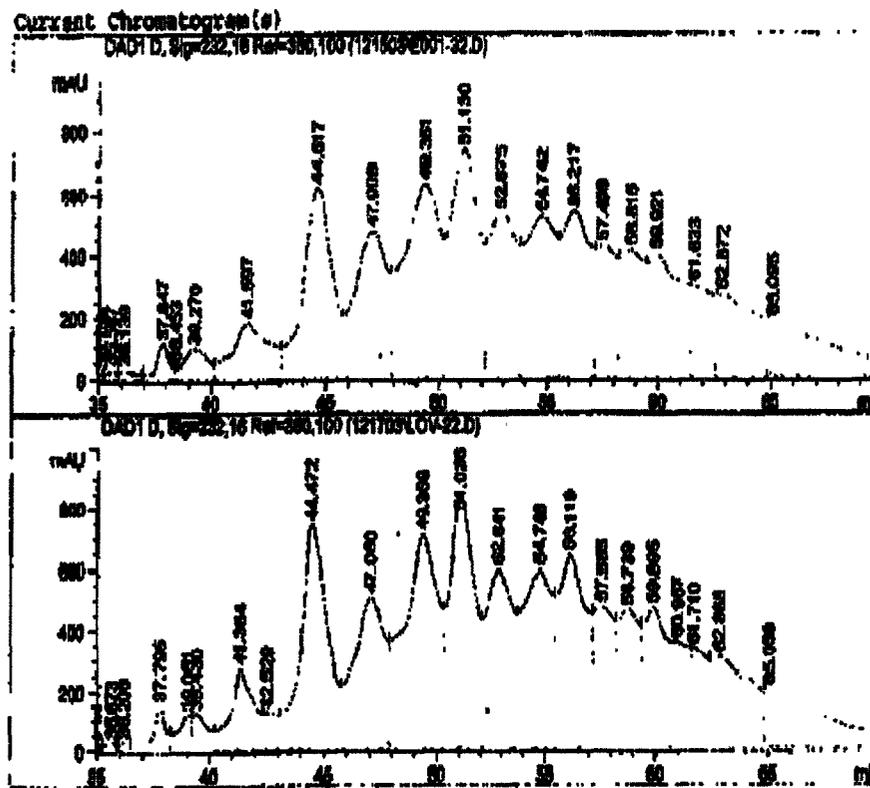


Figure 3 : Experimental CTA-SAX Chromatogram of a Lovenox[®] batch (detection — 232nm ; — 202 – 245nm), Prepared by Aventis²¹

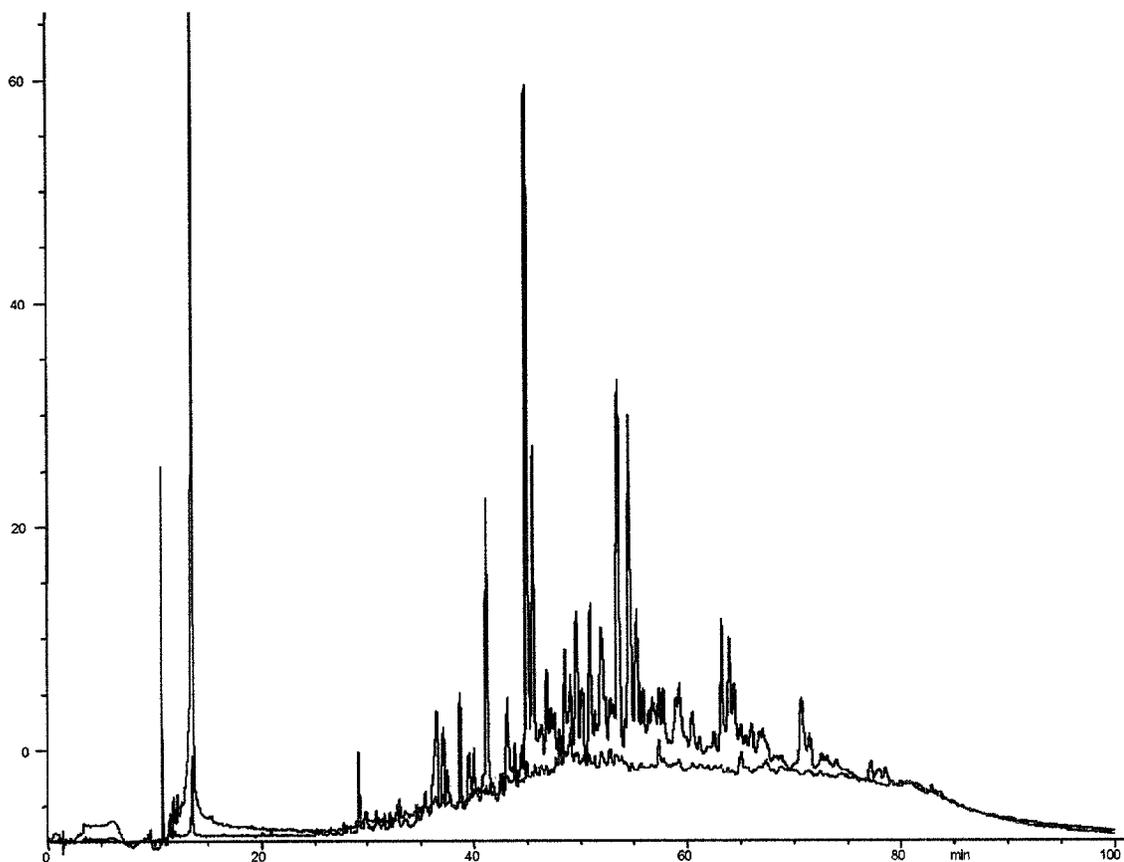
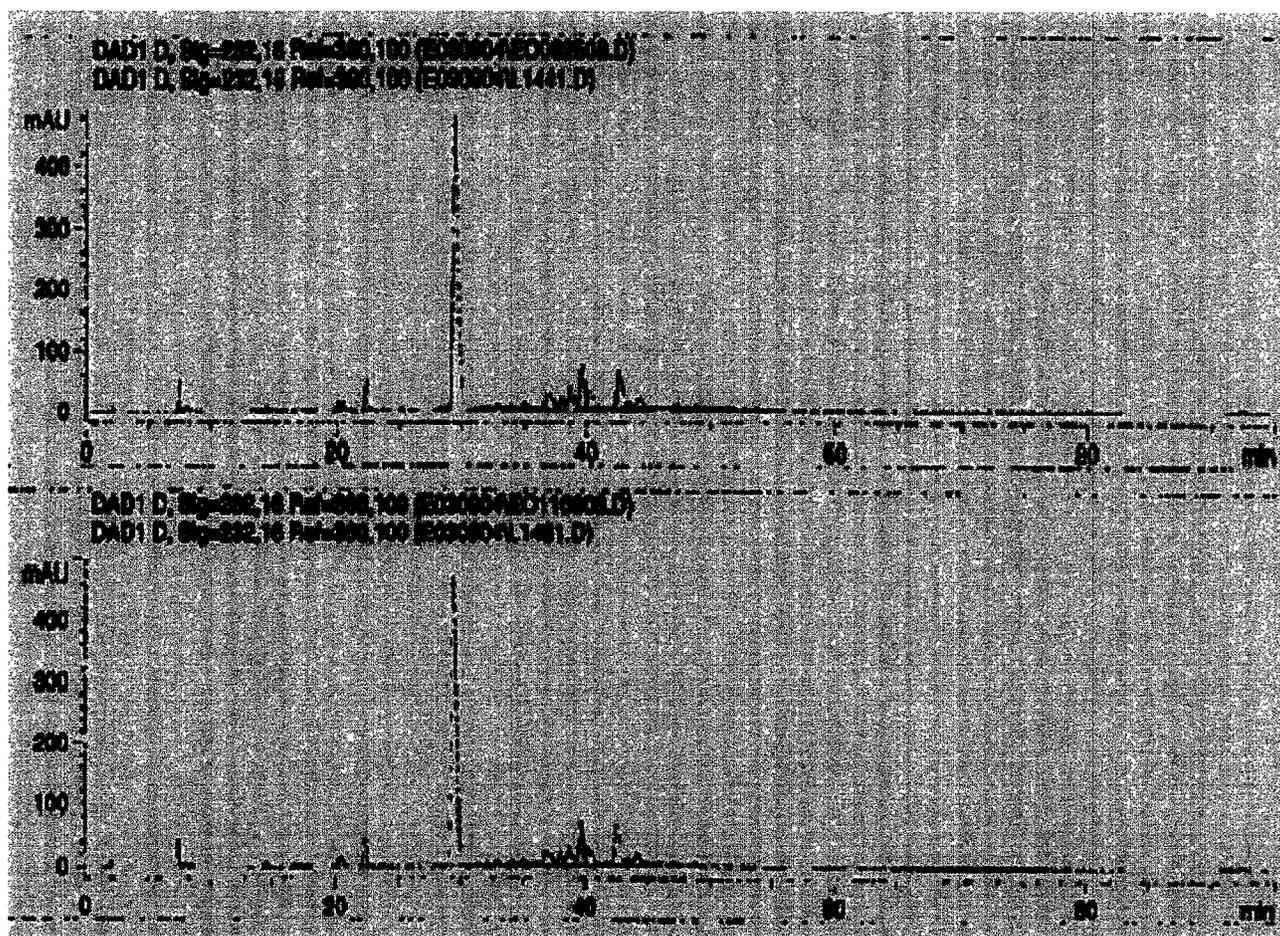


Figure 4 shows Amphastar's chromatograms of the so-called disaccharide building blocks of Lovenox[®] and Amphastar batches. Here again, there are no structures or quantitative data. The main peak eluted at about 30 min is probably the 3 sulfated disaccharide Δ Is. However, the seven other disaccharides of lower sulfation degree should be present in the chromatogram before the main peak (about 30 min). Given the lack of clarity in Amphastar's chromatogram, it is impossible to determine if these low sulfation degree disaccharides are present. Even if they are present, Amphastar's chromatogram makes clear that they would be present in too small

²¹ See P Mourier & C Viskov. Chromatographic analysis and sequencing approach of heparin oligosaccharides using cetyltrimethylammonium dynamically coated stationary phases. *Anal. Biochem.* 2004; 332:299-313.

a quantity, compared to other saccharides eluting around 40 min, which are most probably hexa and tetrasaccharides. It is likely that the mixture chromatographed by Amphastar is not the disaccharide building blocks corresponding to an exhaustively depolymerized sample (an exhaustive depolymerized sample is obtained by digestion with an enzyme mixture of heparinase 1, heparinase 2 and heparinase 3). Instead, Amphastar's chromatogram probably corresponds to a partially depolymerized sample by heparinase 1.

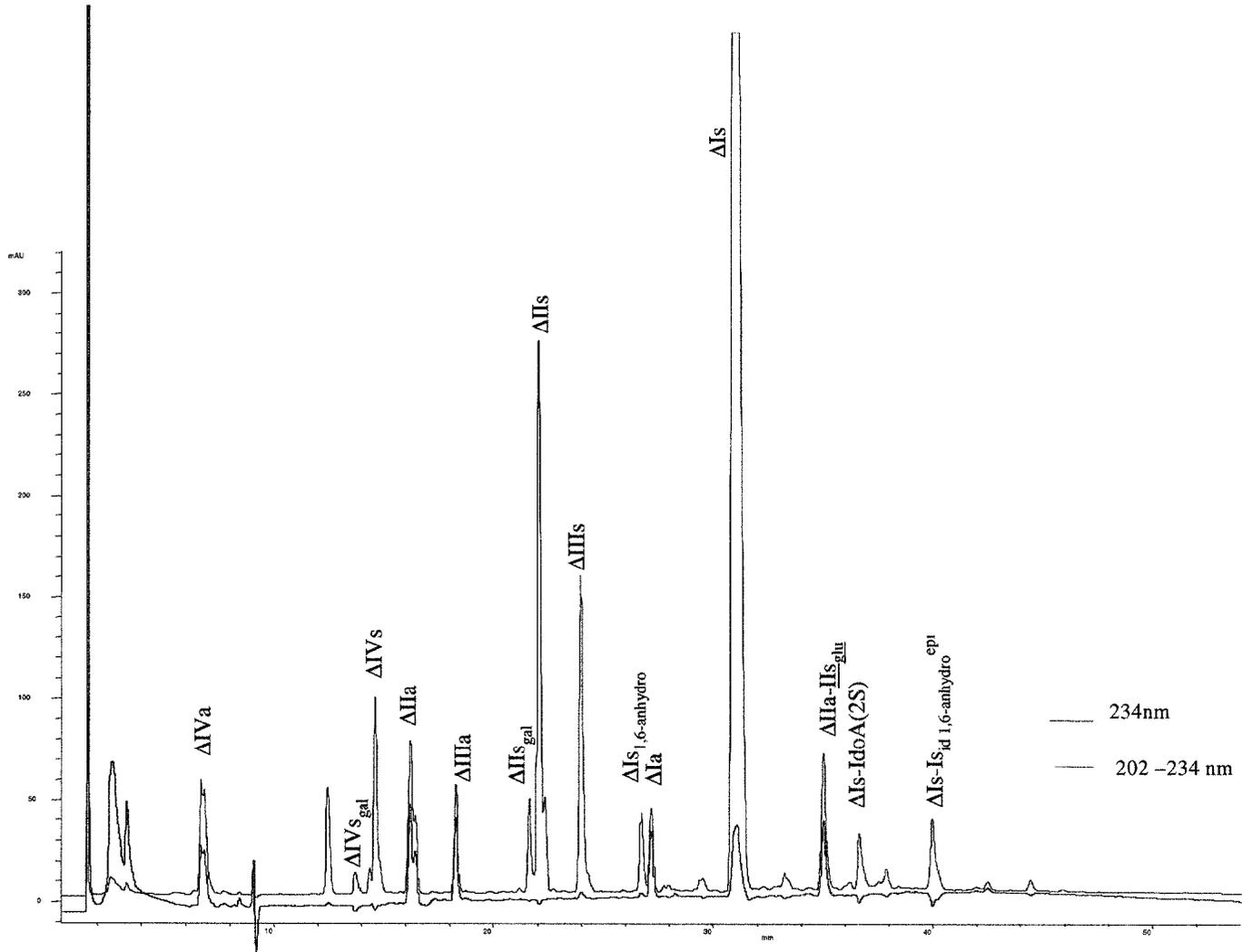
Figure 4 : Chromatograms of "LMWH disaccharide building blocks" in Amphastar document



Finally, Figure 5 shows Aventis' chromatogram of exhaustively digested Lovenox[®]. In this mixture more than 90% (w/w) are disaccharides, with the remaining 10% consisting of heparinase-resistant tri and tetrasaccharides. Those peaks, which correspond to heparinase resistant oligosaccharides, have a cumulated chromatographic area of less than 5% of the entire mixture. In this type of Lovenox[®] sample, ΔIs have a chromatographic area of about 60%.

Contrary to Amphastar's assertions, therefore, Amphastar's chromatograms do not identify LMWH disaccharide building blocks, nor do they demonstrate anything about the structural features of Amphastar LMWH batches. Moreover, they make clear that Amphastar has an incomplete knowledge of the basis of the chromatographic control of an LMWH, i.e. the analysis of its disaccharide building blocks. Because of the poor quality of Amphastar's chromatograms overall, they should not be used to establish that its proposed generic is equivalent to Enoxaparin.

Figure 5 : Chromatogram of an exhaustively depolymerized Lovenox® batch²²



²² Figure excerpted from International Patent Application WO 2004/027087 A2.

2. Dimethyl formamide ("DMF")

Appendix 2 of the Amphastar Comment purports to provide a comparison of active pharmaceutical ingredient (API) between "Amphastar Enoxaparin" and Lovenox[®] per the specifications and analytical methods of the European Pharmacopoeia monograph.²³ In this appendix, Amphastar compared three batches of its proposed generic to three batches of commercially available Lovenox[®]. By presenting data on a series of comparative assays, the appendix attempts to demonstrate chemical and biological identity between the two products.

Amphastar appears, however, to have used contaminated Lovenox[®] in its comparison. One of the tests run by Amphastar in Appendix 2 was a comparison of DMF levels. DMF would most likely be present as a residual solvent, and is generally thought to be undesirable in pharmaceutical products. Aventis does not use DMF in any step of the manufacturing process for Enoxaparin, and the substance is therefore not present either in the API form of Enoxaparin or in the drug product Lovenox[®], or in any intermediate.

Surprisingly, Appendix 2 reveals that Amphastar observed 102 ppm of DMF in Lovenox[®] batch 1446. There is no legitimate reason, however, for the presence of this substance in that batch. Again, Aventis does not use the substance in any part of its manufacturing process.

It is unclear why Amphastar observed DMF in batch 1446. One possibility is analytical error. Another possibility is errors in the steps Amphastar took to prepare the Lovenox[®] batches for analysis during pretreatment by lyophilization. In Appendix 2 Amphastar indicates that all three batches of Enoxaparin (API) were analyzed in "almost white powder" form after the lyophilization step. The presence of DMF suggests that samples have been cross-contaminated during the lyophilization pretreatment.

More importantly, however, the fact that Amphastar observed DMF in tested Enoxaparin batches renders the comparative analysis unreliable. Errors in Amphastar's lyophilization process, discussed above, could have had a significant impact on the tested product. Amphastar therefore cannot use these data to compare its proposed generic to Enoxaparin.

²³ Amphastar Comment, at Appendix 2.

Moreover, Amphastar did not actually use the API form of Lovenox[®] for testing, but rather took the Lovenox[®] drug product and processed it to “re-create” an “API” form of Lovenox[®]. In other words, Amphastar had to somehow extract the API from the Lovenox[®] drug product, raising significant issues of scientific method.

3. Amphastar “Picks and Chooses” Its Batches

In conducting its comparative analysis, Amphastar tested multiple batches of both Lovenox[®] and its proposed generic product. Yet for any given comparison, Amphastar does not present data for all of the batches. Rather, data is provided on some batches for some comparisons, but not for others. It therefore appears that Amphastar may be presenting data only for those batches that provide a favorable comparison.

For example, Appendix 3 provides a synopsis of Amphastar’s equivalence comparisons. In the table for Test 1 (General Physical Properties), Amphastar compares three batches of its product (112002C, 112002D, and 111802A) to the three batches of Lovenox[®] (1446²⁴, 1481, and 15021). In the next test (General Chemical Properties), however, Amphastar uses three different batches of its product (EO093002, EO100202, and EO101402) in its comparison to freeze-dried Lovenox[®]. Amphastar provides no justification, however, for substituting these batches in this particular comparison.

Similarly, in Test 4 of Appendix 3 (Biochemistry; Anti-Xa and AntiXa/Anti-IIa), Amphastar inexplicably substitutes a new batch of its product (112002A) for batch 111802A in the comparison. It then introduces, again without explanation, a new batch of Lovenox[®] (1485) in place of batch 15021. Given the lack of explanation for the substitutions, one could conclude that Amphastar has provided data in any given comparative test only for those batches that provide results most favorable to Amphastar. Without full disclosure of the results for all batches in all comparative analyses, the Amphastar Data must be considered unreliable.

²⁴ Amphastar uses Batch 1446 in all of its comparative analysis in Appendix 3 despite the fact that it is contaminated with DMF. Once again, the presence of DMF in this batch renders all of Amphastar’s analysis in Appendix 3 unreliable.

4. *In Vivo* Studies in Rats Are Not Reliable Predictors for Comparing Products for Regulatory Approval to be Administered to Humans

Amphastar's *in vivo* profile studies comparing the anti-Xa and anti-IIa levels of Enoxaparin and the proposed generic in rats cannot be used to reliably compare the expected *in vivo* anti-Xa and anti-IIa levels in humans. Species differences in blood coagulation systems are well known. Moreover, the rat pharmacokinetics of LMWHs, particularly Enoxaparin, are not comparable to that of humans; thus, the time course of anti-Xa activity in rats should not be automatically assumed to predict clinical effectiveness or safety.²⁵

5. Amphastar's pH Levels Are Inaccurate

Finally, Amphastar's comparative studies in Appendix 2 were conducted using Enoxaparin in almost white powder form. According to the enoxaparin sodium European Pharmacopoeia monograph, pH should be tested on a 1% concentration. In Appendix 3 (table 1), however, Amphastar's comparative study is conducted on the drug product (enoxaparin sodium 10 % concentration solution). Therefore, at two different concentrations, the pH values of enoxaparin sodium and the drug product cannot be the same in contradiction to the pH values shown in both Appendices 2 and 3. This suggests additional flaws in Amphastar's analysis.

C. Conclusions Relating to the Amphastar Testing

In light of the analytical flaws in Amphastar's comparisons detailed above, the Amphastar Data cannot be used to establish that its proposed generic product is equivalent to Enoxaparin. Even without these flaws, Amphastar's tests provide only simple physico-chemical comparison of the Amphastar drug substance and lyophilized Lovenox[®] drug product, rather than a comparison of overall pharmacological activity. In light of the fact that Enoxaparin is not yet completely characterized, and its mechanisms of action not yet fully-understood, the Amphastar Data do not provide a reasonable basis for comparing the two products even without the evident analytical

²⁵ See NC Linhart, MD Laforest, et al. Pharmacokinetic and tissue distribution of ⁹⁹Tc - labeled enoxaparin in rat: Evaluation of dosimetry parameters. *Biomed. Pharmacother.* 1990; 44:317-323. Anti-IIa levels are low and with a reduced time course. This anti-IIa activity is related to the clearance of saccharide chains above 5,000 Da. Clearance of these saccharides in rats is not comparable to that in humans.

flaws. FDA therefore cannot use the Amphastar Data to establish equivalence between the two products.

II. Teva’s Data on Variability in Lovenox’s Saccharide Building Blocks Are Unreliable

On page 3 of the Teva Comment, Teva argues that Aventis’ Citizen Petition and Supplement are “contradicted by the known variability of Lovenox® itself.”²⁶ In support of this claim, Teva excerpts data from Momenta Pharmaceuticals’ International Patent Application WO 03/078960 A2 (the “Momenta Patent Application”). These data contain results of studies, conducted by Momenta, on the variability of the saccharide components that comprise Enoxaparin’s polysaccharide chains (the “Momenta Data”). These results, as presented in the Teva Comment, are provided below:

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

In short, Teva argues that Aventis’ manufacturing process results in wide batch-to-batch variation and, thus, ANDA applicants should not be required to use an equivalent manufacturing process in order to demonstrate “sameness.”

²⁶ Teva Comment, p. 3.

This argument must fail, however, because the Momenta Data are flawed and unreliable. In generating the Momenta Data, Momenta deviated from proper scientific analytical methodology in several respects. A brief discussion of some of these deviations makes clear that the resulting data are flawed, and do not provide a reasonable basis for establishing the level of batch-to-batch variability in Enoxaparin.

A. The Momenta Data Do Not Properly Close Mass Balance

Based on a Capillary Electrophoresis profile of commercially available Lovenox[®] disclosed in the Momenta Patent Application, the Momenta Data identify ten saccharide types in each of the three tested batches. The Momenta Data provides the relative percent area under the curve (“AUC”) for each saccharide type in each of the three tested batches. For example, according to the Momenta Data, the p1 saccharide type constitutes 60.8 percent of Batch 1, with the p2 type constituting 7.0 percent, and so forth. Because the percentages add up to 100 at the bottom of each column, the Momenta Data attempt to close mass balance and represent that the ten saccharide types it has identified constitute all of the saccharide components of Enoxaparin.

The Momenta Data must be inaccurate, however, because Momenta has not identified all of the components of Enoxaparin’s polysaccharide chains and therefore has not properly closed mass balance. For example, the Momenta Data does not identify any components containing the 1,6-anhydro ring structure.²⁷ In the Citizen Petition, however, Aventis demonstrated that the 1,6-anhydro ring structure exists at the reducing end of between 15% and 25% of Enoxaparin’s polysaccharide chains. Clearly, therefore, the Momenta Data do not identify all of the components of Enoxaparin’s chains and have not properly closed mass balance. Furthermore, the Momenta Data assume that AUC corresponds to the mole percentage of each component in attempting to close mass balance. This assumption may not be valid and needs to be tested by preparing standards of each saccharide (p1-p10) and determining the molar absorptivity of each.

Were Momenta’s analysis to include the 1,6-anhydro ring structure components, the percentages assigned to many of the different saccharide types could change. Furthermore, different peaks may be affected differently. For example,

²⁷ The Momenta Patent Application identifies p1 through p7 as disaccharides, and p8 as a tetrasaccharide. P9 and p10 are identified only as “non-natural sugars.” See Momenta Patent Application, at 13-14. These “non-natural sugars” cannot be the 1,6-anhydro ring structure components because they do not constitute a large enough portion of the total Enoxaparin mixture. See footnote 28, *infra*.

depending on why Momenta failed to observe a 1,6-anhydro saccharide, the variation could completely disappear from the small peaks (p2-p10), but be only slightly reduced in the large peak (p1). Because it is unclear why Momenta failed to observe the 1,6-anhydro ring structure, the Momenta Data do not establish batch-to-batch variability in Enoxaparin.

In many cases, proper identification of the 1,6-anhydro ring structure among the components of Enoxaparin could result in the variation percentages tightening considerably. For example, complete analysis (with identification of the 1,6-anhydro components) could cause p7 in Batch 1 to fall to 3.9 and Batch 3 to rise to 3.4.²⁸ This would cause the p7 variation percentage to close to approximately 24%. This further underscores the unreliability of the Momenta Data.

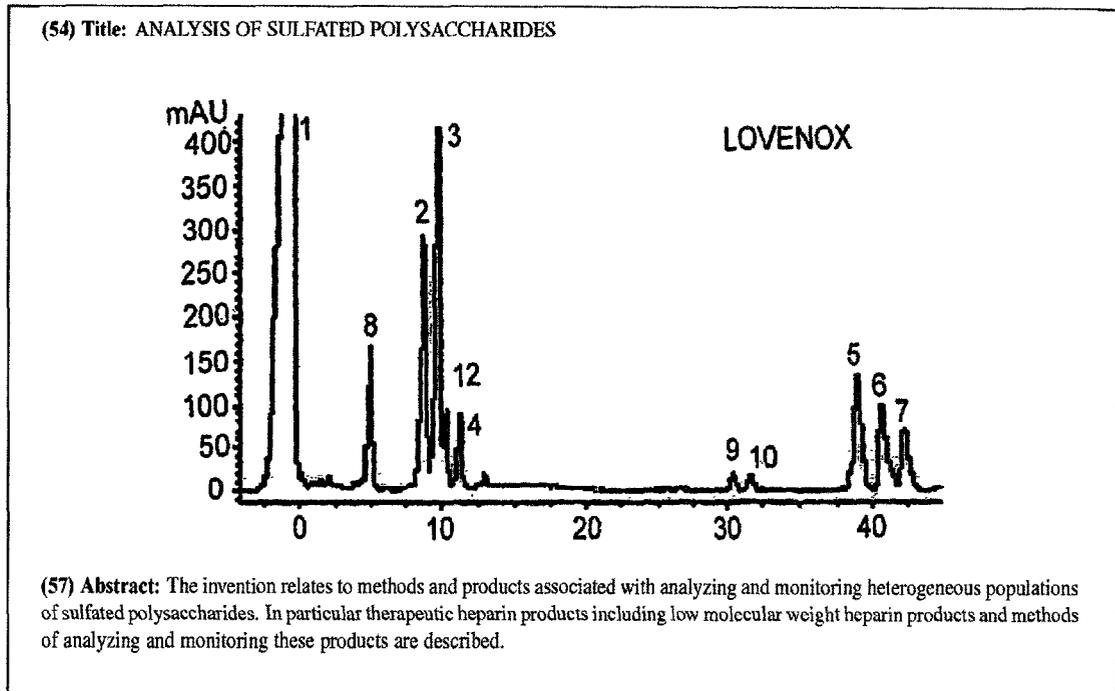
B. Momenta's Analysis Ignores Several Unidentified Peaks

The Capillary Electrophoresis on which the Momenta Data is based, and as printed in the Momenta Patent Application, is replicated below in Figure 6.²⁹

²⁸ As pointed out in the Citizen Petition, from 15% to 25% of the chains comprising Enoxaparin contain 1,6 anhydrosugar ends. Heparinase treatment of Enoxaparin affords a mixture of disaccharides and tetrasaccharides, having an average molecular weight of 900. This means that a single Enoxaparin chain (MW avg 4,500) is broken by heparinase into 5 pieces ($4,500/900 = 5$). For example, on heparinase treatment, 100 Enoxaparin chains would give rise to 500 saccharides, 15 to 25 of which contain 1,6 anhydrosugars. Thus, 3-5% ($15-25/500 \times 100$) of the saccharides should contain 1,6 anhydrosugars.

²⁹ See Momenta Patent Application, at 1.

Figure 6



As is readily apparent, the Momenta Data ignore several minor peaks and shoulders in the chromatogram. For example, there are unidentified peaks at approximately T=2, T=12, and T=25. In addition, there are clear shoulders on virtually all of the peaks that Momenta has identified. These peaks and shoulders suggest that there may be additional unknown and unidentified components in the mixture being analyzed.³⁰ Once again, because Momenta has not taken all of the components of Enoxaparin into account, its AUC percentages for the components it does identify must be inaccurate. For that additional reason, the data cannot be used to support a finding of significant batch-to-batch variation in Enoxaparin.

C. Momenta's Cocktail of Enzymes Introduces Unpredictability

Finally, the Momenta Patent Application indicates that Momenta prepared its Lovenox[®] batches for analysis by depolymerizing Enoxaparin with a

³⁰ This is not surprising in light of the fact that approximately 30% of the Enoxaparin macromolecule has yet to be characterized.

cocktail of enzymes, including heparinases.³¹ Because small oligosaccharide chains such as those contained in Lovenox[®] are poor substrates, heparinases are unpredictable in their ability to act on these chains. This could have added to the variability identified in the Momenta Data.³² In addition, it is unclear from the Momenta Patent Application how much active enzyme was present in the cocktail that Momenta used. These enzymes are thermally unstable and their activity can change with time and storage.³³ To establish the effect that these enzymes would have on batch-to-batch variability, Momenta should have applied rigorous control experiments. The method used by Momenta is part of a patent application, not a validated analytical method, which is strictly controlled. The Momenta Patent Application contains no indication that such controls were applied.

As a result of these flaws in the Momenta Data, it is impossible to rely on that data to establish wide batch-to-batch variation among Enoxaparin's saccharide building blocks. Of course, it should be noted that some degree of variation is expected in any product derived from living organisms. FDA has long recognized that it is usually not possible "to assure by chemical analysis that different batches" of the same biological product "are identical."³⁴ FDA should therefore require any proposed generic applicant to demonstrate that its product is sufficiently equivalent to the pioneer.

III. Amphastar Has Not Identified Any "Critical Changes" to Aventis' Manufacturing Process

The Amphastar Comment points out that between March 1996 and April 2004, Aventis submitted 17 NDA supplements regarding chemistry, manufacturing and

³¹ See Momenta Patent Application, at 97.

³² See KG Rice & RJ Linhardt. Study of Structurally Defined Oligosaccharide Substrates of Heparin and Heparin Monosulfate Lyases. *Carbohydrate Research* 1989; 190:219-233.

³³ See DL Lohse & RJ Linhardt. Purification and Characterization of Heparin Lyases from *Flavobacterium Heparinum*. *J. Biological Chemistry* 1992; 267(34):24347-24355.

³⁴ See *Serono Labs. v. Shalala*, 158 F.3d 1313, 1318 (D.C. Cir. 1998) (quoting Letter from Janet Woodcock to Serono Labs, June 17, 1997 (hereinafter, "Woodcock Letter")).

controls (“CMC”) for Lovenox[®].³⁵ Based on these CMC supplements, Amphastar declares that between March 1996 and April 2004, “Aventis made a critical change for CMC (Chemistry, Manufacturing and Control), on average, once every six (6) months.”³⁶ Thus, Amphastar argues that Aventis has changed its manufacturing process so many times, and so significantly, that Enoxaparin cannot truly be considered to be “process dependent.” We disagree.

Actually, from March 1996 to April 2004, Aventis submitted 24 CMC supplements to its Lovenox[®] NDA, not 17. Of these 24 CMC supplements, however, 16 were solely drug product-related, and thus had no effect whatsoever on the drug substance (enoxaparin sodium). The remaining eight supplements, which were not solely drug product related, are described below:

1. **S-011 (submitted 4/15/96):** Update in testing methods specifications and analytical methods and stability protocols for drug substance
2. **S-022 (submitted 1/26/99):** Addition of a new supplier for starting material
3. **S-023 (submitted 1/26/99):** Expansion of manufacturing site, addition and replacement of equipment, and increased batch size for the drug substance
4. **S-024 (submitted 1/26/99):** New regulatory method for determining residual solvents³⁷
5. **S-038 (submitted 4/6/00):** Addition of alternate analytical test site for release and stability testing of starting material
6. **S-041 (submitted 8/31/00):** Addition of drug substance manufacturing site

³⁵ Amphastar Comment, at 1. Amphastar identified these supplements from FDA’s website on Label and Approval History of Lovenox[®].

³⁶ *Id.*

³⁷ FDA split Aventis’ submission of January 26, 1999 into three separate supplement numbers, S-022, S-023 and S-024. Hence, the three CMC supplements have the same submission date.

7. **S-055 (submitted 7/11/03):** Additional characterization of drug substance structure (1,6-anhydro ring structure at 15% to 25% concentration)
8. **S-059 (submitted 1/23/04):** Transfer of synthesis from one facility to another

As the foregoing makes clear, Amphastar's argument (that Aventis has changed its manufacturing process so many times, and so significantly, that Enoxaparin cannot truly be considered to be "process dependent") is totally without merit.

IV. The Amphastar, Teva, and Hyman Comments Reflect Misunderstandings of Both the Citizen Petition and the Underlying Regulatory Framework

The Amphastar, Teva, and Hyman Comments make several legal arguments in an attempt to discredit Aventis' Citizen Petition and Supplement. As is explained in greater detail below, these arguments reflect fundamental misunderstandings of both the Citizen Petition and Supplement, as well as the underlying legal and regulatory framework for the approval of generic drugs.

A. The Teva and Hyman Comments Mischaracterize *Serono*

Both the Teva and Hyman Comments mischaracterize *Serono Labs v. Shalala*³⁸ ("*Serono*") in an attempt to draw a parallel between Enoxaparin and the menotropins. For example, the Teva Comment states:

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.³⁹

According to Teva, *Serono* dictates that the fact that a pioneer drug is not fully-characterized can play no role in determinations of "sameness." Teva therefore argues

³⁸ 158 F.3d 1313 (D.C. Cir. 1998).

³⁹ Teva Comment, at 5.

that *Serono* requires FDA to approve generic Enoxaparin despite the possible differences in structural fingerprints pointed out in the Citizen Petition and Supplement.⁴⁰

Teva's focus on characterization of the product, however, completely misinterprets FDA's determinations regarding Pergonal (the pioneer drug in *Serono*), and the very limited holding of the *Serono* case. The focus of the *Serono* case was not whether there were differences between the uncharacterized portions of the proposed generic and Pergonal. Instead, the case focused on whether those differences affected safety and effectiveness. FDA concluded that the differences between Pergonal and the proposed generic, "demonstrated no differences in safety and efficacy" and were therefore not clinically significant for Pergonal's intended uses.⁴¹ Whether the active ingredient in Pergonal was fully characterized or not, was not a factor in the decision.

In fact, the *Serono* case makes clear that the fact that a pioneer drug is not fully-characterized can cause a finding that a generic is not the "same" as the pioneer. In examining the menotropins, FDA concluded that Pergonal's lack of characterization should not bar generic products in that particular case because "any potential variations in FSH isoforms between the [generic] and Pergonal *appear not to be clinically significant* for the product's intended uses."⁴² In other words, FDA concluded that the uncharacterized portions of FSH did not meaningfully affect the pharmacological profile of the drug product. By its own reasoning, had FDA had reason to suspect that the variations in the uncharacterized portions of Pergonal might have clinical significance, FDA would have withheld approval of the generic product until that possibility was ruled out. Thus the *Serono* court was not faced with the issue in this case, i.e. where there is reason to believe that the uncharacterized portions do have clinical significance.

Enoxaparin represents a case where the uncharacterized portions likely have clinical significance. In the Citizen Petition and the Supplement, Aventis has pointed to several process dependent structural fingerprints in the newly characterized portions of Enoxaparin, such as, but not limited to, the 1,6-anhydro ring structure and process dependent ATIII binding oligosaccharides. Aventis has presented data that suggest that these known fingerprints may be "clinically significant for the product's

⁴⁰ *Id.* at 5-6.

⁴¹ *Serono*, 158 F.3d at 1320.

⁴² *Id.* (quoting the Woodcock Letter) (emphasis added).

intended uses.”⁴³ The fact that there are process-dependent structural modifications with likely clinical significance in the characterized portions of Enoxaparin gives FDA ample reason to suspect that there may be additional clinically significant modifications in the uncharacterized portions of Enoxaparin.

As a result, until Enoxaparin becomes fully-characterized, the only way to ensure that a generic product contains the same active ingredient as Enoxaparin is to require that the generic manufacturer employ an equivalent manufacturing process or that appropriate clinical trials are performed. Not only is this conclusion warranted by the data Aventis has already presented, it also is fully consistent with the reasoning and holding in *Serono* and the FDA decision it upheld.

B. Any Generic Version of Enoxaparin Must Include the 1,6-Anhydro Ring Structure at the Proper Concentration

In a supplemental new drug application (“sNDA”) approved on July 27, 2004, Aventis identified a 1,6-anhydro ring (bicyclic) structure at the reducing end of all Enoxaparin oligosaccharides bearing 6-O-sulfo groups on the glucosamine moiety and included this structure in its labeling.⁴⁴ This 1,6-anhydro ring structure is a result of Aventis’ particular manufacturing process for Enoxaparin.

In approving this sNDA, FDA confirmed that the 1,6 anhydro ring structure is an essential component of the active ingredient of Lovenox[®]. As a result, FDA cannot approve any generic Enoxaparin product that does not include the 1,6 anhydro ring structure at the proper concentration. To do so would be to approve an ANDA that does not contain the same active ingredient as the reference listed drug as required by section 505(j)(2)(A)(ii)(I).⁴⁵

The “same labeling” requirement of the FD&C Act also requires that any proposed generic contain the 1,6-anhydro ring structure. Section 505(j)(2)(A)(v) requires that the labeling for any proposed ANDA generic product be the same as the

⁴³ See Aventis Citizen Petition, at 12-19; Aventis: Citizen Petition Supplement, at 4-11.

⁴⁴ See Lovenox[®] sNDA S-055 approval letter.

⁴⁵ 21 U.S.C. § 505(j)(2)(A)(ii)(I). The 1,6-anhydro ring structure is an example of a previously uncharacterized portion of Enoxaparin. It is likely that there are other examples of potentially clinically significant process dependent structures in the uncharacterized portion of Enoxaparin

labeling for the reference listed drug.⁴⁶ Any generic product that did not contain the 1,6-anhydro ring structure in its label would not have the same label as the reference listed drug, and therefore would be unapprovable.⁴⁷

Finally, a USP monograph has been published in the November-December 2003 *Pharmacopeial Forum*. This proposal states that “[a]bout 20 percent of the [enoxaparin] materials contain a 1,6-anhydro derivative on the reducing end of the chain, the range being between 15 and 25 percent.”⁴⁸ The USP sets forth minimum standards to which drug products must conform. Therefore, should this proposal become finalized, any drug product claiming to be Enoxaparin that did not conform to this specification could not be labeled as USP and, therefore, would not bear the same labeling as Lovenox and would be ineligible for approval as an ANDA.⁴⁹

C. The FD&C Act Requires That ANDA Applicants Follow an Equivalent Manufacturing Process or Provide Clinical Studies

Both the Hyman and Teva Comments argue that “duplicating an innovator’s manufacturing process is not required by law and is not the standard for demonstrating sameness.”⁵⁰ We disagree. The Act requires that the generic product have the “same” active ingredient as the reference listed drug. More importantly, the Act requires that an ANDA contain “*information to show* that the active ingredient of the new drug is the same as the listed drug.”⁵¹

⁴⁶ 21 U.S.C. § 505(j)(2)(A)(v).

⁴⁷ The Hyman Comment concedes this point. That Comment states that “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. A generic enoxaparin product would be required to conform to the updated labeling in order to obtain FDA approval.” Hyman Comment, at 2 (internal citations omitted).

⁴⁸ 29(6) *Pharmacopeial Forum* 1876 (Nov-Dec. 2003).

⁴⁹ See 21 U.S.C. § 351(b). As discussed below, however, conformance with such standards alone does not necessarily demonstrate the “sameness” of active ingredient required by section 505(j) of the Act.

⁵⁰ Hyman Comment, at 2. See also Teva Comment, at 2 (“Aventis . . . gloss[es] over the fundamental point that ‘sameness’ of manufacturing process is not a requirement for approval of a generic drug under an ANDA”).

⁵¹ 21 U.S.C. § 355(j)(2)(A)(ii)(I) (emphasis added).

The Act does not define what “information” must be shown to establish sameness. Just what “information” an ANDA must contain, therefore, depends on the nature of the active ingredient. For well-known, small molecule chemical drugs, information to demonstrate that the active ingredient is the same may be simply identification of the chemical compound and evidence to show that it conforms with USP standards.

As Teva concedes in its Comment, however, Enoxaparin is a complex product derived from living cells, rather than synthetic chemicals.⁵² The product is made even more complex by a depolymerization process that, among the varying LMWHs on the market today, results in distinct chemical structures and, therefore, differing pharmacological activity and approved indications for clinical use. Thus, simply identifying the active ingredient and confirming that it complies with pharmacopoeial monographs is insufficient to demonstrate that a generic product has the same active ingredient as Enoxaparin.⁵³

In light of this complexity, the only ways that a generic can establish sameness is to use an equivalent manufacturing process or perform the appropriate clinical trials. Thus, far from being “simply not a request that FDA can grant,” Aventis’ request that a generic be required to use an equivalent manufacturing process is a request that FDA is *required* to grant, absent the performance of appropriate clinical trials.

D. Other Arguments in the Teva and Hyman Comments

The Hyman and Teva Comments make several other arguments that require only a brief discussion.

1. Enoxaparin’s Structural Fingerprints are Process Dependent

The Teva Comment claims that the only support that Aventis has offered for the proposition that Enoxaparin’s fingerprints are process dependent “is the statement [in footnote 33 of the CP] that ‘clinical supplies used in a few of the initial [Lovenox] clinical studies . . . were made from batches where some of the conditions

⁵² Teva Comment, at 5.

⁵³ Because the process to amend monographs take time, the European Pharmacopeia has not yet been updated to reflect the 1,6-anhydro ring structure. *See* European Pharmacopoeia, at 1104 (4th Ed. 2002).

(e.g., time and temperature) were modified.”⁵⁴ This is simply not true. The Citizen Petition and the Supplement present ample additional evidence to make clear that Enoxaparin’s structural fingerprints are process dependent.

First, Aventis’ contention that “[e]ach LMWH’s manufacturing process results in particular structural characteristics of its polysaccharide chains” is supported by the signed declaration of Dr. Robert J. Linhardt.⁵⁵ Dr. Linhardt is a world-renowned expert on heparin and LMWHs.⁵⁶

The Citizen Petition and Supplement also clearly explain how the known fingerprints in Enoxaparin are developed as a result of Aventis’ manufacturing process. For example, the Citizen Petition shows how the 1,6-anhydro ring structure is formed through intramolecular nucleophilic substitution during Aventis’ particular depolymerization process.⁵⁷ More importantly, the Citizen Petition explains that by changing certain parameters in its manufacturing process, Aventis scientists constructed two LMWHs similar to Enoxaparin in molecular weight, anti-Xa activity, and anti-Xa/anti-IIa ratio, but with dissimilar concentrations of the 1,6 anhydro ring structure.⁵⁸

Finally, FDA itself has recognized that the varying depolymerization processes used to create LMWHs create chemically distinct drug products. Recognizing these differences, FDA has approved the different LMWHs currently on the market in the United States for different indications. Further, in 1993, FDA issued an alert to physicians stressing that the various LMWHs may not be used interchangeably.⁵⁹ This warning is also found in the approved prescribing information for all currently available LMWHs. Indeed, as evidenced by FDA guidance documents,

⁵⁴ Teva Comment, at 2.

⁵⁵ See Aventis Citizen Petition, at 11, n.34, and attached Declaration of Robert J. Linhardt, Ph.D. (hereinafter, Linhardt Declaration).

⁵⁶ See Linhardt Declaration, *Curriculum Vitae*.

⁵⁷ See Aventis Citizen Petition, at 13.

⁵⁸ *Id.* at 14. The Supplement to the Citizen Petition clearly explains how the process-dependent ATIII binding oligosaccharides are formed as a result of Aventis’ manufacturing process. See Aventis Citizen Petition Supplement, at 4-5.

⁵⁹ See Nightingale SL. Appropriate use of low-molecular-weight heparins (LMWHs). *JAMA* 1993;270(14):1672. *But see* Prandoni P & Nenci GG. Low molecular weight heparins: are they interchangeable? Yes/No. *J. Thromb. Haemost.* 2003; 1:10-13 (citing debate on interchangeability of LMWHs).

the Agency has long-recognized that, “[b]ecause of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), *a biological product was often defined by its manufacturing process...*”⁶⁰ Teva’s assertion that Aventis has offered little or no proof of the process dependency of Enoxaparin’s structural fingerprints is therefore simply inaccurate.

2. Conformance With USP, BP, and EP Monographs for Enoxaparin Does Not Ensure “Sameness”

The Teva Comment points out that monographs exist for Enoxaparin in both the European Pharmacopoeia (EP) and the British Pharmacopoeia (BP) and that a proposed USP monograph has been published in the November-December 2003 *Pharmacopeial Forum*. Teva therefore argues that “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 level of preparation (alkaline depolymerization of heparin benzyl ester).”⁶¹

The Teva Comment undermines its own assertion, however, by pointing out (correctly) that “compliance to compendial tests and specifications is not necessarily sufficient for approval of any ANDA, and . . . FDA may require additional tests and specifications beyond those mandated by USP.”⁶² For the reasons discussed in the Citizen Petition, the Supplement, and this Comment, Enoxaparin provides just such a case.

3. Aventis’ Requests Are Consistent With Legal Precedent and Legislative History, and Are In Furtherance of Public Policy

The Hyman Comment argues that “[f]orcing generic applicants to wait for Enoxaparin to be fully characterized chemically is inconsistent with legal precedent and legislative history, against public policy, and unnecessary.”⁶³ This argument, however, mischaracterizes the Citizen Petition and Supplement. Aventis has never

⁶⁰ FDA, Guidance to Industry Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (April 1996) (emphasis added).

⁶¹ Teva Comment, at 3-4.

⁶² *Id.* at 4. The courts have affirmed FDA’s responsibility to do just that. *See Serono*, 158 F.3d at 1322, n.3 (quoting 57 Fed. Reg. 17950, 17959).

⁶³ Hyman Comment, at 3.

argued that FDA may not approve a generic Enoxaparin product until Enoxaparin is fully-characterized. Rather, Aventis has argued only that until Enoxaparin becomes fully-characterized, FDA must require ANDA applicants either to submit results of clinical tests showing that their product has the same safety and effectiveness profile as Enoxaparin, or to employ a manufacturing process that is equivalent to Aventis' process in order to ensure that the generic product has the same active ingredient as Lovenox.[®]

As demonstrated by the discussion of the *Serono* case both here and in the Citizen Petition and Supplement, these requests are fully-consistent with legal precedent. They are also consistent with the legislative history of Hatch-Waxman, and public policy. The Hyman Comment argues that Hatch-Waxman was aimed to "ensure availability of affordable generic products for the benefit of consumers," and that "[d]elaying availability of generic enoxaparin would be against public policy and inconsistent with legislative intent."⁶⁴

Aventis agrees that these are important public policy goals, which Congress certainly contemplated in enacting Hatch-Waxman. The primary goal of Hatch-Waxman, and the highest interest of public policy, however, is that FDA ensure that any drugs entering the marketplace are safe and effective. Aventis' requests are directed at ensuring that FDA does not approve a generic enoxaparin product that does not share Enoxaparin's effectiveness or that could jeopardize patient safety. Far from being anti-competitive, as the Teva and Hyman Comments suggest, Aventis' requests are therefore fully-consistent with the first goal of Hatch-Waxman and highest priority of public policy.

V. Conclusions

In its Citizen Petition and Supplement, Aventis has identified several structural fingerprints in Enoxaparin. These fingerprints contribute to Enoxaparin's anticoagulant activity, and also have non-anticoagulant effects, which may have clinical significance. In addition, these structural fingerprints are process dependent. A generic product that did not employ an equivalent manufacturing process might not contain these fingerprints at the proper levels and therefore might behave differently than Enoxaparin in ways that are clinically significant for the product's intended uses.

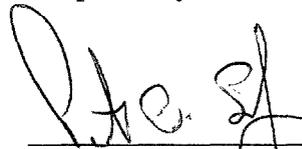
The Amphastar, Hyman, and Teva Comments have presented several arguments, both scientific and legal, in an attempt to draw FDA's attention away from this central argument of the Citizen Petition and Supplement. Not only are these

⁶⁴ *Id.* at 4.

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arguments flawed, as pointed out above, but they also fail to address the central issue of importance in the debate over generic Enoxaparin. Generic enoxaparin sodium products that do not either (a) follow an equivalent manufacturing process, or (b) establish a similar safety and effectiveness profile through clinical trials, might not be the "same" as Enoxaparin. The costs of any such inequivalence could be borne by patients, who take Enoxaparin for the treatment of life-threatening conditions. FDA must therefore require that all proposed generic enoxaparin sodium products take at least one of these measures.

Respectfully submitted,



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