



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services

Food and Drug Administration
Rockville, MD 20857

June 1, 2004

Stephen A. Campbell, Esq.
Senior VP, Regulatory Affairs
Amphastar Pharmaceuticals, Inc.
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

This is in response to your letter dated May 13, 2004, to Lester M. Crawford, Acting Commissioner, Food and Drug Administration (FDA), requesting that the citizen petition filed by Aventis Pharmaceuticals (Docket No. 03P-0064/CP1) concerning Lovenox (enoxaparin sodium injection) be denied and that Amphastar's abbreviated new drug application (ANDA 76-684) be expedited for approval. Your letter was forwarded to my office in the Center for Drug Evaluation and Research (CDER) for response.

Thank you for writing. As I am sure you know, citizen petitions are the way that industry, consumer groups, and individuals can influence FDA to make a change in a regulation or to take other action. A petition requests the FDA Commissioner to establish, amend, or revoke a regulation or order, or to take or not to take any other form of administrative action, under the laws administered by FDA. Citizen petitions are placed in a public docket, allowing for public review and comment. CDER is then required by law to evaluate and respond to the petition.

I have taken the liberty of forwarding your letter (with enclosures) to Dockets Management so that it can be recorded and considered as a comment to Aventis Pharmaceuticals' citizen petition. Citizen petitions with all recorded comments are available on our Dockets Management web page at <http://www.fda.gov/ohrms/dockets/default.htm>.

Again thank you for writing. Please do not hesitate to contact me if I can provide further assistance.

Sincerely,

Donald Dobbs
Division of Drug Information (HFD-240)
Office of Training and Communications
Center for Drug Evaluation and Research
Food and Drug Administration

03P-0064

CZ / ANS



AMPHASTAR PHARMACEUTICALS, INC.

11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone: (909) 980-9484 • Fax: (909) 980-8296

May 13, 2004

Acting Commissioner
Lester M. Crawford, D.V.M., Ph.D.
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane, HF-1
Rockville, Maryland 20857

**RE: Docket No. 03P-0064/CP1 – Enoxaparin Sodium Injection.
Amphastar ANDA 76-684 for Enoxaparin Sodium Injection.**

Dear Dr. Crawford:

On February 19, 2003, Aventis Pharmaceuticals (“Aventis”) filed a Citizen Petition (Docket No. 03P-0064/CP1) 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, through counsel, filed a supplement to its Citizen Petition.

In its lengthy document, Aventis emphasized that its manufacturing process is **stringent and unique**. The structure of the low molecular weight heparins, Enoxaparin, is “**highly sensitive**” to “**Aventis’ process**.” Aventis stated in the Citizen Petition:

Aventis’ manufacturing process creates a highly complex collection of macromolecules with a chemical structure that is unique among currently approved LMWHs. This structure is marked by distinct polysaccharide sequences and structural modifications (or “fingerprints”) that are highly sensitive to Aventis’ process.

However, when Amphastar visited the FDA website on Label and Approval History of Lovenox (brand name for Enoxaparin), Appendix 1, we learned the following:

Between March 1996 and April 2004, the record showed that Aventis had filed:

- “Control Supplement” seven (7) times¹,
- “Manufacturing Change or Addition” nine (9) times², and

¹Approval of Control Supplement #011 (2/24/98); #022 (7/21/99); #024 (7/22/99); #026 (9/14/99); #027 (10/05/99); #039 (10/24/00); #044 (11/30/01).

² Approval of Manufacturing Change or Addition #004 (3/15/96); #012 (10/23/96); #013 (5/16/97); #023 (11/08/99); #032 (1/27/00); #038 (6/20/00); #041 (12/14/00); #042 (7/05/01); #043 (1/23/03).

- “Formulation Revision” one (1) time³.

The total changes amount to seventeen (17) times in eight (8) years (1996-2004). In other words, the available data shows Aventis made a critical change for CMC (Chemistry, Manufacturing and Control), on average, once every six (6) months! Obviously, the “*Aventis’ process*” is not uniquely defined and should not be considered “*highly sensitive.*”

This is just another example of brand-name companies using endless delay tactics in order to keep their drug “Evergreen.” Aventis is wasting the taxpayers’ money and the court’s time with these types of delay tactics.

European Pharmacopeia has published the specification of Enoxaparin Sodium as an Active Pharmaceutical Ingredient (API) for many years.

In March 2003, Amphastar submitted an ANDA (Abbreviated New Drug Application) 76-684 with the FDA for Enoxaparin. The FDA accepted the filing as the first Paragraph IV Patent Challenge to Lovenox. The API for Enoxaparin Sodium utilized for Amphastar’s ANDA 76-684 meets all of the specifications for Enoxaparin Sodium according to European Pharmacopeia (01/2002:1097) as given in Appendix 2. Recently, Amphastar answered all of the FDA’s questions in detail and responded to the FDA ANDA package reviewer. Amphastar’s response to the FDA became an amendment that included:

- 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, HPCL-SAX chromatogram, and HPCL-SEC chromatogram
- Examination of the 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-IIa

These studies (Appendix 3) indicate that Amphastar’s Enoxaparin Sodium is equivalent to Aventis’ Lovenox.

In response to the Paragraph IV notification that it received from Amphastar, Aventis filed a frivolous lawsuit against Amphastar for patent infringement (patent #5,389,618) in August 2003. Their intent is to delay a generic release for 8 years or until at least 2012 (the expiration date of the above-patent). Today, the U.S. market for Lovenox is \$1.2 billion. When the generic versions are available, the price of this drug will be reduced to 1/5 to 1/3 of the current price of Lovenox. If Aventis unfairly blocks the approval of generic Lovenox, it will cost the U.S. consumers \$6.4 billion to \$7.7 billion in the next eight (8) years.

³ Approval of Formulation Revision #030 action date 6/02/00

Therefore, for the reasons cited above, it is respectfully requested that Citizen Petition 2003P-0064-CP1 be denied and that Amphastar's ANDA 76-684 submittal for Enoxaparin be expedited.

Respectfully,

A handwritten signature in cursive script, appearing to read "Stephen A. Campbell".

Stephen A. Campbell, Esq
Senior VP, Regulatory Affairs

cc: Steven Golson, M.D., M.P.H.

Acting Director, Office of Center for Drug Evaluation and Research

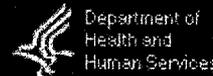
Ms. Helen Winkle, Director of the Office of Pharmaceutical Science

Gary Buehler R. Ph., Director of the Office of Generic Drugs

Jan P. Weir, Esq., Stradling Yocca Carlson & Rauth



U.S. Food and Drug Administration



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Label and Approval History

Drug Name(s) LOVENOX (Brand Name Drug)
FDA Application No. (NDA) 020164
Active Ingredient(s) ENOXAPARIN SODIUM
Company AVENTIS

[Go to Approval History](#)

Label Information

What information does a label include?

Note: Not all labels are available in electronic format from FDA.

The latest approved label (approved 04/21/2004) is *not available* on this site for LOVENOX, NDA no. 020164

View the label approved on 11/17/2000 

- To see if other previously-approved labels are available on this site, go to the "[Approval History](#)" section of this page. **Older labels are for historical information only and should not be used for clinical purposes.**

Approval History

Note: Not all reviews are available in electronic format from FDA.

Appendix - 1

Older labels are for historical information only, and should not be used for clinical purposes.
 Action dates can only be verified from 1984 to the present.

Action Date	Supplement Number	Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
04/21/2004	058	Labeling Revision	Letter 	Label is not available on this site.
04/13/2004	056	Labeling Revision	Letter 	Label is not available on this site.
12/18/2003	048	Labeling Revision	Letter 	Label is not available on this site.
07/01/2003	050	Labeling Revision	Letter 	Label is not available on this site.
06/20/2003	051	Labeling Revision	Letter 	Label is not available on this site.
01/23/2003	043	Manufacturing Change or Addition	Letter 	This supplement type does not usually require new labeling.
01/09/2002	046	Labeling Revision	Letter 	Label is not available on this site.
01/09/2002	045	Labeling Revision	Letter 	Label is not available on this site.
01/09/2002	040	Labeling Revision	Letter 	Label is not available on this site.
11/30/2001	044	Control Supplement		This supplement type does not usually require new labeling.
07/05/2001	042	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
12/14/2000	041	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
11/17/2000	037	Labeling Revision	Label  Letter 	
11/17/2000	036	New or Modified Indication	Label  Letter 	
10/24/2000	039	Control Supplement		This supplement type does not usually require new labeling.

08/03/2000	020	Efficacy Supplement with Clinical Data to Support	Letter 	Label is not available on this site.
06/20/2000	038	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
06/02/2000	030	Labeling Revision		Label is not available on this site.
05/30/2000	034	Efficacy Supplement with Clinical Data to Support	Letter 	Label is not available on this site.
04/04/2000	035	Package Change		Label is not available on this site.
01/27/2000	032	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
11/08/1999	023	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
10/05/1999	031	Labeling Revision		Label is not available on this site.
10/05/1999	027	Control Supplement		This supplement type does not usually require new labeling.
09/28/1999	028	Labeling Revision		Label is not available on this site.
09/14/1999	026	Control Supplement		This supplement type does not usually require new labeling.
07/22/1999	024	Control Supplement		This supplement type does not usually require new labeling.
07/21/1999	022	Control Supplement		This supplement type does not usually require new labeling.
04/20/1999	021	Labeling Revision		Label is not available on this site.
03/03/1999	019	Package Change		Label is not available on this site.
12/31/1998	015	New or Modified Indication	Label  Letter  Review	
03/27/1998	016	New or Modified Indication		Label is not available on this site.
02/24/1998	011	Control Supplement		This supplement type does not usually require new labeling.

01/30/1998	010	New or Modified Indication	<u>Review</u>	Label is not available on this site.
05/27/1997	017	Labeling Revision		Label is not available on this site.
05/27/1997	006	Labeling Revision		Label is not available on this site.
05/16/1997	013	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
05/06/1997	008	New or Modified Indication		Label is not available on this site.
03/07/1997	007	Package Change		Label is not available on this site.
01/27/1997	014	Labeling Revision		Label is not available on this site.
10/23/1996	012	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
06/26/1996	009	Package Change		Label is not available on this site.
03/15/1996	004	Manufacturing Change or Addition		This supplement type does not usually require new labeling.
01/30/1996	005	Labeling Revision		Label is not available on this site.
03/09/1995	002	New or Modified Indication		Label is not available on this site.
03/14/1994	001	Labeling Revision		Label is not available on this site.
03/29/1993	000	Approval	Label  Letter 	
PDF files, marked with an icon  , require the free Adobe Acrobat Reader.				

- **There are no Therapeutic Equivalents**

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Comparison of API between Amphistar Enoxaparin and Lovenox® per Specifications of European Pharmacopoeia

TEST	EP SPECIFICATION	Amphistar			Lovenox®		
		EO093002	EO100202	EO101402	1446	1481	15021
Appearance	White or Almost White Powder	Almost White Powder					
Appearance of Solution:							
Clarity	To pass test	Pass	Pass	Pass	Pass	Pass	Pass
Degree of Coloration	To pass test	Pass	Pass	Pass	pass	pass	pass
Identification:							
A. ¹³ C NMR	Conform to Standard	Conform to std					
B. Anti-Xa/Anti-IIa	3.3-5.3	4.1	4.0	4.3	4.0	3.8	3.8
C. Molecular Weight (MW)							
MW (average)	3500-5500	4837	4723	4876	4408	4463	4595
MW<2000	12.0-20.0%	13.7	14.3	14.9	16.6	16.6	16.0
2000<MW<8000	68.0-88.0%	73.7	73.7	73.0	73.2	72.6	72.3
D. Reaction of Sodium	To pass test	Pass	Pass	Pass	Pass	Pass	Pass
Absorbance at 231nm	14.0-20.0	15.6	15.7	16.2	15.4	16.2	16.3
Benzyl Alcohol	NMT 0.1% (w/w)	0.005	0.005	0.006	0.03	0.03	0.02
Sodium	11.3-13.5% (w/w)	12.3	12.3	12.5	12.4	13.0	13.1
pH	5.5-8.0	7.4	7.3	7.3	6.6	7.2	6.9
Nitrogen	1.5-2.5%	2.2	1.7	2.1	2.0	2.0	1.9
Heavy Metals	NMT 30 ppm	pass	pass	pass	pass	pass	pass
Loss on Drying	NMT 10.0%	2.5	3.0	3.2	N/A	N/A	N/A
[-OSO ₃ ⁻]/[-COO ⁻]	NLT 1.8	2.3	2.3	2.3	N/A	N/A	N/A
Assay							
Anti-Xa activity	90-125 IU/mg	103	102	97	109.0	107.9	103.8
Anti-IIa activity		25	26	23	27	28	27
Residual Solvent:							
Methanol	NMT 3000 ppm	17	0	25	0	0	8
DMF	NMT 880 ppm	0	0	0	102	0	0

N/A : API for Lovenox® was obtained by lyophilization of the finished product, these items were not performed due to the limits of the sample amount



Amphastar Pharmaceuticals, Inc

SYNOPSIS OF EQUIVALENCE COMPARISON OF AMPHASTAR ENOXAPARIN & AVENTIS LOVENOX

Ver. 1.0 5/12, 2004

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Equivalence of physico-chemical properties between Amphastar Enoxaparin vs. Lovenox®

1. General Physical Properties

Test	Appearance of Solution	pH	Absorbance at 231nm
Specification	Colorless to pale yellow solution	5.5 – 7.5	14.0 – 20.0
Amphastar, 112002C	Pass	7.0	15.8
Amphastar, 112002D	Pass	7.0	16.4
Amphastar, 111802A	Pass	6.9	16.3
Average	Pass	7.0	16.2
Lovenox®, 1446	Pass	6.6	15.4
Lovenox®, 1481	Pass	7.2	16.2
Lovenox®, 15021	Pass	6.9	16.3
Average	Pass	6.9	16.0

2. General Chemical Properties

Test	Sodium	Nitrogen	Heavy Metals	Benzyl Alcohol	Methanol	DMF
Specification	11.3 – 13.5% (w/w)	1.5 – 2.5%	NMT 30ppm	NMT 0.1% (w/w)	NMT 3000ppm	NMT 880ppm
Amphastar EO093002	12.3	2.2	pass	0.01	17	0
Amphastar EO100202	12.3	1.7	pass	0.01	0	0
Amphastar EO101402	12.5	2.1	pass	0.01	25	0
Average	12.2	2.0	pass	0.01	14.0	0
Lovenox® 1446	12.4	2.0	pass	0.03	0	102
Lovenox® 1481	13.0	2.0	pass	0.03	0	0
Lovenox® 15021	13.1	1.9	pass	0.02	8	0
Average	12.8	2.0	pass	0.03	2.7	34

Equivalence of physico-chemical properties between Amphastar Enoxaparin vs. Lovenox®

3. Molecular Weight: Average and Distribution

Test	Average Mw	Mw < 2000	2000 ≤ Mw ≤ 8000	Mw > 8000
Specification	3500 - 5500	12.0 – 20.0%	68.0 – 88.0%	< 18.0%
Amphastar, 112002C	4756	14.7	73.9	11.4
Amphastar, 112002D	4775	13.4	75.6	11.0
Amphastar, 111802A	4778	14.3	74.0	11.7
Average	4770	14.1	74.5	11.4
Lovenox®, 1446	4408	16.6	73.2	10.2
Lovenox®, 1481	4463	16.6	72.6	10.8
Lovenox®, 15021	4595	16.0	72.3	11.7
Average	4489	16.4	72.7	10.9

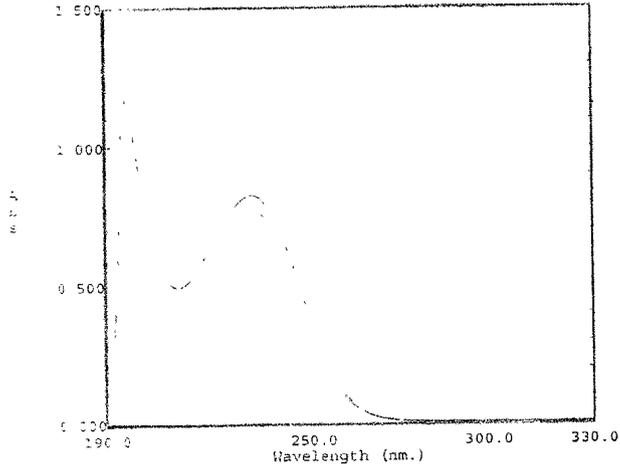
Equivalence in biochemical and biological assay between Amphastar Enoxaparin vs. Lovenox®

4. Biochemistry : Anti-Xa and Anti Xa/Anti-IIa

Test	Anti-Xa	Anti-Xa/Anti-IIa
Concentration 100 mg/mL	Specification	8500 – 13000 IU/mL (Target :10000 IU/mL)
	Amphastar, 112002A	10022
	Amphastar, 112002C	10114
	Amphastar, 112002D	10035
	Average	10057
	Lovenox®, 1446	10898
	Lovenox®, 1481	10788
	Lovenox®, 1485	10786
	Average	10824
Concentration 150 mg/mL	Specification	13000 – 19000 IU/mL (Target : 15000 IU/mL)
	Amphastar, 111802A	14809
	Lovenox®, 15021	15612

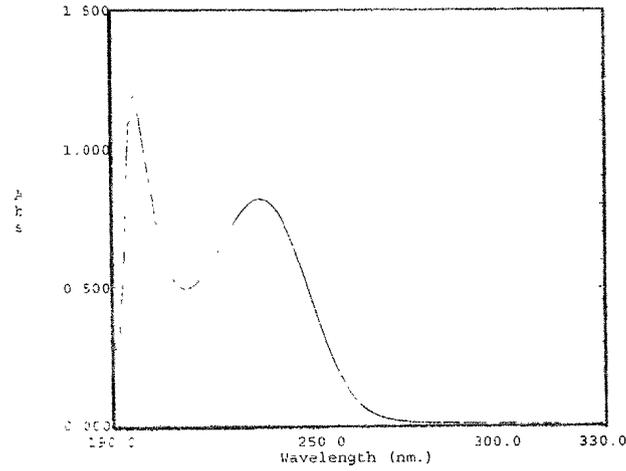
Equivalence Comparison between Amphastar Enoxaparin and Lovenox®

5.1 Characterization : UV spectrum, 3 lots each, Blue - Amphastar Enoxaparin, Red - Lovenox®



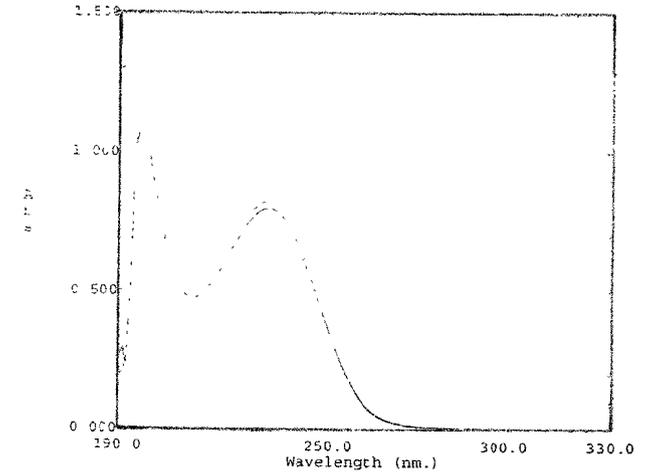
112002D - LV1481

UV spectra for Enoxaparin Sodium Injection lot 112002D and Lovenox lot 1481



111802A - LV-15021

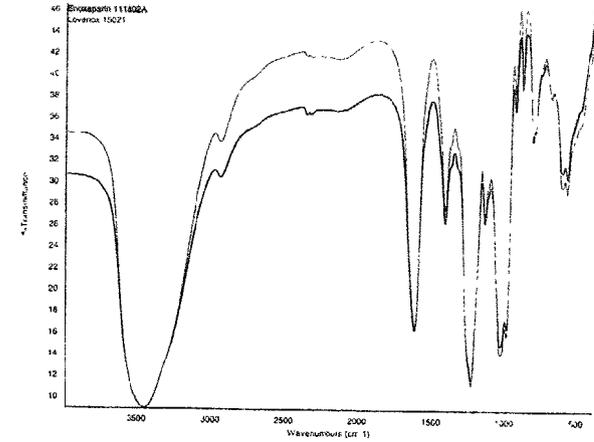
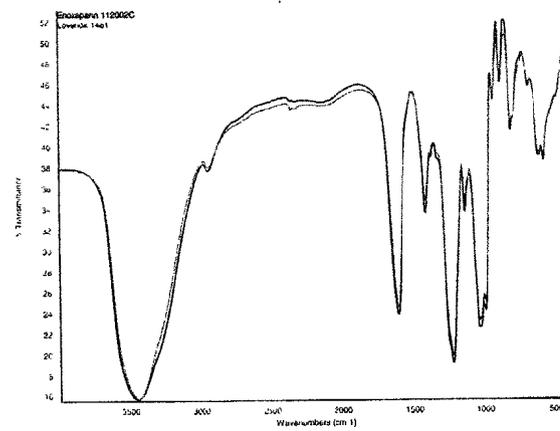
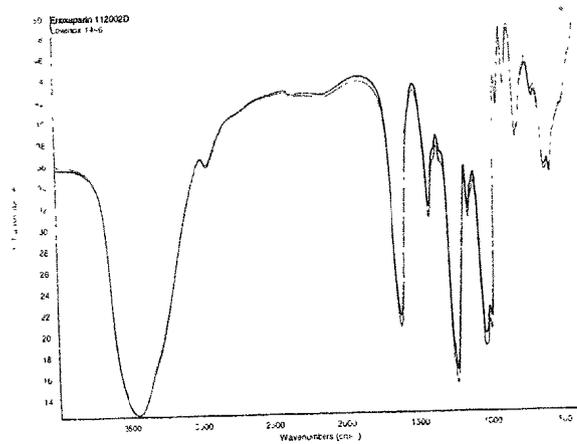
UV spectra for Enoxaparin Sodium Injection lot 111802A and Lovenox lot 15021



112002C - LV1481

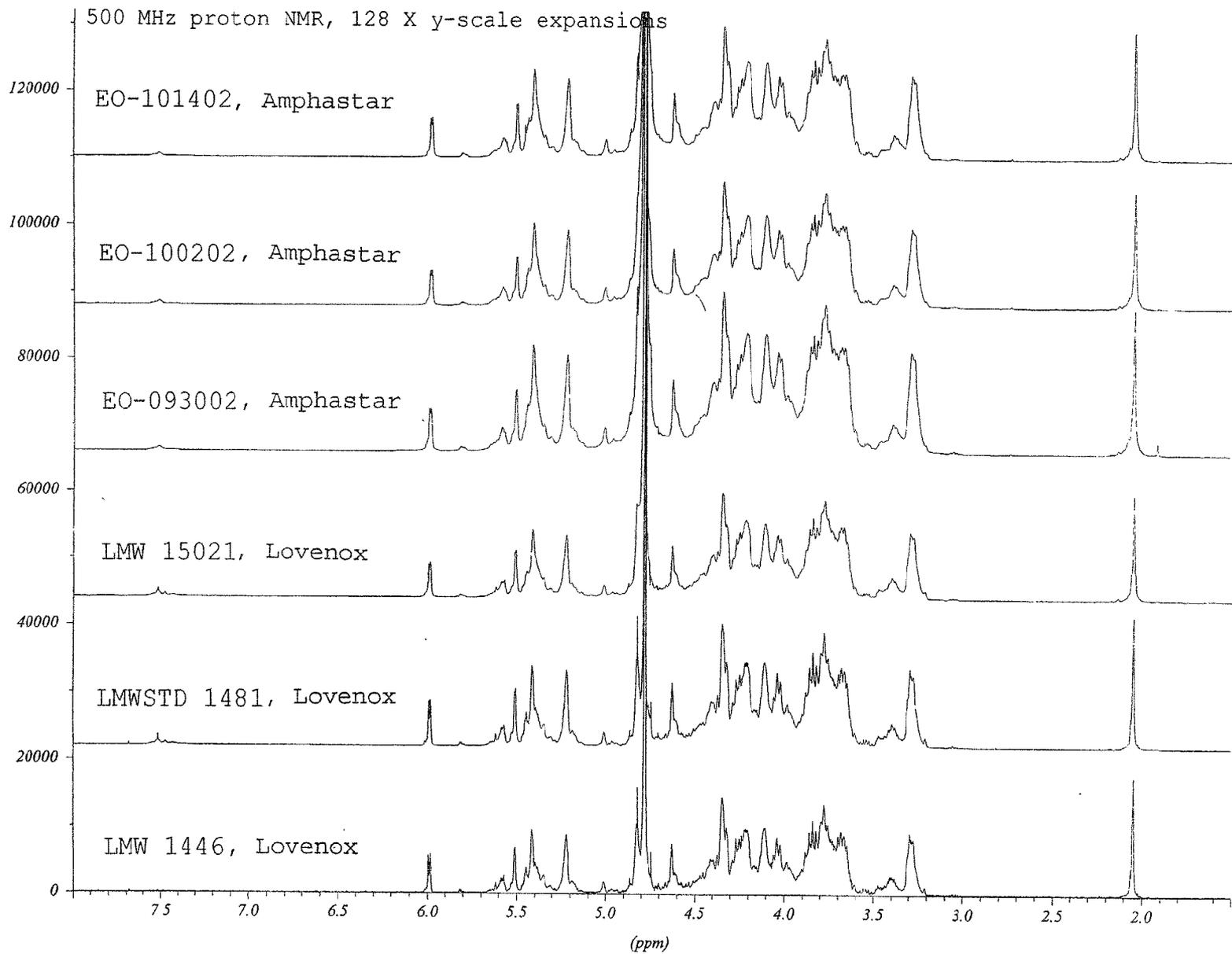
UV spectra for Enoxaparin Sodium Injection lot 112002C and Lovenox lot 1481

5.2 Characterization : FT-IR spectrum, 3 lots each, Blue - Amphastar Enoxaparin, Red - Lovenox®



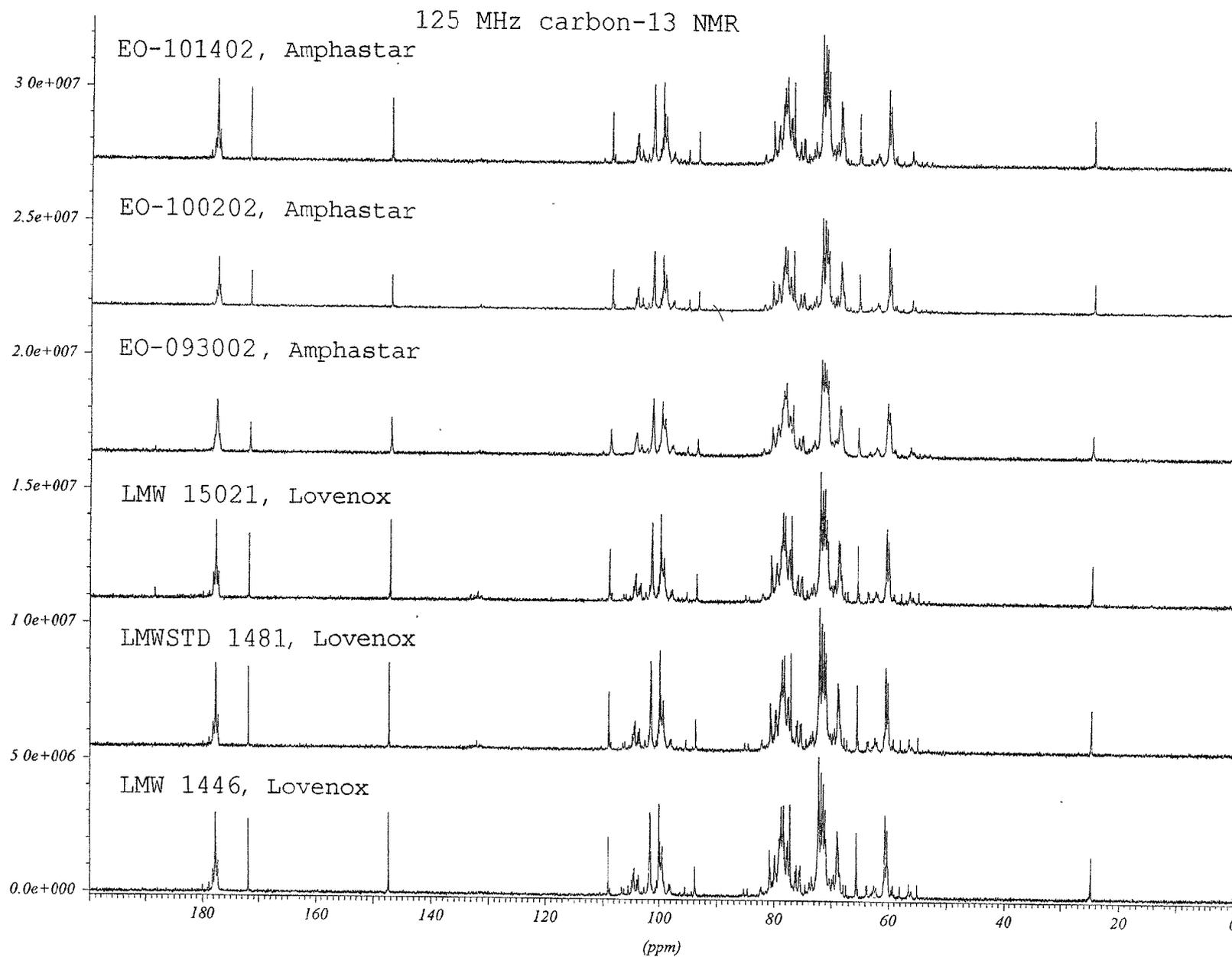
Equivalence Comparison between Amphastar Enoxaparin and Lovenox®

5.3 Characterization : Proton ¹H NMR spectrum, 3 lots each



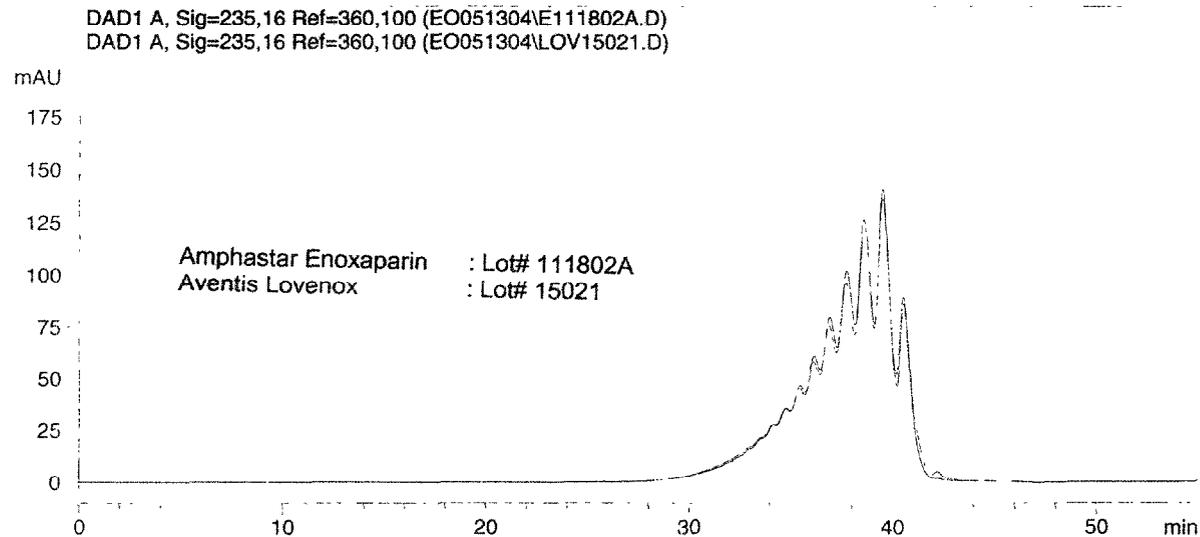
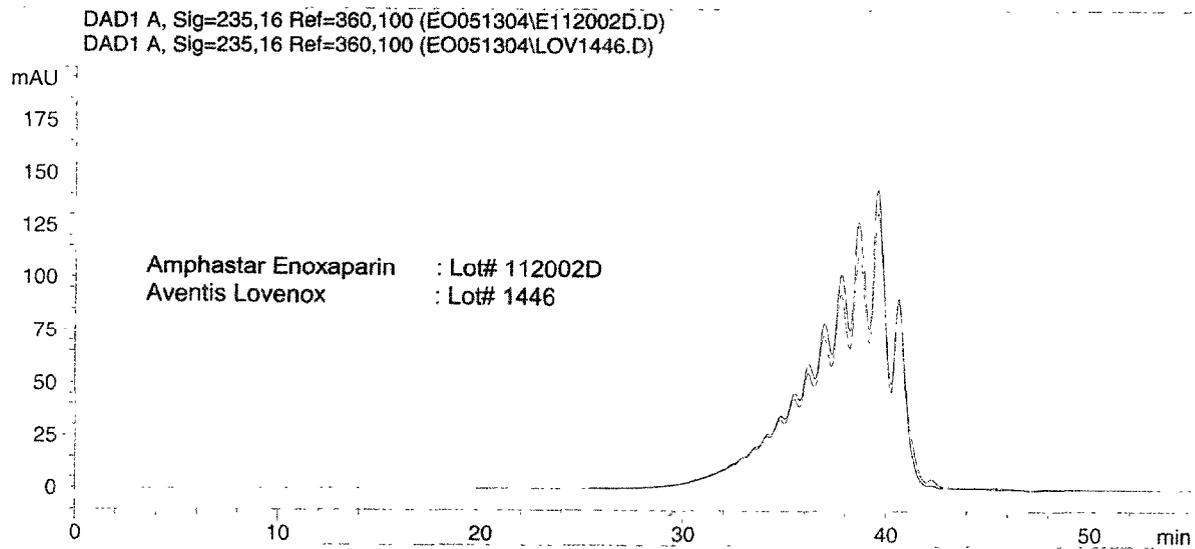
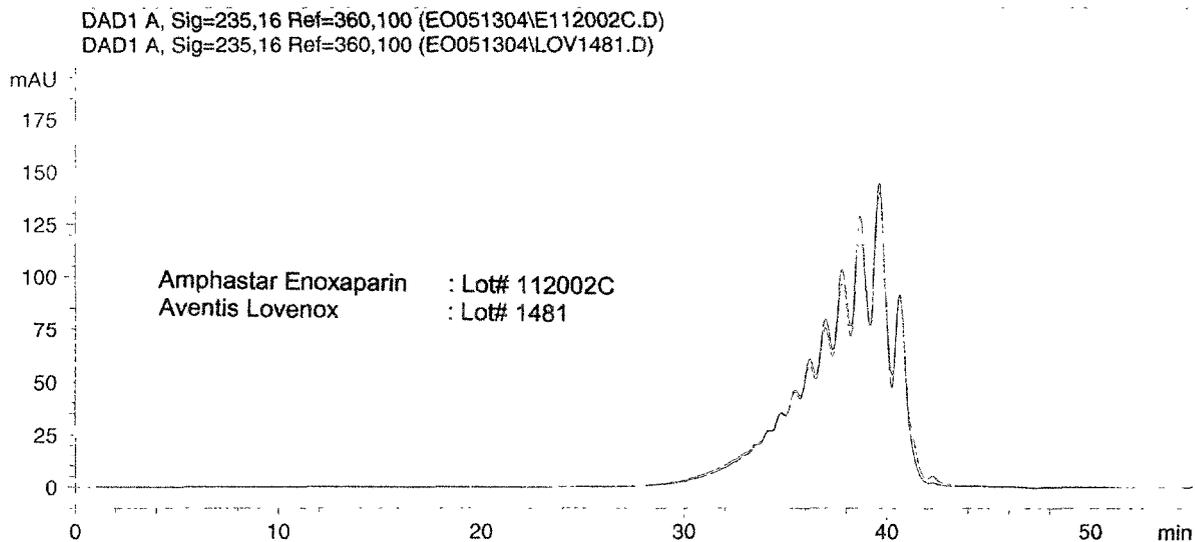
Equivalence Comparison between Amphastar Enoxaparin and Lovenox®

5.4 Characterization : Carbon ¹³ C NMR spectrum

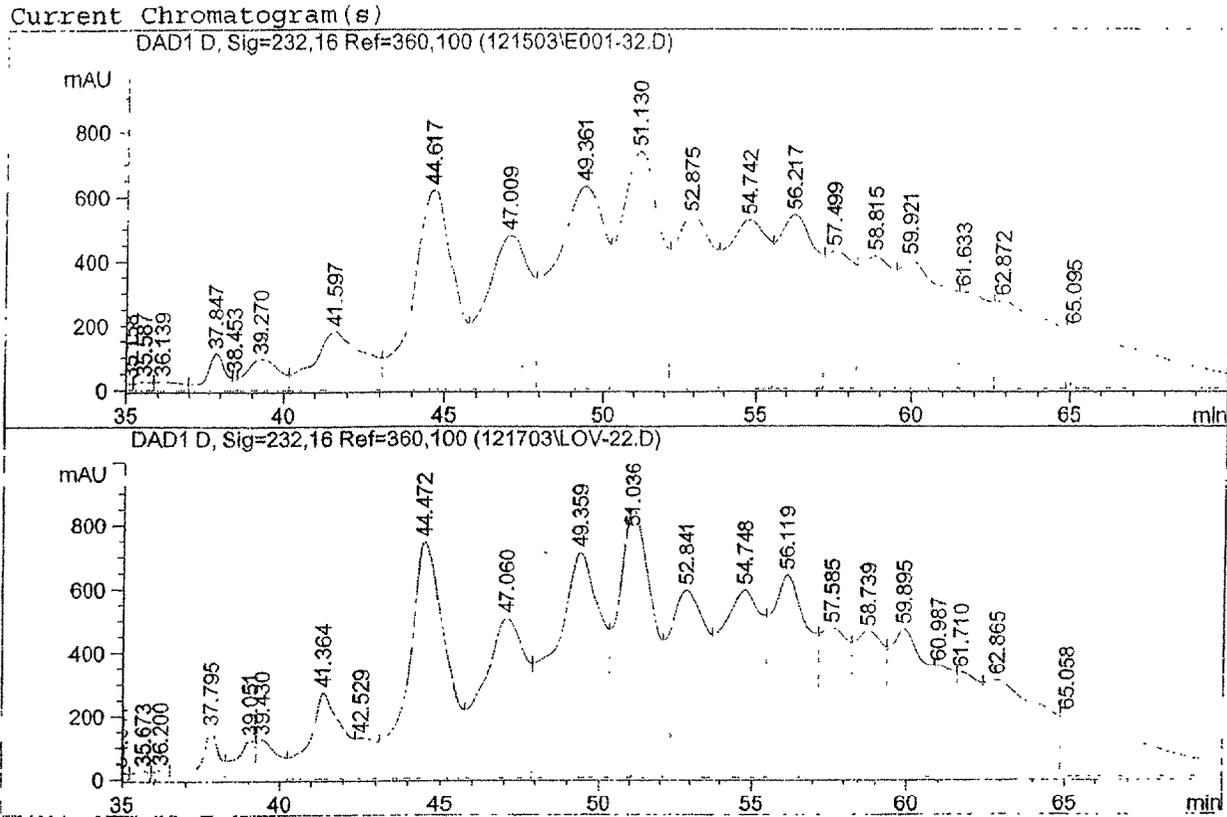


Equivalence Comparison between Amphastar Enoxaparin and Lovenox®

5.5 Characterization : HPLC-SEC Chromatogram, 3 lots each, Blue: Amphastar Enoxaparin, Red: Lovenox®



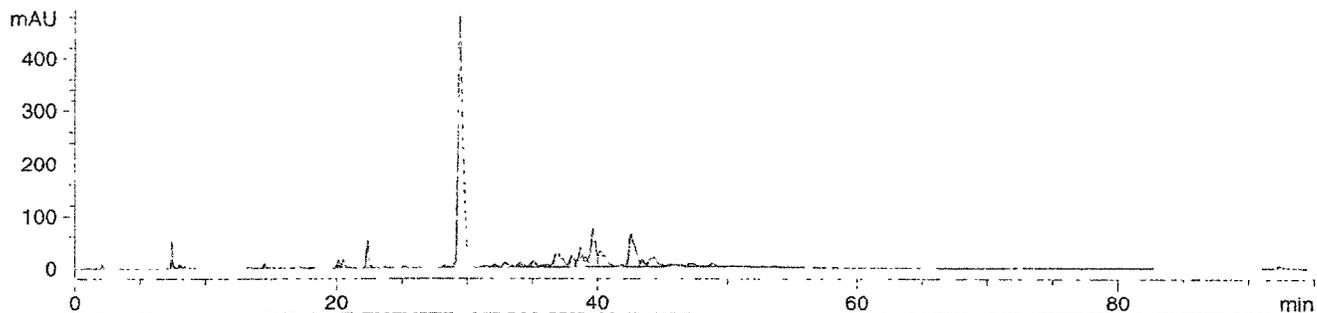
**Equivalence Comparison Between Amphastar Enoxaparin and Aventis Lovenox:
5.6 HPLC-Strong Anion Exchange (HPLC-SAX) Chromatograms**



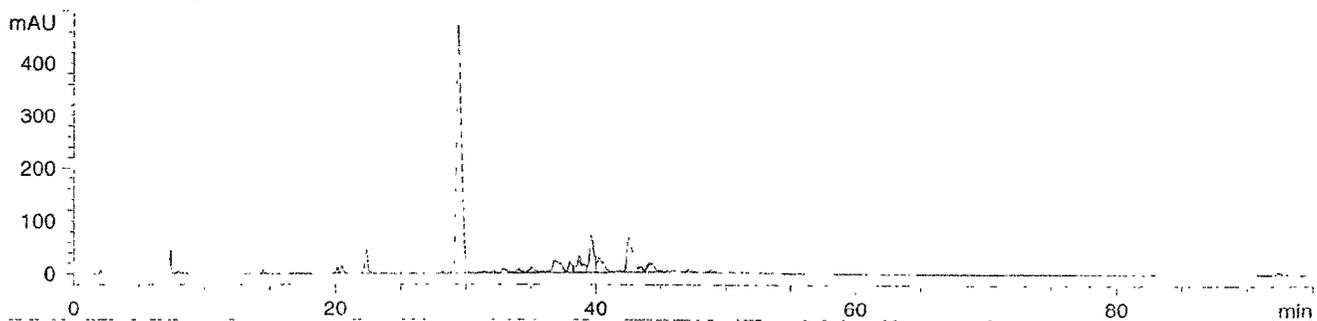
**Upper: Amphastar Enoxaparin
Lower: Aventis Lovenox**

Equivalence Comparison of The Disaccharide Unit Building Blocks Three Lots of Amphastar Enoxaparin (in blue) and Aventis Lovenox (in red)

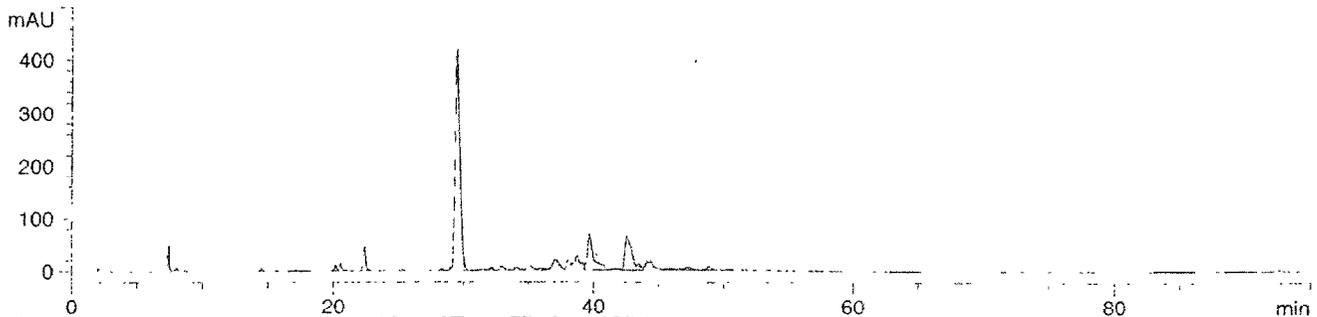
DAD1 D, Sig=232,16 Ref=360,100 (E030904\EO062503.D)
DAD1 D, Sig=232,16 Ref=360,100 (E030904\L1441.D)



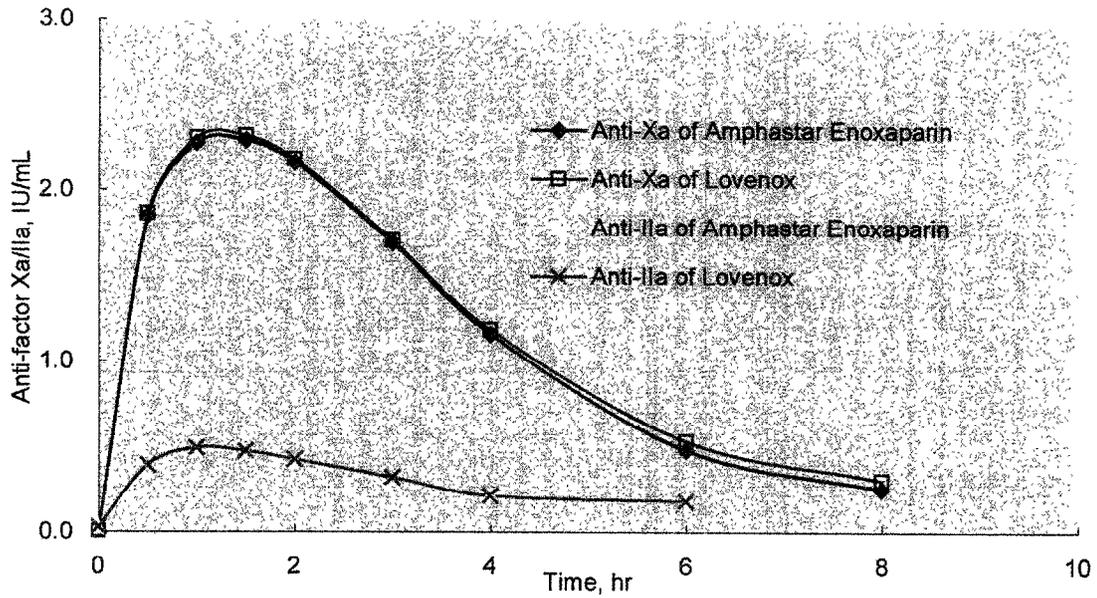
DAD1 D, Sig=232,16 Ref=360,100 (E030904\EO110603.D)
DAD1 D, Sig=232,16 Ref=360,100 (E030904\L1481.D)



DAD1 D, Sig=232,16 Ref=360,100 (E030904\EO093002.D)
DAD1 D, Sig=232,16 Ref=360,100 (E030904\L15021.D)



**In vivo Comparison of Anti-Factor Xa & IIa in Rat Plasma
Between Amphastar Enoxaparin and Lovenox®**



The major statistical results, i.e. the estimation and the 90% confidence intervals for the *in vivo* profiles of a rat model, between Amphastar Enoxaparin and Lovenox®, are summarized in the table below:

Item		Anti-factor Xa		Anti-factor IIa	
		AUC _{0-∞}	A _{max}	AUC _{0-∞}	A _{max}
Estimation	Original, %	97	97	96	98
	Dose-normalized, %	101	102	99	101
90% Confidence Interval	Original, %	89-105	90-104	85-106	92-103
	Dose-normalized, %	93-109	95-109	89-109	95-107