CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076684

CHEMISTRY REVIEWS

ANDA 76-684

Enoxaparin Sodium Injection
30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL, and 150 mg/mL

Amphastar Pharmaceuticals, Inc.

Naiqi Ya, Ph. D.*

Office of Generic Drugs/Division of Chemistry II

Comment [note1]: Replace the yellow highlighted text with the Chemistry Reviewer's name

Comment [note2]: Replace the highlighted text with the name of the clinical review division (for NDA reviews) or the chemistry division (for ANDA reviews)

***Note: This review was completed on October 16, 2003 and the resulting Major letter was issued on October 17, 2003. Due to the unique regulatory status of enoxaparin applications at the time of review, only the deficiency letter was checked into the COMIS system. This review is archived into the DARRTS system by D. Skanchy (the current assigned reviewer to this ANDA) on March 3, 2011 to complete the record. Naiqi Ya and Sau (Larry) Lee (both previously assigned reviewers to this ANDA are signers on this review.**

Table of Contents

Comment [Note3]:
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To automatically have MSWord update the Table of Contents with the correct pagination, Click once anywhere in the Table of Contents (the Table of Contents should now be shaded) and then press either the F9 key or Alt+Shift+U

Chemistry Review Data Sheet

1. ANDA 76-684

2. REVIEW #: 1

3. REVIEW DATE: October 16, 2003

4. REVIEWER: Naiqi Ya, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	March 4, 2003
Amendment (a filing issue)	April 18, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Amphastar Pharmaceuticals, Inc.
Address:	11570 Six Street Rancho Cucamonga, CA 91730
Representative:	Stephen A. Campbell, Esq Sr. Vice President, Regulatory Affairs
Telephone:	(626) 459-5253 (909) 980-9484 ext. 2019

Comment [Note4]:
Please Do Not Change the Order Only the items in bold will be in the template If there are categories that do not apply, these should not be deleted, but should be marked as "N/A" with an explanation as to why the review of the section is not applicable, if not obvious This Review Data Sheet is an integral part of the chemistry review and should always be part of the review documentation

Comment [Note5]:
Add the review number for this review. All reviews for an A/NDA should be numbered sequentially even if the assigned reviewer is changed.

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The date when he review chemist completes the ini ial draft review of the submissions listed under SUBMISSION(S) BEING REVIEWED. Dates should be in the day-month-year format (DD-MMM-YYYY).

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Name of review chemist.

Comment [Note8]:
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Comment [Note10]:
Include the exact address for the applicant. This may be an administrative address, which is different from the actual manufacturing address. Also, include the addresses for the "contact for FDA correspondence" and/or "U.S. Agent", if necessary. ... [3]

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Enoxaparin Sodium

9. LEGAL BASIS FOR SUBMISSION:

The approved enoxaparin sodium injection as Lovenox®, 100 mg/mL and 150 mg/mL in prefilled syringes, manufactured by Aventis Pharmaceuticals Inc. Lovenox® is currently covered by two US patents and one exclusivity:

US Patent No.	Description	Expiration Date
4,692,435	Mucopolysacchride composition having a regulatory action on coagulation, medicament containing some and process of preparation	December 24, 2004
5,389,618	Mixtures of articular LMW heparinic polysaccharides for the prophylaxis/treatment of acute thrombotic events	February 14, 2012

Exclusivity	Description	Expiration Date
I-315	Thromboprophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness	November 17, 2003

The applicant claimed that the US Patent No. 5,389,618 will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. The applicant intends to market this drug product upon approval of the ANDA, but not before expiry of the exclusivity on November 17, 2003.

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120/0.8 mL, and 150 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

Comment [Note11]:
a.Proprietary Name (If not applicable, indicate N/A)
b.Non-Proprietary Name (USAN)
c.Code Name/# (ONDC only)
d.Chem. Type/Submission Priority (ONDC Only)
Chem. Type = (1, 2, 3, 4, 5 or 6)
Submission Priority = S or P
(Standard or Priority; specific link for determining priority: http://www fda gov/cder/mapp/6020-3 pdf)

Comment [note12]:
Type in the proprietary name(s) [a k a , trade name(s)] for the drug product If not applicable, then enter N/A

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Type in the Non-Proprietary name (i e , the USAN name) for the drug product

Comment [Note14]:
The section should include:

For ANDAs:
The Reference Listed Drug (RLD), including the proprietary name, dosage form, strength(s), and NDA holder.
If the ANDA is filed as a result of a Suitability Petition, this should be stated. Because suitability petitions are based on a change from ar ... [4]

Comment [Note15]:
Refer to FDA Form 356h or available references.

Comment [Note16]:
Refer to the CDER Data Standards Manual (General link for MAPP list: http://www.fda.gov/cder/mapp.htm), as needed or, for novel dosage forms, consult Nomenclature Standard ... [5]

Comment [Note17]:
Strength should be defined clearly, (e.g., mg per ml, :g per tablet, or per dose). "Strength" is defined in 21 CFR §210.3(b)(16) as: :
The concentration of the drug ... [6]

Comment [Note18]:
Refer to the CDER Data Standards as needed, e.g., i.v., oral

Comment [Note19]:
Indicate which market place the intended drug product will be marketed

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

__X__SPOTS product – Form Completed

____Not a SPOTS product

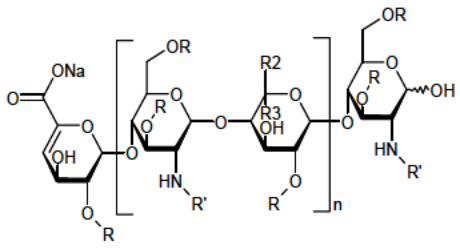
Comment [note20]:
If applicable, fill out the form for special products and deliver to the team leader. The Spots Data Form can be retrieved by clicking on the underlined yellow highlighted text. The team leader should mail the completed form to: ONDC, HFD-800, Room 13B-31 Parklawn.

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Comment [Note21]:

Place the chemical structure on the first page, if possible, so as to maintain he sequence of items. If the structure is larger than a half-page, add an additional page.

Enoxaparin Sodium. 9041-08-1.



n = 1 to 21, R = H or SO_3Na, R' = H or SO_3Na or $COCH_3$
R2 = H and R3 = CO_2Na or R2 = CO_2Na and R3 = H

17. RELATED/SUPPORTING DOCUMENTS:

Comment [Note22]:

DMFs and Other Documents (e.g., INDs, NDAs, related drugs, texts and literature review ar icles which may aid the review of the NDA, but are not required for reference) cited by the applicant on the Form 356h should be listed. Listings of documents should include the application number of he document, and a brief description of how it supports this application.

A. DMFs:

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	II			7			Inactive DM

[1] Action codes for DMF Table:
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7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Wavier requested for an injection dosage		
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

Comment [Note25]:

The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

19. ORDER OF REVIEW

Comment [Note26]:

For OGD only

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to major deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The basic structure is that of heparin, with a series of disaccharide units formed from uronic acid (glyucuronic or iduronic) and glucosamine, substituted in various ways. The most represented disaccharide unit is 4-α-L-iduronic acid-2-*O*-sulfate-α-(1→4)-D-glucosamine-*N*,6-sulfate, with extensive sulfation at position 6 of the amino sugar and at position 2 of the iduronic acid. Some of the amino sugar residues are *N*-acetylated instead of *N*-sulfated, and iduronic acid residues are occasionally nonsulfated.

Enoxaparin sodium is produced by alkaline depolymerization of heparin sodium and exists in an amorphous form of a practically white, hygroscopic powder. It is very soluble in water and decomposes without melting. Its potency is expressed as International Unit of anti-Xa activity/mg and as anti-Xa/anti-IIa activity ratio. The average molecular weight is about 4500 daltons. The molecular weight distribution is: <2000 daltons - ≤20%, 2000 to 8000 daltons - ≥68%, and >8000 daltons - ≤18%.

Enoxaparin Sodium Injection are available in strengths: 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL, and 150 mg/mL. The drug product contains (b) (4) (b) (4), Water for Injection USP, (b) (4) (b) (4). All strengths are packaged in per-filled syringes.

Comment [Note27]:
The primary reviewer should write the Chemistry Executive Summary with the following objectives in mind:
1 To meet the needs of a multiple audience of internal Chemistry management, Team Leaders, Reviewers, Clinical Division Directors, ODE Directors, Office Directors, or others with signatory responsibility This will be especially important when looking back historically on a review decision It can also serve to communicate Chemistry concerns to other CDER disciplines
2 To provide a brief account (1-2 pages) of the important aspects of quality of the drug substance and drug product
3 To discuss any unique scientific and regulatory issues that had a significant effect on the review decision (e g , concerns surrounding a stability issue, an acceptance criteria, dissolution testing, special dosage forms, impurity, stereochemistry)
4 To describe the attributes of the drug product that can affect safety ... [7]

Comment [Note28]:
You should state whether your recommendation is approval, approvable or not approvable from a chemistry review perspective.

Comment [Note29]:
This summary is intended to pull together all the assessments and conclusions made during the chemistry review(s) This summary serves as both an orientation to the review and a stand-alone document communicating the important findings without reiterating the assessment The summary should be a *bottom-line* document without equivocation and should be written in plain language appropriate for educated lay as well as technical audiences The information requested below should be included since the reviewer is expected to be able ... [8]

Comment [Note30]:
•Describe the drug product (name(s), strength(s)/potency, dosage form, sterile, indication, and how it is packaged)
•Describe the drug substance(s) (e g , USAN, retest date) Identify and describe key physicochemical (e g , particle size distribution, solubility, morphic form) and biological properties that can influence batch reproducibility, product performance and/or drug product quality The type and extent of issues will vary with the uniqueness and complexity of the drug substance
•Describe the formulation and dru ... [9]

B. Description of How the Drug Product is Intended to be Used

Lovenox Injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism and for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

C. Basis for Approvability or Not-Approval Recommendation

In order to demonstrate the proposed generic drug product's pharmaceutical equivalence to the innovator brand, the following five criteria need to be met for establishing "sameness" of the drug substance enoxaparin sodium (for details see the draft white paper which describes the criteria OGD will require of ANDA sponsors who wish to demonstrate pharmaceutical equivalence for LMWH):

- Equivalence of physico-chemical properties
- Equivalence of heparin starting material and in the chemical selectivity of depolymerization, as per the drug product labeling
- Equivalence in disaccharide building blocks
- Equivalence in biochemical and biological assays
- Equivalence of *in vivo* pharmacokinetic profiles

The following studies should be included to demonstrate the equivalence of physico-chemical properties including: a) molecular weight distribution via high-performance size exclusion chromatography; b) sodium and molar ratio of sulfate/carboxylate; c) UV spectra; d) ^{1}H and ^{13}C NMR. (b) (4) (b) (4).

To demonstrate equivalence of heparin starting material and in the chemical selectivity of depolymerization, a generic firm needs to use the same heparin source material, i.e. heparin derived from porcine intestinal mucosa, and to depolymerize heparin with a process of equivalent chemical selectivity to that of the innovator such that the resultant fragments have the "same" signature disaccharide terminal end fingerprints and the "same" statistical distribution of main chain disaccharide sequences. (b) (4)

Equivalence in disaccharide building blocks may be achieved by compositional analysis of the disaccharide unit building blocks that constitute the polysaccharide chains. (b) (4)

Comment [Note31]:

Describe the relationship of the recommended dose to the amount of drug product supplied (e g , multiple-dose container, pharmacy bulk package) Describe any unusual preparation of dose prior to administration and indicate any incompatibilities of the drug product with reconstitution diluents or dosage devices List the dosing schedule, proposed strength(s), and maximum daily dose Identify the expiration dating period and recommended storage conditions

Comment [Note32]:

State the reasons for the recommendation If the application is not approval, cite the major chemistry issues and include a discussion of their relationship to the safety and quality of the drug product Include any risk management steps taken

Executive Summary Section

Equivalence in biochemical and biological assays includes analyzing the anti-Xa activity and anti-Xa/anti-IIa ratio between the generic and innovator products. These tests are part of the USP and EP monographs for heparin and enoxaparin. The applicant performs anti-Xa activity and anti-Xa/anti-IIa ratio in the proposed drug substance specifications.

The equivalence of pharmacokinetic profiles is determined by measuring the *in vivo* profiles of two pharmacodynamic markers following subcutaneous drug administration: anti-Xa and anti-IIa. (b) (4)

It is crucial to establish "sameness" between the applicant's drug substance and the innovator's drug substance for this injection drug product before reviewing the drug product part of the application.

The microbiology review, labeling review and establishment inspection are currently pending.

In light of the magnitude of issues pertaining to the drug substance that impact on the safety and efficacy, the application is not approvable due to major deficiencies.

Following this page, 12 pages withheld in full (b)(4)

Chemistry Assessment Section

cc: ANDA 76-684 Original
ANDA 76-684 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/NYa/
HFD-640/SRosencrance/
HFD-640/THinchliffe/

F/T by /

C:\Documents and Settings\skanchyd\Desktop\Amphastar Reviews\76684rev1.doc

TYPE OF LETTER: NOT APPROVABLE - MAJOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J SKANCHY
03/03/2011

NAIQI YA
03/03/2011

SAU L LEE
03/03/2011

THOMAS O HINCHLIFFE
03/03/2011

ANDA 76-684

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Chemistry Review Data Sheet

1. ANDA 76-684

2. REVIEW #: 2

3. REVIEW DATE: March 21, 2005

4. REVIEWER: Naiqi Ya, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	March 4, 2003
Amendment (a filing issue)	April 18, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment	March 22, 2004
Amendment	July 6, 2004
Amendment	August 2, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Amphastar Pharmaceuticals, Inc.
Address: 11570 Six Street
Rancho Cucamonga, CA 91730
Representative: Stephen A. Campbell, Esq
Sr. Vice President, Regulatory Affairs

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Telephone: (626) 459-5253
(909) 980-9484 ext. 2019

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For ANDAs:
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NDA or ANDA number should b ... [4]

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Comment [Note16]:
Strength should be defined clearly, (e.g., mg per ml, :g per tablet, or per dose). "Strength" is defined in 21 CFR §210.3(b)(16) as: :
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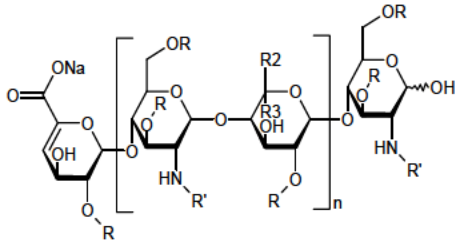

n = 1 to 21, R = H or SO_3Na, R' = H or SO_3Na or $COCH_3$
R2 = H and R3 = CO_2Na or R2 = CO_2Na and R3 = H

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	III	(b) (4)		7			Defer review
	II			7			Review delayed

[1] Action codes for DMF Table:
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The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to major deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The basic structure is that of heparin, with a series of disaccharide units formed from uronic acid (glyucuronic or iduronic) and glucosamine, substituted in various ways. The most represented disaccharide unit is 4-α-L-iduronic acid-2-*O*-sulfate-α-(1→4)-D-glucosamine-*N*,6-sulfate, with extensive sulfation at position 6 of the amino sugar and at position 2 of the iduronic acid. Some of the amino sugar residues are *N*-acetylated instead of *N*-sulfated, and iduronic acid residues are occasionally nonsulfated.

Enoxaparin sodium is produced by alkaline depolymerization of heparin sodium and exists in an amorphous form of a practically white, hygroscopic powder. It is very soluble in water and decomposes without melting. Its potency is expressed as International Unit of anti-Xa activity/mg and as anti-Xa/anti-IIa activity ratio. The average molecular weight is about 4500 daltons. The molecular weight distribution is: <2000 daltons - ≤20%, 2000 to 8000 daltons - ≥68%, and >8000 daltons - ≤18%.

Enoxaparin Sodium Injection are available in strengths: 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL, and 150 mg/mL. The drug product contains (b) (4) (b) (4), Water for Injection USP, (b) (4) (b) (4). All strengths are packaged in per-filled syringes.

Comment [Note26]:
The primary reviewer should write the Chemistry Executive Summary with the following objectives in mind:
1 To meet the needs of a multiple audience of internal Chemistry management, Team Leaders, Reviewers, Clinical Division Directors, ODE Directors, Office Directors, or others with signatory responsibility This will be especially important when looking back historically on a review decision It can also serve to communicate Chemistry concerns to other CDER disciplines
2 To provide a brief account (1-2 pages) of the important aspects of quality of the drug substance and drug product
3 To discuss any unique scientific and regulatory issues that had a significant effect on the review decision (e g , concerns surrounding a stability issue, an acceptance criteria, dissolution testing, special dosage forms, impurity, stereochemistry)
4 To describe the attributes of the drug product that can affect safety ... [7]

Comment [Note27]:
You should state whether your recommendation is approval, approvable or not approvable from a chemistry review perspective.

Comment [Note28]:
This summary is intended to pull together all the assessments and conclusions made during the chemistry review(s) This summary serves as both an orientation to the review and a stand-alone document communicating the important findings without reiterating the assessment The summary should be a *bottom-line* document without equivocation and should be written in plain language appropriate for educated lay as well as technical audiences The information requested below should be included since the reviewer is expected to be able ... [8]

Comment [Note29]:
•Describe the drug product (name(s), strength(s)/potency, dosage form, sterile, indication, and how it is packaged)
•Describe the drug substance(s) (e g , USAN, retest date) Identify and describe key physicochemical (e g , particle size distribution, solubility, morphic form) and biological properties that can influence batch reproducibility, product performance and/or drug product quality The type and extent of issues will vary with the uniqueness and complexity of the drug substance
•Describe the formulation and dru ... [9]

B. Description of How the Drug Product is Intended to be Used

Lovenox Injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism and for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

C. Basis for Approvability or Not-Approval Recommendation

The studies provided in the submission are insufficient to establish equivalence. The following detailed studies should be provided:

a) (b) (4)

b)

c)

d)

e)

f)

Based on your equivalence studies of generic low molecular weight heparins, the Office of Generic Drugs has the following additional recommendations:

a) (b) (4)

b)

c)

It is crucial to establish "sameness" between the applicant's drug substance and the innovator's drug substance for this injection drug product before reviewing the drug product part of the application.

Comment [Note30]:

Describe the relationship of the recommended dose to the amount of drug product supplied (e g , multiple-dose container, pharmacy bulk package) Describe any unusual preparation of dose prior to administration and indicate any incompatibilities of the drug product with reconstitution diluents or dosage devices List the dosing schedule, proposed strength(s), and maximum daily dose Identify the expiration dating period and recommended storage conditions

Comment [Note31]:

State the reasons for the recommendation If the application is not approval, cite the major chemistry issues and include a discussion of their relationship to the safety and quality of the drug product Include any risk management steps taken

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The microbiology review, labeling review and establishment inspection are currently pending.

In light of the magnitude of issues pertaining to the drug substance that impact on the safety and efficacy, the application is not approvable due to major deficiencies.

Following this page, 12 pages withheld in full (b)(4)

cc: ANDA 76-684 Original
ANDA 76-684 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/NYa/
HFD-640/SRosencrance/DSkanchy for 3/21/05
HFD-640/THinchliffe/3/21/05

F/T by TOH/3/21/05

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TYPE OF LETTER: NOT APPROVABLE - MAJOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J SKANCHY
03/03/2011

NAIQI YA
03/03/2011

SAU L LEE
03/03/2011

THOMAS O HINCHLIFFE
03/03/2011

ANDA 076684

Enoxaparin Sodium Injection

Amphastar Pharmaceuticals, Inc.

Sau (Larry) Lee, Ph.D. and
David Skanchy, Ph.D.

Science, Staff, Immediate Office and DCIV
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 076684

2. REVIEW #: 3

3. REVIEW DATE: July 21, 2011

4. REVIEWER(s): Sau (Larry) Lee, Ph.D. and David Skanchy, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	March 4, 2003
Amendment (a filing issue)	April 18, 2003
Major Amendment	March 22, 2004
Amendment	July 6, 2004
Amendment	August 2, 2004

Note that these submissions were reviewed by Naiqi Ya in CR#1 and CR#2.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment*	May 11, 2005
Amendment*	June 30, 2005
Amendment*	July 14, 2005
Amendment*	February 21, 2006
Amendment*	March 18, 2006
Amendment*	March 31, 2006
Amendment*	April 3, 2006
Amendment*	May 19, 2006
Amendment*	May 25, 2006
Amendment*	June 4, 2006
Amendment*	July 10, 2006
Amendment*	July 12, 2006

Amendment*	July 16, 2006
Amendment*	July 18, 2006
Amendment*	September 20, 2006
Amendment*	October 2, 2006
Amendment*	October 27, 2006
Amendment*	November 3, 2006
Amendment*	November 6, 2006
Amendment*	November 7, 2006
Amendment*	November 29, 2006
Amendment*	December 19, 2006
Amendment*	March 11, 2007
Amendment*	March 29, 2007
Amendment*	April 11, 2007
Amendment*	April 19, 2007
Amendment*	December 6, 2007
Amendment*	February 18, 2008
Amendment*	February 19, 2008
Amendment*	March 31, 2008
Amendment*	April 20, 2008
Amendment*	May 8, 2008
Amendment*	June 18, 2008
Amendment*	June 30, 2008
Amendment*	July 01, 2008
Amendment*	July 10, 2008
Amendment*	July 22, 2008
Amendment*	July 30, 2008

Amendment*	August 06, 2008
Amendment*	August 26, 2008
Amendment*	September 28, 2008
Amendment*	October 09, 2008
Amendment*	October 24, 2008
Amendment*	October 25, 2008
Amendment*	November 05, 2008
Amendment*	December 02, 2008
Amendment*	December 04, 2008
Amendment*	February 03, 2009
Amendment*	February 09, 2009
Amendment*	April 15, 2009
Amendment*	April 16, 2009
Amendment*	June 18, 2009
Amendment*	September 18, 2009
Amendment*	November 9, 2009
Amendment#	August 19, 2010
Amendment#	March 24, 2011
Amendment (product samples)#	April 21, 2011
Amendment#	July 01, 2011

*Reviewed by Sau (Larry) Lee
#Reviewed by David Skanchy

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Amphastar Pharmaceuticals, Inc.
Address:	11570 Six Street Rancho Cucamonga, CA 91730
Representative:	Stephen A. Campbell, Esq Sr. Vice President, Regulatory Affairs
Telephone:	(626) 459-5253 (909) 980-9484 ext. 2019

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lovenox®
b) Non-Proprietary Name (USAN): Enoxaparin Sodium Injection

9. LEGAL BASIS FOR SUBMISSION:

The approved enoxaparin sodium injection is Lovenox (100 mg/mL and 150 mg/mL) in prefilled syringes, manufactured by Sanofi-aventis Pharmaceuticals Inc. Lovenox is currently covered by two US patents:

US Patent No.	Description	Expiration Date
4,692,435	Mucopolysaccharide composition having a regulatory action on coagulation, medicament containing some and process of preparation	December 24, 2004
5,389,618	Method for the prevention and/or treatment of thrombotic episodes, such as myocardial infarction, in a human patient and method for the prevention of venous thrombosis in a postoperative human patient.	February 14, 2012
RE38743	Method for the prevention and/or treatment of thrombotic episodes, such as myocardial infarction, in a human patient and method for the prevention of venous thrombosis in a postoperative human patient.	February 14, 2012

Exclusivity	Description	Expiration Date
I-315	Thromboprophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness	November 17, 2003

The ANDA 076684 applicant claimed that US Patents 5,389,618 and RE38743 will not be infringed by the manufacture, use, or sale of the drug product for which this abbreviated new drug application (ANDA) is submitted. The applicant intends to market this drug product upon approval of the ANDA, but not before expiry of the exclusivity on November 17, 2003.

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:

100 mg/mL: 30 mg/0.3 mL
40 mg/0.4 mL
60 mg/0.6 mL
80 mg/0.8 mL
100 mg/1.0 mL

150 mg/mL: 120 mg/0.8 mL
150 mg/1.0 mL

13. ROUTE OF ADMINISTRATION:

14. Rx/OTC DISPENSED: __X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

__X__SPOTS product – Form Completed

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See section S.1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		1	Adequate	June 15, 2011	Reviewed by B. Scott
	II			1	Adequate	April 6, 2011	Reviewed by D. Skanchy

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	2/06/06	B. Pillari
EES	Acceptable	6/23/2011	OC
Methods Validation	Not Applicable		
Labeling	Acceptable	6/07/11	L. Kwok
Bioequivalence	Acceptable	08/05/09	Z. Z. Wahba
Immunogenicity consult (OBP)	Acceptable	09/16/09	D. Verthelyi
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		
CDRH syringe consult	Complete	6/21/2011	N. Thakur

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 076684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC perspective. All disciplines complete.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Low molecular weight heparins[1] (LMWHs), such as enoxaparin sodium, are manufactured through a controlled depolymerization of heparin sodium.[2] Both LMWHs and heparin sodium act as anticoagulants by inactivating both factor Xa and factor IIa in the coagulation cascade.[3,4] Other mechanisms may also account for the anticoagulant activity of these drugs. For example, heparin sodium and LMWHs are known to promote the release of tissue factor pathway inhibitor (TFPI), which prevents the progression of the coagulation cascade.[5] In comparison to heparin sodium, LMWHs possess a longer half-life, a more predictable anticoagulant response, and reduced side effects. Accordingly, LMWHs do not require frequent laboratory monitoring and are more amenable than heparin sodium for use in out-of-hospital settings.

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[1] There are four approved NDAs for LMWHs: Lovenox (enoxaparin sodium, NDA 020164), Fragmin (dalteparin sodium, NDA 020287), Normiflo (ardeparin sodium, NDA 020227 that was withdrawn in 2001 at the request of the manufacturer) and Innohep (tinzaparin sodium, NDA 020484). The active ingredients in these LMWH products are derived from different modes of depolymerization yielding drug products containing active pharmaceutical ingredients with different distribution of oligosaccharide chain lengths and sequences as well as different chemical modifications at the terminal ends of these oligosaccharide chains. These LMWH products are regarded as having different active pharmaceutical ingredients.

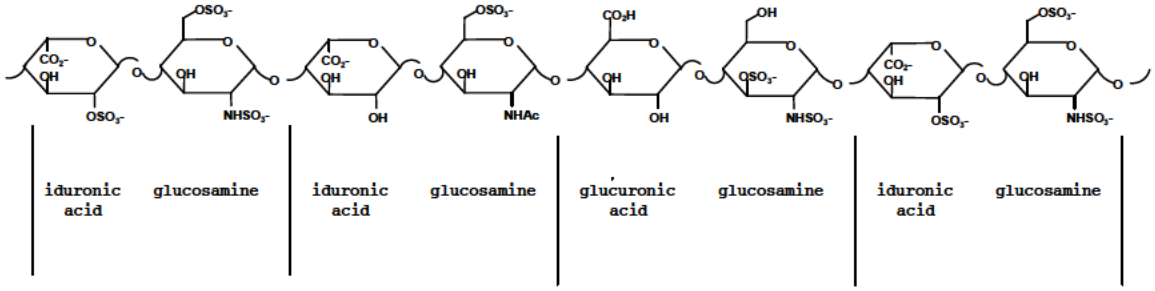
[2] Linhardt et al., *Semin. Thromb. Hemost.* (1999) 25 S3:5-16.

[3] Factor Xa is a protein factor in the coagulation cascade that activates prothrombin (factor II) into thrombin (factor IIa). Thrombin is a factor in the coagulation cascade that converts fibrinogen to fibrin monomers, which eventually self-associate and are cross-linked during clot formation (blood coagulation).

[4] Lin, R. and Hu, Z., 2000, Hematologic Disorders, in Melmon and Merrelli's Clinical Pharmacology, Carruthers et al., eds., 4th ed., New York: McGraw Hill, 737-797.

[5] Hirsh et al., *Chest.* (2001) 119:64S-94S.

Enoxaparin sodium is a sodium salt of a low-molecular weight heparin (LMWH) produced by alkaline depolymerization of benzyl ester derivatives of heparin derived from porcine intestinal mucosa. This depolymerization process involves the esterification of the carboxyl group of heparin sodium followed by a chemical cleavage by β-elimination. Enoxaparin sodium shares the characteristics of a basic structure of heparin sodium (see the figure below). Similar to heparin sodium, enoxaparin sodium is a heterogeneous mixture of oligosaccharides that consist of variably repeating disaccharide units and vary in the chain length and sequence. Each disaccharide unit is comprised of an uronic acid (D-glucuronic or L-iduronic) linked to D-glucosamine via a 1-4 glycosidic bond. Four positions of the disaccharide unit can be chemically modified. For example, three positions, C2 of the uronic acid, C3 and C6 of the glucosamine can be O-sulfated. In addition, C2 of the glucosamine can be N-acetylated or N-sulfated. The most represented disaccharide unit is 4-α-L-iduronic acid-2-*O*-sulfate-α-(1→4)-D-glucosamine-*N*,6-sulfate, with extensive sulfation at position 6 of the amino sugar and at position 2 of the L-iduronic acid.



Disaccharide repeating units present in heparin. These repeating units are composed of glucosamine and an uronic acid (either iduronic or glucuronic acid) with the linkage sequence: [(1→4) α-D-glucosaminyl – (1→4) β-D-hexuronosyl]$_n$.

Enoxaparin sodium has a distinctly different molecular weight distribution and a different ratio of Anti-factor Xa and Anti-factor IIa activities. In addition, it has unique chemical modifications (or fingerprints) at the terminal ends of the chains, such as $\Delta^{4,5}$-uronate structure and 1,6-anhydro ring structure at the non-reducing and reducing ends, respectively. These unique structural fingerprints at the terminal ends of the chains are a direct result of the cleavage reaction used to manufacture enoxaparin sodium.[6] Thus, these chemical modifications provide an additional dimension of heterogeneity that may not be present in heparin sodium. However, the clinical relevance of these chemical fingerprints is currently not known.

Based upon the above description, the heterogeneity of enoxaparin sodium comes from 1) polydispersity of the chain length, 2) the chemical heterogeneity associated with the modified disaccharide units, and 3) the chemical heterogeneity of the "natural" disaccharide units and corresponding sequences in internal main chains. In order to demonstrate drug substance sameness, the heterogeneity associated with this drug substance must be taken into consideration.

[6] Linhardt et al., *Semin. Thromb. Hemost.* (1999) 25 S3:5-16.

Enoxaparin sodium exists in an amorphous form of a practically white, hygroscopic powder. It is very soluble in water and decomposes without melting. Its potency is expressed as International Unit of Anti-factor Xa activity/mg and Anti-factor IIa activity/mg, and as Anti-factor Xa/Anti-factor IIa activity ratio. The weight-average molecular weight is about 4500 daltons (Da), the range being between 3,800 and 5,000 Da. The molecular weight distribution is:

<2000 Da:	12.0–20.0%
2000 to 8000 Da:	68.0–82.0%
>8000 Da:	≤18.0%

Enoxaparin sodium injection is a sterile aqueous solution, which is available in seven different strengths: 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1.0 mL, 120 mg/0.8 mL, and 150 mg/1.0 mL. The drug product contains enoxaparin sodium drug substance, Water for injection, USP , and (b) (4) (b) (4). All strengths are packaged in pre-filled syringes.

B. Description of How the Drug Product is Intended to be Used

Lovenox is for subcutaneous and intravenous use.

Lovenox is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in patients undergoing hip replacement surgery, during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Lovenox is indicated for:

- the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium;
- the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

Lovenox is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

Lovenox has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute STEMI receiving thrombolysis and being managed medically or with Percutaneous Coronary Intervention (PCI).

C. Basis for Approvability or Not-Approval Recommendation

The active ingredient in the proposed generic enoxaparin sodium injection has been shown to be chemically equivalent to that in the innovator product, Lovenox®, by demonstrating its equivalence of physicochemical properties (including chain mapping), heparin starting material, the mode of depolymerization, disaccharide units, fragment mapping, sequence of oligosaccharides, biochemical/biological assays, and *in vivo* pharmacodynamic profiles to Lovenox®. The analytical methods used for these studies were validated, including their specificity (negative controls) and precision (intermediate precision).

The drug substance release specifications include all critical attributes of enoxaparin sodium. The applicant has demonstrated a good understanding of process parameters that are essential for manufacturing the drug substance chemically equivalent to Lovenox®. The applicant investigated the effects of the critical process parameters such as the degree of esterification (DOE), water content, base (NaOH) concentration, depolymerization temperature and time on the drug substance critical attributes (e.g., molecular weight distribution, anti-Xa activity, and modified disaccharide building blocks). Based on the data and information provided in the ANDA, the applicant is required to incorporate the characterization tests that were used to demonstrate drug substance sameness at the molecular level, including disaccharide mapping, chain mapping, and NMR analysis of the ratio of hydroxyl and sulfated $\Delta^{4,5}$-uronate moieties at the non-reducing end of oligosaccharide chains, as formal API release tests.

With regard to the drug product, as this is a relatively simple formulation which is qualitatively and quantitatively (Q_1&Q_2) the same as the RLD (contains the active ingredients dissolved in water), the manufacturing process of drug products should not have any impact on the drug substance identity. It is also acceptable in the context of sterility assurance based upon the recommendation made by the Microbiology division.

The drug product specifications include all the essential tests, and are found to be adequate. The proposed tests and acceptance criteria for the drug product are mostly based upon the USP.

All testing results for the drug product stability studies are within their acceptance criteria, and no trends were observed. A tentative 24 month expiry period has been granted for the drug product.

This ANDA is approvable from a CMC perspective. DBE, immunogenicity review, labeling, EES and microbiology are acceptable.

Following this page, 70 pages withheld in full (b)(4)

A APPENDICES

A.1 Facilities and Equipment (biotech only)

N/A

A.2 Adventitious Agents Safety Evaluation

See Microbiology Reviews for this ANDA and supporting DMF's.

A.3 Novel Excipients

N/A

R REGIONAL INFORMATION

R.1 Executed Batch Records

Provided.

R.2 Comparability Protocols

N/A

R.3 Methods Validation Package

Provided. No FDA validation is required per policy.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Acceptable.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Categorical exclusion

III. List Of Deficiencies To Be Communicated

N/A – Application is approveable for CMC.

II. Administrative

A. Reviewer's Signature

B. Endorsement Block

DSkanchy/7/21/2011
SLee/
ARaw/
NYa/
THinchliffe/

C. CC Block

Following this page, 3 pages withheld in full (b)(4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J SKANCHY
07/21/2011

SAU L LEE
07/25/2011

ANDRE S RAW
07/25/2011

NAIQI YA
07/25/2011

THOMAS O HINCHLIFFE
07/25/2011