CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-857

Name: Enoxaparin Sodium Injection USP, 100 mg/mL
(packaged in 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1 mL)

and

Enoxaparin Sodium Injection USP, 150 mg/mL
(packaged in 120 mg/0.8 mL and 150 mg/1 mL)

-Prefilled Single-dose Syringes with Automatic Safety Device
-Preservative-Free

Sponsor: Sandoz Inc.

Approval Date: July 23, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 077857

Sandoz Inc.
Attention: Marcy Macdonald
Director, Regulatory Affairs
2555 West Midway Blvd.
Broomfield, CO 80020

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 26, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Enoxaparin Sodium Injection USP, 100 mg/mL, [packaged in 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/ 1 mL], and 150 mg/mL [packaged in 120 mg/0.8 mL and 150 mg/1 mL] (Prefilled Single-dose Syringes with Automatic Safety Device) (Preservative-Free).

Reference is made to your amendments dated July 6, August 31, September 7, October 5, November 9, November 17, November 29, December 28, 2006; January 5, February 20, February 27, March 23, March 26, June 8, September 19, October 26, 2007; February 13, February 27, June 2, June 13, September 23, September 25, November 20, November 21, December 12, 2008; January 20, February 27, March 2, March 12, March 20, April 8, May 21, June 1, June 3, June 19, June 25, July 1, August 6, September 18, September 30, October 7, October 21, December 1, and December 30, 2009; and January 13, January 18, March 15, April 28, and May 26, 2010. Reference is also made to your communications dated June 22, and September 8, 2006; multiple amendments (47 submissions) dated January 3, 2007 through March 9, 2007; and June 13, and September 16, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Office of Generic Drugs has determined that your Enoxaparin Sodium Injection USP, 100 mg/mL and 150 mg/mL, (Preservative-Free), meets the standards for

approval (including those for active ingredient sameness and bioequivalence) and, therefore, is therapeutically equivalent to the reference listed drug (RLD), Lovenox Injection, 100 mg/mL and 150 mg/mL, respectively, (Preservative-Free), of Sanofi Aventis US, LLC (Sanofi).

The reference listed drug (RLD) upon which you have based your ANDA, Sanofi's Lovenox Injection, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 5,389,618 (the '618 patent) and RE38743 (the '743 patent) expire on February 14, 2012.

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '618 and '743 patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Enoxaparin Sodium Injection, 100 mg/mL, 150 mg/mL (Prefilled Single Dose Syringes with Automatic Safety Device), under this ANDA. You have notified the agency that Sandoz, Inc. (Sandoz) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Sandoz for infringement of the '618 and '743 patents in the United States District Court for the Central District of California [Aventis Pharma S.A. and Aventis Pharmaceuticals, Inc.v. Sandoz Inc., Civil Action Nos. CV-07-2558 (previously CV-06-3671) and CV-06-4858]. As noted below, these patents were found to be unenforceable.

With respect to 180-day generic drug exclusivity for Enoxaparin Sodium Injection, 100 mg/mL and 150 mg/mL (Prefilled Single Dose Syringes with Automatic Safety Device), ANDAs containing paragraph IV certifications and referencing Lovenox were submitted to FDA before the passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173) (MMA). Therefore, 180-day exclusivity for drug products referencing Lovenox is governed by section 505(j)(5)(B)(iv) of the Act as in effect before passage of the MMA. See section 1102(b)(1) of the MMA. In accordance with the applicable exclusivity provisions, any 180-day exclusivity for these products was triggered on October 2, 2008, when the Federal Circuit issued the Mandate with respect to its decision in Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc. (525 F.3d. 1334; Fed. Cir. May 14, 2008) affirming the district court's finding that the '618 and '743 patents are unenforceable due to inequitable conduct. The 180-day period expired on March

31, 2009. Therefore, under section 505(j)(5)(B)(iii) your ANDA is eligible for approval.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

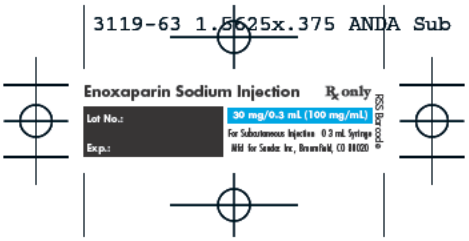
KEITH O WEBBER
07/23/2010

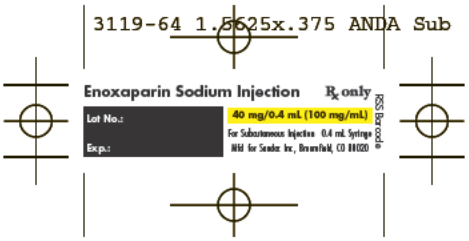
CENTER FOR DRUG EVALUATION AND RESEARCH

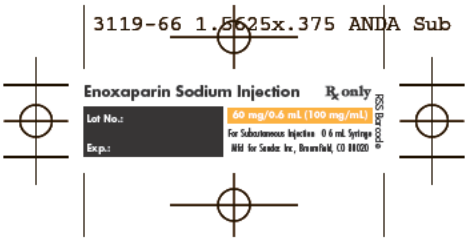
APPLICATION NUMBER:

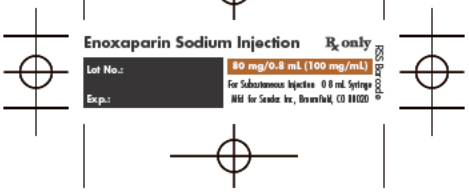
ANDA 77-857

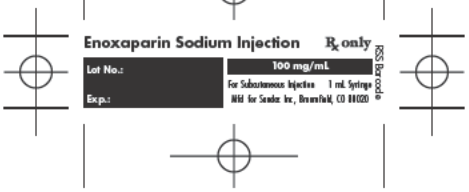
LABELING

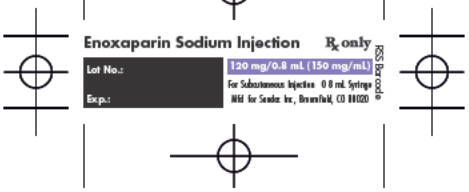


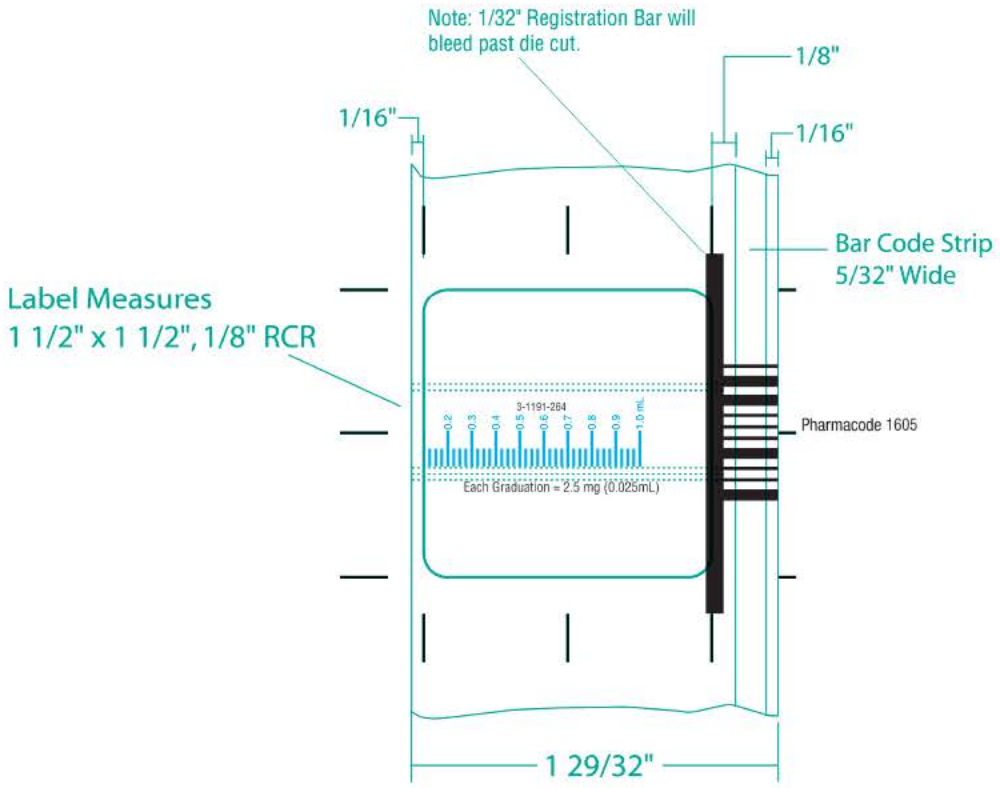












(b) (4)

Proof E

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Fold Size:

Paper Weight/Stock Description: **CLEAR BOPP**

Standard or Mini Pharmacode: **Standard 1605**

Note: This digital proof is to show size, copy placement and color breaks. Actual colors will be matched on press to approved color standards and/or PMS color swatches.

Approved By

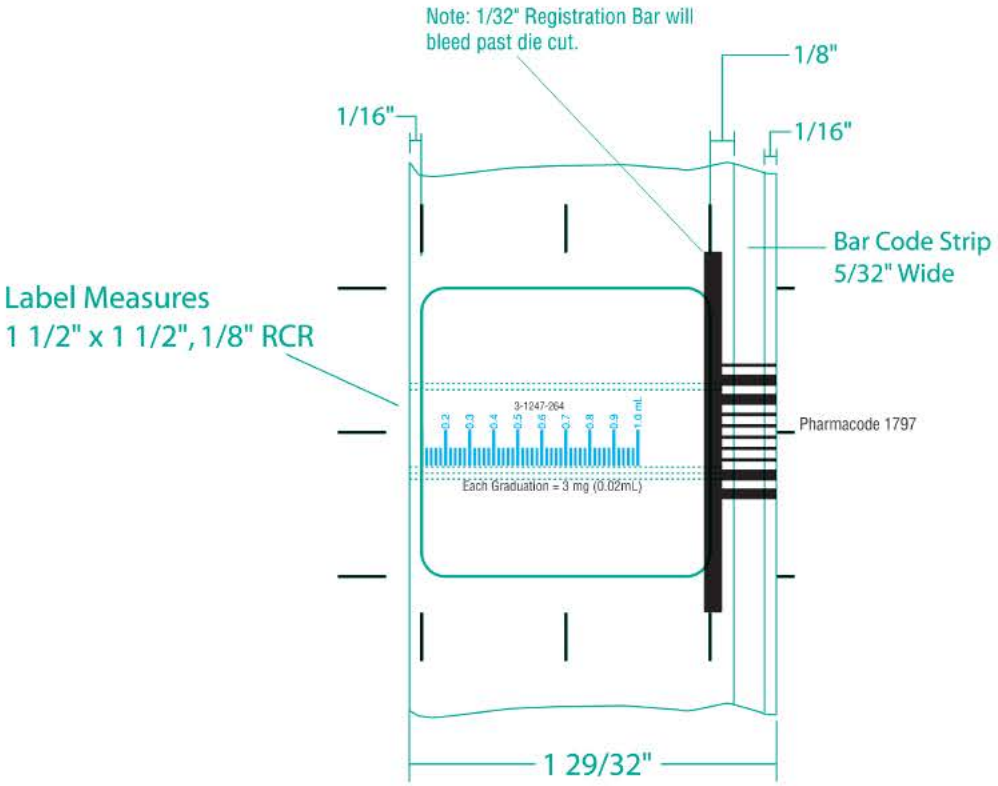
Customer: Date:

☐ **Art OK to print** ☐ **Another proof required**

☐ **See Attached**

Note: We must have a signed proof before we can begin production.

The printed piece may not be a perfect match to a PDF. The finished piece should be verified against the customer approved hard copy or a signed hard copy proof.



(b) (4)

Proof E

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Fold Size:

Paper Weight/Stock Description: **CLEAR BOPP**

Standard or Mini Pharmacode: **Standard 1797**

Note: This digital proof is to show size, copy placement and color breaks. Actual colors will be matched on press to approved color standards and/or PMS color swatches.

Approved By

Customer: Date:

☐ **Art OK to print** ☐ **Another proof required**

☐ **See Attached**

Note: We must have a signed proof before we can begin production.

The printed piece may not be a perfect match to a PDF. The finished piece should be verified against the customer approved hard copy or a signed hard copy proof.

Enoxaparin Sodium Injection

30 mg/0.3 mL (100 mg/mL)

Single Dose Syringe with Automatic Safety Device
For Subcutaneous Injection
One 0.3 mL Syringe

NDC 0781-3119-63
℞ only

SANDOZ

Each syringe contains 30 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.
Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Mfd. by Baxter Pharmaceutical Solutions, Bloomington, IN 47403 for Sandoz Inc., Broomfield, CO 80020
ISS 07-2005M

Lot No.:

Exp.:

Enoxaparin Sodium Injection

40 mg/0.4 mL (100 mg/mL)

Single Dose Syringe with Automatic Safety Device
For Subcutaneous Injection
One 0.4 mL Syringe

NDC 0781-3119-64

R_x only

SANDOZ

Each syringe contains 40 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.
Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Mfd. by Baxter Pharmaceutical Solutions, Bloomington, IN 47403 for Sandoz Inc., Broomfield, CO 80020
ISS 07-2005M

Lot No.:

Exp.:

Enoxaparin Sodium Injection

60 mg/0.6 mL (100 mg/mL)

Single Dose Syringe with Automatic Safety Device
For Subcutaneous Injection
One 0.6 mL Syringe

NDC 0781-3119-66

Rx only

SANDOZ

Each syringe contains 60 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Mfd. by Baxter Pharmaceutical Solutions, Bloomington, IN 47403 for Sandoz Inc., Broomfield, CO 80020
ISS 07-2005M

Lot No.:

Exp.:

Enoxaparin Sodium Injection

80 mg/0.8 mL (100 mg/mL)

Single Dose Syringe with Automatic Safety Device
For Subcutaneous Injection
One 0.8 mL Syringe

NDC 0781-3119-68

R_x only

SANDOZ

Each syringe contains 80 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Mfd. by Baxter Pharmaceutical Solutions, Bloomington, IN 47403 for Sandoz Inc., Broomfield, CO 80020
ISS 07-2005M

Lot No.:

Exp.:

Enoxaparin Sodium Injection

100 mg/mL

Single Dose Syringe with Automatic Safety Device
For Subcutaneous Injection
One 1 mL Syringe

NDC 0781-3119-69

Rx only

SANDOZ

Each syringe contains 100 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Mfd. by Baxter Pharmaceutical Solutions, Bloomington, IN 47403 for Sandoz Inc., Broomfield, CO 80020
ISS 07-2005M

Lot No.:

Exp.:

Enoxaparin Sodium Injection

120 mg/0.8 mL (150 mg/mL)

Single Dose Syringe with Automatic Safety Device
For Subcutaneous Injection
One 0.8 mL Syringe

NDC 0781-3121-68

Rx only

SANDOZ

Each syringe contains 120 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.02 mL graduation equals 3 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Mfd. by Baxter Pharmaceutical Solutions, Bloomington, IN 47403 for Sandoz Inc., Broomfield, CO 80020
ISS 07-2005M

Lot No.:

Exp.:

Enoxaparin Sodium Injection

150 mg/mL

Single Dose Syringe with Automatic Safety Device
For Subcutaneous Injection
One 1 mL Syringe

NDC 0781-3121-69

Rx only

SANDOZ

Each syringe contains 150 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.02 mL graduation equals 3 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Mfd. by Baxter Pharmaceutical Solutions, Bloomington, IN 47403; Dist. by Sandoz Inc., Princeton, NJ 08540
ISS 07-2005M

Lot No.:

Exp.:

ANDA SUBMISSION

NDC 0781-3119-63

Enoxaparin Sodium Injection

30 mg/0.3 mL (100 mg/mL)

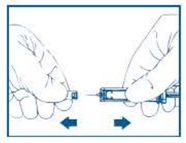
Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.3 mL Syringes **Rx only**

SANDOZ

Directions for Use of Enoxaparin Sodium Injection Single Dose Syringe with Automatic Safety Device:

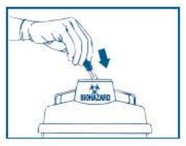


1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.



5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:

- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

NDC 0781-3119-63

Enoxaparin Sodium Injection

30 mg/0.3 mL (100 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.3 mL Syringes **Rx only**

SANDOZ

Lot No.:

Exp.:

Enoxaparin Sodium Injection

Rx only

Each syringe contains 30 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

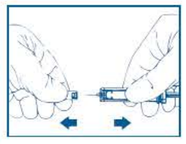
Manufactured by
Baxter Pharmaceutical Solutions
Bloomington, IN 47403

Manufactured for
Sandoz Inc.
Broomfield, CO 80020

ISS 07-2005M

ANDA SUBMISSION

Directions for Use of Enoxaparin Sodium Injection Single Dose Syringe with Automatic Safety Device:



1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

NDC 0781-3119-64

Enoxaparin Sodium Injection

40 mg/0.4 mL (100 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.4 mL Syringes

℞ only

SANDOZ

NDC 0781-3119-64

Enoxaparin Sodium Injection

40 mg/0.4 mL (100 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.4 mL Syringes **℞ only**

N 3 0781-3119-64 7

SANDOZ

Lot No.:

Exp.:

NDC 0781-3119-64

Enoxaparin Sodium Injection

40 mg/0.4 mL (100 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.4 mL Syringes **℞ only**

SANDOZ

Enoxaparin Sodium Injection

℞ only

Each syringe contains 40 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by
Baxter Pharmaceutical Solutions
Bloomington, IN 47403

Manufactured for
Sandoz Inc.
Broomfield, CO 80020

ISS 07-2005M

ANDA SUBMISSION

SANDOZ

Ten 0.6 mL Syringes Rx only

For Subcutaneous Injection

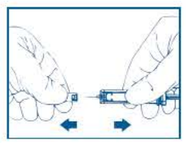
Single Dose Syringes with Automatic Safety Device

60 mg/0.6 mL (100 mg/mL)

Enoxaparin Sodium Injection

NDC 0781-3119-66

Directions for Use of Enoxaparin Sodium Injection Single Dose Syringe with Automatic Safety Device:



1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

NDC 0781-3119-66

Enoxaparin Sodium Injection

60 mg/0.6 mL (100 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.6 mL Syringes Rx only

N 3 0781-3119-66 1

SANDOZ

Lot No.:

Exp.:

Enoxaparin Sodium Injection

Rx only

Each syringe contains 60 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by
Baxter Pharmaceutical Solutions
Bloomington, IN 47403

Manufactured for
Sandoz Inc.
Broomfield, CO 80020

ISS 07-2005M

ANDA SUBMISSION

NDC 0781-3119-68

Enoxaparin Sodium Injection

80 mg/0.8 mL (100 mg/mL)

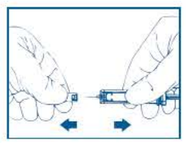
Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.8 mL Syringes **℞ only**

SANDOZ

Directions for Use of Enoxaparin Sodium Injection Single Dose Syringe with Automatic Safety Device:



1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

NDC 0781-3119-68

Enoxaparin Sodium Injection

80 mg/0.8 mL (100 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.8 mL Syringes **℞ only**

SANDOZ

N 3 0781-3119-68 5

SANDOZ

Lot No.:

Exp.:

Enoxaparin Sodium Injection

℞ only

Each syringe contains 80 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

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Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.8 mL Syringes **℞ only**

SANDOZ

ANDA SUBMISSION

NDC 0781-3119-69

Enoxaparin Sodium Injection

100 mg/mL

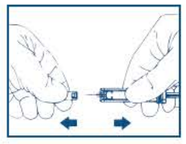
Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 1 mL Syringes **Rx only**

SANDOZ

Directions for Use of Enoxaparin Sodium Injection Single Dose Syringe with Automatic Safety Device:



1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

NDC 0781-3119-69

Enoxaparin Sodium Injection

100 mg/mL

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 1 mL Syringes **Rx only**

SANDOZ

NDC 0781-3119-69

Enoxaparin Sodium Injection

100 mg/mL

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 1 mL Syringes **Rx only**

N 3 0781-3119-69 2

SANDOZ

Lot No.:

Exp.:

Enoxaparin Sodium Injection

Rx only

Each syringe contains 100 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

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ISS 07-2005M

SANDOZ

Rx only

Ten 0.8 mL Syringes

For Subcutaneous Injection

Single Dose Syringes with Automatic Safety Device

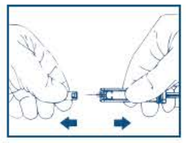
Enoxaparin Sodium Injection

120 mg/0.8 mL (150 mg/mL)

NDC 0781-3121-68

ANDA SUBMISSION

Directions for Use of Enoxaparin Sodium Injection Single Dose Syringe with Automatic Safety Device:



1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:

- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

NDC 0781-3121-68

Enoxaparin Sodium Injection

120 mg/0.8 mL (150 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.8 mL Syringes

Rx only

SANDOZ

NDC 0781-3121-68

Enoxaparin Sodium Injection

120 mg/0.8 mL (150 mg/mL)

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 0.8 mL Syringes Rx only

N 3 0781-3121-68 8

SANDOZ

Lot No.:

Exp.:

Enoxaparin Sodium Injection

Rx only

Each syringe contains 120 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.02 mL graduation equals 3 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

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ISS 07-2005M

NDC 0781-3121-69

Enoxaparin Sodium Injection

150 mg/mL

Single Dose Syringes with Automatic Safety Device

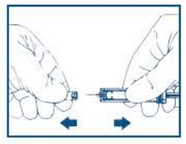
For Subcutaneous Injection

Ten 1 mL Syringes **Rx only**

SANDOZ

ANDA SUBMISSION

Directions for Use of Enoxaparin Sodium Injection Single Dose Syringe with Automatic Safety Device:



1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:

- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

NDC 0781-3121-69

Enoxaparin Sodium Injection

150 mg/mL

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 1 mL Syringes **Rx only**

SANDOZ

NDC 0781-3121-69

Enoxaparin Sodium Injection

150 mg/mL

Single Dose Syringes with Automatic Safety Device

For Subcutaneous Injection

Ten 1 mL Syringes **Rx only**

N 3 0781-3121-69 5

SANDOZ

Lot No.:

Exp.:

Enoxaparin Sodium Injection

Rx only

Each syringe contains 150 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.02 mL graduation equals 3 mg enoxaparin sodium injection.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

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SANDOZ

Enoxaparin Sodium Injection

Rx only

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use enoxaparin sodium injection safely and effectively. See full prescribing information for enoxaparin sodium injection.

Enoxaparin sodium injection for subcutaneous use

Initial U.S. Approval: 1993

WARNING: SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [see *Warnings and Precautions (5.1)* and *Drug Interactions (7)*].

- - - - - - RECENT MAJOR CHANGES - - - - - -

Boxed Warning, Warnings and Precautions (5.1) (12/2009)

- - - - - - INDICATIONS AND USAGE - - - - - -

Enoxaparin sodium injection is a low molecular weight heparin [LMWH] indicated for:

Prophylaxis of deep vein thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness (1.1)
Inpatient treatment of acute DVT with or without pulmonary embolism (1.2)
Outpatient treatment of acute DVT without pulmonary embolism. (1.2)
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction [MI] (1.3)
Treatment of acute ST-segment elevation myocardial infarction [STEMI] managed medically or with subsequent percutaneous coronary intervention [PCI] (1.4)

- - - - - - DOSAGE AND ADMINISTRATION - - - - - -

Indication	Standard Regimen (2.1, 2.3)
DVT prophylaxis in abdominal surgery	40 mg SC once daily up to 12 days
DVT prophylaxis in knee replacement surgery	30 mg SC every 12 hours up to 14 days
DVT prophylaxis in hip replacement surgery	30 mg SC every 12 hours or 40 mg SC once daily up to 14 days
DVT prophylaxis in medical patients	40 mg SC once daily up to 14 days
Inpatient treatment of acute DVT with or without pulmonary embolism	1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily (with warfarin) up to 17 days
Outpatient treatment of acute DVT without pulmonary embolism	1 mg/kg SC every 12 hours (with warfarin) up to 17 days
Unstable angina and non-Q-wave MI	1 mg/kg SC every 12 hours (with aspirin) 2 to 8 days
Acute STEMI in patients <75 years of age [For dosing in subsequent PCI, see *Dosage and Administration (2.1)*]	30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC every 12 hours at least 8 days (with aspirin)
Acute STEMI in patients ≥75 years of age	0.75 mg/kg SC every 12 hours (no bolus) at least 8 days (with aspirin)

(continued)

- Adjust the dose for patients with severe renal impairment (2.2, 8.7)

- - - - - - DOSAGE FORMS AND STRENGTHS - - - - - -

100 mg/mL concentration (3.1):
- Prefilled syringes: 30 mg/0.3 mL, 40 mg/0.4 mL
- Graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL

150 mg/mL concentration (3.2):
- Graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/mL

- - - - - - CONTRAINDICATIONS - - - - - -

- Active major bleeding (4)
- Thrombocytopenia with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium (4)
- Hypersensitivity to enoxaparin sodium (4)
- Hypersensitivity to heparin or pork products (4)

- - - - - - WARNINGS AND PRECAUTIONS - - - - - -

- Increased risk of hemorrhage: Use with caution in patients at risk (5.1)
- Percutaneous coronary revascularization: Obtain hemostasis at the puncture site before sheath removal (5.2)
- Concomitant medical conditions: Use with caution in patients with bleeding diathesis, uncontrolled arterial hypertension or history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction, or hemorrhage (5.3)
- History of heparin-induced thrombocytopenia: Use with caution (5.4)
- Thrombocytopenia: Monitor thrombocytopenia closely (5.5)
- Interchangeability with other heparins: Do not exchange with heparin or other LMWHs (5.6)
- Pregnant women with mechanical prosthetic heart valves and their fetuses, may be at increased risk and may need more frequent monitoring and dosage adjustment (5.7)

- - - - - - ADVERSE REACTIONS - - - - - -

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

- - - - - - DRUG INTERACTIONS - - - - - -

Discontinue agents which may enhance hemorrhage risk prior to initiation of enoxaparin sodium injection or conduct close clinical and laboratory monitoring (5.9, 7).

- - - - - - USE IN SPECIFIC POPULATIONS - - - - - -

- Severe renal impairment: Adjust dose for patients with creatinine clearance <30 mL/min (2.2, 8.7)
- Geriatric Patients: Monitor for increased risk of bleeding (8.5)
- Patients with mechanical heart valves: Not adequately studied (8.6)
- Hepatic Impairment: Use with caution (8.8)
- Low-weight patients: Observe for signs of bleeding (8.9)

See 17 for PATIENT COUNSELING INFORMATION

Revised: April 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SPINAL/EPIDURAL HEMATOMAS

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [see *Warnings and Precautions (5.1)* and *Drug Interactions (7)*].

1 INDICATIONS AND USAGE

1.1 Prophylaxis of deep vein thrombosis

Enoxaparin sodium injection is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
- in patients undergoing abdominal surgery who are at risk for thromboembolic complications [see *Clinical Studies (14.1)*].
- 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.

1.2 Treatment of Acute Deep Vein Thrombosis

Enoxaparin sodium injection 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.

1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-wave Myocardial Infarction

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

1.4 Treatment of Acute ST-Segment Elevation Myocardial Infarction

Enoxaparin sodium injection, when administered concurrently with aspirin, has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction (STEMI) receiving thrombolysis and being managed medically or with percutaneous coronary intervention (PCI).

2 DOSAGE AND ADMINISTRATION

All patients should be evaluated for a bleeding disorder before administration of enoxaparin sodium injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring enoxaparin sodium injection activity, routine monitoring of coagulation parameters is not required [see *Warnings and Precautions (5.9)*].

For subcutaneous use, enoxaparin sodium injection should not be mixed with other injections or infusions.

For intravenous use (i.e., for treatment of acute STEMI), enoxaparin sodium injection can be mixed with normal saline solution (0.9%) or 5% dextrose in water.

Enoxaparin sodium injection is not intended for intramuscular administration.

2.1 Adult Dosage

Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of enoxaparin sodium injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been administered in clinical trials.

Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of enoxaparin sodium injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, it is recommended that continued prophylaxis with enoxaparin sodium injection 40 mg once a day be administered by SC injection for 3 weeks. The usual duration of administration is 7 to 10 days; up to 14 days administration has been administered in clinical trials.

Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of enoxaparin sodium injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of enoxaparin sodium injection has been administered in the controlled clinical trial.

Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of enoxaparin sodium injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of enoxaparin sodium injection is **1 mg/kg every 12 hours** administered SC or **1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of enoxaparin sodium injection). Enoxaparin sodium injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of enoxaparin sodium injection administration has been administered in controlled clinical trials.

Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of enoxaparin sodium injection is **1 mg/kg** administered SC **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with enoxaparin sodium injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days; up to 12.5 days of enoxaparin sodium injection has been administered in clinical trials. [See *Warnings and Precautions (5.2)* and *Clinical Studies (14.5)*].

Treatment of Acute ST-Segment Elevation Myocardial Infarction: In patients with acute ST-segment elevation myocardial infarction, the recommended dose of enoxaparin sodium injection is a **single IV bolus of 30 mg** plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours (maximum 100 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining doses). Dosage adjustments are recommended in patients ≥75 years of age [see *Dosage and Administration (2.3)*]. All patients should receive aspirin as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated.

When administered in conjunction with a thrombolytic (fibrin-specific or non-fibrin specific), enoxaparin sodium injection should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. In the pivotal clinical study, the enoxaparin sodium injection treatment duration was 8 days or until hospital discharge, whichever came first. An optimal duration of treatment is not known, but it is likely to be longer than 8 days.

For patients managed with percutaneous coronary intervention (PCI): If the last enoxaparin sodium injection SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last enoxaparin sodium injection SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of enoxaparin sodium injection should be administered [see *Warnings and Precautions (5.2)*].

2.2 Renal Impairment

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in Table 1 [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

Table 1

Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30mL/minute)

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Treatment of acute ST-segment elevation myocardial infarction in patients <75 years of age, when administered in conjunction with aspirin	30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC once daily.
Treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, when administered in conjunction with aspirin	1 mg/kg administered SC once daily (**no** initial bolus)

2.3 Geriatric Patients with Acute ST-Segment Elevation Myocardial Infarction

For treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, **do not use an initial IV bolus**. Initiate dosing with **0.75 mg/kg SC every 12 hours (maximum 75 mg for the first two doses only, followed by 0.75 mg/kg dosing for the remaining doses)** [see *Use in Specific Populations (8.5)* and *Clinical Pharmacology (12.3)*].

No dose adjustment is necessary for other indications in geriatric patients unless kidney function is impaired [see *Dosage and Administration (2.2)*].

2.4 Administration

Enoxaparin sodium injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

Enoxaparin sodium injection must not be administered by intramuscular injection. Enoxaparin sodium injection is intended for use under the guidance of a physician.

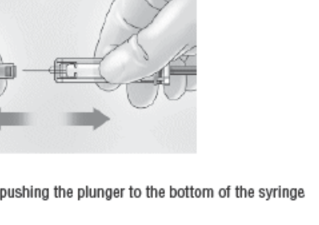
For subcutaneous administration, patients may self-inject only if their physicians determine that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique: Patients should be lying down and enoxaparin sodium injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.

Enoxaparin sodium injection prefilled syringes and graduated prefilled syringes are for single, one-time use only and are available with a system that shields the needle after injection.

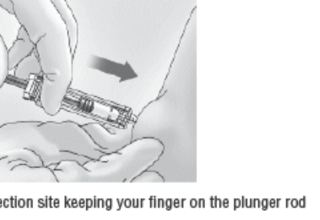
1. Remove the needle shield by pulling it straight off the syringe (see Figure A). If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

Figure A



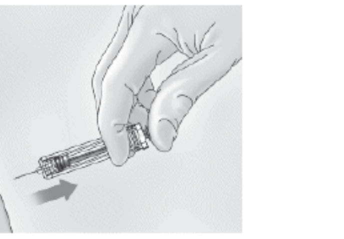
2. Inject using standard technique, pushing the plunger to the bottom of the syringe (see Figure B).

Figure B



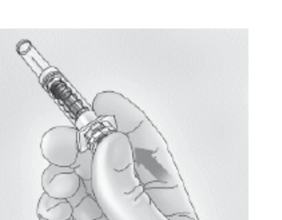
3. Remove the syringe from the injection site keeping your finger on the plunger rod (see Figure C).

Figure C



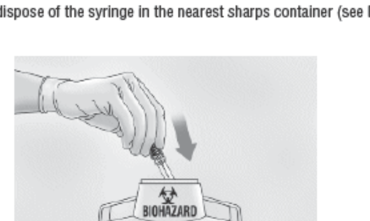
4. Orient the needle away from you and others, and activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation (see Figure D).

Figure D



5. Immediately dispose of the syringe in the nearest sharps container (see Figure E).

Figure E



NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.

Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

Intravenous (Bolus) Injection Technique: For intravenous injection, the multiple-dose vial should be used. Enoxaparin sodium injection should be administered through an intravenous line. Enoxaparin sodium injection should not be mixed or co-administered with other medications. To avoid the possible mixture of enoxaparin sodium injection with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of enoxaparin sodium injection to clear the port of drug. Enoxaparin sodium injection may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

3 DOSAGE FORMS AND STRENGTHS

Enoxaparin sodium injection is available in two concentrations:

3.1 100 mg / mL Concentration

-Prefilled Syringes 30 mg / 0.3 mL, 40 mg / 0.4 mL

-Graduated Prefilled Syringes 60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / 1 mL

3.2 150 mg / mL Concentration

-Graduated Prefilled Syringes 120 mg / 0.8 mL, 150 mg / 1 mL

4 CONTRAINDICATIONS

- Active major bleeding.
- Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium.
- Known hypersensitivity to enoxaparin sodium (*e.g.*, pruritus, urticaria, anaphylactic/anaphylactoid reactions) [see *Adverse Reactions (6.2)*].
- Known hypersensitivity to heparin or pork products.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Hemorrhage

Cases of epidural or spinal hematomas have been reported with the associated use of enoxaparin sodium injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting hemostasis such as NSAIDs, with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity [see *Boxed Warning, Adverse Reactions (6.2)* and *Drug Interactions (7)*].

Enoxaparin sodium injection should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

Bleeding can occur at any site during therapy with enoxaparin sodium injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

5.2 Percutaneous Coronary Revascularization Procedures

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction, and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between enoxaparin sodium injection doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation [see *Dosage and Administration (2.1)*].

5.3 Use of Enoxaparin Sodium Injection with Concomitant Medical Conditions

Enoxaparin sodium injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage.

5.4 History of Heparin-induced Thrombocytopenia

Enoxaparin sodium injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

5.5 Thrombocytopenia

Thrombocytopenia can occur with the administration of enoxaparin sodium injection.

Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given enoxaparin sodium injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials.

Platelet counts less than 50,000/mm³ occurred at a rate of 0.1% in patients given enoxaparin sodium injection, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, enoxaparin sodium injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death [see *Warnings and Precautions (5.4)*].

5.6 Interchangeability with Other Heparins

Enoxaparin sodium injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

5.7 Pregnant Women with Mechanical Prosthetic Heart Valves

The use of enoxaparin sodium injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed [see *Use in Specific Populations (8.6)*].

5.9 Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with enoxaparin sodium injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of enoxaparin sodium injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Enoxaparin sodium injection in patients with significant renal impairment. If during enoxaparin sodium injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of enoxaparin sodium injection [see *Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following serious adverse reactions are also discussed in other sections of the labeling:
- Spinal/epidural hematoma [see *Boxed Warning* and *Warnings and Precautions (5.1)*]
- Increased Risk of Hemorrhage [see *Warnings and Precautions (5.1)*]
- Thrombocytopenia [see *Warnings and Precautions (5.5)*]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

During clinical development for the approved indications, 15,918 patients were exposed to enoxaparin sodium. These included 1,228 for prophylaxis of deep vein thrombosis following abdominal surgery in patients at risk for thromboembolic complications, 1,368 for prophylaxis of deep vein thrombosis following hip or knee replacement surgery, 711 for prophylaxis of deep vein thrombosis in medical patients with severely restricted mobility during acute illness, 1,578 for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, 10,176 for treatment of acute ST-elevation myocardial infarction, and 857 for treatment of deep vein thrombosis with or without pulmonary embolism. Enoxaparin sodium doses in the clinical trials for prophylaxis of deep vein thrombosis following abdominal or hip or knee replacement surgery or in medical patients with severely restricted mobility during acute illness ranged from 40 mg SC once daily to 30 mg SC twice daily. In the clinical studies for prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction doses were 1 mg/kg every 12 hours and in the clinical studies for treatment of acute ST-segment elevation myocardial infarction enoxaparin sodium doses were a 30 mg IV bolus followed by 1 mg/kg every 12 hours SC.

Hemorrhage

The incidence of major hemorrhagic complications during enoxaparin sodium injection treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with enoxaparin sodium injection [see Tables 2 to 7].

Table 2

Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

Indications	Enoxaparin Sodium Injection 40 mg q.d. SC	Heparin 5000 U q8h SC
	Dosing Regimen	
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

Table 3

Major Bleeding Episodes Following Hip or Knee Replacement Surgery[1]

Indications	Enoxaparin Sodium Injection 40 mg q.d. SC	Enoxaparin Sodium Injection 30 mg q12h SC	Heparin 15,000 U/24h SC
	Dosing Regimen		
Hip Replacement Surgery Without Extended Prophylaxis[2]		n = 786 31 (4%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis			
Peri-operative Period[3]	n = 288 4 (2%)		
Extended Prophylaxis Period[4]	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis[2]		n = 294 3 (1%)	n = 225 3 (1%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.

[2] Enoxaparin sodium injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

[3] Enoxaparin sodium injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

[4] Enoxaparin sodium injection 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the enoxaparin sodium injection patients versus 1.8% of the placebo patients.

Table 4

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness[1]

Indications	Enoxaparin Sodium Injection[2] 20 mg q.d. SC	Enoxaparin Sodium Injection[2] 40 mg q.d. SC	Placebo[2]
	Dosing Regimen		
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

[2] The rates represent major bleeding on study medication up to 24 hours after last dose.

Table 5

Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment[1]

Indication	Enoxaparin Sodium Injection 1.5 mg/kg q.d. SC	Enoxaparin Sodium Injection 1 mg/kg q12h SC	Heparin aPTT Adjusted I.V. Therapy
	Dosing Regimen[2]		
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

[2] All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of enoxaparin sodium injection or standard heparin therapy and continuing for up to 90 days.

Table 6

Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Enoxaparin Sodium Injection[1] 1 mg/kg q12h SC	Heparin[1] aPTT Adjusted I.V. Therapy
	Dosing Regimen	
Unstable Angina and Non-Q-Wave MI[2,3]	n = 1578 17 (1%)	n = 1529 18 (1%)

[1] The rates represent major bleeding on study medication up to 12 hours after dose.

[2] Aspirin therapy was administered concurrently (100 to 325 mg per day).

[3] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Table 7

Major Bleeding Episodes in Acute ST-Segment Elevation Myocardial Infarction

Indication	Enoxaparin Sodium Injection[1] Initial 30 mg IV bolus followed by 1 mg/kg q12h SC	Heparin[1] aPTT Adjusted IV Therapy
	Dosing Regimen	
Acute ST-Segment Elevation Myocardial Infarction	n = 10176 n (%)	n = 10151 n (%)
- Major bleeding (including ICH) [2]	211 (2.1)	138 (1.4)
- Intracranial hemorrhages (ICH)	84 (0.8)	66 (0.7)

[1] The rates represent major bleeding (including ICH) up to 30 days

[2] Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by ≥ 5 g/dL. ICH were always considered major.

Elevations of Serum Aminotransferases

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with enoxaparin sodium injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Enoxaparin sodium injection should be interpreted with caution.

Local Reactions

Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of enoxaparin sodium injection.

Adverse Reactions in Patients Receiving Enoxaparin Sodium Injection for Prophylaxis or Treatment of DVT, PE:

Other adverse reactions that were thought to be possibly or probably related to treatment with enoxaparin sodium injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the enoxaparin sodium injection group, are provided below [see Tables 8 to 11].

Table 8

Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium Injection-Treated Patients Undergoing Abdominal or Colorectal Surgery

Adverse Reaction	Enoxaparin Sodium Injection 40 mg q.d. SC n = 1228 % Severe	Total	Heparin 5000 U q8h SC n = 1234 % Severe	Total
	Dosing Regimen			
Hemorrhage	<1	7	<1	6
Anemia	<1	3	<1	3
Ecchymosis	0	3	0	3

Table 9

Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium Injection-Treated Patients Undergoing Hip or Knee Replacement Surgery

	Dosing Regimen									
	Enoxaparin Sodium Injection 40 mg q.d. SC				Enoxaparin Sodium Injection 30 mg q12h SC		Heparin 15,000 U/24h SC		Placebo q12h SC	
	Peri-Operative Period n = 288[1] %		Extended Prophylaxis Period n = 131[2] %		n = 1080 %		n = 766 %		n = 115 %	
Adverse Reaction	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Fever	0	8	0	0	<1	5	<1	4	0	3
Hemorrhage	<1	13	0	5	<1	4	1	4	0	3
Nausea					<1	3	<1	2	0	2
Anemia	0	16	0	<2	<1	2	2	5	<1	7
Edema					<1	2	<1	2	0	2
Peripheral edema	0	6	0	0	<1	3	<1	4	0	3

[1] Data represent enoxaparin sodium injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received enoxaparin sodium injection peri-operatively in an unblinded fashion in one clinical trial.

[2] Data represent enoxaparin sodium injection 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Table 10

Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium Injection-Treated Medical Patients With Severely Restricted Mobility During Acute Illness

Adverse Reaction	Enoxaparin Sodium Injection 40 mg q.d. SC n = 360 %	Placebo q.d. SC n = 362 %
	Dosing Regimen	
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

Table 11

Adverse Events Occurring at ≥2% Incidence in Enoxaparin Sodium Injection-Treated Patients Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

	Dosing Regimen					
	Enoxaparin Sodium Injection 1.5 mg/kg q.d. SC n = 298 %		Enoxaparin Sodium Injection 1 mg/kg q12h SC n = 559 %		Heparin aPTT Adjusted I.V. Therapy n = 544 %	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Injection Site Hemorrhage	0	5	0	3	<1	<1
Injection Site Pain	0	2	0	2	0	0
Hematuria	0	2	0	<1	<1	2

Adverse Events in Enoxaparin Sodium Injection-Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction:

Non-hemorrhagic clinical events reported to be related to enoxaparin sodium injection therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic events, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC enoxaparin sodium injection than in patients treated with IV heparin.

Serious adverse events with enoxaparin sodium injection or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the enoxaparin sodium injection group are provided below [see Table 12].

Table 12

Serious Adverse Events Occurring at ≥0.5% Incidence in Enoxaparin Sodium Injection-Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction

Adverse Event	Enoxaparin Sodium Injection 1 mg/kg q12h SC n = 1578 n (%)	Heparin aPTT Adjusted IV Therapy n = 1529 n (%)
	Dosing Regimen	
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

Adverse Reactions in Enoxaparin Sodium Injection-Treated Patients with Acute ST-Segment Elevation Myocardial Infarction:

In a clinical trial in patients with acute ST-segment elevation myocardial infarction, the only adverse reaction that occurred at a rate of at least 0.5% in the enoxaparin sodium injection group was thrombocytopenia (1.5%).

6.2 Post-Marketing Experience

There have been reports of epidural or spinal hematoma formation with concurrent use of enoxaparin sodium injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis.

Local reactions at the injection site (*e.g.*, nodules, inflammation, oozing), systemic allergic reactions (*e.g.*, pruritus, urticaria, anaphylactic/anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thrombocytopenia with thrombosis [see *Warnings and Precautions (5.5)*] have been reported.

Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues). Very rare cases of hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate reliably their frequency or to establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

Whenever possible, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of enoxaparin sodium injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring [see *Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes the potential of enoxaparin sodium injection to increase the risk of developmental abnormalities the above background risk.

Fetal Risk Summary

Enoxaparin sodium injection does not cross the placenta, and is not expected to result in fetal exposure to the drug. Human data from a retrospective cohort study, which included 693 live births, suggest that enoxaparin sodium injection does not increase the risk of major developmental abnormalities. Based on animal data, enoxaparin is not predicted to increase the risk of major developmental abnormalities (see *Data*).

Clinical Considerations

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see *Warnings and Precautions (5.7)* and *Use in Specific Populations (8.6)*]. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches [see *Boxed Warning*]. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

It is not known if monitoring of anti-Factor Xa activity and dose adjustment (by weight or anti-Factor Xa activity) of enoxaparin sodium injection affect the safety and the efficacy of the drug during pregnancy.

Data

Human Data - There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received enoxaparin sodium injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been conducted [see *Warnings and Precautions (5.7)*].

Animal Data - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 15 times the recommended human dose (by comparison with 2 mg/kg as the maximum recommended daily dose). There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether enoxaparin sodium injection is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from enoxaparin sodium injection, a decision should be made whether to discontinue nursing or discontinue enoxaparin sodium injection, taking into account the importance of enoxaparin sodium injection to the mother and the known benefits of nursing.

8.4 Pediatric Use

Safety and effectiveness of enoxaparin sodium injection in pediatric patients have not been established.

8.5 Geriatric Use

Prevention of Deep Vein Thrombosis in hip, knee and abdominal surgery; treatment of Deep Vein Thrombosis, Prevention of ischemic complications of unstable angina and non-Q-Wave myocardial infarction

Over 2800 patients, 65 years and older, have received enoxaparin sodium injection in pivotal clinical trials. The efficacy of enoxaparin sodium injection in the geriatric (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of enoxaparin sodium injection were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when enoxaparin sodium injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of enoxaparin sodium injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving enoxaparin sodium injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin sodium injection between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Enoxaparin sodium injection should be used with care in geriatric patients who may show delayed elimination of enoxaparin. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered [see *Warnings and Precautions (5.9)* and *Clinical Pharmacology (12.3)*].

Treatment of Acute ST-Segment Elevation Myocardial Infarction

In the clinical study for treatment of acute ST-segment elevation myocardial infarction, there was no evidence of difference in efficacy between patients ≥75 years of age (n = 1241) and patients less than 75 years of age (n = 9015). Patients ≥75 years of age did not receive a 30 mg IV bolus prior to the normal dosage regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours [see *Dosage and Administration (2.3)*]. The incidence of bleeding complications was higher in patients ≥65 years of age as compared to younger patients (<65 years).

8.6 Patients with Mechanical Prosthetic Heart Valves

The use of enoxaparin sodium injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism [see *Warnings and Precautions (5.7)*].

8.7 Renal Impairment

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*]. In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia [see *Adverse Reactions (6.2)*].

8.8 Hepatic Impairment

The impact of hepatic impairment on enoxaparin's exposure and antithrombotic effect has not been investigated. Caution should be exercised when administering enoxaparin to patients with hepatic impairment.

8.9 Low-Weight Patients

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Accidental overdosage following administration of enoxaparin sodium injection may lead to hemorrhagic complications. Injected enoxaparin sodium may be largely neutralized by the slow IV injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of enoxaparin sodium injected: 1 mg protamine sulfate should be administered to neutralize 1 mg enoxaparin sodium injection, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of enoxaparin sodium injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

If at least 12 hours have elapsed since the last enoxaparin sodium injection, protamine administration may not be required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

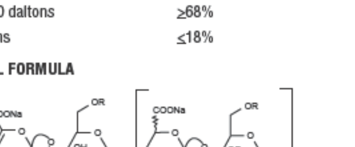
11 DESCRIPTION

Enoxaparin sodium injection is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin. The pH of the injection is 5.5 to 7.5.

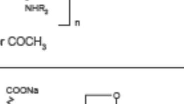
Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain. The drug substance is the sodium salt. The average molecular weight is about 4500 daltons. The molecular weight distribution is:

<2000 daltons	≤20%
2000 to 8000 daltons	≥68%
>8000 daltons	≤18%

STRUCTURAL FORMULA



R_1 H or SO_3Na and R_2 SO_3Na or $COCH_3$

R	X*= 15 to 25%		n= 0 to 20
	100 - X	H	n =1 to 21

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

Enoxaparin Sodium Injection 100 mg/mL Concentration contains 10 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1000 IU [with reference to the W.H.O. Second International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

Enoxaparin Sodium Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. Second International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The enoxaparin sodium injection prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection. [See *Dosage and Administration (2)* and *How Supplied (16)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enoxaparin is a low molecular weight heparin which has antithrombotic properties.

12.2 Pharmacodynamics

In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean ± SD, 14.0 ± 3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean±SD, 1.22 ± 0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose (100 mg / mL concentration), administered SC every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n = 1607). A 30 mg IV bolus immediately followed by a 1 mg/kg SC administration resulted in aPTT post-injection values of 50 seconds. The average aPTT prolongation value on Day 1 was about 16% higher than on Day 4.

12.3 Pharmacokinetics

Absorption. Pharmacokinetic trials were conducted using the 100 mg/mL formulation. Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 mcg/mL) and 0.38 IU/mL (3.83 mcg/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg given SC, based on anti-Factor Xa activity is approximately 100% in healthy subjects.

A 30 mg IV bolus immediately followed by a 1 mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 84% of steady-state levels. Steady state is achieved on the second day of treatment.

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges [see *Dosage and Administration (2)*]. After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once-daily regimens in healthy volunteers, the steady state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics. After repeated subcutaneous administration of the 1 mg/kg twice daily regimen, the steady state is reached from day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

Although not studied clinically, the 150 mg/mL concentration of enoxaparin sodium is projected to result in anticoagulant activities similar to those of 100 mg/mL and 200 mg/mL concentrations at the same enoxaparin dose. When a daily 1.5 mg/kg SC injection of enoxaparin sodium was given to 25 healthy male and female subjects using a 100 mg/mL or a 200 mg/mL concentration the following pharmacokinetic profiles were obtained [see Table 13]:

Table 13
Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg SC Once Daily Doses of Enoxaparin Sodium Using 100 mg/mL *or* 200 mg/mL Concentrations

	Concentration	Anti-Xa	Anti-IIa	Heptest	aPTT
A_{max} (IU/mL or Δsec)	100 mg/mL	1.37 (±0.23)	0.23 (±0.05)	105 (±17)	19 (±5)
	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	111 (±17)	22 (±7)
	90% CI	102-110%		102-111%	
t_{max}** (h)	100 mg/mL	3 (2-6)	4 (2-5)	2.5 (2-4.5)	3 (2-4.5)
	200 mg/mL	3.5 (2-6)	4.5 (2.5-6)	3.3 (2-5)	3 (2-5)
AUC (ss) (h*IU/mL or h* Δ sec)	100 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)	
	200 mg/mL	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)	
	90% CI	105-112%		103-109%	

* Means ± SD at Day 5 and 90% Confidence Interval (CI) of the ratio

** Median (range)

Distribution. The volume of distribution of anti-Factor Xa activity is about 4.3 L.

Elimination. Following intravenous (IV) dosing, the total body clearance of enoxaparin is 26 mL/min. After IV dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after a single SC dose to about 7 hours after repeated dosing. Significant anti-Factor Xa activity persists in plasma for about 12 hours following a 40 mg SC once a day dose.

Following SC dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min.

Metabolism. Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

Special Populations

Gender: Apparent clearance and A_{max} derived from anti-Factor Xa values following single SC dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters has not been conclusively identified; however, body weight may be a contributing factor.

Geriatric: Apparent clearance and A_{max} derived from anti-Factor Xa values following single and multiple SC dosing in geriatric subjects were close to those observed in young subjects. Following once a day SC dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value. [see *Dosage and Administration (2.3)* and *Use in Specific Populations (8.5)*].

Renal Impairment: A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50–80 mL/min) and moderate (creatinine clearance 30-50 mL/min) renal impairment after repeated subcutaneous 40 mg once-daily doses. In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC at steady-state is significantly increased on average by 65% after repeated subcutaneous 40 mg once-daily doses [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.7)*].

Hemodialysis: In a single study, elimination rate appeared similar but AUC was two-fold higher than control population, after a single 0.25 or 0.5 mg/kg intravenous dose.

Hepatic Impairment: Studies with enoxaparin in patients with hepatic impairment have not been conducted and the impact of hepatic impairment on the exposure to enoxaparin is unknown [see *Use in Specific Populations (8.8)*].

Weight: After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady-state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while A_{max} is not increased.

When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 40 mg dose, that anti-Factor Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects [see *Use in Specific Populations (8.9)*].

Pharmacokinetic interaction: No pharmacokinetic interaction was observed between enoxaparin and thrombolytics when administered concomitantly.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

13.2 Animal Toxicology and/or Pharmacology

A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

13.3 Reproductive and Developmental Toxicology

Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day corresponding to 211 mg/m^2/day and 410 mg/m^2/day in rats and rabbits respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin.

14 CLINICAL STUDIES

14.1 Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications

Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE).

In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Asian and 0.4% others. Enoxaparin sodium injection 40 mg SC, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5000 U every 8 hours SC in reducing the risk of DVT. The efficacy data are provided below [see Table 14].

Table 14
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

	Dosing Regimen	
Indication	**Enoxaparin Sodium Injection** 40 mg q.d. SC n (%)	**Heparin** 5000 U q8h SC n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures Total VTE[1] (%)	56 (10.1) (95% CI[2]: 8 to 13)	63 (11.3) (95% CI: 9 to 14)
DVT Only (%)	54 (9.7) (95% CI: 7 to 12)	61 (10.9) (95% CI: 8 to 13)

[1] VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
[2] CI = Confidence Interval

In a second double-blind, parallel group study, enoxaparin sodium injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below [see Table 15].

Table 15
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Colorectal Surgery

	Dosing Regimen	
Indication	**Enoxaparin Sodium Injection** 40 mg q.d. SC n (%)	**Heparin** 5000 U q8h SC n (%)
All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures Total VTE[1](%)	48 (7.1) (95% CI[2]: 5 to 9)	45 (6.7) (95% CI: 5 to 9)
DVT Only (%)	47 (7.0) (95% CI: 5 to 9)	44 (6.5) (95% CI: 5 to 8)

[1] VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
[2] CI = Confidence Interval

14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

Enoxaparin sodium injection has been shown to reduce the risk of post-operative deep vein thrombosis (DVT) following hip or knee replacement surgery.

In a double-blind study, enoxaparin sodium injection 30 mg every 12 hours SC was compared to placebo in patients with hip replacement. A total of 100 patients were randomized in the study and all patients were treated. Patients ranged in age from 41 to 84 years (mean age 67.1 years) with 45% men and 55% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued for 10 to 14 days after surgery. The efficacy data are provided below [see Table 16].

Table 16
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

	Dosing Regimen	
Indication	**Enoxaparin Sodium Injection** 30 mg q12h SC n (%)	**Placebo** q12h SC n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)
Treatment Failures Total DVT (%)	5 (10)[1]	23 (46)
Proximal DVT (%)	1 (2)[2]	11 (22)

[1] p value versus placebo = 0.0002
[2] p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of enoxaparin sodium injection in patients with hip replacement. A total of 572 patients were randomized in the study and 568 patients were treated. Patients ranged in age from 31 to 88 years (mean age 64.7 years) with 63% men and 37% women. Patients were 93% Caucasian, 6% Black, <1% Asian, and 1% others. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The efficacy data are provided below [see Table 17].

Table 17
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

	Dosing Regimen		
Indication	**10 mg q.d. SC** n (%)	**30 mg q12h SC** n (%)	**40 mg q.d. SC** n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)
Treatment Failures Total DVT (%)	40 (25)	22 (11)[1]	27 (14)
Proximal DVT (%)	17 (11)	8 (4)[2]	9 (5)

[1] p value versus enoxaparin sodium injection 10 mg once a day = 0.0008
[2] p value versus enoxaparin sodium injection 10 mg once a day = 0.0168

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens. In a double-blind study, enoxaparin sodium injection 30 mg every 12 hours SC was compared to placebo in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the study and 131 patients were treated, of which 99 had total knee replacement and 32 had either unicompartmental knee replacement or tibial osteotomy. The 99 patients with total knee replacement ranged in age from 42 to 85 years (mean age 70.2 years) with 36.4% men and 63.6% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued up to 15 days after surgery. The incidence of proximal and total DVT after surgery was significantly lower for enoxaparin sodium injection compared to placebo. The efficacy data are provided below [see Table 18].

Table 18
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery

	Dosing Regimen	
Indication	**Enoxaparin Sodium Injection** 30 mg q12h SC n (%)	**Placebo** q12h SC n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures Total DVT (%)	5 (11)[1] (95% CI[2]: 1 to 21)	32 (62) (95% CI: 47 to 76)
Proximal DVT (%)	0 (0)[3] (95% Upper CL[4]: 5)	7 (13) (95% CI: 3 to 24)

[1] p value versus placebo = 0.0001
[2] CI = Confidence Interval
[3] p value versus placebo = 0.013
[4] CL = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium injection 30 mg every 12 hours SC in patients undergoing elective knee replacement surgery was compared to heparin 5000 U every 8 hours SC. A total of 453 patients were randomized in the study and all were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.6% others. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for enoxaparin sodium injection compared to heparin.

Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin sodium injection 40 mg SC, initiated up to 12 hours prior to surgery for the prophylaxis of post-operative DVT. At the end of the peri-operative period, all patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin sodium injection 40 mg (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 69.4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium injection compared to placebo. The efficacy data are provided below [see Table 19].

Table 19
Efficacy of Enoxaparin Sodium Injection in the Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

	Post-Discharge Dosing Regimen	
Indication (Post-Discharge)	**Enoxaparin Sodium Injection** 40 mg q.d. SC n (%)	**Placebo** q.d. SC n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Treatment Failures Total DVT (%)	6 (7)[1] (95% CI[2]: 3 to 14)	18 (20) (95% CI: 12 to 30)
Proximal DVT (%)	5 (6)[3] (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)

[1] p value versus placebo = 0.008
[2] CI= Confidence Interval
[3] p value versus placebo = 0.537

In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin sodium injection 40 mg SC, initiated up to 12 hours prior to surgery. All patients were examined for clinical signs and symptoms of venous thromboembolic (VTE) disease. In a double-blind design, patients without clinical signs and symptoms of VTE disease were randomized to a post-discharge regimen of either enoxaparin sodium injection 40 mg (n = 131) once a day SC or to placebo (n = 131) for 3 weeks. A total of 262 patients were randomized in the study double-blind phase and all patients were treated. Patients ranged in age from 44 to 87 years (mean age 68.5 years) with 43.1% men and 56.9% women. Similar to the first study the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium injection compared to placebo, with a statistically significant difference in both total DVT (enoxaparin sodium injection 21 [16%] versus placebo 45 [34%]; p = 0.001) and proximal DVT (enoxaparin sodium injection 8 [6%] versus placebo 28 [21%]; p = <0.001).

14.3 Prophylaxis of Deep Vein Thrombosis In Medical Patients with Severely Restricted Mobility During Acute Illness

In a double blind multicenter, parallel group study, enoxaparin sodium injection 20 mg or 40 mg once a day SC was compared to placebo in the prophylaxis of deep vein thrombosis (DVT) in medical patients with severely restricted mobility during acute illness (defined as walking distance of <10 meters for ≤3 days). This study included patients with heart failure (NYHA Class III or IV); acute respiratory failure or complicated chronic respiratory insufficiency (not requiring ventilatory support): acute infection (excluding septic shock); or acute rheumatic disorder [acute lumbar or sciatic pain, vertebral compression (due to osteoporosis or tumor), acute arthritic episodes of the lower extremities]. A total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged in age from 40 to 97 years (mean age 73 years) with equal proportions of men and women. Treatment continued for a maximum of 14 days (median duration 7 days). When given at a dose of 40 mg once a day SC, enoxaparin sodium injection significantly reduced the incidence of DVT as compared to placebo. The efficacy data are provided below [see Table 20].

Table 20
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis in Medical Patients With Severely Restricted Mobility During Acute Illness

	Dosing Regimen		
Indication	**Enoxaparin Sodium Injection** 20 mg q.d. SC n (%)	**Enoxaparin Sodium Injection** 40 mg q.d. SC n (%)	**Placebo** n (%)
All Treated Medical Patients During Acute Illness	351 (100)	360 (100)	362 (100)
Treatment Failure[1] Total VTE[2] (%)	43 (12.3)	16 (4.4)	43 (11.9)
Total DVT (%)	43 (12.3) (95% CI[3] 8.8 to 15.7)	16 (4.4) (95% CI[3] 2.3 to 6.6)	41 (11.3) (95% CI[3] 8.1 to 14.6)
Proximal DVT (%)	13 (3.7)	5 (1.4)	14 (3.9)

[1] Treatment failures during therapy, between Days 1 and 14.
[2] VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
[3] CI = Confidence Interval

At approximately 3 months following enrollment, the incidence of venous thromboembolism remained significantly lower in the enoxaparin sodium injection 40 mg treatment group versus the placebo treatment group.

14.4 Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

In a multicenter, parallel group study, 900 patients with acute lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) enoxaparin sodium injection 1.5 mg/kg once a day SC, (ii) enoxaparin sodium injection 1 mg/kg every 12 hours SC, or (iii) heparin IV bolus (5000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 60.7 years) with 54.7% men and 45.3% women. All patients also received warfarin sodium (dose adjusted according to PT to achieve an International Normalization Ratio [INR] of 2.0 to 3.0), commencing within 72 hours of initiation of enoxaparin sodium injection or standard heparin therapy, and continuing for 90 days. Enoxaparin sodium injection or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both enoxaparin sodium injection regimens were equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism (DVT and/or PE). The efficacy data are provided below [see Table 21].

Table 21
Efficacy of Enoxaparin Sodium Injection in Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

	Dosing Regimen[1]		
Indication	**Enoxaparin Sodium Injection** 1.5 mg/kg q.d. SC n (%)	**Enoxaparin Sodium Injection** 1 mg/kg q12h SC n (%)	**Heparin** aPTT Adjusted I.V. Therapy n (%)
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Patient Outcome Total VTE[2] (%)	13 (4.4)[3]	9 (2.9)[3]	12 (4.1)
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

[1] All patients were also treated with warfarin sodium commencing within 72 hours of enoxaparin sodium injection or standard heparin therapy.
[2] VTE = venous thromboembolic event (DVT and/or PE).
[3] The 95% Confidence Intervals for the treatment differences for total VTE were:
enoxaparin sodium injection once a day versus heparin (-3.0 to 3.5)
enoxaparin sodium injection every 12 hours versus heparin (-4.2 to 1.7).

Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT were randomized to enoxaparin sodium injection or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outpatient exclusion criteria included the following: inability to receive outpatient heparin therapy because of associated co-morbid conditions or potential for non-compliance and inability to attend follow-up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but ONLY enoxaparin sodium injection patients were permitted to go home on therapy (72%). A total of 501 patients were randomized in the study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8 years) with 60.5% men and 39.5% women. Patients were randomized to either enoxaparin sodium injection 1 mg/kg every 12 hours SC or heparin IV bolus (5000 IU) followed by a continuous infusion administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also received warfarin sodium as described in the previous study. Enoxaparin sodium injection or standard heparin therapy was administered for a minimum of 5 days. Enoxaparin sodium injection was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are provided below [see Table 22].

Table 22
Efficacy of Enoxaparin Sodium Injection in Treatment of Deep Vein Thrombosis

	Dosing Regimen[1]	
Indication	**Enoxaparin Sodium Injection** 1 mg/kg q12h SC n (%)	**Heparin** aPTT Adjusted IV Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome Total VTE[2] (%)	13(5.3)[3]	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	3 (1.2)

[1] All patients were also treated with warfarin sodium commencing on the evening of the second day of enoxaparin sodium injection or standard heparin therapy.
[2] VTE = venous thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]).
[3] The 95% Confidence Intervals for the treatment difference for total VTE was: enoxaparin sodium injection versus heparin (-5.6 to 2.7).

14.5 Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction

In a multicenter, double-blind, parallel group study, patients who recently experienced unstable angina or non-Q-wave myocardial infarction were randomized to either enoxaparin sodium injection 1 mg/kg every 12 hours SC or heparin IV bolus (5000 U) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study, and 3107 patients were treated. Patients ranged in age from 25-94 years (median age 64 years), with 33.4% of patients female and 66.6% male. Race was distributed as follows: 89.8% Caucasian, 4.8% Black, 2.0% Asian, and 3.5% other. **All** patients were also treated with aspirin 100 to 325 mg per day. Treatment was initiated within 24 hours of the event and continued until clinical stabilization, revascularization procedures, or hospital discharge, with a maximal duration of 8 days of therapy. The combined incidence of the triple endpoint of death, myocardial infarction, or recurrent angina was lower for enoxaparin sodium injection compared with heparin therapy at 14 days after initiation of treatment. The lower incidence of the triple endpoint was sustained up to 30 days after initiation of treatment. These results were observed in an analysis of both all-randomized and all-treated patients. The efficacy data are provided below [see Table 23].

Table 23
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (Combined Endpoint of Death, Myocardial Infarction, or Recurrent Angina)

	Dosing Regimen[1]			
Indication	**Enoxaparin Sodium Injection** 1 mg/kg q12h SC n (%)	**Heparin** aPTT Adjusted IV Therapy n (%)	**Reduction** (%)	**p Value**
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint[2] 48 Hours	96 (6.1)	112 (7.3)	1.2	0.120
14 Days	261 (16.5)	303 (19.8)	3.3	0.017
30 Days	313 (19.8)	358 (23.4)	3.6	0.014

[1] All patients were also treated with aspirin 100 to 325 mg per day.
[2] Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

The combined incidence of death or myocardial infarction at all time points was lower for enoxaparin sodium injection compared to standard heparin therapy, but did not achieve statistical significance. The efficacy data are provided below [see Table 24].

Table 24
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (Combined Endpoint of Death or Myocardial Infarction)

	Dosing Regimen[1]			
Indication	**Enoxaparin Sodium Injection** 1 mg/kg q12h SC n (%)	**Heparin** aPTT Adjusted IV Therapy n (%)	**Reduction** (%)	**p Value**
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint[2] 48 Hours	16 (1.0)	20 (1.3)	0.3	0.126
14 Days	76 (4.8)	93 (6.1)	1.3	0.115
30 Days	96 (6.1)	118 (7.7)	1.6	0.069

[1] All patients were also treated with aspirin 100 to 325 mg per day.
[2] Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

In a survey one year following treatment, with information available for 92% of enrolled patients, the combined incidence of death, myocardial infarction, or recurrent angina remained lower for enoxaparin sodium injection versus heparin (32.0% vs 35.7%).

Urgent revascularization procedures were performed less frequently in the enoxaparin sodium injection group as compared to the heparin group, 6.3% compared to 8.2% at 30 days (p = 0.047).

14.6 Treatment of Acute ST-Segment Elevation Myocardial Infarction

In a multicenter, double-blind, double-dummy, parallel group study, patients with acute ST-segment elevation myocardial infarction (STEMI) who were to be hospitalized within 6 hours of onset and were eligible to receive fibrinolytic therapy were randomized in a 1:1 ratio to receive either enoxaparin sodium injection or unfractionated heparin.

Study medication was initiated between 15 minutes before and 30 minutes after the initiation of fibrinolytic therapy. Unfractionated heparin was administered beginning with an IV bolus of 60 U/kg (maximum 4000 U) and followed with an infusion of 12 U/kg per hour (initial maximum 1000 U per hour) that was adjusted to maintain an aPTT of 1.5 to 2 times the control value. The IV infusion was to be given for at least 48 hours. The enoxaparin dosing strategy was adjusted according to the patient's age and renal function. For patients younger than 75 years of age, enoxaparin was given as a single 30 mg intravenous bolus plus a 1 mg/kg SC dose followed by an SC injection of 1 mg/kg every 12 hours. For patients at least 75 years of age, the IV bolus was not given and the SC dose was reduced to 0.75 mg/kg every 12 hours. For patients with severe renal insufficiency (estimated creatinine clearance of less than 30 mL per minute), the dose was to be modified to 1 mg/kg every 24 hours. The SC injections of enoxaparin were given until hospital discharge or for a maximum of eight days (whichever came first). The mean treatment duration for enoxaparin was 6.6 days. The mean treatment duration of unfractionated heparin was 54 hours.

When percutaneous coronary intervention was performed during study medication period, patients received antithrombotic support with blinded study drug. For patients on enoxaparin, the PCI was to be performed on enoxaparin (no switch) using the regimen established in previous studies, *i.e.* no additional dosing, if the last SC administration was less than 8 hours before balloon inflation, IV bolus of 0.3 mg/kg enoxaparin if the last SC administration was more than 8 hours before balloon inflation.

All patients were treated with aspirin for a minimum of 30 days. Eighty percent of patients received a fibrin-specific agent (19% tenecteplase, 5% reteplase and 55% alteplase) and 20% received streptokinase.

Among 20,479 patients in the ITT population, the mean age was 60 years, and 76% were male. Racial distribution was: 87% Caucasian, 9.8% Asian, 0.2% Black, and 2.8% other. Medical history included previous MI (13%), hypertension (44%), diabetes (15%) and angiographic evidence of CAD (5%). Concomitant medication included aspirin (95%), beta-blockers (86%), ACE inhibitors (78%), statins (70%) and clopidogrel (27%). The MI at entry was anterior in 43%, non-anterior in 56%, and both in 1%.

The primary efficacy end point was the composite of death from any cause or myocardial re-infarction in the first 30 days after randomization. Total follow-up was one year.

The rate of the primary efficacy end point (death or myocardial re-infarction) was 9.9% in the enoxaparin group, and 12.0% in the unfractionated heparin group, a 17% reduction in the relative risk, (P=0.000003) [see Table 25].

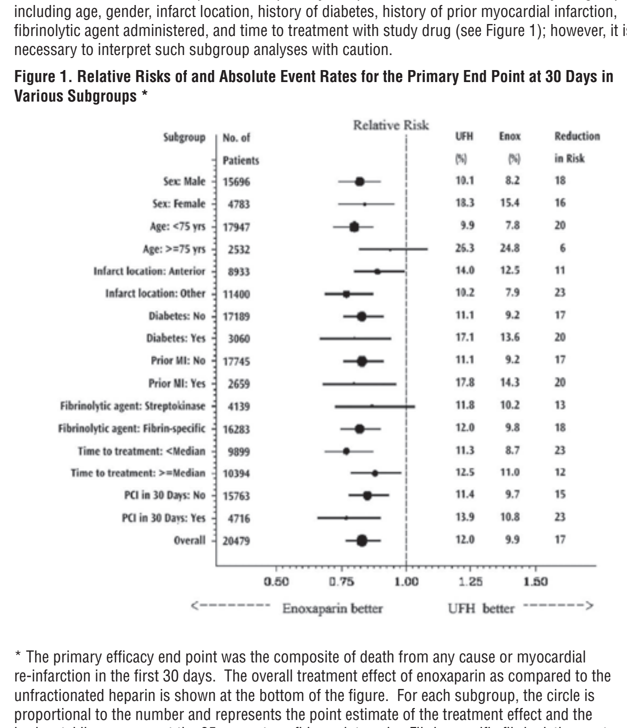
Table 25
Efficacy of Enoxaparin Sodium Injection in the Treatment of Acute ST-Segment Elevation Myocardial Infarction

	Enoxaparin (N=10,256)	**UFH (N=10,223)**	**Relative Risk (95% CI)**	**P Value**
Outcome at 48 hours	n (%)	n (%)		
Death or Myocardial Re-infarction	478 (4.7)	531 (5.2)	0.90 (0.80 to 1.01)	0.08
Death	383 (3.7)	390 (3.8)	0.98 (0.85 to 1.12)	0.76
Myocardial Re-infarction	102 (1.0)	156 (1.5)	0.65 (0.51 to 0.84)	<0.001
Urgent Revascularization	74 (0.7)	96 (0.9)	0.77 (0.57 to 1.04)	0.09
Death or Myocardial Re-infarction or Urgent Revascularization	548 (5.3)	622 (6.1)	0.88 (0.79 to 0.98)	0.02
Outcome at 8 Days				
Death or Myocardial Re-infarction	740 (7.2)	954 (9.3)	0.77 (0.71 to 0.85)	<0.001
Death	559 (5.5)	605 (5.9)	0.92 (0.82 to 1.03)	0.15
Myocardial Re-infarction	204 (2.0)	379 (3.7)	0.54 (0.45 to 0.63)	<0.001
Urgent Revascularization	145 (1.4)	247 (2.4)	0.59 (0.48 to 0.72)	<0.001
Death or Myocardial Re-infarction or Urgent Revascularization	874 (8.5)	1181 (11.6)	0.74 (0.68 to 0.80)	<0.001
Outcome at 30 Days				
Primary efficacy endpoint (Death or Myocardial Re-infarction)	**1017 (9.9)**	**1223 (12.0)**	**0.83 (0.77 to 0.90)**	**0.000003**
Death	708 (6.9)	765 (7.5)	0.92 (0.84 to 1.02)	0.11
Myocardial Re-infarction	352 (3.4)	508 (5.0)	0.69 (0.60 to 0.79)	<0.001
Urgent Revascularization	213 (2.1)	286 (2.8)	0.74 (0.62 to 0.88)	<0.001
Death or Myocardial Re-infarction or Urgent Revascularization	1199 (11.7)	1479 (14.5)	0.81 (0.75 to 0.87)	<0.001

Note: Urgent revascularization denotes episodes of recurrent myocardial ischemia (without infarction) leading to the clinical decision to perform coronary revascularization during the same hospitalization. CI denotes confidence intervals.

The beneficial effect of enoxaparin on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, fibrinolytic agent administered, and time to treatment with study drug (see Figure 1); however, it is necessary to interpret such subgroup analyses with caution.

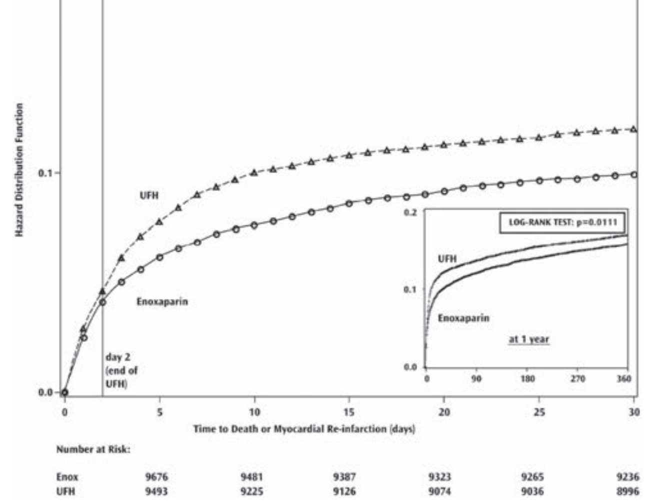
Figure 1. Relative Risks of and Absolute Event Rates for the Primary End Point at 30 Days in Various Subgroups *



* The primary efficacy end point was the composite of death from any cause or myocardial re-infarction in the first 30 days. The overall treatment effect of enoxaparin as compared to the unfractionated heparin is shown at the bottom of the figure. For each subgroup, the circle is proportional to the number and represents the point estimate of the treatment effect and the horizontal lines represent the 95 percent confidence intervals. Fibrin-specific fibrinolytic agents included alteplase, tenecteplase and reteplase. Time to treatment indicates the time from the onset of symptoms to the administration of study drug (median, 3.2 hours).

The beneficial effect of enoxaparin on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2).

Figure 2 - Kaplan-Meier plot - death or myocardial re-infarction at 30 days - ITT population



There is a trend in favor of enoxaparin during the first 48 hours, but most of the treatment difference is attributed to a step increase in the event rate in the UFH group at 48 hours (seen in Figure 2), an effect that is more striking when comparing the event rates just prior to and just subsequent to actual times of discontinuation. These results provide evidence that UFH was effective and that it would be better if used longer than 48 hours. There is a similar increase in endpoint event rate when enoxaparin was discontinued, suggesting that it too was discontinued too soon in this study.

The rates of major hemorrhages (defined as requiring 5 or more units of blood for transfusion, or 15% drop in hematocrit or clinically overt bleeding, including intracranial hemorrhage) at 30 days were 2.1% in the enoxaparin group and 1.4% in the unfractionated heparin group. The rates of intracranial hemorrhage at 30 days were 0.8% in the enoxaparin group 0.7% in the unfractionated heparin group. The 30-day rate of the composite endpoint of death, myocardial re-infarction or ICH (a measure of net clinical benefit) was significantly lower in the enoxaparin group (10.1%) as compared to the heparin group (12.2%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Enoxaparin sodium injection is available in two concentrations [see Tables 26 and 27]:

Table 26
100 mg/mL Concentration

Dosage Unit / Strength[1]	Anti-Xa Activity[2]	Package Size (per carton)	Label Color	NDC #
Prefilled Syringes[3] 30 mg / 0.3 mL	3000 IU	10 syringes	Medium Blue	0781-3119-63
40 mg / 0.4 mL	4000 IU	10 syringes	Yellow	0781-3119-64
Graduated Prefilled Syringes[3] 60 mg / 0.6 mL	6000 IU	10 syringes	Orange	0781-3119-66
80 mg / 0.8 mL	8000 IU	10 syringes	Brown	0781-3119-68
100 mg / mL	10,000 IU	10 syringes	Black	0781-3119-69

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. Enoxaparin sodium injection 30 and 40 mg prefilled syringes, and 60, 80, and 100 mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection**.
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. Second International Low Molecular Weight Heparin Reference Standard.
[3] Each enoxaparin sodium injection prefilled syringe is for single, one-time use only and is affixed with a 27 gauge x 1/2 inch needle.

Table 27
150 mg/mL Concentration

Dosage Unit / Strength[1]	Anti-Xa Activity[2]	Package Size (per carton)	Syringe Label Color	NDC #
Graduated Prefilled Syringes[3] 120 mg / 0.8 mL	12,000 IU	10 syringes	Purple	0781-3121-68
150 mg / mL	15,000 IU	10 syringes	Navy Blue	0781-3121-69

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. Enoxaparin sodium injection 120 mg and 150 mg graduated prefilled syringes contain **15 mg enoxaparin sodium per 0.1 mL** Water for Injection.
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. Second International Low Molecular Weight Heparin Reference Standard.
[3] Each enoxaparin sodium injection graduated prefilled syringe is for single, one-time use only and is affixed with a 27 gauge x 1/2 inch needle.

Store at 20° - 25°C (68°C - 77°F) (see USP Controlled Room Temperature).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

17 PATIENT COUNSELING INFORMATION

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs, platelet inhibitors, or other anticoagulants, they should be informed to watch for signs and symptoms of spinal or epidural hematoma, such as tingling, numbness (especially in the lower limbs) and muscular weakness. If any of these symptoms occur the patient should contact his or her physician immediately.

Additionally, the use of aspirin and other NSAIDs may enhance the risk of hemorrhage. Their use should be discontinued prior to enoxaparin therapy whenever possible; if co-administration is essential, the patient's clinical and laboratory status should be closely monitored [see *Drug Interactions (7)*].

Patients should also be informed:

- of the instructions for injecting enoxaparin sodium injection if their therapy is to continue after discharge from the hospital.
- it may take them longer than usual to stop bleeding.
- they may bruise and/or bleed more easily when they are treated with enoxaparin sodium injection.
- they should report any unusual bleeding, bruising, or signs of thrombocytopenia (such as a rash of dark red spots under the skin) to their physician [see *Warnings and Precautions (5.1, 5.5)*].
- to tell their physicians and dentists they are taking enoxaparin sodium injection and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken [see *Warnings and Precautions (5.3)*].
- to tell their physicians and dentists of all medications they are taking, including those obtained without a prescription, such as aspirin or other NSAIDs [see *Drug Interactions (7)*].

04-2010

Manufactured by
Baxter Pharmaceutical Solutions LLC
for
Sandoz Inc.
Princeton, NJ 08540

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: August 26, 2005 (original)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. 100 mg/mL and 150 mg/mL strengths- delete "1" appearing with "mL". (100 mg/mL and 150 mg/mL)

   b. The RLD supplement approved on March 7, 2005 (NDA 20-164/S-063) provides for revision of the graduation statements for Lovenox® 120 mg and 150 mg strengths from "Each 0.025 mL graduation equals 3.75 mg enoxaparin sodium injection." to "Each 0.02 mL graduation equals 3 mg enoxaparin sodium injection." Please update your labels and labeling to be in accord.

   c. 60 mg/0.6 mL strength only: In the HOW SUPPLIED section of the insert labeling, the syringe label color for the 60 mg/0.6 mL strength is described as "orange". The label and labeling submitted in the August 26, 2005 submission may be mistaken as yellow/gold. We encourage you to choose another shade of orange.

   d. The syringe labels and peel lid labeling are blurry and difficulty to read. Please ensure that the final printed labels and labeling are true to color, size and clarity.

2. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. On page 3137 of your original submission, you stated: "A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths." Please submit the label with the graduated markings for our review. If possible, please mail us samples of the syringe with the syringe label and graduated markings to facilitate our review.

   b. Include the net quantity on your labels.

   c. Include the route of administration on your labels.

3. PEEL LID LABELING (One syringe)

   Refer to GENERAL COMMENTS

4. CARTON LABELING (10 syringes)

   Directions for use: Please confirm if the directions and explanations of the activation of the safety system are true for your product.

5. INSERT

   a. GENERAL COMMENTS

      i. We note that you reference the "W.H.O. Second International Low Molecular Weight Heparin

Reference Standard" throughout your insert, whereas the RLD references the "W.H.O. First International Low Molecular Weight Heparin Reference Standard". Please explain.

ii. Please note that USAN names are common nouns and should be treated as such in a text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.

b. CLINICAL PHARMACOLOGY, Clinical Trials

i. Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, third paragraph, fifth sentence-revise to read "Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery."

ii. Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE), second paragraph-revise the ninth and tenth sentences to read "Enoxaparin sodium injection or standard heparin therapy was administered for a minimum of 5 days. Enoxaparin sodium injection was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism."

iii. CONTRAINDICATIONS, second paragraph: delete [redacted] (b) (4).

c. DOSAGE AND ADMINISTRATION, title of the table: "...<30 mL/minute)" [add a space between "30" and "mL"]

Please revise your labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

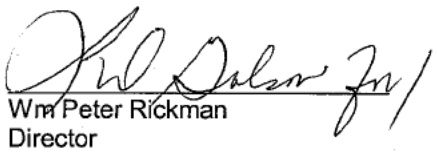
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTE TO CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 20-164/S-055 and S-053, approved 7/23/04 and 10/20/04. Statement regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling because Sandoz has not applied for approval for the benzyl alcohol preserved multi-dose presentation of the enoxaparin sodium injection.

   NDA 20-164/S-063 approved on March 7, 2005 provides for correction of an apparent inconsistency between the carton and blister foil labeling for the Lovenox® 120 mg and 150 mg strength pre-filled syringes (graduation statements) and the labeling on the pre-filled syringes. Specifically, "Each 0.025 mL graduation equals 3.75mg enoxaparin sodium injection." was revised to read "Each 0.02 mL graduation equals 3mg enoxaparin sodium injection." We will ask Sandoz to revise their labels and labeling to be in accord.

   Drug product not subject to USP 29 monograph (checked 5/31/06)

2. PATENT and EXCLUSIVITY

Patent Data – NDA 20-164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	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	III [Vol. A1.1, pg. 15]	None
RE38743	2/14/12	U-545		III [Vol. A1.1, pg. 15]	

Exclusivity Data– NDA 20-164

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

3. Manufacturer-
   Baxter Pharmaceutical Solutions LLC
   Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
   100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes, 60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes 300 mg/3mL multiple dose vial;
   150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

   The ANDA is proposing the following strengths;
   100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes 60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
   150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
   Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
   NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
   ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]
   USP – not USP

7. Dispensing Recommendations:
   NDA – None
   ANDA – None
   USP – not USP

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. **A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths.** A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: We will ask Sandoz to submit the label with the calibrations for our review. *(After the firm submits the labels with the graduations, need to ask chemist: Are the calibrations on the graduated syringes accurate?)*

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

Date of Review: May 31, 2006 Date of Submission: August 26, 2005 (original)

Primary Reviewer: Ruby Wu Date: 6/1/06

Team Leader: Lillie Golson Date: 6/2/06

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cc: ANDA: 77-857
DUP/DIVISION FILE
HFD-613/RWu/LGolson(no cc)
V:\FIRMSNZ\SANDOZ\LTRS&REV\77857.na1.L.doc
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: July 6, 2006 (amendment)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Graduated markings for 60, 80, and 100 mg strengths: revise "Graduation 0.025 mL" to read "Each Graduation = 2.5 mg (0.025 mL)"
   b. Graduated markings for 120 and 150 mg strengths: revise "Graduation=3 mg (0.02 mL)" to read "Each Graduation = 3 mg (0.02 mL)" [spacing]

2. PEEL LID LABELING (One syringe)

   150 mg/mL strength only- delete "1" appearing with "mL" (i.e., 150 mg/mL)

3. CARTON LABELING (10 syringes)

   Satisfactory in final print.

4. INSERT

   GENERAL COMMENT: 100 mg/mL and 150 mg/mL strengths- delete "1" appearing with "mL" (100 mg/mL and 150 mg/mL)

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

NOTE TO CHEMIST:

Are the calibrations for the graduated syringes accurate?

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 20-164/S-055 and S-053, approved 7/23/04 and 10/20/04. Statement regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling because Sandoz has not applied for approval for the benzyl alcohol preserved multi-dose presentation of the enoxaparin sodium injection.

   NDA 20-164/S-063 approved on March 7, 2005 provides for correction of an apparent inconsistency between the carton and blister foil labeling for the Lovenox® 120 mg and 150 mg strength pre-filled syringes (graduation statements) and the labeling on the pre-filled syringes. Specifically, "Each 0.025 mL graduation equals 3.75mg enoxaparin sodium injection." was revised to read "Each 0.02 mL graduation equals 3mg enoxaparin sodium injection." We will ask Sandoz to revise their labels and labeling to be in accord.

   Drug product not subject to USP 29 monograph (checked 11/2/06)

2. PATENT and EXCLUSIVITY

Patent Data – NDA 20-164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	METHOD FOR THE PREVENTION AND/OR TREATMENT OF THROMBOTIC EPISODES, SUCH AS MYOCARDIAL NFARCTION, IN A HUMAN PATIENT AND METHOD FOR THE PREVENTION OF VENOUS THROMBOSIS IN A POSTOPERATIVE HUMAN PATIENT	III [Vol. A1.1, pg. 15]	None
RE38743	2/14/12	U-545		III [Vol. A1.1, pg. 15]	

Exclusivity Data– NDA 20-164

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

3. Manufacturer-
   Baxter Pharmaceutical Solutions LLC
   Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
   100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes,
   60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
   300 mg/3mL multiple dose vial;
   150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

   The ANDA is proposing the following strengths;
   100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
   60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
   150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
   Components: Enoxaparin, water for injection (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
   NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
   ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]
   USP – not USP

7. Dispensing Recommendations:
   NDA – None
   ANDA – None
   USP – not USP

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)

"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]

Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

Date of Review: November 2, 2006 Date of Submission: July 6, 2006 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

ANDA: 77-857
V:\FIRMSNZ\SANDOZ\LTRS&REV\77857.na2.L.doc
Review

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

/s/

Ruby Wu
11/6/2006 04:36:41 PM
MEDICAL OFFICER

Lillie Golson
11/7/2006 04:00:51 PM
MEDICAL OFFICER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: November 29, 2006 (amendment)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.
   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)

   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT

   Satisfactory in draft.

Please submit your insert labeling in final print electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

NOTE TO CHEMIST:

Are the calibrations for the graduated syringes accurate?

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 20-164/S-055 and S-053, approved 7/23/04 and 10/20/04. Statement regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling because Sandoz has not applied for approval for the benzyl alcohol preserved multi-dose presentation of the enoxaparin sodium injection.

   NDA 20-164/S-063 approved on March 7, 2005 provides for correction of an apparent inconsistency between the carton and blister foil labeling for the Lovenox® 120 mg and 150 mg strength pre-filled syringes (graduation statements) and the labeling on the pre-filled syringes. Specifically, "Each 0.025 mL graduation equals 3.75mg enoxaparin sodium injection." was revised to read "Each 0.02 mL graduation equals 3mg enoxaparin sodium injection." We will ask Sandoz to revise their labels and labeling to be in accord.

   Drug product not subject to USP 29 monograph (checked 11/2/06)

2. PATENT and EXCLUSIVITY

Patent Data – NDA 20-164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	METHOD FOR THE PREVENTION AND/OR TREATMENT OF THROMBOTIC EPISODES, SUCH AS MYOCARDIAL NFARCTION, IN A HUMAN PATIENT AND METHOD FOR THE PREVENTION OF VENOUS THROMBOSIS IN A POSTOPERATIVE HUMAN PATIENT	III [Vol. A1.1, pg. 15]	None
RE38743	2/14/12	U-545		III [Vol. A1.1, pg. 15]	

Exclusivity Data– NDA 20-164

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

3. Manufacturer-
   Baxter Pharmaceutical Solutions LLC
   Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
   100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes,
   60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
   300 mg/3mL multiple dose vial;
   150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

   The ANDA is proposing the following strengths;
   100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
   60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
   150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
   Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
   NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
   ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]
   USP – not USP

7. Dispensing Recommendations:
   NDA – None
   ANDA – None
   USP – not USP

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

Date of Review: December 13, 2006 Date of Submission: November 29, 2006

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

ANDA: 77-857
V:\FIRMSNZ\SANDOZ\LTRS&REV\77857.na3.L.doc
Review

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

/s/

Ruby Wu
12/18/2006 09:13:52 AM
MEDICAL OFFICER

Lillie Golson
12/21/2006 04:52:47 PM
MEDICAL OFFICER

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: February 20, 2007 and February 27, 2007 (amendments)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   *****There is a note to the chemist pending*****

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT
   Satisfactory in final print as submitted in the February 27, 2007 amendment.

Revisions needed post-approval: No.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Lovenox® Injection
NDA Number: 20-164
NDA Drug Name: Enoxaparin Sodium Injection
NDA Firm: Aventis
Date of Approval of NDA Insert and supplement #: NDA 20-164/SCP-070 approved January 12, 2007
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides

NOTE TO CHEMIST:

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 28, 2007 9:21 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

Can you confirm if this has been addressed? Once the firm submits the insert labeling correctly, I should be able to write up an approval summary...

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, November 02, 2006 3:10 PM
To: Ya, Naiqi
Subject: 77-857 Sandoz

Sandoz's graduated markings are not on the syringe itself...but on a label...refer to EDR, 7/6/06 submission, "graduation labels". Can you also verify the graduated markings are accurate:

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 20-164/SCP-070 approved January 12, 2007. SCP-070 provides for a change in multiple dose vial labeling as well as minor editorial revisions. Sandoz has not applied for approval for the benzyl alcohol preserved multi-dose presentation of the enoxaparin sodium injection. Therefore, changes approved in NDA 20-164/SCP-070 does not affect Sandoz's labeling and statement regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling.

   NDA 20-164/S-063 approved on March 7, 2005 provides for correction of an apparent inconsistency between the carton and blister foil labeling for the Lovenox® 120 mg and 150 mg strength pre-filled syringes (graduation statements) and the labeling on the pre-filled syringes. Specifically, “Each 0.025 mL graduation equals 3.75mg enoxaparin sodium injection.” was revised to read “Each 0.02 mL graduation equals 3mg enoxaparin sodium injection.” Sandoz has incorporated these changes in their labeling.

   Drug product not subject to USP 29 monograph (checked 3/5/07)

2. PATENT and EXCLUSIVITY

Patent Data – NDA 20-164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	METHOD FOR THE PREVENTION AND/OR TREATMENT OF THROMBOTIC EPISODES, SUCH AS MYOCARDIAL NFARCTION, IN A HUMAN PATIENT AND METHOD FOR THE PREVENTION OF VENOUS THROMBOSIS IN A POSTOPERATIVE HUMAN PATIENT	IV	None
RE38743	2/14/12	U-545		IV	

Exclusivity Data– NDA 20-164

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

MQ Notes:

- 10/2/06 PA: Rc'd ltr dated 9/8/06 for notice of PIV cert sent 6/22/06 on patents '618 and '743. RR received 6/26/06. Litigation filed in U.S. Court 8/4/06 on both patents. IM
- 7/7/06 PA: Rc'd ltr dated 6/22/06 for patent amendment for '618 and '743 patents. Change from PIII to PIV. Both expire 2/14/12. Awaiting notice of RR./IM

3. Manufacturer-
Baxter Pharmaceutical Solutions LLC
Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes,
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
300 mg/3mL multiple dose vial;
150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

The ANDA is proposing the following strengths;
100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]
USP – not USP

7. Dispensing Recommendations:
NDA – None
ANDA – None
USP – not USP

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

Date of Review: March 5, 2007 Date of Submission: February 27, 2007

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

ANDA: 77-857
V:\FIRMSNZ\SANDOZ\LTRS&REV\77857.ap.L.doc
Review

Following this page, 25 pages withheld in full - (b)(4) Draft Labeling

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

/s/

Ruby Wu
3/7/2007 02:55:01 PM
MEDICAL OFFICER

Lillie Golson
3/8/2007 01:03:16 PM
MEDICAL OFFICER

Supersedes the approval summary signed off 3/8/07

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: June 13, 2008 (amendment)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.
   There is a note to the chemist pending*

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT
   Satisfactory in final print as submitted in the June 13, 2008 amendment.
   SPL provided in the June 13, 2008 amendment

Revisions needed post-approval: No.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Lovenox® Injection
NDA Number: 20-164
NDA Drug Name: Enoxaparin Sodium Injection
NDA Firm: Aventis

Date of Approval of NDA Insert and supplement #: NDA 20-164/SLR-075 approved May 16, 2007
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides

NOTE TO CHEMIST:

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, July 03, 2008 9:48 AM
To: Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

HI Naiqi,

Please confirm if the graduated markings are accurate.

Thanks,

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 28, 2007 9:21 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

Can you confirm if this has been addressed? Once the firm submits the insert labeling correctly, I should be able to write up an approval summary...

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, November 02, 2006 3:10 PM
To: Ya, Naiqi
Subject: 77-857 Sandoz

Sandoz's graduated markings are not on the syringe itself...but on a label...refer to EDR, 7/6/06 submission, "graduation labels". Can you also verify the graduated markings are accurate:

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 20-164/SLR-075 approved May 16, 2007. This supplement provides for the use of Lovenox (enoxaparin sodium) Injection for the treatment of acute ST-segment elevation myocardial infarction (STEMI). The insert is also in PLR format.

   On December 15, 2006 (received December 18, 2006) sanofi-aventis submitted labeling supplement S-075 in conjunction with the Type 6 NDA 22-138 (submitted November 17, 2006; received November 17, 2006; approved May 16, 2007) for a new indication of acute ST-segment Elevation Myocardial Infarction (STEMI). The new indication also added a new route of administration (i.e., intravenous) in addition to the approved subcutaneous route of administration. S-075 was approved on May 16, 2007.

   NDA 20-164/S-063 approved on March 7, 2005 provides for correction of an apparent inconsistency between the carton and blister foil labeling for the Lovenox® 120 mg and 150 mg strength pre-filled syringes (graduation statements) and the labeling on the pre-filled syringes. Specifically, “Each 0.025 mL graduation equals 3.75mg enoxaparin sodium injection.” was revised to read “Each 0.02 mL graduation equals 3mg enoxaparin sodium injection.” Sandoz has incorporated these changes in their labeling.

   The products in this ANDA do not contain benzyl alcohol. Therefore, statement regarding hypersensitivity to benzyl alcohol is not required in Amphastar's labeling.

   Drug product not subject to USP 31 monograph (checked 7/3/08)

2. PATENT and EXCLUSIVITY

Patent Data – NDA 20-164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	METHOD FOR THE PREVENTION AND/OR TREATMENT OF THROMBOTIC EPISODES, SUCH AS MYOCARDIAL NFARCTION, IN A HUMAN PATIENT AND METHOD FOR THE PREVENTION OF VENOUS THROMBOSIS IN A POSTOPERATIVE HUMAN PATIENT	IV	None
RE38743	2/14/12	U-545		IV	

Exclusivity Data– NDA 20-164

Code	Reference	Expiration	Labeling Impact
I-533/S-075	ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)	*MAY 16,2010*	*Carve-out per June 13, 2008 amendment*

STEMI is protected by exclusivity I-533. The route of administration for all other indications is SC. For STEMI, the drug product may be administered IV or SC. Sandoz is choosing to carve-out the indication for STEMI. Therefore, Sandoz carved-out all information pertaining to the IV administration of the drug product.

MQ Notes:

- 10/2/06 PA: Rc'd ltr dated 9/8/06 for notice of PIV cert sent 6/22/06 on patents '618 and '743. RR received 6/26/06. Litigation filed in U.S. Court 8/4/06 on both patents. IM
- 7/7/06 PA: Rc'd ltr dated 6/22/06 for patent amendment for '618 and '743 patents. Change from PIII to PIV. Both expire 2/14/12. Awaiting notice of RR./IM

3. Manufacturer-
Baxter Pharmaceutical Solutions LLC
Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes,
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
300 mg/3mL multiple dose vial;
150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

The ANDA is proposing the following strengths;
100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]
USP – not USP

7. Dispensing Recommendations:
NDA – None
ANDA – None
USP – not USP

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]

Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

10. Citizen Petition
There is a citizen petition pending for enoxaparin sodium injection (Docket 03-P-0065-CP1) submitted on February 19, 2003 by Covington & Burling on behalf of Aventis Pharmaceuticals. Response pending.

Summary: Petition requests that FDA withhold approval of any ANDA for a generic Lovenox until enoxaparin is fully characterized, unless manufacturing process is equivalent to Aventis' or applicant demonstrates S&E thru clinical trials

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Date of Review: July 3, 2008 Date of Submission: June 13, 2008

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

ANDA: 77-857
V:\FIRMSNZ\SANDOZ\LTRS&REV\77857.ap2.L.doc
Review

Following this page, 25 pages withheld in full - (b)(4) Draft Labeling

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

/s/

Ruby Wu
7/9/2008 09:58:55 AM
LABELING REVIEWER

Lillie Golson
7/9/2008 02:01:14 PM
LABELING REVIEWER

Supersedes the approval summary signed off 7/9/2008

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: September 23, 2008 (amendment)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   There is a note to the chemist pending*

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT
   Satisfactory in final print as submitted in the September 23, 2008 amendment.
   SPL provided in the September 23, 2008 amendment

Revisions needed post-approval: Yes. The following post-approval comment will be emailed to the firm after the review has been signed-off. The revision may be submitted in the annual report.

You may delete "RECENT MAJOR CHANGES" from the HIGHLIGHT section. The RLD has already removed the listing in their labeling.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lovenox® Injection

NDA Number: 20-164

NDA Drug Name: Enoxaparin Sodium Injection

NDA Firm: Aventis

Date of Approval of NDA Insert and supplement #: NDA 20-164/SLR-080 approved July 16, 2008

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

NOTE TO CHEMIST:

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 09, 2008 2:50 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Larry,

Any updates?

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, July 09, 2008 1:22 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Larry,

I'm inquiring about the prefilled syringe (single-use). The syringe has graduated markings and I was wonderful if the markings are accurate.

Ruby

From: Lee, Sau
Sent: Wednesday, July 09, 2008 1:19 PM
To: Ya, Naiqi; Wu, Ruby (Chi-Ann)
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Ruby,

We haven't review the multiple-use dosage form yet.

Larry

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, July 03, 2008 9:48 AM
To: Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

HI Naiqi,

Please confirm if the graduated markings are accurate.

Thanks,

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 28, 2007 9:21 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

Can you confirm if this has been addressed? Once the firm submits the insert labeling correctly, I should be able to write up an approval summary...

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, November 02, 2006 3:10 PM
To: Ya, Naiqi
Subject: 77-857 Sandoz

Sandoz's graduated markings are not on the syringe itself...but on a label...refer to EDR, 7/6/06 submission, "graduation labels". Can you also verify the graduated markings are accurate:

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 20-164/SLR-080 approved July 16, 2008.

   The products in this ANDA do not contain benzyl alcohol. Therefore, statement regarding hypersensitivity to benzyl alcohol is not required in Amphastar's labeling.

   Drug product not subject to USP 31 monograph (checked 10/9/08)

2. PATENT and EXCLUSIVITY

Patent Data – NDA 20-164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	METHOD FOR THE PREVENTION AND/OR TREATMENT OF THROMBOTIC EPISODES, SUCH AS MYOCARDIAL NFARCTION, IN A HUMAN PATIENT AND METHOD FOR THE PREVENTION OF VENOUS THROMBOSIS IN A POSTOPERATIVE HUMAN PATIENT	IV	None
RE38743	2/14/12	U-545		IV	

Exclusivity Data– NDA 20-164

Code	Reference	Expiration	Labeling Impact
I-533/S-075	ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)	*MAY 16,2010*	***Carve-out*** *per June 13, 2008 amendment*

STEMI is protected by exclusivity I-533. The route of administration for all other indications is SC. For STEMI, the drug product may be administered IV or SC. Sandoz is choosing to carve-out the indication for STEMI. Therefore, Sandoz carved-out all information pertaining to the IV administration of the drug product.

MQ Notes:

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- 7/7/06 PA: Rc'd ltr dated 6/22/06 for patent amendment for '618 and '743 patents. Change from PIII to PIV. Both expire 2/14/12. Awaiting notice of RR./IM

3. Manufacturer-
Baxter Pharmaceutical Solutions LLC
Bloomington IN 47403 [Vol. A1.4, pg. 1412]

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100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes,
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
300 mg/3mL multiple dose vial;
150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

The ANDA is proposing the following strengths;
100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]
USP – not USP

7. Dispensing Recommendations:
NDA – None
ANDA – None
USP – not USP

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

10. Citizen Petition
There is a citizen petition pending for enoxaparin sodium injection (Docket 03-P-0065-CP1) submitted on February 19, 2003 by Covington & Burling on behalf of Aventis Pharmaceuticals. Response pending.

Summary: Petition requests that FDA withhold approval of any ANDA for a generic Lovenox until enoxaparin is fully characterized, unless manufacturing process is equivalent to Aventis' or applicant demonstrates S&E thru clinical trials

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Date of Review: October 9, 2008 Date of Submission: September 23, 2008

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

Following this page, 25 pages withheld in full - (b)(4) Draft Labeling

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

/s/

Ruby Wu
10/15/2008 09:36:44 AM
LABELING REVIEWER

Lillie Golson
10/16/2008 02:12:10 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	77-857
Date of Submissions:	September 18, 2009 (amendment)
Applicant's Name:	Sandoz, Inc.
Established Name:	Enoxaparin Sodium Injection USP, 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT
   You have chosen to carve-out information pertaining to the indication protected by exclusivity I-533. Please make the following revisions:
   a. 6.1: Revise the third paragraph to read
   [redacted] (b) (4)
   b. 12.2: Upon further consideration, please delete [redacted] (b) (4)
   c. 12.3: Upon further consideration, please delete " [redacted] (b) (4)

[redacted] (b) (4)

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

NOTE TO CHEMIST:

From: Lee, Sau
Sent: Saturday, October 11, 2008 11:09 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Ruby,

I mentioned to Naiqi last time. I will follow up and let you know.

Regards,
Larry

****
Sau (Lawrence) Lee, Ph.D.
Chemical Engineer
Food and Drug Administration
Office of Generic Drugs
7519 Standish Place
Rockville, MD 20855
Phone: 240-276-9321
****

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 09, 2008 2:50 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Larry,

Any updates?

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, July 09, 2008 1:22 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

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Ruby,

We haven't review the multiple-use dosage form yet.

Larry

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Please confirm if the graduated markings are accurate.

Thanks,

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 28, 2007 9:21 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

Can you confirm if this has been addressed? Once the firm submits the insert labeling correctly, I should be able to write up an approval summary...

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Subject: 77-857 Sandoz

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- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 20-164/SLR-083 approved July 23, 2009.

   The products in this ANDA do not contain benzyl alcohol. Therefore, statement regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling.

   USP 32 monograph (checked 9/11/09)
   Enoxaparin Sodium Injection
   Packaging and storage— Preserve in single-dose or multiple-dose containers in Type I glass. Store between 20 and 25 , excursions permitted between 15 and 30 .
   Labeling— Label it to indicate the amount (mg) of Enoxaparin Sodium in the total volume of contents. The label states also that the Enoxaparin Sodium starting material is porcine derived.

   From: Wu, Ruby (Chi-Ann)
   Sent: Thursday, November 20, 2008 8:53 AM
   To: 'caryn.mccullough@sandoz.com'
   Cc: Hinchliffe, Thomas
   Subject: RE: Enoxaparin - ANDA 77-857

   Good morning Caryn,

   Adding "USP" to the established name is an annual reportable change. Please send a new correspondence to your ANDA with a commitment to add "USP" post-approval.

   Thanks,

   Ruby

   From: caryn.mccullough@sandoz.com [mailto:caryn.mccullough@sandoz.com]
   Sent: Wednesday, November 19, 2008 4:52 PM
   To: Wu, Ruby (Chi-Ann)
   Subject: Enoxaparin - ANDA 77-857

   Hi Ruby,

   We have a question regarding the USP designation for Enoxaparin Sodium Injection. The USP monograph goes in to effect on December 1st, but our labels currently do not include the USP

designation. Will we be expected to update our labeling now, or can we launch with product after December 1st that is not labeled as USP? Our product meets the USP requirements.

Thanks for your help.

Caryn

Caryn McCullough
Regulatory Affairs

REMS: none (checked 9/11/09)
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

2. PATENT and EXCLUSIVITY

Patent Data – NDA 20-164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	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	IV	None
RE38743	2/14/12	U-545		IV	

Exclusivity Data– NDA 20-164

Code	Reference	Expiration	Labeling Impact
I-533/S-075	ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)	*MAY 16,2010*	***Carve-out*** *per June 13, 2008 amendment*

STEMI is protected by exclusivity I-533. The route of administration for all other indications is SC. For STEMI, the drug product may be administered IV or SC. Sandoz is choosing to carve-out the indication for STEMI. Therefore, Sandoz carved-out all information pertaining to the IV administration of the drug product.

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- 7/7/06 PA: Rc'd ltr dated 6/22/06 for patent amendment for '618 and '743 patents. Change from PIII to PIV. Both expire 2/14/12. Awaiting notice of RR./IM

3. Manufacturer-
Baxter Pharmaceutical Solutions LLC
Bloomington IN 47403 [Vol. A1.4, pg. 1412]

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100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes, 60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes 300 mg/3mL multiple dose vial;
150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

The ANDA is proposing the following strengths;
100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes 60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]

7. Dispensing Recommendations:
NDA – None
ANDA – None

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
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ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

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Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

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There is a citizen petition pending for enoxaparin sodium injection (Docket 03-P-0065-CP1) submitted on February 19, 2003 by Covington & Burling on behalf of Aventis Pharmaceuticals. Response pending.

Summary: Petition requests that FDA withhold approval of any ANDA for a generic Lovenox until enoxaparin is fully characterized, unless manufacturing process is equivalent to Aventis' or applicant demonstrates S&E thru clinical trials

---

Date of Review: October 3, 2009 Date of Submission: September 18, 2009

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

ANDA: 77-857

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

CHI-ANN Y WU
10/15/2009

LILLIE D GOLSON
10/15/2009

Supersedes the approval summary signed off 10/16/2008

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 077857

Date of Submissions: October 21, 2009 (amendment)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   There is a note to the chemist pending*

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT
   Satisfactory in final print as submitted in the October 21, 2009 amendment.

Revisions needed post-approval: No.

NOTE TO CHEMIST:

From: Lee, Sau
Sent: Saturday, October 11, 2008 11:09 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Ruby,

I mentioned to Naiqi last time. I will follow up and let you know.

Regards,
Larry

****
Sau (Lawrence) Lee, Ph.D.
Chemical Engineer
Food and Drug Administration
Office of Generic Drugs
7519 Standish Place
Rockville, MD 20855
Phone: 240-276-9321
****

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 09, 2008 2:50 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Larry,

Any updates?

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, July 09, 2008 1:22 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Larry,

I'm inquiring about the prefilled syringe (single-use). The syringe has graduated markings and I was wonderful if the markings are accurate.

Ruby

From: Lee, Sau
Sent: Wednesday, July 09, 2008 1:19 PM
To: Ya, Naiqi; Wu, Ruby (Chi-Ann)
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Ruby,

We haven't review the multiple-use dosage form yet.

Larry

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, July 03, 2008 9:48 AM
To: Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

HI Naiqi,

Please confirm if the graduated markings are accurate.

Thanks,

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 28, 2007 9:21 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

Can you confirm if this has been addressed? Once the firm submits the insert labeling correctly, I should be able to write up an approval summary...

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, November 02, 2006 3:10 PM
To: Ya, Naiqi
Subject: 77-857 Sandoz

Sandoz's graduated markings are not on the syringe itself...but on a label...refer to EDR, 7/6/06 submission, "graduation labels". Can you also verify the graduated markings are accurate:

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA 020164/SLR-083 approved July 23, 2009.

   The products in this ANDA do not contain benzyl alcohol. Therefore, statement regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling.

   USP 32 monograph (checked 11/2/09)
   According to the USP bulletin (http://www.usp.org/USPNF/notices/enoxaparinSodiumInjectionApril2009.html), the monograph will become official December 1, 2009

   Enoxaparin Sodium Injection
   Packaging and storage— Preserve in single-dose or multiple-dose containers in Type I glass. Store between 20 and 25 , excursions permitted between 15 and 30 .
   Labeling— Label it to indicate the amount (mg) of Enoxaparin Sodium in the total volume of contents. The label states also that the Enoxaparin Sodium starting material is porcine derived.

   From: Wu, Ruby (Chi-Ann)
   Sent: Thursday, November 20, 2008 8:53 AM
   To: 'caryn.mccullough@sandoz.com'
   Cc: Hinchliffe, Thomas
   Subject: RE: Enoxaparin - ANDA 77-857

   Good morning Caryn,

   Adding "USP" to the established name is an annual reportable change. Please send a new correspondence to your ANDA with a commitment to add "USP" post-approval.

   Thanks,

   Ruby

   From: caryn.mccullough@sandoz.com [mailto:caryn.mccullough@sandoz.com]
   Sent: Wednesday, November 19, 2008 4:52 PM
   To: Wu, Ruby (Chi-Ann)
   Subject: Enoxaparin - ANDA 77-857

   Hi Ruby,

We have a question regarding the USP designation for Enoxaparin Sodium Injection. The USP monograph goes in to effect on December 1st, but our labels currently do not include the USP designation. Will we be expected to update our labeling now, or can we launch with product after December 1st that is not labeled as USP? Our product meets the USP requirements.

Thanks for your help.

Caryn

_____

Caryn McCullough
Regulatory Affairs

REMS: none (checked 11/2/09)
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

2. PATENT and EXCLUSIVITY

Patent Data – NDA 020164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	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	IV	None
RE38743	2/14/12	U-545		IV	

Exclusivity Data– NDA 020164

Code	Reference	Expiration	Labeling Impact
I-533/S-075	ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)	*MAY 16,2010*	***Carve-out*** *per June 13, 2008 amendment*

STEMI is protected by exclusivity I-533. The route of administration for all other indications is SC. For STEMI, the drug product may be administered IV or SC. Sandoz is choosing to carve-out the indication for STEMI. Therefore, Sandoz carved-out all information pertaining to the IV administration of the drug product.

MQ Notes:

- 10/2/06 PA: Rc'd ltr dated 9/8/06 for notice of PIV cert sent 6/22/06 on patents '618 and '743. RR received 6/26/06. Litigation filed in U.S. Court 8/4/06 on both patents. IM
- 7/7/06 PA: Rc'd ltr dated 6/22/06 for patent amendment for '618 and '743 patents. Change from PIII to PIV. Both expire 2/14/12. Awaiting notice of RR./IM

3. Manufacturer-
Baxter Pharmaceutical Solutions LLC
Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes, 60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes 300 mg/3mL multiple dose vial;
150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

The ANDA is proposing the following strengths;

100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes

150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]

7. Dispensing Recommendations:
NDA – None
ANDA – None

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

10. Citizen Petition
There is a citizen petition pending for enoxaparin sodium injection (Docket 03-P-0065-CP1) submitted on February 19, 2003 by Covington & Burling on behalf of Aventis Pharmaceuticals. Response pending.

Summary: Petition requests that FDA withhold approval of any ANDA for a generic Lovenox until enoxaparin is fully characterized, unless manufacturing process is equivalent to Aventis' or applicant demonstrates S&E thru clinical trials

---

Date of Review: November 2, 2009 Date of Submission: October 21, 2009

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

ANDA: 077857

Following this page, 25 pages withheld in full - (b)(4) Draft Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

CHI-ANN Y WU
11/23/2009

LILLIE D GOLSON
11/23/2009

Supersedes the approval summary signed off 11/23/09

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 077857

Date of Submissions: December 30, 2009 (amendment)

Applicant's Name: Sandoz, Inc.

Established Name: Enoxaparin Sodium Injection USP, 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   There is a note to the chemist pending*

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT
   Satisfactory in final print as submitted in the December 30, 2009 amendment.

Revisions needed post-approval: Yes. The following post-approval editorial changes will be emailed to the firm after the ANDA has been approved:

- Add a vertical line on the left edge for new or modified text listed under “Recent Major Changes” [refer to 21 CFR 201.57(d)(9)].
- 6.1: "Thrombocytopenia [see Warnings and Precautions (5.5)]"

NOTE TO CHEMIST:

From: Ya, Naiqi
Sent: Wednesday, January 06, 2010 3:14 PM
To: Wu, Ruby (Chi-Ann)
Cc: Raw, Andre; Lee, Sau; Hinchliffe, Thomas; Golson, Lillie D
Subject: RE: 77-857 Sandoz

Hi Ruby,

Larry and I checked the firm's ANDA again and found that a test for accuracy of syringes is included in the release specification for the packaging materials. It's acceptable from the CMC point view.

Thanks,

Naiqi

From: Lee, Sau
Sent: Saturday, October 11, 2008 11:09 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Ruby,

I mentioned to Naiqi last time. I will follow up and let you know.

Regards,
Larry

****
Sau (Lawrence) Lee, Ph.D.
Chemical Engineer
Food and Drug Administration
Office of Generic Drugs
7519 Standish Place
Rockville, MD 20855
Phone: 240-276-9321
****

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 09, 2008 2:50 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Larry,

Any updates?

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, July 09, 2008 1:22 PM
To: Lee, Sau; Ya, Naiqi
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Hi Larry,

I'm inquiring about the prefilled syringe (single-use). The syringe has graduated markings and I was wonderful if the markings are accurate.

Ruby

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To: Ya, Naiqi; Wu, Ruby (Chi-Ann)
Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

Ruby,

We haven't review the multiple-use dosage form yet.

Larry

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, July 03, 2008 9:48 AM
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Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

HI Naiqi,

Please confirm if the graduated markings are accurate.

Thanks,

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 28, 2007 9:21 AM
To: Wu, Ruby (Chi-Ann); Ya, Naiqi
Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

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Subject: 77-857 Sandoz

Sandoz's graduated markings are not on the syringe itself...but on a label...refer to EDR, 7/6/06 submission, "graduation labels". Can you also verify the graduated markings are accurate:

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA NDA 020164/S-085 approved December 23, 2009. This “Prior Approval” supplemental new drug application provides for revisions to the boxed warning, recent major changes and warnings and precautions sections of package insert.

   The products in this ANDA do not contain benzyl alcohol. Therefore, statement regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling.

   USP 32 monograph (checked 1/5/10)
   According to the USP bulletin (http://www.usp.org/USPNF/notices/enoxaparinSodiumInjectionApril2009.html), the monograph became official December 1, 2009

   Enoxaparin Sodium Injection
   Packaging and storage— Preserve in single-dose or multiple-dose containers in Type I glass. Store between 20 and 25 , excursions permitted between 15 and 30 .
   Labeling— Label it to indicate the amount (mg) of Enoxaparin Sodium in the total volume of contents. The label states also that the Enoxaparin Sodium starting material is porcine derived.

   From: Wu, Ruby (Chi-Ann)
   Sent: Thursday, November 20, 2008 8:53 AM
   To: 'caryn.mccullough@sandoz.com'
   Cc: Hinchliffe, Thomas

Subject: RE: Enoxaparin - ANDA 77-857

Good morning Caryn,

Adding "USP" to the established name is an annual reportable change. Please send a new correspondence to your ANDA with a commitment to add "USP" post-approval.

Thanks,

Ruby

From: caryn.mccullough@sandoz.com [mailto:caryn.mccullough@sandoz.com]
Sent: Wednesday, November 19, 2008 4:52 PM
To: Wu, Ruby (Chi-Ann)
Subject: Enoxaparin - ANDA 77-857

Hi Ruby,

We have a question regarding the USP designation for Enoxaparin Sodium Injection. The USP monograph goes in to effect on December 1st, but our labels currently do not include the USP designation. Will we be expected to update our labeling now, or can we launch with product after December 1st that is not labeled as USP? Our product meets the USP requirements.

Thanks for your help.

Caryn

Caryn McCullough
Regulatory Affairs

REMS: none (checked 1/5/10)
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

2. PATENT and EXCLUSIVITY

Patent Data – NDA 020164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	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	IV	None
RE38743	2/14/12	U-545		IV	

Exclusivity Data– NDA 020164

Code	Reference	Expiration	Labeling Impact
I-533/S-075	ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)	*MAY 16,2010*	***Carve-out*** *per June 13, 2008 amendment*

STEMI is protected by exclusivity I-533. The route of administration for all other indications is SC. For STEMI, the drug product may be administered IV or SC. Sandoz is choosing to carve-out the indication for STEMI. Therefore, Sandoz carved-out all information pertaining to the IV administration of the drug product.

MQ Notes:

- 10/2/06 PA: Rc'd ltr dated 9/8/06 for notice of PIV cert sent 6/22/06 on patents '618 and '743. RR received 6/26/06. Litigation filed in U.S. Court 8/4/06 on both patents. IM
- 7/7/06 PA: Rc'd ltr dated 6/22/06 for patent amendment for '618 and '743 patents. Change from PIII to PIV. Both expire 2/14/12. Awaiting notice of RR./IM

3. Manufacturer-
Baxter Pharmaceutical Solutions LLC
Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes,
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
300 mg/3mL multiple dose vial;
150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

The ANDA is proposing the following strengths;
100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]

7. Dispensing Recommendations:
NDA – None
ANDA – None

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for our review. ***(chemist needs to verify if the calibrations are accurate)***

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

10. Citizen Petition
There is a citizen petition pending for enoxaparin sodium injection (Docket 03-P-0065-CP1) submitted on February 19, 2003 by Covington & Burling on behalf of Aventis Pharmaceuticals. Response pending.

Summary: Petition requests that FDA withhold approval of any ANDA for a generic Lovenox until enoxaparin is fully characterized, unless manufacturing process is equivalent to Aventis' or applicant demonstrates S&E thru clinical trials

---

Date of Review: January 5, 2010 Date of Submission: December 30, 2009

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

Following this page, 25 pages withheld in full - (b)(4) Draft Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

CHI-ANN Y WU
01/13/2010

LILLIE D GOLSON
01/13/2010

Supersedes the approval summary signed off 1/13/10

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 077857
Date of Submission: April 28, 2010 (amendment)
Applicant's Name: Sandoz, Inc.
Established Name: Enoxaparin Sodium Injection USP, 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

APPROVAL SUMMARY

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Do you have Final Printed Labels and Labeling? Yes

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT

The indication for STEMI is protected by exclusivity I-533 which expires May 16, 2010.

CIRCUMSTANCE	INSERT THAT WILL BE USED ON THE COMMERCIAL BATCH
ANDA is approved BEFORE the expiration of the STEMI exclusivity	Insert submitted on December 30, 2009 that does NOT include info specific to the STEMI indication.
ANDA is approved AFTER the expiration of the STEMI exclusivity	Insert submitted on April 28, 2010 that DOES include info specific to the STEMI indication.

Revisions needed post-approval: Yes. The following post-approval changes will be emailed to the firm (caryn.mccullough@sandoz.com) after the review has been signed off.

Please make the following revisions to the insert labeling submitted on April 28, 2010. Revised labeling should be submitted as a "Supplement-Changes Being Effected".

- Add a vertical line on the left edge for new or modified text listed under "Recent Major Changes" [refer to 21 CFR 201.57(d)(9)].
- 2.4 Administration: Please add the following as the second paragraph- "The use of a tuberculin syringe or equivalent is recommended when using enoxaparin sodium injection multiple-dose vials to assure withdrawal of the appropriate volume of drug."
- 3 Dosage Forms and Strength: revise "XX mg/1 mL" to read "XX mg/mL"

*** The treatment of STEMI may involve IV bolus administration of the drug product using the multi-dose vial, followed by subcutaneous injections. Sandoz has carved-out information pertaining to benzyl alcohol warnings since the prefilled syringes do not contain benzyl alcohol. However, information pertaining to the use of MDV and IV bolus administration is helpful…Sandoz has left most of this information in, except for the sentence above in section 2.4. Therefore, we'll ask Sandoz to add the information back.*

NOTE TO CHEMIST:

From: Ya, Naiqi
Sent: Wednesday, January 06, 2010 3:14 PM
To: Wu, Ruby (Chi-Ann)
Cc: Raw, Andre; Lee, Sau; Hinchliffe, Thomas; Golson, Lillie D
Subject: RE: 77-857 Sandoz

Hi Ruby,

Larry and I checked the firm's ANDA again and found that a test for accuracy of syringes is included in the release specification for the packaging materials. It's acceptable from the CMC point view.

Thanks,

Naiqi

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Cc: Raw, Andre
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Hi Ruby,

I mentioned to Naiqi last time. I will follow up and let you know.

Regards,
Larry

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Sau (Lawrence) Lee, Ph.D.
Chemical Engineer
Food and Drug Administration
Office of Generic Drugs
7519 Standish Place
Rockville, MD 20855
Phone: 240-276-9321
****

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Cc: Raw, Andre
Subject: RE: 77-857 Sandoz

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Any updates?

Ruby

From: Wu, Ruby (Chi-Ann)
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Cc: Raw, Andre
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We haven't review the multiple-use dosage form yet.

Larry

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Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

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Ruby

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Cc: Hinchliffe, Thomas
Subject: RE: 77-857 Sandoz

Can you confirm if this has been addressed? Once the firm submits the insert labeling correctly, I should be able to write up an approval summary...

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, November 02, 2006 3:10 PM
To: Ya, Naiqi
Subject: 77-857 Sandoz

Sandoz's graduated markings are not on the syringe itself...but on a label...refer to EDR, 7/6/06 submission, "graduation labels". Can you also verify the graduated markings are accurate:

- 60, 80, and 100 mg strengths: Each Graduation = 2.5 mg (0.025 mL)
- 120 and 150 mg strengths: Each Graduation = 3 mg (0.02 mL)

FOR THE RECORD:

1. Review based on the labeling of Lovenox ® Injection, NDA NDA 020164/S-085 approved December 23, 2009. This “Prior Approval” supplemental new drug application provides for revisions to the boxed warning, recent major changes and warnings and precautions sections of package insert.

   Sandoz's prefilled syringes do not contain benzyl alcohol. Therefore, statements regarding hypersensitivity to benzyl alcohol is not required in Sandoz's labeling.

   USP 32 monograph (checked 4/29/10)
   According to the USP bulletin (http://www.usp.org/USPNF/notices/enoxaparinSodiumInjectionApril2009.html), the monograph became official December 1, 2009

   Enoxaparin Sodium Injection
   Packaging and storage— Preserve in single-dose or multiple-dose containers in Type I glass. Store between 20 and 25 , excursions permitted between 15 and 30 .
   Labeling— Label it to indicate the amount (mg) of Enoxaparin Sodium in the total volume of contents. The label states also that the Enoxaparin Sodium starting material is porcine derived.

   From: Wu, Ruby (Chi-Ann)
   Sent: Thursday, November 20, 2008 8:53 AM
   To: 'caryn.mccullough@sandoz.com'
   Cc: Hinchliffe, Thomas

Subject: RE: Enoxaparin - ANDA 77-857

Good morning Caryn,

Adding "USP" to the established name is an annual reportable change. Please send a new correspondence to your ANDA with a commitment to add "USP" post-approval.

Thanks,

Ruby

From: caryn.mccullough@sandoz.com [mailto:caryn.mccullough@sandoz.com]
Sent: Wednesday, November 19, 2008 4:52 PM
To: Wu, Ruby (Chi-Ann)
Subject: Enoxaparin - ANDA 77-857

Hi Ruby,

We have a question regarding the USP designation for Enoxaparin Sodium Injection. The USP monograph goes in to effect on December 1st, but our labels currently do not include the USP designation. Will we be expected to update our labeling now, or can we launch with product after December 1st that is not labeled as USP? Our product meets the USP requirements.

Thanks for your help.

Caryn

Caryn McCullough
Regulatory Affairs

REMS: none (checked 4/29/10)
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

2. PATENT and EXCLUSIVITY

Patent Data – NDA 020164

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5389618	2/14/12	U-545	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	IV	None
RE38743	2/14/12	U-545		IV	

MQ Notes:

- 10/2/06 PA: Rc'd ltr dated 9/8/06 for notice of PIV cert sent 6/22/06 on patents '618 and '743. RR received 6/26/06. Litigation filed in U.S. Court 8/4/06 on both patents. IM
- 7/7/06 PA: Rc'd ltr dated 6/22/06 for patent amendment for '618 and '743 patents. Change from PIII to PIV. Both expire 2/14/12. Awaiting notice of RR./IM

Exclusivity Data– NDA 020164

Code	Reference	Expiration	Labeling Impact
I-533/S-075	ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)	*MAY 16,2010*	*Carve-out per June 13, 2008 amendment. See April 28, 2010 amendment below.*

STEMI is protected by exclusivity I-533. The route of administration for all other indications is SC. For STEMI, the drug product may be administered IV or SC. Sandoz is choosing to carve-out the indication for STEMI. Therefore, Sandoz carved-out all information pertaining to the IV administration of the drug product. However, if

the ANDA is approved after the expiration of I-533, the firm has committed (in the April 28, 2010 amendment) to use insert that does include the STEMI indication.

April 28, 2010 amendment: In this amendment, the firm provided revised labeling to include information pertaining to STEMI.

CIRCUMSTANCE	INSERT THAT WILL BE USED ON THE COMMERCIAL BATCH
ANDA is approved BEFORE the expiration of the STEMI exclusivity	Insert submitted on December 30, 2009 that does NOT include info specific to the STEMI indication.
ANDA is approved AFTER the expiration of the STEMI exclusivity	Insert submitted on April 28, 2010 that DOES include info specific to the STEMI indication.

The physician insert labeling for this product has been revised to include information on Exclusivity Code I-533 which will be expiring May 16, 2010. Sandoz labeling previously did not include information pertaining to Exclusivity Code I-533, ST-segment Elevation Myocardial Infarction (STEMI). Since this exclusivity expires soon, we have revised our insert to include all text related to STEMI. However, Sandoz will not use this labeling until after the exclusivity has expired. If Sandoz should get approval of its application prior to May 16, 2010, we will withdraw this labeling amendment and use our currently filed labeling that does not include the STEMI indication information.

3. Manufacturer-
Baxter Pharmaceutical Solutions LLC
Bloomington IN 47403 [Vol. A1.4, pg. 1412]

4. The RLD is available in the following strengths:
100mg/mL - 30 mg/0.3mL ampules, 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes,
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
300 mg/3mL multiple dose vial;
150 mg/mL- 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

The ANDA is proposing the following strengths;
100mg/mL- 30 mg/0.3mL and 40 mg/0.4mL-prefilled syringes
60 mg/0.6mL, 80 mg/0.8mL, 100 mg/mL graduated prefilled syringes
150 mg/mL - 120 mg/0.8 mL, 150 mg/mL graduated prefilled syringes

5. The inactives are accurately listed in the DESCRIPTION section
Components: Enoxaparin, water for injection, (b) (4) [Vol. A1.1, pg. 387]

6. Storage Conditions:
NDA – Store at 25 °C(77 °F); excursions permitted to15°-30°C (59°-86°F). [see USP].
ANDA – Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]

7. Dispensing Recommendations:
NDA – None
ANDA – None

8. Container Closure -
Container- 1 mL clear glass, type 1, 27 ga 1/2 inch
Closure- 1 mL long stopper black (b) (4)
"The primary packaging component consist of a type 1 glass syringe with a fixed needle and rigid needle shield and a stopper, a plunger rod is applied to the stopper. A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths. A (b) (4) safety needle shield is (b) (4) on each syringe. ..Each syringe is individually packaged in a thermoform tray with a paper lid. Ten syringes are (b) (4) packaged in a carton." [Vol. A1.7, pg. 3137]
Calibration:
RLD: The RLD has the calibrations on the syringe itself.
ANDA: Sandoz submitted the labels with the calibrations for CMC review.

9. Finished Product Description-
Clear, colorless to pale yellow solution essentially free from visible particulate matter [Vol. A1.7, pg. 3222]

10. Citizen Petition
There is a citizen petition pending for enoxaparin sodium injection (Docket 03-P-0065-CP1) submitted on February 19, 2003 by Covington & Burling on behalf of Aventis Pharmaceuticals. Response pending.

Summary: Petition requests that FDA withhold approval of any ANDA for a generic Lovenox until enoxaparin is fully characterized, unless manufacturing process is equivalent to Aventis' or applicant demonstrates S&E thru clinical trials

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Date of Review: April 29, 2010 Date of Submission: April 28, 2010

Primary Reviewer: Ruby Wu

Team Leader: Lillie Golson

ANDA: 077857

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

CHI-ANN Y WU
05/05/2010

LILLIE D GOLSON
05/05/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

CHEMISTRY REVIEWS

ANDA 77-857

Enoxaparin Sodium Injection, 100 mg/mL and 150 mg/mL

Sandoz Inc.

Sau Lawrence Lee, Ph.D
Immediate Office/Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-857

2. REVIEW #: 1

3. REVIEW DATE: March 31, 2006:

4. REVIEWER: Sau Lawrence Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August-26-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	2555 West Midway Blvd. Broomfield, CO 80020
Representative:	Beth Brannan, Director, Regulatory Affairs Director, Regulatory Affairs
Telephone:	(720) 810-0129
Fax:	(303) 438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Enoxaparin Sodium
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only): N/A

- Chem. Type: N/A
- Submission Priority: N/A

9. LEGAL BASIS FOR SUBMISSION:

Lovenox® Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120/0.8 mL and 150 mg/mL) are the reference listed drug held by Aventis Pharmaceuticals, Inc. (Sanofi-Aventis) (NDA 20-164).

Sandoz certifies that U.S. Patents 5,389,618 and RE38,743 will both expire on February 14, 2012. The applicant requests approval of this ANDA effective after expiration of these patents (Paragraph III Certification).

Sandoz certifies that there are no listed exclusivities for the referenced product.

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, and 100 mg/mL)
150 mg/mL (120/0.8 mL and 150 mg/mL)

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

___X___SPOTS product – Form Completed

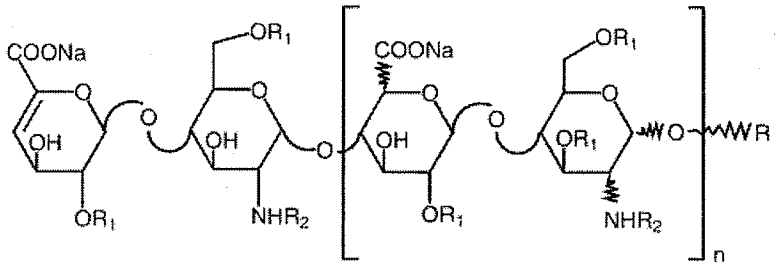
_____Not a SPOTS product

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

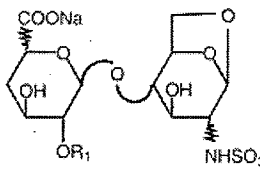
Chemical Name: Enoxaparin Sodium

Molecular Weight Distribution: < 2000 Da: 12.0–20.0%
2000–8000 Da: 68.0–82.0%
> 8000 Da: ≤ 18%

Structural Formula:



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

R	X* = 15 to 25%		n = 0 to 20
	100 - X	II	n = 1 to 21

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
18557	II	Sandoz GmbH	Heparin Sodium	7			Defer review

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Microbiology	Pending		
EES	Withhold	6-12-06	J.D. Ambrogio
Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Pending		
EA	Not Applicable		
Radiopharmaceutical	Not Applicable		

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:

Chemistry Review for ANDA 77-857

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Drug Substance

Due to the heterogeneous nature of enoxaparin sodium, the compendial standards for enoxaparin (as defined by the European Pharmacopeia (EP), British Pharmacopeia (BP), and U.S. Pharmacopeia-Pharmacopeial Forum (USP-PF)) are not sufficient to ensure pharmaceutical equivalence of a generic enoxaparin to the reference listed drug (RLD). For these reasons, OGD prescribes additional standards that are material to "sameness" of the drug substance. OGD concludes that based on the aggregate weight of scientific evidence, a proposed generic enoxaparin product has the same active ingredient as that in Lovenox if the proposed product meets the following five criteria:

- Equivalence of physicochemical properties
- Equivalence of heparin starting material and in mode of depolymerization
- Equivalence in disaccharide building blocks, sequence of oligosaccharide species, and fragment mapping
- Equivalence in biochemical and biological assays
- Equivalence of in-vivo pharmacodynamic profiles

Although the sponsor has provided a substantial amount of data to demonstrate the chemical equivalence of its proposed generic drug product and Lovenox® (RLD), additional information is needed in order to equivocally show the drug substance sameness, as defined by the five criteria listed above. This information should include:

- (b) (4)

In addition, the Office of Generic Drugs (OGD) has the following recommendations:

- [redacted] (b) (4)

In light of the magnitude of issues pertaining to the drug substance that can impact the drug safety and efficacy, the application is ***not approvable*** due to deficiencies listed above.

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

Not Applicable

II. Summary of Chemistry Assessments

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

Since enoxaparin sodium is produced by alkaline depolymerization of heparin sodium, it shares the characteristics of a basic structure of heparin sodium. Enoxaparin sodium is a heterogeneous mixture of oligosaccharides, consisting of variably repeating disaccharide units. Similar to heparin sodium, each disaccharide unit is comprised of an uronic acid (D-glyucuronic or L-iduronic) linked to D-glucosamine via 1-4 glycosidic bond. Four positions of the disaccharide unit can be chemically modified. 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.

Unlike heparin sodium, enoxaparin 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 chemical modifications provide an additional dimension of heterogeneity that is not present in heparin sodium, since they are a direct result of the cleavage reaction used to produce enoxaparin sodium.

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 ex-

pressed 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 Da:	≤20%
2000 to 8000 Da:	≥68%
>8000 Da:	≤18%

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/mL, 120 mg/0.8 mL, and 150 mg/mL. The drug product contains enoxaparin sodium (active ingredient), water for injection, (b) (4) (b) (4). All strengths are packaged in pre-filled syringes.

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

Enoxaparin sodium injection 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.

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

Enoxaparin sodium injection 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.

C. Basis for Approvability or Not-Approval Recommendation:

One (or two) paragraph summary of major deficiencies cited

Following this page, 46 pages withheld in full - (b)(4)

III. List Of Deficiencies To Be Communicated

ANDA: 77-857 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Enoxaparin Sodium, 100 mg/mL ad 150 mg/mL

The deficiencies presented below represent MAJOR deficiencies.

1. The following deficiencies have been identified with respect to the information provided regarding drug substance "sameness" of your proposed enoxaparin sodium to Lovenox.

a. (b) (4)

b.

c.

d.

e.

f.

g. (b) (4)

h.

i.

j.

2. (b) (4)

Please be advised that the review of the remainder of the application is deferred until the submission of the information on the active ingredient as requested above.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-857 Original
ANDA 77-857 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-600/SLee/ Signature 7/5/06
HFD-600/ARaw/ 7/5/06
HFD-640/NYa/6/26/06 7/5/06
HFD-640/THinchliffe/Y.Kong for THinchliffe 7/6/06

F/T by /rad6/28/06

V:\FIRMSNZ\Sandoz\ltrs&rev\77857rev1.doc

TYPE OF LETTER: NOT APPROVABLE - MAJOR

ANDA 77-857

Enoxaparin Sodium Injection

Sandoz Inc.

Sau Lawrence Lee, Ph.D.
Office of Generic Drugs
Immediate Office

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-857

2. REVIEW #: 2

3. REVIEW DATE: March 30, 2006

4. REVIEWER: Sau Lawrence Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	August 29, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August 26, 2005
Major Amendment	August 31, 2006
Telephone Amendment	October 05, 2006
Telephone Amendment	November 9, 2006
Telephone Amendment	November 29, 2006
Telephone Amendment	March 23, 2007
Telephone Amendment	March 26, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	2555 West Midway Blvd. Broomfield, CO 80020
Representative:	Beth Brannan Director, Regulatory Affairs
Telephone:	(720) 810-0129

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:

Lovenox® Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120/0.8 mL and 150 mg/mL) are the reference listed drug held by Aventis Pharmaceuticals, Inc. (Sanofi-Aventis) (NDA 20-164).

Sandoz certifies that U.S. Patents 5,389,618 and RE38,743 will both expire on February 14, 2012. The applicant requests approval of this ANDA effective after expiration of these patents (Paragraph III Certification).

Sandoz certifies that there are no listed exclusivities for the referenced product.

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, and 100 mg/mL.

150 mg/mL: 120/0.8 mL and 150 mg/mL.

13. ROUTE OF ADMINISTRATION:

14. Rx/OTC DISPENSED: __X_ Rx ___OTC

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

_____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
18557	II	Sandoz GmbH	Heparin Sodium	7	Pending		Minor deficiencies issued
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	May 18, 2005	The DMF (b) (4) was reviewed by A. Al-Hakim and was found to be adequate.

[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

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	11/01/05	J.D. Ambrogio
Methods Validation	Acceptable	03/26/07	S.L. Lee
Labeling	Acceptable	03/05/07	R. Wu
Bioequivalence	Acceptable	11/17/06	Z.Z. Wahba
EA	Not Applicable		

Radiopharmaceutical	Not Applicable		

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 77-857

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Pending.

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

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.

---

[1] There are four approved NDAs for LMWHs: Lovenox (enoxaparin sodium) (NDA # 20-164), Fragmin (dalteparin sodium) (NDA # 20-287), Normiflo (ardeparin sodium) (NDA # 20-227) (withdrawn in 2001 at the request of the manufacturer) and Innohep (tinzaparin sodium) (NDA # 20-484). The active ingredients in these LMWH products are derived from different modes of depolymerization yielding drug products containing active 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 ingredients.

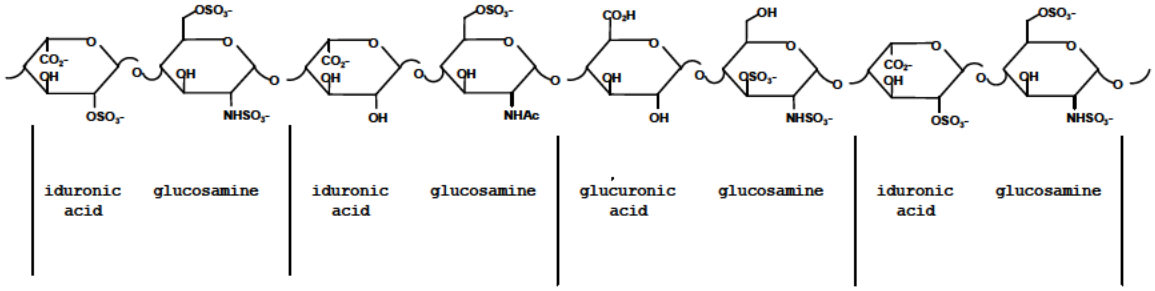
[2] Linhardt et al., *Semin. Thromb. Hemost.* (1999) 25 S3:5-16.

[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 the 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 1-4 glycosidic bond. Four positions of the disaccharide unit can be chemically modified. 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]$_n$.

However, unlike heparin sodium, enoxaparin sodium has a distinctly different molecular weight distribution and a different ratio of Anti-Xa and Anti-IIa activities. In addition, it has unique chemical modifications (or fingerprints) at the terminal ends of a chain, 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 is not present in heparin sodium. However, the clinical relevance of these chemical fingerprints is not known.

Based upon the above description, the heterogeneity of enoxaparin sodium comes from 1) polydispersity of the chain length, 2) the chemical diversity associated with the modified disaccharide units, and 3) the chemical diversity 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-Xa activity/mg and as anti-Xa/anti-IIa activity ratio. The weight-average molecular weight is about 4500 daltons (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/mL, 120 mg/0.8 mL, and 150 mg/mL. The drug product contains enoxaparin sodium (active ingredient), water for injection, (b) (4) (b) (4) All strengths are packaged in pre-filled syringes.

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

Enoxaparin sodium injection 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.

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

Enoxaparin sodium injection 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.

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 DMF 18557 for the heparin starting material is adequate. The specifications for the heparin sodium include all essential tests per USP criteria. The main impurities associated with the heparin starting material, such as (b) (4) and (b) (4) (b) (4), were monitored and controlled.

The applicant has demonstrated a good understanding of the drug substance manufacturing process and critical process parameters.

The drug substance release specifications include all critical attributes of enoxaparin sodium.

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.

The drug product specifications include all the essential tests. The proposed tests and acceptance criteria for the drug product are based upon the USP-PF. It is found to be adequate. When the proposed USP monograph becomes official, the applicant commits to comply with all USP compendial specifications pertaining to the drug product.

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.

The approval of this applicant is pending due to minor deficiencies in microbiology and DMF for the heparin starting material.

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II. Administrative

A. Reviewer's Signature

B. Endorsement Block

SLee/10-23-06
ARaw/10-23-06
NYa/10-23-06

C. CC Block

Outside Firms Including Contract Testing Laboratories

Site	Function
Momenta Pharmaceuticals Inc. 675 West Kendall Street Cambridge, MA 02142	Perform the primary and secondary characterization tests for demonstrating drug substance sameness.
Baxter Pharmaceutical Solutions LLC 927 S. Curry Pike Road Bloomington, IN 47402	Manufactured drug product. Performed and/or may perform testing of drug substance, excipients, drug product, and drug product stability testing.
	(b) (4)

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

SAU L LEE
05/24/2010

ANDRE S RAW
05/25/2010

THOMAS O HINCHLIFFE
07/20/2010

NAIQI YA
07/20/2010

ANDA 077857

Enoxaparin Sodium Injection

Sandoz Inc.

Sau (Larry) Lee, Ph.D.
Science Staff, Immediate Office
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 077857

2. REVIEW: #3

3. REVIEW DATE: July 19, 2010

4. REVIEWER: Sau (Larry) Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	August 26, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August 26, 2005
Amendment	August 31, 2006
Amendment	October 05, 2006
Amendment	November 9, 2006
Amendment	November 29, 2006
Amendment	March 23, 2007
Amendment	March 26, 2007
Amendment	September 19, 2007
Amendment	June 2, 2008
Amendment	September 23, 2008
Amendment	November 20, 2008
Amendment	November 21, 2008
Amendment	December 12, 2008
Amendment	February 27, 2009
Amendment	March 2, 2009
Amendment	June 19, 2009
Amendment	June 25, 2009
Amendment	August 06, 2009
Amendment	September 30, 2009
Amendment	October 7, 2009
Amendment	December 01, 2009

Amendment	January 13, 2010
Amendment	January 28, 2010
Amendment	May 26, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	2555 West Midway Blvd. Broomfield, CO 80020
Representative:	Jean Domenico Manager Manager, Regulatory Affairs
Telephone:	(303) 438-4242
Fax:	(303) 438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:

ANDA submitted on 8/29/2005, BOS=Lovenox Injection NDA 20164, PII to '435, PIII to '618 and 'RE743. ANDA ack for filing on 8/29/2005(LO dated 10/24/2005), strengths accepted are 100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL pfs and 150 mg/mL, 0.8 mL and 1 mL pfs. Patent amendment submitted on 6/23/2006-Sandoz amends from PIII to PIV on the '618 and 'RE743. Patent Amendment submitted on 9/11/2006-RR from Sanofi Aventis in Bridgewater, NJ, notice also sent via DHL to Sanofi Aventis in Paris France with notice delivered on 6/26/2006 signed and dated 6/26/2006, suit filed in the D of NJ on 8/4/2006 for infringement of the 'RE743, CA #06-CV-3671. On 1/3/2007 the sponsor submitted a PIV cert to the '445 patent(not a listed patent), Sandoz continued to provide serial certifications to this patent through 3/9/2007. On 6/16/2008 the firm provided a revised exclusivity statement which communicated their intent to omit claims related to the I-533 exclusivity. Patent amendment submitted on 9/17/2008-Sandoz informs the Agency that CA 06-3671 from the D of NJ was transferred to CA and assigned case # 07-2558, Sandoz provided copies of signed court orders dated 8/28/2008 in which Sandoz Motion for Summary Judgment of Unenforceability was granted and final judgment with prejudice in favor of Sandoz was entered, these orders applied to CA #07-2558 and 06-4858 both in the D of CA, Central District. OGD notes that the orders entered by the DC of CA were dated after the Judgement was entered by the CAFC in Sanofi v. Amphastar and TEVA in which the court entered the order on 5/14/2008. The mandate associated with the CAFC ruling was issued on 10/2/2008 which finalized the order. This issuance of the mandate served as a

trigger of 180 day exclusivity. Minimally the issuance of the Mandate triggered the 180 day exclusivity of Amphastar which is associated with the '618 patent.

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: Subcutaneous and intravenous

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
018557	II	Sandoz GmbH	Heparin Sodium	1	Adequate	December 16, 2009	
(b) (4)	II	(b) (4)		1	Adequate	May 18, 2005	

		(b) (4)			(CMC) January 18, 2008 (MICRO)	

[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

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	02/04/08	P. Dexter
EES	Acceptable	07/15/10	N.L. Rolli
Methods Validation	Acceptable	01/30/10	S.L. Lee
Labeling	Acceptable	03/05/07	R. Wu
Bioequivalence	Acceptable	11/17/06	Z.Z. Wahba
Immunogenicity	Acceptable	09/22/09	S. Verthelyi
EA	Acceptable (categorical exclusion)	01/30/10	S.L. Lee
Radiopharmaceutical	Not Applicable		

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 077857

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC perspective.

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

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) (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 (APIs) 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.

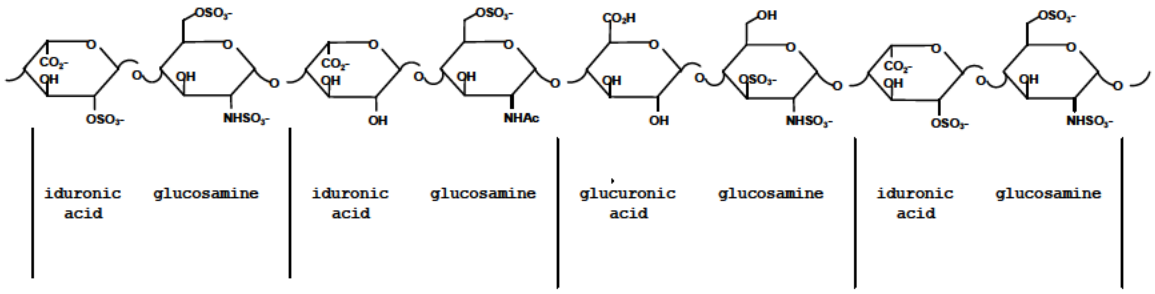
[2] Linhardt et al., *Semin. Thromb. Hemost.* (1999) 25 S3:5-16.

[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 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 the 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 building blocks and vary in the chain length and sequence. Each disaccharide building block is comprised of an uronic acid (D-glucuronic or L-iduronic) linked to D-glucosamine via 1-4 glycosidic bond. Four possible positions of the disaccharide unit can be chemically modified. For example, 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 building blocks present in heparin. These repeating units are composed of glucosamine and 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 distinct molecular weight distribution and ratio of Anti-factor Xa and Anti-factor IIa activities. In addition, enoxaparin sodium has unique chemical modifications (or fingerprints) at the terminal ends of a chain, such as $\Delta^{4,5}$-uronate structure at the non-reducing and 1,6-anhydro ring structure at the reducing ends, respectively. These unique chemical modifications at the terminal ends of the chains can be related to the cleavage reaction used to manufacture enoxaparin sodium and the manufacturing conditions.[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 modified chemical fingerprints is currently not known.

Based upon the above description, the heterogeneity of enoxaparin sodium comes from 1) the polydispersity of the chain length, 2) the chemical heterogeneity associated with the "modified" disaccharide building blocks, and 3) the chemical heterogeneity of the "natural" disaccharide building blocks and their corresponding sequences in internal

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

main chains. Demonstration of drug substance sameness must take into consideration the heterogeneity associated with enoxaparin sodium drug substance.

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, Water for Injection, USP, (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 (enoxaparin sodium) in the proposed enoxaparin sodium injection drug product was shown to be equivalent[7] to that in the reference listed drug (RLD), Lovenox, by meeting the following criteria:

- Equivalence of physicochemical properties, including molecular weight distribution and chain mapping
- Equivalence of heparin source material and mode of depolymerization
- Equivalence in disaccharide building blocks, fragment mapping, sequence of oligosaccharides
- Equivalence in biochemical and biological assays
- Equivalence of *in vivo* pharmacodynamic profiles

The analytical methods used to demonstrate equivalence of the proposed enoxaparin sodium and Lovenox were validated, including their specificity (negative controls) and precision (intermediate precision).

The Sandoz GmbH heparin source material ("Heparin Sodium, USP") described in Drug Master File (DMF 18557) is adequate for use as a raw material in the manufacture of a generic version of Lovenox (b) (4). The release tests and specifications for the Sandoz GmbH heparin source material comply with the current USP monograph for heparin sodium.

The ANDA 077857 applicant demonstrated an adequate understanding of the manufacturing process of enoxaparin sodium drug substance and an adequate control of critical process parameters.

[7] Section 505(j)(2)(A)(ii)(I) of the Act states that an ANDA must contain information to show that the active ingredient[7] of the generic drug product is the "same" as that of the listed drug.

The drug substance release tests and specifications include critical attributes of enoxaparin sodium and comply with all USP specifications pertaining to enoxaparin sodium.

With regard to the drug product, as this is a relatively simple formulation which is qualitatively (Q_1) and quantitatively (Q_2) the same as the RLD (contains the active ingredients dissolved in water), the drug product manufacturing process does not affect the drug substance identity.

The drug product release tests and specifications include critical attributes of enoxaparin sodium injection and comply with all USP specifications pertaining to enoxaparin sodium injection.

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

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

SAU L LEE
07/19/2010

ANDRE S RAW
07/19/2010

NAIQI YA
07/19/2010

THOMAS O HINCHLIFFE
07/20/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-857
Drug Product Name	Enoxaparin Sodium Injection
Strengths	100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL), and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL)
Applicant Name	Sandoz Inc.
Contact Information	Bet Brannan 2555 West Midway Blvd Broomfield, CO 80020 Phone 303-438-4237 Fax 303-438-4600
Submission Date(s)	08/26/06
Amendment Date(s)	09/07/06
Reviewer	Z.Z. Wahba, Ph.D.
First Generic	No

Review of an Amendment

I. Executive Summary

This is a review of a fasting in vivo bioequivalence (BE) study. This application references the reference listed drug (RLD) Lovenox® (Enoxaparin Sodium Injection) Injection, 100 mg/mL and 150 mg/mL. The BE study was a two-way crossover design, comparing a dose of 1x100 mg/mL of the test and reference products in healthy adult males and females (n = 38). The firm requests waiver for in vivo BE studies on the 150 mg/mL strength.

The firm has provided the statistical analysis of the in vivo pharmacodynamic markers of the drug, anti-factor Xa, anti-factor IIa, Heptest® and aPTT, with anti-factor Xa being the primary endpoint.

The results (point estimate, 90% CI) of the fasting BE study for the primary endpoint, anti-factor Xa are LAUCt of 1.13, 111.56-114.21%; LAUCi of 1.12, 110.85-113.54%; and LCmax of 1.11, 105.94-115.84%.

The formulation for the 150 mg/mL strength is proportionally similar to the 100 mg/mL strength which underwent bioequivalence study. However, request for waiver of in vivo biostudy on the 150 mg/mL strength is not granted at this time as the BE study is deficient.

The application is **incomplete** due to several deficiencies cited in the deficiency section of this review.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Enoxaparin Sodium Injection, 100 mg/mL &150 mg/mL
Reference Product	Lovenox® (enoxaparin sodium) Injection, 100 mg/mL &150 mg/mL
RLD Manufacturer	Aventis Pharma
NDA No.	20-164
RLD Approval Date	01-23-03
Indication	Indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism; indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin; and indicated for: the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium, and the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

B. PK/PD Information

Enoxaparin is a low molecular weight heparin (LMWH) obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Low Molecular Weight Heparins

are administered via subcutaneous injection and in contrast to heparin, possess a longer half-life, more predictable anticoagulant response, and reduced side effects.

Bioavailability	92%
Food Effect	N/A
Tmax	1-5 hours
Metabolism	Metabolized in the liver with metabolites unidentified.
Excretion	Excreted in the urine as unchanged drug and metabolites
Half-life	4-5 hours
Relevant OGD or DBE History	The DBE drug file contains two applications (ANDA 76-684, Amphastar; and ANDA (b) (4)); and a citizen petition (Docket No. 03P-0064/CP).

The OGD current requirements for demonstrating the pharmaceutical equivalence ("sameness") between a generic drug formulation and the RLD product of this drug are as follows (per the Chemistry Deficiency letter to Amphastar - ANDA 76-684, dated October 17, 2003, see below the communicated deficiency comments):

1) Equivalence of physico-chemical properties

   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.

2) Equivalence of heparin starting material and in the chemical selectivity of depolymerization, as per the drug product labeling

   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.

3) Equivalence in disaccharide building blocks

   Equivalence in disaccharide building blocks may be achieved by compositional analysis of the disaccharide unit building blocks that constitute the polysaccharide chains. This should include a direct determination of some sequence of the major oligosaccharide species present in both generic and innovator's products.

4) Equivalence in biochemical and biological assays

Equivalence in biochemical and biological assays includes analyzing the anti-Xa activity and anti-Xa/anti-IIa ratio between

the generic and innovator products.

5) Equivalence of in vivo pharmacokinetic profiles

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.

A generic product of Low Molecular Weight Heparins (LMWH) should be demonstrated for its pharmaceutical equivalence or "sameness" to the RLD product before its bioequivalence to the RLD product is considered.

DBE Review Decision on ANDA 76-684:
The DBE has established PK equivalence requirements for enoxaparin sodium injection based on the geometric mean ratio and confidence intervals for the primary end point anti-Xa (v:\firmsam\amphastart\ltrs&rev\\76684a0403.doc). In addition, the DBE recommends that the statistical analysis of anti-lla, Heptest® and aPTT data should be provided in the submission.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	Yes	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Table 3. Bioanalytical Method Validation for Anti-Xa Activity in Sodium Citrate Human Plasma

Information requested	Data
Bioanalytical method validation report location	(b) (4) (report revision 1 dated 18 Mar 2005)
Analyte	Low Molecular Weight Heparin (based anti-Xa activity)
Internal standard (IS)	Not Applicable (no IS)
Method description	Low molecular weight heparins are used for the prevention and treatment of thromboembolic diseases. The quantitative determination of plasma LMWH levels by the measurement of their anti-Xa activity is a useful tool for the monitoring treatment efficacy. This procedure is carried out with an (b) (4)
Limit of quantitation	0.030 IU/mL
Average recovery of drug (%)	Not Applicable (no extraction)
Average recovery of IS (%)	Not Applicable (no IS, no extraction)
Standard curve concentrations	0.020 to 0.500 IU/mL
QC concentrations (units/mL)	0.030, 0.040, 0.080, 0.140, 0.286 and 0.400 IU/mL
QC Intra-batch precision range (%)	4.4 to 17.3%
QC Intra-batch accuracy range (%)	Not Applicable
QC Inter-batch precision range (%)	0.0 to 12.5%
QC Inter-batch accuracy range (%)	-9.0 to 7.5%
Bench-top stability (hrs)	20 hours at ambient temperature
Stock stability (days)	157 days in Tris EDTA buffer at -80°C
Processed stability (hrs)	Not Applicable
Freeze-thaw stability (cycles)	4 cycles at -80°C
Long-term storage stability (days)	18 days at -20°C, 180 days at -80°C
Dilution integrity	20-fold
Selectivity	Failed to meet acceptance criteria

Table 3 (cont'd). Bioanalytical Method Validation for Anti-IIa Activity in Sodium Citrate Human Plasma

Information requested	Data
Bioanalytical method validation report location	(b) (4) (report dated 02 March 2005)
Analyte	Low Molecular Weight Heparin (based on anti-IIa activity)
Internal standard (IS)	Not Applicable (no IS)
Method description	Low molecular weight heparins are used for the prevention and treatment of thromboembolic diseases. The quantitative determination of plasma LMWH levels by the measurement of their anti-IIa activity is a useful tool for the monitoring treatment efficacy. The procedure is carried out with an (b) (4)
Limit of quantitation	0.030 IU/mL
Average recovery of drug (%)	Not Applicable (no extraction)
Average recovery of IS (%)	Not Applicable (no IS, no extraction)
Standard curve concentrations	0.020 to 0.500 IU/mL
QC concentrations	0.030, 0.050, 0.080, 0.139, 0.284 and 0.400 IU/mL
QC Intra-batch precision range (%)	2.7 to 20.9%
QC Intra-batch accuracy range (%)	Not Applicable
QC Inter-batch precision range (%)	0.0 to 6.0%
QC Inter-batch accuracy range (%)	-6.7 to 2.1%
Bench-top stability (hrs)	20 hours at ambient temperature
Stock stability (days)	157 days in Tris EDTA buffer at -80°C
Processed stability (hrs)	Not Applicable
Freeze-thaw stability (cycles)	4 cycles at -80°C
Long-term storage stability (days)	18 days at -20°C, 175 days at -80°C
Dilution integrity	25-fold
Selectivity	Failed to meet acceptance criteria

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	AA23230
Study Design	Randomized, Single-Dose, Two-way Crossover under fasting conditions
No. of subjects enrolled	40 (38+2 alternates)
No. of subjects completing	39
No. of subjects analyzed	38
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 15 Female: 23
Test product	Sandoz' Enoxaparin Sodium Injection
Reference product	Lovenox® (enoxaparin sodium) Injection
Strength tested	100 mg/ mL
Dose	100 mg (1 x 100 mg/mL)

Enoxaparin Dose: 1 x 1 mL of a 100 mg/mL enoxaparin sodium subcutaneous injection (100 mg enoxaparin sodium) Geometric Means*, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (AA23230)				
Anti-factor Xa				
Parameters	Test	Reference	Ratio	90% C.I.
AUC 0-t	15.586	13.821	112.8	111.4 – 114.1
AUCinf	15.950	14.215	112.2	110.9 – 113.6
Cmax	1.237528	1.117079	110.8	105.9 – 115.8
Ratio of Anti-factor Xa/Anti-factor IIa				
Parameters	Test	Reference	Ratio	90% C.I.
AUC 0-t	11.2087	12.7199	88.1	85.0 – 91.3
AUCinf	9.0602	9.9350	91.2	86.0 – 96.7
Cmax	7.95118	8.95200	88.8	85.1 – 92.7
APTT for Enoxaparin**				
Parameters	Test	Reference	Ratio	90 C.I.
AUC 0-t	1140.58	1125.90	101.3	100.7 – 101.9
Cmax	40.088	38.674	103.7	101.0 – 106.4
Enoxaparin Anti-factor Xa (Heptest® Assay)**				
Parameters	Test	Reference	Ratio	90 C.I.
AUC 0-t	6.9259	7.2918	95.0	90.5 – 99.7
AUCinf	9.4460	9.6999	97.4	90.3 – 105.0
Cmax	0.7874	0.8687	90.6	86.0 – 95.6
Anti-factor IIa**				
Parameters	Test	Reference	Ratio	90 C.I.
AUC 0-t	1.39054	1.08655	128.0	123.7 – 132.4
AUCinf	1.77788	1.45427	122.3	115.3 – 129.6
Cmax	0.155641	0.124785	124.7	117.7 – 132.1

*Geometric least-squares means are reported

** Not bioequivalence endpoints

Note: The 90% C.I. values provided by the firm (above table) are similar to the results obtained by the reviewer (see the Appendix section).

Study No. AA23230 Additional information in Volumes(s), Page(s)								
Anti-factor Xa								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Above Acceptable Range	5.0	4.0	0.4	0.4	5.0	4.0	0.4	0.4
QMV	15.0	20.0	1.3	1.8	15.0	20.0	1.3	1.8
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	20.0	24.0	1.8	2.1	20.0	24.0	1.8	2.1
Anti-factor IIa								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
QMV	11.0	10.0	1.0	0.9	11.0	10.0	1.0	0.9
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	11.0	10.0	1.0	0.9	11.0	10.0	1.0	0.9

QMV: Questionable multiple values (%CV between replicate values >20)

Did use of recalculated plasma concentration data change study outcome? No (No PK repeats)

NOTE: Only anti-Xa is considered the primary endpoint marker. The firm has also submitted statistical data for the secondary endpoints, e.g., anti-IIa, Heptest® and aPTT. These data were also reviewed.

F. Formulation

Location in appendix	Section IV.B, Page 17
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	-

G. In Vitro Dissolution

N/A

H. Waiver Request(s)

Strengths for which waivers requested	150 mg/mL
Regulation cited	21 CFR 320.22(b)(1)
Proportional to strength tested in vivo (yes or no)	N/A
Dissolution is acceptable (yes or no)	N/A
Waiver granted (yes or no)	The waiver request is not considered at the present time pending determination of pharmaceutical equivalence of the test product.

I. Deficiency Comments

The firm is requested to submit the following items:

1. A complete report of pre-study assay method validation data should be submitted including long-term stability data for anti-Xa and anti-IIa in frozen plasma samples for a storage period equivalent to the maximum freezer storage duration of the actual study samples. Stability data for processed and unprocessed samples in refrigerator, on benchtop or autosampler, if applicable, freeze thaw stability and stock solution stability data should also be submitted. Dilution integrity study using QC samples should also be submitted.

2. A list of reassay samples, with original and repeat values, and reasons for reassaying as well as reasons for selecting the final reported values.

3. All raw numerical data for the anti-Xa and anti-IIa assays.

4. Any correlation coefficients for the calibration curves.

5. All dilution QCs used in the analysis and repeat analysis of actual samples, with dilution magnitude and assay values included.

6. The certificate of analysis for the test and reference lots used in the study: The certificate of analysis should include assay results of enoxaparin sodium, anti-Xa activity, anti-IIa activity and anti-Xa/anti-IIa ratio.

6. The analytical assay dates for the BE study (from the first plasma sample analyzed the last plasma sample analyzed) were not provided.

7. The standard operating procedures (SOPs) describing the chromogenic assays of anti-factor Xa and anti-factor IIa.

J. Recommendations

The in vivo PK equivalence study conducted by Sandoz Inc. comparing its test product, Enoxaparin Sodium Injection, 100 mg/mL, lot #900321, with the RLD product, Aventis' Lovenox® Injection, 100 mg/mL, lot #1606, is incomplete for the reasons cited in the deficiency section. The request for waiver of in vivo biostudy on the 150 mg/mL strength is not granted at this time.

The firm should be informed of the deficiency comments and recommendation.

Zakaria Z. Wahba, Ph.D. Date:
Review Branch III

Chandra S. Chaurasia, Ph.D. Date
Acting Team Leader, Review Branch III

Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information (p 1, vol. A1.13)	
Study Number	MDS Pharma Services Project AA23230
Study Title	Randomized, Single-Dose, Two-way Crossover under fasting conditions
Clinical Site	MDS Pharma Services, Saint-Laurent, Montréal, Canada
Principal Investigator	Gaetano Morelli, M.D.
Study/Dosing Dates	Period-1: 06/01/05; Period-2: 06/08/05
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	Not provided
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	Not provided

Treatment ID	**Test**	**Reference**
Test or Reference	T	R
Product Name	Enoxaparin Sodium	Lovenox®
Manufacturer	Sandoz	Aventis Pharma
Batch/Lot No.	900321 (BPS lot #900729)	1606
Manufacture Date	04/01/05	N/A
Expiration Date	N/A	01/07
Strength	100 mg/1 mL	100 mg/1 mL
Dosage Form	Injection	Injection
Batch Size	* (b) (4)	N/A
Potency	Not provided	Not provided
Content Uniformity (mean, %CV)	Not provided	Not provided
Formulation	See Appendix Section B	
Dose Administered	100 mg (1x100 mg/mL)	100 mg (1x100 mg/mL)
Route of Administration	Subcutaneous Injection	

*Information from the Chemistry review.

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	Yes (see the appendix section, the information in the plasma data file)
Blood Sampling Times	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24 and 36 hours post-dose
Blood Volume Collected/Sample	1 x 4.5 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, and stored at -80°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours predose until 4 hours postdose
Length of Confinement	10 hours predose until 36 hours postdose
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.

Comments on Study Design: The study design is incomplete due to the deficiencies cited in the deficiency section.

6. Clinical Results

Table 1 Demographics of Study Subjects

	Test Product N=39	Reference Product N=39
Age (Years)		
Mean±SD	33.4 ± 9.8	33.4 ± 9.8
Range	18 - 50	18 - 50
Age Groups		
18-39	27 (69.2%)	27 (69.2%)
40-64	12 (30.8%)	12 (30.8%)
Sex		
Female	24 (61.5%)	24 (61.5%)
Male	15 (38.5%)	15 (38.5%)
Race		
Caucasian	39 (100.0%)	39 (100.0%)

	Test Product N=39	Reference Product N=39
Frame		
Large	4 (10.3%)	4 (10.3%)
Medium	28 (71.8%)	28 (71.8%)
Small	7 (17.9%)	7 (17.9%)
Weight (kg)		
Mean±SD	68.1 ± 10.5	68.1 ± 10.5
Range	53.1 - 88.5	53.1 - 88.5
Height (cm)		
Mean±SD	170.4 ± 8.7	170.4 ± 8.7
Range	157 - 188	157 - 188
Elbow Breadth (cm)		
Mean±SD	6.6 ± 0.6	6.6 ± 0.6
Range	5.8 - 8.1	5.8 - 8.1

Table 2 Dropout Information

(Info. on p 25, vol. A1.3)

Subject No.	Reason	Period	Replaced?
28	The subject was withdrawn from the study for personal reasons in Period-1.	P-1	No

Table 3 Study Adverse Events

Adverse Event (Classified according to MedDRA Version 8.0) System Organ Class Preferred Term	Test		Reference		Total	
Number of Subjects Dosed	40	(100%)	39	(100%)	40	(100%)
Number of Subjects Without Adverse Events	30	(75%)	34	(87.2%)	28	(70%)
Number of Subjects With Adverse Events	10	(25%)	5	(12.8%)	12	(30%)
General disorders and administration site conditions	8	(20%)	5	(12.8%)	10	(25%)
Injection site haemorrhage	2	(5%)	2	(5.1%)	3	(7.5%)
Venipuncture site pain	2	(5%)	1	(2.6%)	3	(7.5%)
Injection site pain	2	(5%)	0	(0%)	2	(5%)
Vessel puncture site bruise	2	(5%)	1	(2.6%)	2	(5%)
Asthenia	1	(2.5%)	0	(0%)	1	(2.5%)
Feeling cold	1	(2.5%)	1	(2.6%)	1	(2.5%)
Injection site swelling	0	(0%)	1	(2.6%)	1	(2.5%)

Adverse Event (Classified according to MedDRA Version 8.0) System Organ Class Preferred Term	Test	Reference	Total
Nervous system disorders	3 (7.5%)	1 (2.6%)	3 (7.5%)
Dizziness	3 (7.5%)	0 (0%)	3 (7.5%)
Headache	1 (2.5%)	1 (2.6%)	1 (2.5%)
Renal and urinary disorders	0 (0%)	1 (2.6%)	1 (2.5%)
Dysuria	0 (0%)	1 (2.6%)	1 (2.5%)
Renal pain	0 (0%)	1 (2.6%)	1 (2.5%)
Gastrointestinal disorders	0 (0%)	1 (2.6%)	1 (2.5%)
Nausea	0 (0%)	1 (2.6%)	1 (2.5%)
Vomiting	0 (0%)	1 (2.6%)	1 (2.5%)

Note: Subject #28 (T-trt, P-1) experienced a mild episode of vomiting lasted for 1 minute (7 hrs post dosing). The subject (#28) was withdrawn from the study for personal reasons in Period-1.

Comments: The adverse events of the test and reference products are comparable. No serious adverse events were reported during the study.

Table 4 Protocol Deviations

There were 30 blood-collection samples with reported sampling time delay. All delays observed were short duration (1-5 minutes delay), except 2 samples were reported delays of 8-13 minutes. The reported deviations were judged to have no significant impact on the study.

Comments on Dropouts/Adverse Events/Protocol Deviations: No serious adverse events or major protocol deviations occurred to alter the study outcome.

Table 5 Assay Quality Control – Within Study

(info on pp 594, 665, vol. C1.14)	Anti-Factor Xa	Anti-Factor IIa
QC Conc. (IU /mL)	0.080, 0.138, 0.285, 0.400	0.080, 0.138, 0.285
Inter day Precision (%CV)	5.1-28.4	3.7-5.7
Inter day Accuracy (%)	97.0-102.8	97.5-104.6
Cal. Standards Conc. (IU/mL)	0.020, 0.030, 0.040, 0.060, 0.085, 0.125, 0.204, 0.300, 0.400, and 0.500	0.020, 0.030, 0.050, 0.070, 0.100, 0.150, 0.204, 0.300, 0.400, and 0.500

Inter day Precision (%CV)	3.3-21.3	2.2-15.2
Inter day Accuracy (%)	97.0-105.4	81.2-108.8
Linearity Range (range of R^2 values)	Not provided	Not provided

Comments on Study Assay Quality Control: Incomplete.

Comments on Chromatograms:

No chromatogram was submitted since this is not a chromatographic method. However, there were no raw numerical data submitted (See Deficiency Comments).

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
(b) (4)	07/29/04	Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	The firm did not provide a list of reassay samples with original and repeat values, and reasons for reassaying as well as for selecting the final reported values.
Did recalculation of plasma concentrations change the study outcome?	N/A. Reassay values were not identified in the analytical report.
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	

Summary/Conclusions, Study Assays: See Deficiency Comments.

d) Pharmacokinetic Results

NOTE: The following results were based on the final assay values provided by the firm in the current submission. Pharmacodynamic (PD) reassay values were not identified by the firm in the current report and therefore, could not be confirmed for their validity. As the information concerning PD reassay values become available, the study results will be verified accordingly.

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented below:

Anti-Factor Xa (n=38)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	16.18	17.46	14.42	17.21	1.12
AUCT	15.83	17.77	14.02	17.64	1.13
CMAX	1.28	26.60	1.14	20.67	1.12
KE	0.13	24.42	0.13	27.95	1.06
THALF	5.43	22.57	5.87	26.81	0.93
TMAX	5.00	32.22	4.55	22.67	1.10

MEAN1=Test, MEAN2=Reference

UNIT: AUC=IU.hr/mL, CMAX=IU/mL, TMAX=hrs, THALF=hrs

Anti-Factor IIa (n=38)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	1.82	25.26	1.51	19.01	1.20
AUCT	1.45	30.19	1.13	28.85	1.28
CMAX	0.17	40.10	0.13	30.16	1.28
KE	0.20	34.62	0.17	40.52	1.15
THALF	4.02	42.36	5.02	59.21	0.80
TMAX	5.66	31.90	5.74	33.33	0.99

Anti-Factor Xa/Anti-Factor IIa Ratio (n=38)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	9.25	12.79	9.90	14.37	0.93
AUCT	11.38	17.02	12.91	17.56	0.88
CMAX	8.08	17.11	9.08	16.64	0.89

Table 9 Least Square Geometric Means and 90% Confidence Intervals

Anti-Factor Xa (n=38)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	15.95	14.22	1.12	110.85	113.54
LAUCT	15.59	13.82	1.13	111.56	114.21
LCMAX	1.24	1.12	1.11	105.94	115.84

Anti-Factor IIa (n=38)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	1.78	1.45	1.22	115.27	129.64
LAUCT	1.39	1.09	1.28	123.74	132.36
LCMAX	0.16	0.12	1.25	117.75	132.12

Anti-Factor Xa/anti-Factor IIa Ratio (n=38)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
AUCI	9.12	10.04	0.91	85.30	96.40
AUCT	11.38	12.91	0.88	84.70	91.52
CMAX	8.08	9.08	0.89	85.21	92.75

Table 10 Additional Study Information

	Anti-Factor Xa	Anti-Factor IIa
Root mean square error, AUC_{0-t}	0.030279	0.086857
Root mean square error, $AUC\infty$	0.030958	0.148704
Root mean square error, Cmax	0.115319	0.113607
Ke and AUCi determined for how many subjects?	All subjects	23 subjects
Do you agree or disagree with firm's decision?	Yes agree	Yes agree
Indicate the number of subjects with the following:	-	-
-measurable drug concentrations at 0 hr	None	None
-first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	None	None

Comments on Pharmacokinetic Analysis: The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

- The 90% confidence intervals for AUCt, AUCi, and Cmax of the primary endpoint marker anti-factor Xa were within the acceptable range of 80-125%; however, the application is incomplete due to the deficiencies cited in the deficiency section.

- Note: The reviewer calculated the Xa/anti-factor IIa ratio and it was found within the acceptable range of 80-125

- The statistical analysis information on the secondary marker anti-factor IIa is present in this review for information only and was used to calculate the Xa/anti-factor IIa ratio.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Anti-Factor Xa (n=38)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.5	0.45	41.41	0.42	34.61	1.08
1	0.74	31.13	0.68	25.88	1.09
2	0.99	30.73	0.92	26.88	1.07
3	1.14	29.36	1.04	24.05	1.10
4	1.21	27.61	1.10	21.51	1.10
5	1.19	27.79	1.08	20.49	1.10
6	1.14	24.98	1.04	20.19	1.09
7	1.09	23.76	1.00	18.17	1.10
8	1.03	22.31	0.91	19.84	1.12
10	0.83	19.07	0.75	20.72	1.11
12	0.66	23.76	0.57	26.30	1.17
16	0.35	33.41	0.28	32.83	1.25
24	0.10	30.16	0.09	30.47	1.11
36	0.03	67.77	0.03	76.34	1.07

Anti-Factor IIa (n=38)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.5	0.04	53.92	0.04	47.54	1.14
1	0.07	48.89	0.06	41.96	1.22
2	0.11	46.98	0.09	30.79	1.21
3	0.13	50.21	0.11	36.85	1.21
4	0.14	45.37	0.12	33.89	1.21
5	0.14	51.85	0.11	33.20	1.26
6	0.14	42.15	0.11	30.51	1.25
7	0.14	37.13	0.11	32.16	1.28
8	0.14	33.74	0.11	35.36	1.29
10	0.10	33.24	0.08	31.25	1.22
12	0.07	29.39	0.05	46.58	1.32
16	0.02	139.71	0.01	198.62	2.08
24	0.00	.	0.00	.	.
36	0.00	.	0.00	.	.

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

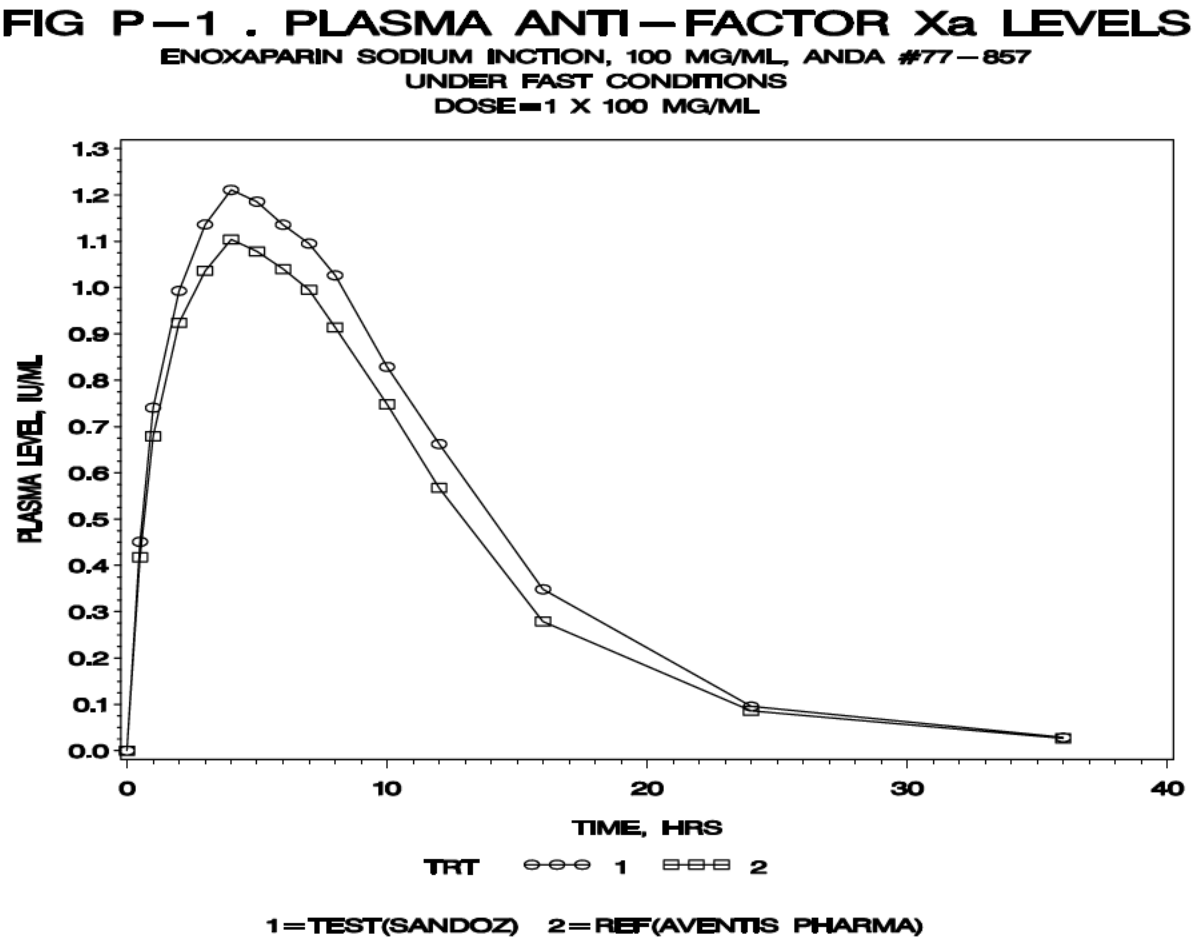
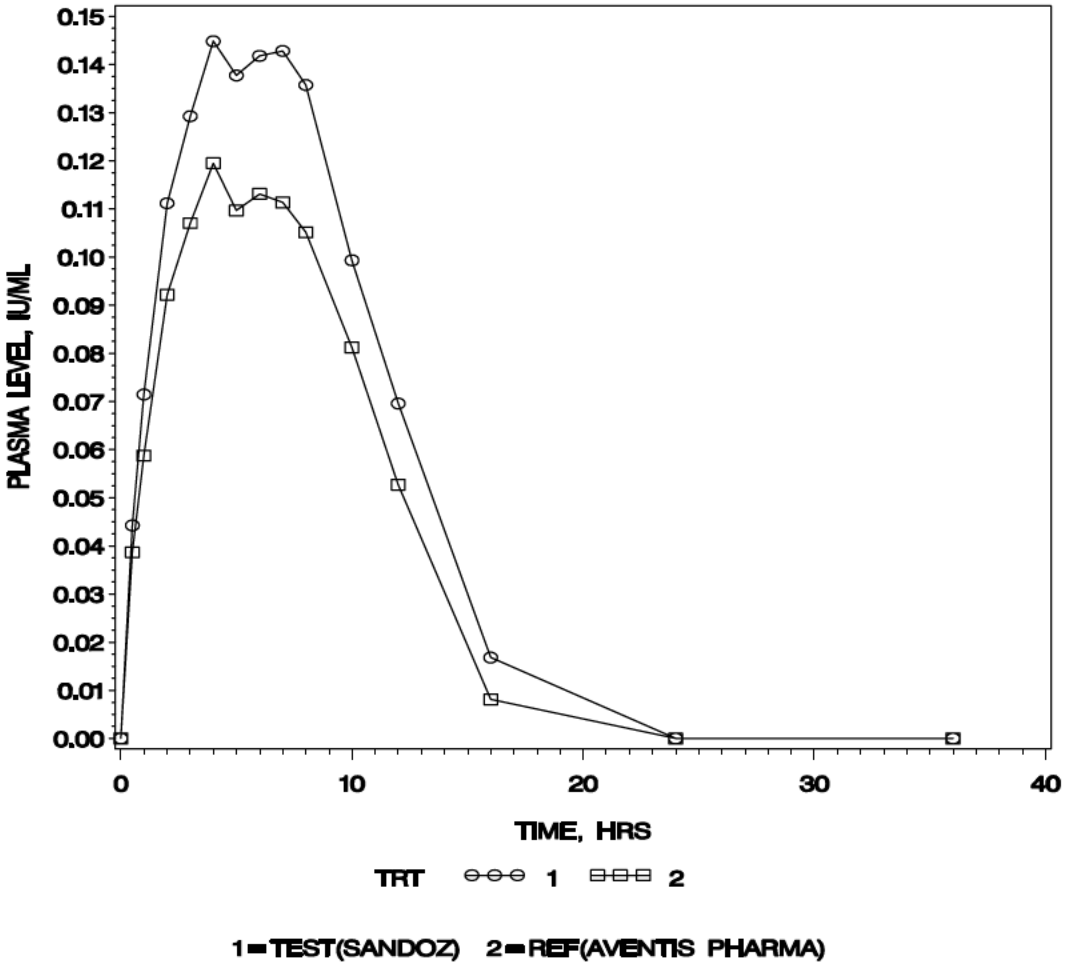


FIG P-2 . PLASMA ANTI-FACTOR IIa LEVELS

ENOXAPARIN SODIUM INCTION, 100 MG/ML, ANDA #77-857
UNDER FAST CONDITIONS
DOSE=1 X 100 MG/ML



B. Formulation Data

Enoxaparin Sodium Injection, 100 mg/mL			
Ingredient	**Grade**	**Per mL**	**Per g[b]**
Enoxaparin Sodium[a]		100 mg	0.10 g
Water for Injection USP	USP/EP	q.s.	(b) (4)
(b) (4)			
Total	-	1.0 mL	

[a]Ajusted for Anti-Xa activity and loss on drying
[b]Density (b) (4)
(b) (4)

Enoxaparin Sodium Injection, 150 mg/mL			
Ingredient	**Grade**	**Per mL**	**Per g[b]**
Enoxaparin Sodium[a]		150 mg	0.15 g
Water for Injection USP	USP/EP	q.s.	(b) (4)
(b) (4)			
Total	-	1.0 mL	

[a]Ajusted for Anti-Xa activity and loss on drying
[b]Density (b) (4)
(b) (4)

	RLD Lovenox® Enoxaparin Sodium Injection	**Generic Drug Enoxaparin Sodium Injection**
Active Ingredient	Enoxaparin sodium	Enoxaparin sodium
Inactive Ingredient	Water for injection	Water for injection
Strength How supplied	100 mg/mL Prefilled Syringe 30 mg/0.3 mL 40 mg/0.4 mL Graduated Prefilled Syringe 60 mg/0.6 mL 80 mg/0.8 mL 100 mg/1.0 mL	100 mg/mL Prefilled Syringe 30 mg/0.3 mL 40 mg/0.4 mL Graduated Prefilled Syringe 60 mg/0.6 mL 80 mg/0.8 mL 100 mg/1.0 mL
	150 mg/mL Graduated Prefilled Syringe 120 mg/0.8 mL 150 mg/1.0 mL	150 mg/mL Graduated Prefilled Syringe 120 mg/0.8 mL 150 mg/1.0 mL
Composition	100 mg/mL strength 10 mg enoxaparin sodium 0.1 mL water for injection Anti-factor Xa activity-1000 IU	100 mg/mL strength 10 mg enoxaparin sodium 0.1 mL water for injection Anti-factor Xa activity-1000 IU

	RLD Lovenox® Enoxaparin Sodium Injection	Generic Drug Enoxaparin Sodium Injection
	150 mg/mL strength 15 mg enoxaparin sodium 0.1 mL water for injection Anti-factor Xa activity-1500 IU	150 mg/mL strength 15 mg enoxaparin sodium 0.1 mL water for injection Anti-factor Xa activity-1500 IU

Comments on the formulation:

The formulation for the proposed generic drug product contains the same active and inactive ingredients at the same concentration, and is manufactured and filled in the same package configurations, sizes and strengths as Lovenox®.

The formulation statement provided above is also satisfactory by the Chemistry review, (V:\firmsnz\Sandoz\ltrs&rev\77857R01.doc).

C. Dissolution Data

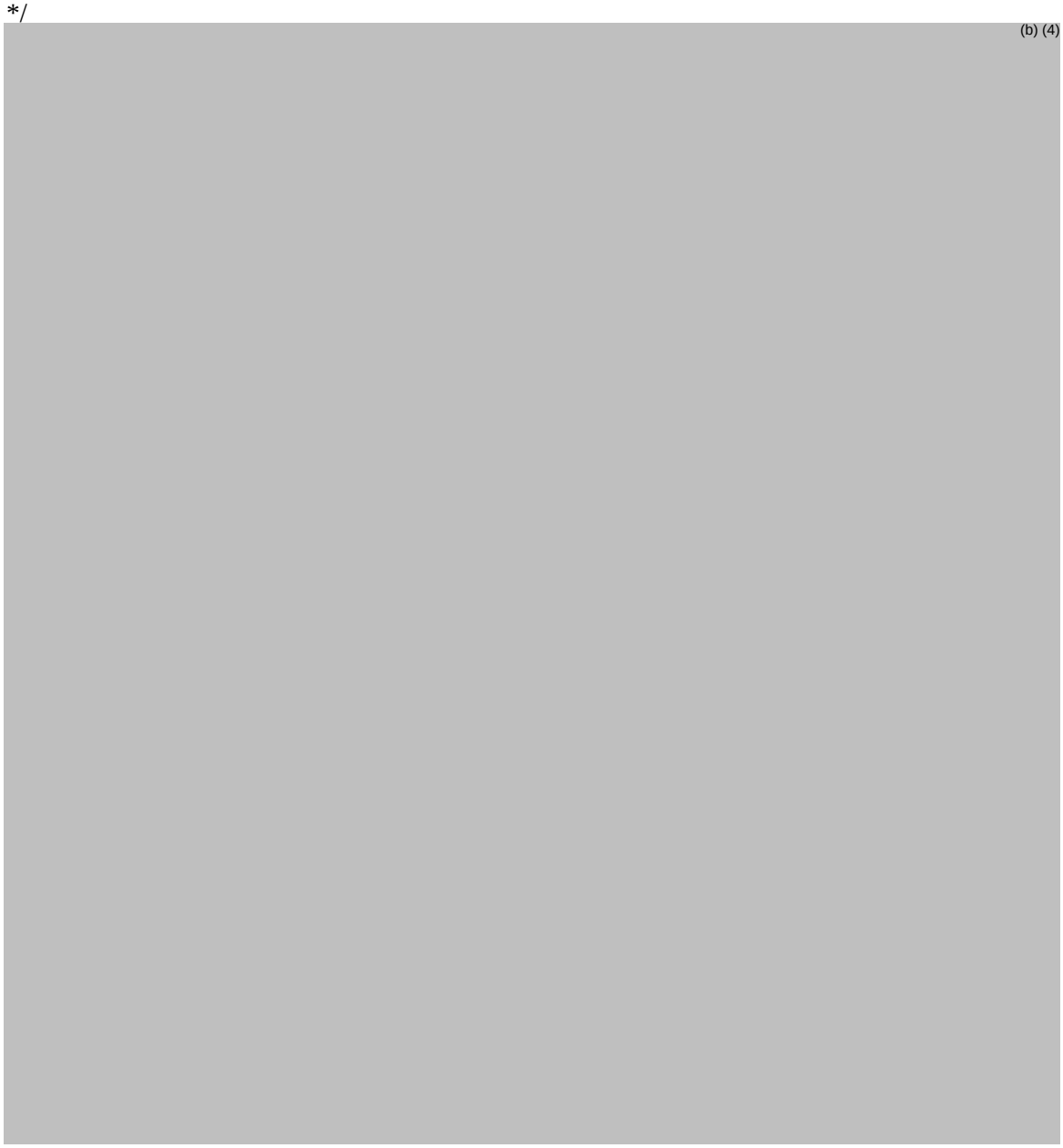
N/A

D. Attachments

Plasma and PK data (Fasting study for Anti-factor Xa)

/* Anti-Factor_aXa s per seq trt c1 c2 c3 c4 c5 c6 c7 c8 c9 c10 c11 c12 c13 c14 c15 AUC0T AUCINF CMAX TMAX HALFLIFE KEL */

(b) (4)



Following this page, 2 pages withheld in full - (b)(4)

(b) (4)

SAS Code (Fasting study for Anti-factor Xa)

(b) (4)

Following this page, 37 pages withheld in full - (b)(4) SAS data

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-857 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Enoxaparin Sodium Injection, 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL)
150 mg/mL (120 mg/0.8 mL and 150 mg/mL)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified and additional information is requested:

1. You have stated in the Bioanalytical Method validation CTD format Tables (Anti-Xa and Anti-IIa) that the selectivity has failed to meet acceptance criteria. Please clarify.

2. Please submit a complete report of pre-study assay method validation data including long-term stability data for Anti-Xa and Anti-IIa in frozen plasma samples for a storage period equivalent to the maximum freezer storage duration of the actual study samples. Stability data for processed and unprocessed samples in refrigerator, on benchtop or autosampler, if applicable, freeze thaw stability and stock solution stability data should also be submitted.

3. Please provide a complete list of reassay samples, with original and repeat values (including subject number, period, type of treatment, blood sampling times), and reasons for the reassays including reasons for selecting the final reported values.

4. Please submit all raw numerical data for the anti-Xa and anti-lla assays.

5. Please submit any correlation coefficients for the calibration curves.

6. Please submit all dilution QCs used in the analysis and repeat analysis of actual samples, with dilution magnitude and assay values included.

7. Please confirm that the actual sampling times were used for calculating the pharmacodynamic parameter concentrations.

8. Please submit the certificate of analysis for the test and reference lots used in the study. The certificate of analysis should include assay results of anti-Xa activity, anti-IIa activity and anti-Xa/anti-IIa ratio.

9. Please provide the start and finish dates for the sample analyses of the BE study.

10. Please provide the standard operating procedures (SOPs) describing how the chromogenic assays of anti-factor Xa and anti-factor IIa are conducted.

Note: It would be helpful for the DBE if the response to the above deficiencies was submitted electronically in MSWord format in addition to the hard copy.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CBIOEQUIVALENCE - Incomplete Submission Date: 08/26/06

For the 100 mg/mL strength

1. FASTING STUDY (STF)
   Clinical: MDS Pharma Services
   Analytical: (b) (4)
   Strength: 100 mg/1 mL
   Outcome: IC

2. Waiver
   Strength: 150/1 mL
   Outcome: IC

Outcome Decisions: Incomplete

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

/s/

Zakaria Z. Wahba
10/26/2006 02:56:23 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
10/26/2006 07:09:52 PM
BIOPHARMACEUTICS

Barbara Davit
10/26/2006 07:20:45 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-857
Drug Product Name	Enoxaparin Sodium Injection
Strengths	100 mg/mL, and 150 mg/mL
Applicant Name	Sandoz Inc.
Contact Information	Bet Brannan 2555 West Midway Blvd Broomfield, CO 80020 Phone 303-438-4237 Fax 303-438-4600
Submission Date(s)	(Original submission date: 08/26/05; Amendment date: 09/07/06)
Amendment Date(s)	11/17/06
Reviewer	Z.Z. Wahba, Ph.D.
First Generic	No

Review of an Amendment

I. Executive Summary

This application references the reference listed drug (RLD) Lovenox® (Enoxaparin Sodium Injection) Injection, 100 mg/mL and 150 mg/mL.

This amendment contains the firm's response to deficiencies cited in the original submission (DFS file: N 077857 N 000 26-Aug-2005). The original application contained the results of fasting bioequivalence (BE) study on the 100 mg/mL of the test and reference products. The 90% confidence interval results of the fasting BE study was within the acceptable range limits of 80-125% (DFS file: N 077857 N 000 26-Aug-2005).

In this amendment, the firm provided an acceptable response to the deficiencies cited in the original submission. The formulation for the 150 mg/mL strength is proportionally similar to the 100 mg/mL strength which underwent bioequivalence study. The 150 mg/mL strength is deemed to be bioequivalent to the RLD Lovenox® Injection, 150 mg/mL, per 21 CFR 320.24 (b)(6).

The application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Enoxaparin Sodium Injection, 100 mg/mL &150 mg/mL
Reference Product	Lovenox® (enoxaparin sodium) Injection, 100 mg/mL &150 mg/mL
RLD Manufacturer	Aventis Pharma
NDA No.	20-164
RLD Approval Date	01-23-03
Indication	Indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism; indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin; and indicated for: the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium, and the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	N/A	
Single-dose fed	N/A	
Steady-state	N/A	
In vitro dissolution	N/A	
Waiver requests	N/A	
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies	N/A	
Amendments	Yes	1

C. Formulation

The formulation was previously submitted and reviewed (see (DFS file: N 077857 N 000 26-Aug-2005).

D. Waiver Request(s):

Strengths for which waivers are requested	150 mg/mL
Regulation cited	21 CFR 320.24 (b) (6)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	-

E. Responses to Deficiency Comments

Deficiency comments are as stated in the DBE review of the original submission (DFS file: N 077857 N 000 26-Aug-2005)

FDA Deficiency Comment #1

You have stated in the Bioanalytical Method validation CTD format Tables (Anti-Xa and Anti-IIa) that the selectivity has failed to meet acceptance criteria. Please clarify.

Firm's Response to the Deficiency Comment #1

The selectivity failed to meet acceptance criteria stated in (b) (4) SOP (b) (4) (b) (4). Based on the SOP acceptance criteria, the precision and accuracy of at least 80% (8 out of 10) of the individual human plasma matrix lots tested must be within ±25% at the LLQC and ±20% at the HQC. These plasma lots are used to prepare the appropriate dilutions.

Results:

For Anti-Xa; Of the 10 lots of human plasma tested, none met acceptance criteria at both the LLQC and HQC levels. All 10 individual human plasma lots tested as blank (i.e., when prepared with no analyte - 0 IU/mL) and generated anti-Xa values below the LLOQ of the method. Five out of ten (5/10) and 2/10 have acceptable recovery at the LLQC and HQC level, respectively.

For Anti-IIa; Of the 10 lots tested, 50% (5 out of 10) of the individual human plasma lots met criteria at both the LLQC and HQC levels (less than 80% of the lots). All 10 tested as blank (i.e., when prepared with no analyte - 0 IU/mL) and generated anti-IIa values below the LLOQ of the method. Nine out of ten (9/10) and 6/10 have acceptable recovery at the LLQC and HQC level, respectively.

Impact assessment on the data:

(b) (4) acknowledges that there is a human plasma matrix lot-to-lot variation when introducing low molecular weight heparin (LMWH) at the LLOQ and HQC levels as demonstrated in the selectivity evaluations assessed in the method validations for both anti-IIa and anti-Xa chromogenic methods. Both of these methods only measure the free form of LMWH in human plasma matrix.

In this study, as the same subject received each of the two investigational products (reference and generic product) in a cross-over design, the effects of human plasma matrix interference is obviated since the relative anti-Xa and anti-IIa profiles of the two investigational compared within a single subject. Selectivity would be of greater concern if treatments were compared between independent groups of subjects or if absolute values for anti-Xa and anti-IIa activities were compared between individual subjects.

DBE's Comment on the Deficiency Comment #1

The firm's response is acceptable.

FDA Deficiency Comment #2

Please submit a complete report of pre-study assay method validation data including long-term stability data for Anti-Xa and Anti-IIa in frozen plasma samples for a storage period equivalent to the maximum freezer storage duration of the actual study samples. Stability data for processed and unprocessed samples in refrigerator, on bench top or autosampler, if applicable, freeze thaw stability and stock solution stability data should also be submitted.

Firm's Response to the Deficiency Comment #2

The complete validation report for LMWH anti-Xa and anti-IIa activity assays, including stability and dilution integrity studies for each method is Provided in Attachment 1 (The 11/17/06 Amendment-1, pages 9-71).

DBE's Comment on the Deficiency Comment #2

The firm's response is acceptable.

FDA Deficiency Comment #3

Please provide a complete list of reassay samples, with original and repeat values (including subject number, period, type of treatment, blood sampling times), and reasons for the reassays including reasons for selecting the final reported values.

Firm's Response to the Deficiency Comment #3

The list of re-assay samples was included (The 11/17/06 Amendment-2). There were 44 out of 1140 (3.5%) re-assay samples. The initial values of these samples were not valid due to questionable multiple values (%CV between replicate values > 20) and above acceptable range.

DBE's Comment on the Deficiency Comment #3
The repeated samples did not compromise the integrity of the study. The firm's response is acceptable.

FDA Deficiency Comment #4

Please submit all raw numerical data for the anti-Xa and anti-lla assays.

Firm's Response to the Deficiency Comment #4

Hard copies of raw data for all assays related to sample analysis for each method were provided in this amendment (For: anti-Xa assays see Attachment-7, pages 330-927; For anti-IIa see Attachment-8, pages 928-1424).

DBE's Comment on the Deficiency Comment #4
The firm's response is acceptable.

FDA Deficiency Comment #5

Please submit any correlation coefficients for the calibration curves.

Firm's Response to the Deficiency Comment #5

Correlation coefficients for the calibration curves for each method were included in Attachment 3 (pages 75-77). The correlation coefficient values of the calibration curves for anti-Xa and anti-IIa were 0.9985 and 0.9983, respectively.

DBE's Comment on the Deficiency Comment #5

The firm's response is acceptable.

FDA Deficiency Comment #6

Please submit all dilution QCs used in the analysis and repeat analysis of actual samples, with dilution magnitude and assay values included.

Firm's Response to the Deficiency Comment #6

Dilution QCs (DHQC) were added to any batch (plate) that included diluted samples (b) (4). The DHQC, which was prepared on the day of the assay, was generated in (b) (4) dilutions due to space limitations on the plate, in order to run complete subject profiles on a single plate. Dilution QCs were not used for batch acceptance but for the acceptance of the dilutions in the batch; if both replicates of the dilution QC failed, those samples covered by the DHQC would be rejected (dilution table for anti-X method was provided in Attachment-4, pages 78-80). There were no diluted needed for anti-IIa analysis.

DBE's Comment on the Deficiency Comment #6

The firm's response is acceptable.

FDA Deficiency Comment #7

Please confirm that the actual sampling times were used for calculating the pharmacodynamic parameter concentrations.

Firm's Response to the Deficiency Comment #7

All blood samples were assumed to been taken at the nominal times, unless the actual sampling times exceeded the deviation windows outlined below. The following deviation windows were permitted:

Nominal Time	Reporting Standard
0.0-0.5 h	+/- 30 seconds
> 0.5-2.0 h	+/- 60 seconds
> 2.0-8.0 h	+/- 2 minutes
> 8.0-24 h	+/- 5 minutes
> 24-36 h	+/- 10 minutes

These times were adjusted in the anti-factor IIa, anti-factor Xa (chromogenic assay) and enoxaparin anti-factor Xa (Heptest® assay) data sets used for pharmacodynamic and statistical analyses to reflect the actual times (accurate to within ± 0.01 hour) at which the samples were obtained.

DBE's Comment on the Deficiency Comment #7
The firm's response is acceptable.

FDA Deficiency Comment #8

Please submit the certificate of analysis for the test and reference lots used in the study. The certificate of analysis should include assay results of anti-Xa activity, anti-IIa activity and anti-Xa/anti-IIa ratio.

Firm's Response to the Deficiency Comment #8

The requested certificates of analysis for the test and reference products in the study were included in the Attachment-5. The anti-Xa activity for the test product (lot #900321) is within 5% of the RLD (lot #1606). The activity values are 10081 IU/mL and 10193 IU/mL, respectively.

	anti-Xa activity	*anti-IIa activity*	*anti-Xa/anti-IIa ratio*
Test product (lot #900321)	10081 IU/mL	2626.4 IU/mL	3.9
RLD (lot #1606)	10193 IU/mL	2815.4 IU/mL	3.6

DBE's Comment on the Deficiency Comment #8
The firm's response is acceptable.

FDA Deficiency Comment #9

Please provide the start and finish dates for the sample analyses of the BE study.

Firm's Response to the Deficiency Comment #9

For Anti-Xa: 07/05/05 to 07/26/05
For Anti-IIa: 07/05/05 to 07/29/05

DBE's Comment on the Deficiency Comment #9
The firm's response is acceptable.

FDA Deficiency Comment #10

Please provide the standard operating procedures (SOPs) describing how the chromogenic assays of anti-factor Xa and anti-factor IIa are conducted.

Firm's Response to the Deficiency Comment #10

The requested SOPs were provided in Attachment-6.

DBE's Comment on the Deficiency Comment #10
The firm's response is acceptable.

F. Recommendation

1. The in vivo PK equivalence study conducted by Sandoz Inc. comparing its test product, Enoxaparin Sodium Injection, 100 mg/mL, lot #900321, with the RLD product, Aventis' Lovenox® Injection, 100 mg/mL, lot #1606, is acceptable. The study demonstrates that under fasting conditions, Sandoz' Enoxaparin Sodium Injection, 100 mg/mL, is bioequivalent to the reference product, Aventis' Lovenox® Injection, 100 mg/mL.

2. Based on the data submitted, the 150 mg/mL strength is deemed to be bioequivalent to the RLD Lovenox® Injection, 150 mg/mL, per 21 CFR 320.24 (b)(6).

Zakaria Z. Wahba, Ph.D. Date:
Division of Bioequivalence
Review Branch III

Chandra Chaurasia, Ph.D. Date:
Division of Bioequivalence
Review Branch III

Dale P. Conner, Pharm. D. Date:
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-857 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Enoxaparin Sodium Injection, 100 mg/mL and 150 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet, and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCE - Acceptable

Submission Date: 11/17/06

1. Study Amendment (STA)

Strength: all
Outcome: AC

Outcome Decisions: AC - Acceptable

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

/s/

Sarah M. Robertson
12/28/2006 12:51:21 PM
BIOPHARMACEUTICS
Signing for Dr. Zakaria Z. Wahba

Chandra S. Chaurasia
12/28/2006 01:06:28 PM
BIOPHARMACEUTICS

Barbara Davit
12/28/2006 02:08:10 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	077857		
Drug Product Name	Enoxaparin Sodium Injection		
Strength (s)	100 mg/mL, and 150 mg/mL		
Applicant Name	Sandoz Inc.		
Address	2555 West Midway Blvd. Broomfield, CO 80020		
Applicant's Point of Contact	Jean Domenico, Manager, Regulatory Affairs 2555 W. Midway Blvd., Broomfield, Colorado 80038-0446		
Contact's Phone #	303-438-4237		
Contact's Fax #	303-438-4600		
Submission Date(s)	Original submission date: 08/26/2006; Amendments dates: 09/07/2006 and 11/17/2006		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	N/A		
Study Type (s)	N/A		
Strength(s)	N/A		
Clinical Site	N/A		
Clinical Site Address	N/A		
Analytical Site	N/A		
Analytical Address	N/A		
OUTCOME DECISION	ADEQUATE		

ADDENDUM TO A REVIEWED APPLICATION

(ANDA 077857 - Original submission date: 08/26/2006;
Amendments date: 09/07/2006 and 11/17/2006)

The Division of Bioequivalence (DBE) reviews of the application 077857, Sandoz Inc.'s Enoxaparin Sodium Injection, 100 mg/mL and 150 mg/mL, refer to fasting in vivo bioequivalence study (MDS Pharma Services Project AA23230) [DARRTS: 077857 REV-BIOEQ-01(General Review), Submit/Final Date 10/26/2006 and 12/28/2006]. The in vivo study conducted in support of this ANDA supports a finding of pharmaceutical equivalence between Sandoz Inc.'s Enoxaparin Sodium Injection and the corresponding reference listed drug (RLD) Lovenox®. Thus, the correct term "pharmacokinetic/pharmacodynamic (PK/PD) equivalence study" should replace the term "in vivo bioequivalence study" in all DBE reviews of ANDA 077857. Therefore, a review of fasting in vivo "bioequivalence" study data is actually a review of "PK/PD equivalence" study data.

In addition, since the RLD, Lovenox® (Enoxparin Sodium) Injection is a parenteral solution and the test products, Enoxaparin Sodium Injection, 100 mg/mL and 150 mg/mL contain qualitatively (Q_1) and quantitatively (Q_2) the same active and inactive ingredients at the same concentrations as the RLD, Lovenox® (Enoxparin Sodium) Injection, 100 mg/mL and 150 mg/mL, respectively, in vivo study requirements for both strengths of Sandoz Inc.'s 100 mg/mL and 150 mg/mL, can be waived under 21 CFR 320.22(b)(1). Therefore, the DBE grants the wavier request for in vivo bioequivalence study requirements for the 150 mg/mL strength based on 21 CFR 320.22(b)(1) and not based on 21 CFR 324(b)(6) as mentioned in the ANDA 077857 review [DARRTS: 077857 REV-BIOEQ-01(General Review), Submit/Final Date 12/28/2006]. Finally, the DBE grants the waiver request for the in vivo bioequivalence study requirements for the 100 mg strength based on 21 CFR 320.22(b)(1).

OUTCOME

ANDA: 77857

Completed Assignment for 77857 ID: 11589

Reviewer: Wahba, Zakaria Date Completed:
Verifier: , Date Verified:
Division: Division of Bioequivalence
Description:

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
11589	8/26/2005	Other	Study Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY
ANDA 77857

Study Amendment/Addendum	
Addendum to BE study	1
Total Complexity Points	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

ZAKARIA Z WAHBA
07/09/2010

MOHEB H MAKARY
07/09/2010

BARBARA M DAVIT
07/09/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review
Review for HFD-600

March/14/2007

ANDA: 77-857

Drug Product Name
Proprietary: N/A
Non-proprietary: Enoxaparin Sodium Injection
Drug Product Classification: N/A
Review Number: #1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
08/26/05	08/29/05	N/A	01/23/07
*08/31/2006	09/01/06	N/A	01/30/07
**12/28/06	12/29/06	N/A	01/23/07

*Major Amendment (CMC)
**Unsolicited Amendment (Microbiology)

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
N/A	N/A	N/A

Applicant/Sponsor
Name: Sandoz, Inc.
Address: 2555 W. Midway Blvd.
P.0 Box 446
Broomfield, CO 80038-0446
Representative: Beth Brannan
Telephone: 720-810-0129

Name of Reviewer: Paul L. Dexter

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Original ANDA.

2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product.

3. **MANUFACTURING SITE:** Baxter Pharmaceutical Solutions LLC.
927 South Curry Pike
Bloomington, IN 47403

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, Subcutaneous, single dose. Available in a 1ml syringe in two concentrations: **100mg/ml** (30mg/0.3ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/1.0ml) and **150 mg/ml** (120mg/0.8ml, 150mg/1.0ml).

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the prophylaxis of deep vein thrombosis, ischemic complications of unstable angina and non-Q-wave myocardial infarction (when administered with aspirin), treatment of acute deep vein thrombosis with our without pulmonary embolism (when administered with warfarin sodium).

B. **SUPPORTING/RELATED DOCUMENTS: DMF** (b) (4) , and **DMF 18557** for information in support of Heparin Sodium use.

C. **REMARKS:** The 12/28/06 Unsolicited Amendment – Microbiology provides information for the inclusion of a new Filling Line # (b) (4) for the subject drug product. Filling Line (b) (4) will be used in addition to the Filling Line # (b) (4) described in the original ANDA.

filename: 77-857.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

[redacted]

B. Brief Description of Microbiology Deficiencies – (b) (4)

[redacted]

C. Assessment of Risk Due to Microbiology Deficiencies –
The safety risk associated with the microbiology deficiencies is considered high.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / Paul L. Dexter
Microbiology Team Leader / Lynne A. Ensor, Ph.D.

C. CC Block
cc: Field Copy

Following this page, 22 pages withheld in full - (b)(4)

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA: 77-857 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Enoxaparin Sodium Injection

A. Microbiology Deficiencies:

1. (b) (4)

2.

3.

4.

5.

Following this page, 1 page withheld in full - (b)(4)

10. (b) (4)

11.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. (b) (4)

2. With regard to organization of this submission, we note that the ANDA is comprised of entire volumes of information not subdivided to facilitate retrieval of specific information and/or documents by the reviewer. For future submissions, please consider using labeled tabs and page numbers to separate subsections and documents within the ANDA and ANDA amendments. Furthermore, if referring to a document in another ANDA section, please include the page number of its location. For expediency of review, the best case scenario is to include all sterility assurance information in the Sterility Assurance Section XXII.

3. We note that the submission relies very heavily on SOPs and reports to describe the (b) (4) processes rather than providing the pertinent information in the narrative. It should be noted that often

qualification reports and SOPs do not sufficiently describe the production parameters and acceptance criteria, so these cannot be relied upon for this information. In future, we would recommend that the pertinent information such as the sterilization process parameters and acceptance criteria be summarized in the narrative.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs

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

/s/

Paul Dexter
3/16/2007 01:54:10 PM
MICROBIOLOGIST

Bonnie McNeal
3/16/2007 02:10:10 PM
MICROBIOLOGIST
Checked for submission links only.

Lynne Ensor
3/19/2007 07:44:12 AM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-600

July/13/2007

ANDA: 77-857

Drug Product Name
Proprietary: N/A
Non-proprietary: Enoxaparin Sodium Injection
Drug Product Classification: N/A
Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
06/8/07	06/11/07	N/A	06/15/07

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
*12/28/06	1	03/14/07
**08/31/2006	1	03/14/07
8/26/05	1	03/14/07

*Unsolicited Amendment (Microbiology)
**Major Amendment (CMC)

Applicant/Sponsor
Name: Sandoz, Inc.
Address: 2555 W. Midway Blvd.
P.0 Box 446
Broomfield, CO 80038-0446
Representative: Beth Brannan
Telephone: 720-810-0129

Name of Reviewer: Paul L. Dexter

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Original ANDA.

2. **SUBMISSION PROVIDES FOR:** Response to Agency's deficiency letter.

3. **MANUFACTURING SITE:** Baxter Pharmaceutical Solutions LLC.
927 South Curry Pike
Bloomington, IN 47403

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, Subcutaneous, single dose. Available in a 1ml syringe in two concentrations: **100mg/ml** (30mg/0.3ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/1.0ml) and **150 mg/ml** (120mg/0.8ml, 150mg/1.0ml).

5. **METHOD(S) OF STERILIZATION:** [redacted] (b) (4).

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the prophylaxis of deep vein thrombosis, ischemic complications of unstable angina and non-Q-wave myocardial infarction (when administered with aspirin), treatment of acute deep vein thrombosis with our without pulmonary embolism (when administered with warfarin sodium).

B. **SUPPORTING/RELATED DOCUMENTS: DMF** [redacted] (b) (4), and **DMF 18557** for information in support of Heparin Sodium use.

C. **REMARKS:** None.

filename: 77-857a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –DMF (b) (4) is deficient.

C. Assessment of Risk Due to Microbiology Deficiencies –
The safety risk associated with the microbiology deficiencies is considered high.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / Paul L. Dexter
Microbiology Team Leader / Lynne A. Ensor, Ph.D.

C. CC Block
cc: Field Copy

Following this page, 11 pages withheld in full - (b)(4)

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA: 77-857 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Enoxaparin Sodium Injection

A. Microbiology Deficiencies:

1. DMF [redacted] (b) (4) has been recently reviewed and was found deficient. The DMF holder has been notified.
2. DMF [redacted] (b) (4) indicates that there are [redacted] (b) (4) of components for Enoxaparin Sodium Injection in ANDA 77-857.
3. In regard to the [redacted] (b) (4) .

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs

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

/s/

Paul Dexter
7/16/2007 12:32:06 PM
MICROBIOLOGIST

Mark Anderson
7/16/2007 01:55:12 PM
MICROBIOLOGIST

Checked for correct linking

Lynne Ensor
7/16/2007 01:57:31 PM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-600

January/28/2008

ANDA: 77-857

Drug Product Name
Proprietary: N/A
Non-proprietary: Enoxaparin Sodium Injection
Drug Product Classification: N/A
Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
10/26/07	10/29/07	N/A	11/13/07

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
6/8/07	2	7/13/07
*12/28/06	1	03/14/07
**08/31/2006	1	03/14/07
8/26/05	1	03/14/07

*Unsolicited Amendment (Microbiology)
**Major Amendment (CMC)

Applicant/Sponsor
Name: Sandoz, Inc.
Address: 2555 W. Midway Blvd.
P.0 Box 446
Broomfield, CO 80038-0446
Representative: Beth Brannan
Telephone: 720-810-0129

Name of Reviewer: Paul L. Dexter

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Amendment # 2.

2. **SUBMISSION PROVIDES FOR:** Response to Agency's deficiency letter.

3. **MANUFACTURING SITE:** Baxter Pharmaceutical Solutions LLC.
927 South Curry Pike
Bloomington, IN 47403

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, Subcutaneous, single dose. Available in a 1ml syringe in two concentrations: **100mg/ml** (30mg/0.3ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/1.0ml) and **150 mg/ml** (120mg/0.8ml, 150mg/1.0ml).

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the prophylaxis of deep vein thrombosis, ischemic complications of unstable angina and non-Q-wave myocardial infarction (when administered with aspirin), treatment of acute deep vein thrombosis with our without pulmonary embolism (when administered with warfarin sodium).

B. **SUPPORTING/RELATED DOCUMENTS: DMF** (b) (4) for (b) (4) (b) (4).

C. **REMARKS:** None.

filename: 77-857a2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) [redacted] .

B. Brief Description of Microbiology Deficiencies – None identified

C. Assessment of Risk Due to Microbiology Deficiencies –
No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / LCDR Paul L. Dexter, M.S.
Microbiology Team Leader / Neal J. Sweeney, Ph.D.

C. CC Block
cc: Field Copy

Following this page, 1 page withheld in full - (b)(4)

Response: (b) (4) for the 100mg/ml concentrated subject drug, and for the 150mg/ml concentrated subject drug.

Acceptable

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

/s/

Paul Dexter
2/4/2008 08:32:21 AM
MICROBIOLOGIST

Mark Anderson
2/4/2008 11:44:35 AM
MICROBIOLOGIST

Checked for correct linking

Neal Sweeney
2/4/2008 02:44:29 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

OTHER REVIEWS

MEMORANDUM

DATE: Monday, June 29, 2009

FROM: Daniela Verthelyi, Division of Therapeutic Proteins, OBP

THROUGH: Amy Rosenberg, Division Director, Division of Therapeutic Proteins, OBP
Steven Kozlowski, Office of Biotechnology Products

TO: File for Sandoz Momenta

RE: ANDA 77-857 Potential immunogenicity of low molecular weight heparins

Sponsor: Sandoz Inc.

Address:	2555 W. Midway Blvd. P.O. Box 446 Broomsfield, CO 80038-0446
Representative:	Kalpana Rao Vanam Vice President, Regulatory Affairs
Telephone:	303-438-4237

Product: Enoxaparin Sodium Injection
Presentation: Enoxaparin sodium is presented as a pre-filled syringe for SC administration in doses of 30mg/0.3mL to 150mg/ml.
Indication: Prophylaxis of Deep Vein Thrombosis

- Treatment of Acute Deep Vein Thrombosis
- Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-wave Myocardial Infarction.

Dose and route: 40mg/day or 30 mg /12 hs or 1mg/kg/12 hs. SC

Recommendation: The data submitted regarding i. the ability of enoxaparin to form complexes with PF4, ii. screening for the presence of impurities that could stimulate the immune system directly, iii. assessment of the activation of human PBMC, and iv) the induction of antibodies to the product in a murine model does not indicate that Sandoz/Momenta's enoxaparin (SME) would be more immunogenic than the registered licensed drug (RLD), however the a number of concerns limit the interpretation of the data as detailed below:

1) regarding concerns that the source of the crude Heparin may impact on the potential immunogenicity of the product, it is important to note that all of the data provided by the Sponsor corresponded to product lots that (b) (4)

However, if the Sponsor commits to meeting at least USP standards for every lot

of crude heparin (b) (4), this may be sufficient to prevent deficient lots to be used to make final product.
2) Several lots of the RLD showed impurities that were evident in the silver stained SDS-PAGE gels. These were no present in the lots of enoxaparin from Sandoz-Moment that were submitted for evaluation. While we presume that absence of impurities is better in terms of product immunogenicity, their potential impact quenching an immune response has not been formally investigated.
3) The sponsor has suggested that they do not want to have release specifications for impurities for drug product release. Instead, they want to apply the new USP criteria to qualify the crude heparin. (b) (4) of protein in the source of heparin. There is no scientific justification for allowing (b) (4) protein and the Sponsors have not validated the clearance of protein in excess of what can be allowed in their starting material. *I recommend that as a the Sponsor is requested to commit to characterize the levels of protein as part of the release specifications using validated acceptable methods for every lot of product or to demonstrate that the any protein present in their staring material is cleared in excess by their manufacturing process.*
4) As detailed below, each of the methods utilized to characterize the complexes have individual weaknesses that hinder the interpretation of the data. For example, average complex diameters were submitted from the PCS rather than the diameter of small, intermediate, and large complexes; the recovery for the SEC methods was poor (~50%), and A280 is not a suitable method for measuring the diameter of the individual complexes. Despite this, and since their weaknesses are not overlapping, comprehensive analysis of the data provided does not suggest that the complexes formed by PF4 and the Sandoz/Momenta enoxaparin commercial size lots significant differ from those formed by the RLD.
5) While differences between innovator and generic product would have suggested increased risk for immune responses and the need to perform clinical studies, the reverse does not hold: Similarity in the observed responses (between innovator and generic products) reduces the risk of unexpected immune responses but does not fully ensure that the risk of developing an immune response to the product will be equivalent in patients.

Therefore, while I recommend that the product be approved, I do so with some reservations due to the absence of data from lots derived from a (b) (4) source and some methodological weaknesses in the individual tests carried out to characterize the complexes. I further recommend that before approval the Sponsor is required to adopt rigorous acceptance criteria for every lot of crude heparin (b) (4), and that specifications for protein impurities be incorporated as part of the drug product lot release criteria or that the Sponsors validate the clearance of protein in excess of what can be allowed in their starting material.

The ensuing review contains a brief summary of the original Review of the data conducted on October 2008 followed by the evaluation of the responses to the questions posed by the Agency in a telecom on March 6th, 2009, and the evaluation of additional data provided for lots that included crude heparin derived from an additional source (b) (4).

Summary of the findings:

Question 1: *HIT is mediated by antibodies to the PF4-heparin complex. Although Sandoz/Momenta used sophisticated approaches to show the sameness of its active ingredient to that in Lovenox, the presence of impurities may affect the interaction of enoxaparin with PF4. Please compare the ability of your product with that of the innovator product to bind to and form complexes with the chemokine PF4, and characterize the size and charge of the resulting complexes. Please include in your studies product lots that are newly released as well as those that are close to expiry date.*

Sandoz/Momenta compared the binding of PF4 to RLD and Enoxaparin Sodium Injection by Plasmon resonance and determined the size and charge of the complexes using a series of orthogonal analytical methods that measure complex size over a range of PHRs as well as the PHR that has neutral charge. The Sponsor contends that PCS and A_{280} light absorption profiles were used to determine complex size changes as a function of PHR, whereas SEC-UV, SEC-MALS, and AUC were used at a single PHR to characterize the size of the intermediate and large complexes formed. All the analyses were performed using 2-4 lots of the RLD to establish an acceptable range of comparability and 9 lots of the Sandoz's enoxaparin (SE). The Sponsors had proposed an acceptance range of (b) (4) % of the lowest and (b) (4)% over the highest value of the RLD results. Given that only 2-4 RLD lots were utilized, of which at least two had evidence of variable undefined impurities, the results were evaluated using more stringent cutoffs (within (b) (4)% of the range of the RLD and absence of statistical difference). Of note, each one of the assays used has weaknesses that hinder the interpretation of the data: for example, average complex diameters were submitted from the PCS rather than the diameter of small, intermediate, and large complexes; the recovery for the SEC methods was poor (~50%), and A280 is not a suitable method for measuring the diameter of the individual complexes. Despite this, comprehensive analysis of the data provided does not suggest that the complexes formed by PF4 and the Sandoz/Momenta enoxaparin commercial size lots significant differ from those formed by the RLD.

Question 2:

a. Please quantify the level of protein impurities utilizing a highly sensitive method.

b. *Please characterize any protein impurities in your product as compared to the innovator product. These studies should have a high sensitivity and be capable of comparing patterns of protein impurities. This could be achieved using discriminating 2D gels, HPLC, or immunoassays. Data from sensitive assays that demonstrate a similar pattern of impurities would support the contention that the generic product is similar with regard to impurity content. Data demonstrating the extent of impurity removal during the manufacturing process could also be of value.*

c. *Please provide information on process removal of nucleic acids and lipids. Significant residual materials may require further comparative characterization.*

d. *Impurities leaching from container closure systems can potentially contribute to the immunogenicity of products. Please assess differences in leachables arising from the syringes used by the generic and innovator products and determine whether they affect immunogenicity, or provide a rationale for why such studies are not needed. Please include in your studies product lots that are newly released as well as those that* Appears this way on original.

Sandoz assessed the presence of impurities using 2 RLD lots, 9 enoxaparin lots and 12 lots of the unfractionated heparin (UFH) using the rationale that the absence of impurities in the UFH supports the absence of impurities in the more refined material. Total protein content was assessed using precipitation with trichloroacetic acid (LOD: (b) (4) ppm or (b) (4) ug/ 100mg dose), SDS-PAGE with Coomassie and silver stain was performed for individual proteins (LOD (b) (4) /g). The low levels of

protein observed in UFH suggest that the manufacturing process for heparin results in degradation of protein. Clearance studies to establish the level of protein clearance were not submitted.
Studies to assess for the presence of lipid impurities included Capillary Gas Chromatography with Mass Spectrometry detection (GC-MS). No lipids were evident at the LOD (LOD: > (b) (4) /g). DNA content was assessed by Threshold® Total DNA Assay System (LOD (b) (4) ng/dose) and all lots were reported to be negative. No raw data were provided.
Overall, the lots seem remarkably devoid of impurities as all the tests fall within the observed parameters for the RLD. The sole exception is that the RLD shows a smear on the SDS-PAGE gels that appears not to be of protein origin. The impact of this change on product immunogenicity is unknown. The Sponsor states that the container closure used is the same as the RLD and assessment of leachable seems adequate. The Sponsor's analysis of leachable substances is acceptable. There appears to be a reasonably low risk for adverse impact on product quality and patient safety due to material potentially leaching from the components of container closure system into the product. Impurities found include (b) (4) (specification: NMT (b) (4) % of DS) and traces of (b) (4) .
Regarding the request that the sponsor incorporate specifications for impurities for product release, the Sponsors has proposed to (b) (4) using the USP monograph draft as acceptance criteria for their starting material (enoxaparin drug substance). Since the Sponsor has control over the manufacturing process (from the staring material downstream) this approach seems acceptable. However, since there are data that show that protein impurities occur in LMWH, *I recommend asking for protein clearance studies, demonstrating how much protein can be cleared by the process as well as the setting of release specifications for this parameter.*

Question 3:

i. Development of an in vitro assay to compare the immunomodulatory (adjuvant-like) effect of the generic and innovator products. For example, assays could be used to assess the immune responses elicited by an antigen in the presence and absence of generic or innovator low molecular weight heparins to examine whether they affect immune responses similarly. The addition of suboptimal levels of innate immune agonists such as LPS or CpG ODN to the system may be helpful in amplifying any immunomodulatory effect of the product.

The sponsor assessed the ability of enoxaparin to induce or enhance an inflammatory response using human PBMCs. Results show increased TNFα with increasing levels of LMWH, but no differences between RLD and enoxaparin lots. Similarly no significant differences were evident between the product and the RLD when assessing recall T cell activation in vitro using Tetanus toxoid as an antigen in the presence or absence of enoxaparin, alone or with suboptimal levels of TLR agonists CpG ODN and LPS. Although initial studies were performed with PBMC from a single donor, data from two additional donors were submitted to the file with similar results. Similarly, the TNFa induction by the product alone in different concentrations was provided in response to the Agency's request showing similar TNFa levels upon stimulation.

ii. Development of an animal model to determine whether the products, alone or in complex with PF4, are similarly immunogenic in vivo. While animal models do not necessarily predict immunogenicity in humans, differences in the immune response would signal that the two molecules are regarded as different by the immune system.

The induction of antibodies to complexes of human PF4 and enoxaparin was evaluated in mice immunized with the complex under different regimens. The mouse to mouse variability is significant,

hindering the detection of any differences. However, no evidence of increased or accelerated immunogenicity was evident in mice that received PF4:LMWH complexes using SME or the RLD. Similarly, no significant differences between the RLD and the product lots were evident when enoxaparin was used as an adjuvant in vivo in mice to assess whether it could act to enhance the immunogenicity of a protein antigen (KLH).Missing from the data provided is the evaluation of the adjuvant properties of LMWH lots in the absence of additional adjuvants (Np CpG ODN or LPS).

Background:

Introduction:

Enoxaparin is low molecular weight heparin (LMWH) comprised of a diverse mixture of many oligosaccharide chains. LMWH inactivate both factor Xa and factor IIa, and promote the release of tissue factor pathway inhibitor (TFPI), which prevents the progression of the coagulation cascade. There are 4 approved NDAs for LMWHs: Lovenox (enoxaparin sodium) (NDA # 20-164), Fragmin (dalteparin sodium) (NDA # 20-287), Normiflo (ardeparin sodium) (NDA # 20-227) (withdrawn in 2001 at the request of the manufacturer),[1] and Innohep (tinzaparin sodium) (NDA # 20-484). They are not therapeutically equivalent and are not considered to be interchangeable. The active ingredients in these LMWH products are derived from different modes of depolymerization (i.e., cleavage by alkaline β-elimination of the benzyl ester derivative of heparin) yielding drug products containing active ingredients with different distributions of oligosaccharide sequences and different chemical modifications at the terminal ends of these oligosaccharide chains. FDA originally approved Aventis' new drug application (NDA) for Lovenox (enoxaparin sodium injection, NDA # 20-164) in 1993 for the prophylaxis and treatment of deep vein thrombosis. Lovenox is the RLD for Sandoz/Momenta's enoxaparin sodium (SEE).

The manufacture of Enoxaparin Sodium Injection is (b) (4) depicted in Figure 1.

(b) (4)

Immune responses to heparin can cause Heparin-induced thrombocytopenia (HIT). HIT is a relatively common iatrogenic thrombotic disorder caused by antibodies to platelet factor 4 (PF4) complexed to unfractionated heparin or LMWH. HIT is caused by IgG antibodies that bind to neoepitopes on platelet factor 4 (PF4) released from activated platelets that develop when it forms complexes with heparin. Anti-PF4-Heparin complex antibodies develop in over 50% of heparin-treated patients (3-4 Units/mL) undergoing surgery involving cardiopulmonary bypass (CPB). Among approved heparins, asymptomatic seroconversion is greatest in patients that receive

unfractionated heparin in various clinical settings (*8–50%) and is lesser with exposure to low molecular-weight heparins (*1–8%) or the synthetic pentasaccharide, fondaparinux (*1–3%). Only a fraction of patients with antibodies go on to develop HIT (1-5% incidence) and the incidence is lower in patients receiving LMWH (0.2-0.5%). Why some patients go on to develop HIT, but others do not, is not understood. Anti-PF4/heparin antibodies may induce thrombocytopenia in HIT by activating platelets through FcγRIIa. Therefore, some anti-PF4/heparin antibodies may be more pathogenic than others based on differences in titer, avidity, isotype or epitope-binding site(REILLY et al., 2006). The increased incidence of HIT in patients undergoing cardiopulmonary surgery is associated with higher circulating levels of PF4 (560-750 ng/mL) (Suvarna et al., 2007).

PF4 structure: PF4, also known as CXCL4, is an abundant 70 amino acid, 7800 Da protein with two disulfide bonds, no tryptophan or methionine residues, two histidines, and a single tyrosine. The PF4 monomer is comprised of a glutamate-rich N-terminal, a relatively hydrophobic sequence containing three anti-parallel β-sheets, and a carboxy-terminal α- helical amphipathic structure containing two pairs of adjacent lysines separated by two amino acids. PF4 exists in solution in a concentration-dependent mixture of monomers, dimers and tetramers. The PF4 tetramer forms a cylindrical structure displaying an equatorial ring of positively charged amino acids derived from the carboxy-terminus α-helices as well as internal cationic amino acids that, in turn, attract negatively charged heparin molecules to wrap circumferentially around the cylinder. PF4 is stored in the alpha granules of platelets where it is found in complex with the chondroitin sulfate (CS) containing proteoglycan serglycin (Slungaard, 2005). PF4/CS complexes are released when platelets are activated. It is presumed that heparin, being more anionic than CS, displaces the endogenous GAG, forming PF4/ heparin complexes instead (Cines et al., 2007). OS-CS is as negative as heparin.

Complex formation**:** The autoantibodies that cause HIT recognize neoepitopes in PF4 that are expressed when complexed with heparin and other anionic glycosaminoglycans (GAGs). The size of PF4/heparin macromolecules is governed by the molar ratios of the reactants. Maximal complex size occurs at molar ratios of PF4:heparin at which surface charge is neutral (~1:1)(Suvarna et al., 2007). Assembly of macromolecular complexes is influenced profoundly by small changes in the stoichiometric ratio of PF4:heparin (PF4:heparin ratio or PHR) (Suvarna et al., 2007). At a 1:1 molar ratio, PF4 and UFH form ultralarge (>670 kD) neutrally charged complexes that bind multiple IgG molecules/complex. Whether these complexes are the most highly immunogenic is controversial(Rauova et al., 2005; Suvarna et al., 2007). Low molecular weight heparin (LMWH) is less antigenic and forms ultralarge complexes less efficiently and mostly at supratherapeutic concentrations.
Studies show that in mice immunized with PF4-Hepain complexes that differ in size and/or zeta potential, antibody formation varies inversely with heparin concentration and is most robust in animals immunized with complexes displaying a net positive zeta-potential (Suvarna et al., 2007). A recent study in C57Bl/6 mice shows that PF4/heparin complexes formed at higher PHRs (PHR 26:1 or PHR 20:1 or 10:1) caused the most robust seroconversion, where those formed at low PHRs or high heparin concentrations (PHR 1:5 or PHR 1:10) were the least immunogenic. Antibody responses were more robust in mice immunized with PF4/heparin complexes expressing a positive zeta potential (Suvarna et al., 2007)

REVIEW OF CURENT SUBMISSION: Complete response to FDA's requests regarding the potential immunogenicity of Enoxaparin Sodium Injection Drug Product.

1. Product lots used:

1.1 Enoxaparin: Nine lots of Enoxaparing and 4 lots of RLD were utilized. In addition, 12 lots of unfractionated heparin were used to address Question 2. *No criteria are provided of how these lots (SME or RLD) were chosen.*

Table 3. Enoxaparin Sodium Injection Lots Tested in this Amendment

Parameter	Enoxaparin Sodium Injection Syringe Lots								
Lot number	900322	900490	902392	906559	906616	907811	908099	907966	907967
Concentration (mg/mL)	100	150	100	150	100	100	100	100	100
Mass/syringe (mg)	80	150	100	120	30	30	100	80	60
Date of manufacture	Mar 2005	Apr 2005	Apr 2006	May 2007	May 2007	Sep 2007	Oct 2007	Oct 2007	Oct2007
DP lot scale (syringes/lot)	(b) (4)								
Lot expiry status	Beyond expiry			Near or at mid-cycle			Recently manufactured		
Stability data	2 yr[3]	2 yr[3]	2 yr[3]	12 mo	12 mo	6 mo	6 mo	6 mo	6 mo
DS manufacturing scale	(b) (4)								
DS lot(s) used in DP manufacture	0503X043	0503X043	0509X090 0511X001 0507X121	0602X963 0602X964	0602X964 0602X113	0703X104	0705X951	0705X951 0705X952	0705X952
Currently designated for commercial supply (pending ANDA approval)	No	No	No	No	No	No	Yes	Yes	Yes

Table 4. RLD Lots Tested in this Amendment

Parameter		RLD Lots			
Lot number		8998	1737	1905	1923
Concentration (mg/mL)		100	100	100	100
Mass/syringe (mg)		80	150	100	120
Date of expiry		Jun 2008	Feb 2009	Aug 2010	Sep 2010
FDA Request # (topic)	**Amendment Section**				
1 (PF4 interactions)	5	X	X	X	X
2a,b,c (impurities)	6.1 to 6.8	ND[1]	ND[1]	X	X
2d (leachables studies)[1]	6.10	NA[2]	NA[2]	NA[2]	NA[2]
3i (in vitro studies)	7	X	X	X	X
3ii (in vivo study)	8	X	ND[1]	X	X

[1] ND: Not done. Sandoz/Momenta's limited inventory of RLD Lots 8998 and 1737 restricted analyses of these lots.

[2] NA: Not applicable. RLD lots used in the leachables studies are described in Table 29

Table 5. Unfractionated Heparin USP Lots Tested in this Amendment

Unfractionated Heparin USP Lot (Sandoz GmbH)		Enoxaparin Sodium Drug Substance Lot (b) (4)
Lot Number	**Manufacture Date**	**Lot Number[1]**
735004007	June 2004	0412X028, 0502X095, 0503X043
735004010	August 2004	0507X120, 0507X121, 0507X122
735004012	October 2004	0509X090, 0511X001
732005001	October 2005	0602X112, 0602X962, 0602X963
732005002	May 2005	0602X964, 0602X113
732006003	May 2006	0703X104, 0705X951
732006004	July 2006	0705X951, 0705X952
732006005	July 2006	0705X952
732006008	December 2006	0710X094
732007005	March 2007	N/A[2]
732007007	April 2007	N/A[2]
732007008	April 2007	N/A[2]

[1] Drug Substance lots are listed that are derived from UFH lots listed on the left

[2] Manufacture of Enoxaparin Sodium Drug Substance is either in progress or is planned from the UFH lot (designated for commercial use).

UFH starting material lots are (b) (4) for the manufacture of Enoxaparin Sodium Drug.

The criteria for (b) (4) is not stated and therefore I cannot assess whether there can be a potential impact on product immunogenicity.

Table 6. Starting Material Lots for Enoxaparin Sodium Injection Lots

UFH Starting Material Lot	Enoxaparin Sodium Injection Lot								
	Drug Product Lot (at or near expiry)			Drug Product Lot (mid-cycle)			Drug Product Lot (recently manufactured)		
	900322	902392	900490	906559	906616	907811	908099[b]	907966[b]	907967[b]
735004007	X[a]		X						
735004010		X							
735004012		X							
732005001				X					
732005002				X	X				
732006003						X	X	X	
732006004							X	X	X
732006005								X	X
732006008	DRUG PRODUCT LOTS DERIVED FROM THESE UFH LOTS HAVE NOT YET BEEN MANUFACTURED								
732007005									
732007007									
732007008									

[a] X: UFH starting material lot was used to manufacture Drug Substance lot(s) used to manufacture Drug Product lot(s)
[b] These Drug Product lots are currently designated for commercial distribution (pending FDA approval)

Source of Heparin:

Lot	UFH
900322	735004007
902392	735004010 735004012
900490	735004007
906559	732005001 732005002
906616	732005002
907811	732006003
908099	732006003 732006004
907966	732006003 732006004 732006005
907967	732006004 732006005

(b) (4)

Reviewer's comments: Except for lot 732006003, all UFH (b) (4)

1.2 Admixtures:

Aliquots from three Enoxaparin Sodium Injection lots (900322, 906559 and 908099) were each mixed with equal amounts of one specific RLD lot (1905) to form three specific admixtures (admixture 1, 2 and 3 respectively). The Enoxaparin Sodium Injection lots were selected to represent Drug Product lots that were beyond expiry (Lot 900322), near mid-cycle (Lot 906559) or recently manufactured (Lot 908099). (See Table 3 for lot details). The RLD lot (1905, Table 4) was selected, based on RLD sample availability.

1.3 PF4

Source (b) (4)

The lots exhibit some variability:

Following this page, 33 pages withheld in full - (b)(4)

Questions posed to the Sponsor in March, 2009:

Question 1:

Your studies show that the individual lots of PF4 used have differences in the percent of monomer, dimer, trimer and tetramer. Please comment on how these differences impact on the analytical and functional studies to characterize the PF4-heparin complexes. After qualifying the (b) (4) *PF4,* (b) (4) *product was used for certain studies. Please clarify the source of PF4 that was used for each study and confirm that all the PF4 used was similarly qualified.*

a. Your studies show that the individual lots of PF4 used have differences in the amounts of monomer, dimer, trimer and tetramer. Please comment on how these differences impact on the analytical and functional studies performed to characterize the PF4-heparin complexes.

b. After qualifying the (b) (4) *PF4,* (b) (4) *PF4 was used for certain studies. Please clarify the source of PF4 that was used for each study and confirm that all the PF4 used was similarly qualified.*

c. Please confirm that the same lot of PF4 was used in all head to head studies.

Question 2: *Please state the criteria used to* (b) (4).

Question 3: Please state the origin of each lot.

Question 4: The retention time and molecular weight of the intermediate complexes formed with Sandoz Enoxaparin appear to be marginally smaller (83.5kDa to 80kDa) as assessed by SEC-HLPC. T test shows=0.02(pp 428-429). Please comment.

Question 5 As you assess complex formation. Please comment on how stable are the complexes formed. The work of Suvarna et al. suggests that complexes at optimal ratios to form large complexes may self- assemble over time.

1- *The SEC recovery is low. Please comment on whether the SEC disrupts the complex.*

2- *Regarding your assessment of complex size by PCS:*

a. *Please submit examples of the raw readout of the PCS for your product and the RLD at the different PHR.*

b. *Please confirm that the numbers provided correspond to the average complex size including large, intermediate and smaller complexes.*

c. *Please submit a table with the diameter of each of these for review if available.*

3- *Regarding your assessment of complex size by A280:*

d. *Please clarify why PH complexes have absorbance at 280 if neither PF4 nor heparin do. Does this assay reflect absorbance or turbidity?*

e. How does the A280 show complex size? Please explain how you derive complex sizes (in nm) from absorbance and how you differentiate the amount of PF4 that is in complex from the complex size.

f. PHR_{max} in table 2 is 1 for all the RLD lots but ranges from 0.8 to 1.2 for SME. Please comment on the accuracy of the method.

4- *Please submit a table detailing the complex charge for each PHR as assessed by z-potential for assessment.*

5- *Please submit better copies of the gels to assess total proteins stained with colloidal blue, as the images included in this submission are hard to interpret. For example, no band is visible for the de-staining control.*

6- *Please establish specifications for impurities and include them as part of your release testing.*

7- *Please clarify whether the in vitro studies were conducted using PBMC from a single donor. If so, please confirm using a second donor.*

8- *Some of the lots appear to induce higher levels of TNFα production by PBMC in culture. Please comment.*

9- *Please provide a rationale for the levels of LPS and CpG ODN used in the in vitro proliferation studies (TT).*

10- *Thymidine uptake is highest in cells stimulated with LMWH. Is the increase in T cell proliferation antigen dependant? Is it dose dependant? Can you provide an explanation of the reduced proliferation when LPS is added to the conditions?*

11- *For the in vivo studies you have provided the antibody titers for the mice treated with LMWH in the presence of adjuvants. Please provide an assessment of the response to the product in the absence of LPS or CpG ODN.*

12- *Please comment on the high variability in the antibody response. Is this due to the time point when the antibody levels were assessed? /Does this high variability within groups maintain in time?*

13- *Please provide a (dose dependent) assessment of the adjuvant effect of the different lots of LMWH (your and the RLD's) in the absence of CpG ODN or LPS.*

On May… 2009, Sandoz Momenta submitted a response to the questions raised by this review. The following is the review of these answers:

Regarding question #1:" .. does FDA consider the data analyses and acceptance criteria described in this amendment to sufficiently address FDA's requests"
The Agency provided the following comments:

1 *Regarding the PF4 source:*

a. *Your studies show that the individual lots of PF4 used have differences in the percent of monomer, dimer, trimer and tetramer. Please comment on how these differences impact on the analytical and functional studies performed to characterize the PF4-heparin complexes.*

b. *After qualifying the (b) (4) PF4, (b) (4) PF4 was used for certain studies. Please clarify the source of PF4 that was used for each study and confirm that all the PF4 used was similarly qualified.*

c. *Please confirm that the same lot of PF4 was used in all head to head studies.*

Data provided by the Sponsor on May 2009:
Sandoz states that the criteria to qualify the lots of PF4 were:
1. Protein concentration – Determined by the BCA assay
2. Protein purity / integrity – Determined by SDS-PAGE with silver staining
3. Ability to form tetramers / higher-order oligomers in the absence of LMWH – Determined by chemical cross-linking and gel analysis (referred to as the "crosslinking assay").
4. LMWH binding efficiency – Determined by a surface plasmon resonance (SPR) kinetic assay.

Sponsor uses 3 lots that have 38%, 57% and 96% trimer/tetramer in the absence of LMWH (Source: (b) (4) and Momenta) to show that despite their ability to form complexes in the absence of LMWH, the different PRF4s have similar increase/decrease turbidity at multiple PHR in the presence of LMWH. They do this by comparing the absorbance at A280 of PF4 and LMWH at different PHRs. The lots used are (b) (4) 090243 + RLD (Lot 1905), shown in green, or Momenta (12-8- 2008, shown in red) or (b) (4) (Lot 0.90243, shown in blue) together with RLD lot 1910. No controls are included to assess the sensitivity of the method to detect changes, the sensitivity of this method to assess complex formation had been previously questioned. In addition, the binding of the 3 lots of PF4 (b) (4) 447-077, JR538-194-1 and

Table 2. Cross-Linking Results for Multiple PF4 Lots

PF4 source	Vendor Lot #	Momenta Lot #	Ability to form tetramers	Monomer (%)	Dimer (%)	Trimer and Tetramer (%)[1]
(b) (4)	090243	447-077[2]	Yes	35%	27%	38%
Momenta	N/A	04DEC08[3]	Yes	3%	1%	96%
(b) (4)	090243	JR538-194-1[3]	Yes	11%	32%	57%
	Q0613[3]	N/A	Yes	15%	30%	55%
	054/08B	LX504-187[2]	Yes	29%	36%	35%

[1] The cross-linking assay does not readily resolve trimers and tetramers. However, there is a strong literature precedent supporting a monomer-dimer-tetramer equilibrium for PF4 in solution (Mayo et al., 1989) [2].
[2] These lots were used for the studies submitted in the OIA
[3] A Momenta-produced PF4 lot and a different resuspension of the (b) (4) PF4 lot were not used for the experiments presented in the OIA. Data from these two preparations are included in this response.

Momenta 4-12-08) to LMWH were shown to have similar initial binding rates by surface Plasmon resonance. Only the association rates were provided. *No data is provided to support the approval of any of the PF4 lots except for Table 2 (bellow) which shows that the different lots of PF4 had very different composition of monomers, dimmers, tetramers in the absence of LMWH. Sponsor states that the % of monomer vs dimmer vs tri/tetramer has no impact on analytical and functional studies and provides some data to support this.*

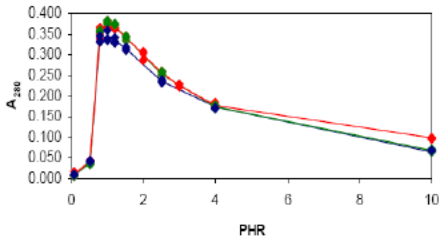


Figure 1. Comparison of A_{280} Light Absorption Profiles for Three PF4 Lots Combined with LMWH

PHR = PF4 tetramer:LMWH ratio. The A_{280} profile shown in green was generated with (b) (4) PF4 (Momenta Lot 447-077) and RLD Lot 1905 (data on file); this profile is extracted from the profiles presented in Figure 10 of the OIA, pg 58. The two other profiles [Momenta PF4; Momenta Lot 04DEC08 (red) and (b) (4) PF4; Momenta Lot JR538-194-1 (blue)] were generated with RLD Lot 1910 (data on file). The data are identical between the upper and lower plots; only the x-axis scales are different.

Conclusion for Question 1a, b &c: The data provided does not adequately explain the reason for the different ratios of monomer:dimmer : trimer/tetramer nor does it really demonstrate that the different sources of PF4 do not impact on the results. The studies performed are missing positive and negative controls to enable the interpretation of the data. Lastly, several of the studies were performed using the PF4 from (b) (4) (b) (4) or from R&D, not included in the above tables. Together this hinders th e interpretation of any data on the characterization of the PF4-enoxaparin complexes. On the other hand, the Sponsor states that for each study the same lot of PF4 was used for Sandoz-Momenta enoxaparin (SME) and the RLD. Of note, the different sources of PF4 could be linked to the differences observed in the kinetics of complex formation demonstrated by the A280 and PCS methods.

Regarding question #2:"
The Agency provided the following comments:

2. With reference to your assessment of complex formation, please comment on the stability of the complexes formed. The work of Suvarna et al. suggests that the size of complexes may change over time.

The Sponsor agrees with the Agency that the complexes change with time and states that this was taken into account when qualifying the A280 assay, PCS and Zeta potential assays. The Sponsor assures the Agency that the studies with enoxaparin and the RLD were performed in parallel using comparable incubation and reading times across groups. The sponsor presented data where they examined the stability of the complexes by A280, PCS and Zeta potential and each assay was performed when the complexes were stable. As shown bellow, the Sponsor chose various times depending on the assay. It is unclear why different techniques would show that the complex formation stabilizes at different time points.

A280 graph shows that the maximal absorbance diminishes with time after 30 minutes. This is the opposite of what is published by Suvarna et.al, where measurement of the particle size by grew from about 500nm to about 9000nm in 3 hours. Is the decrease due to dissolving of the complexes or precipitation? Or is it due to decreased turbidity of larger complexes? Again, there are no controls to compare the profile with. Based on this data the sponsors state that they conducted all A280 at 30 minutes. In addition, the data provided was performed using only RLD lot 1898

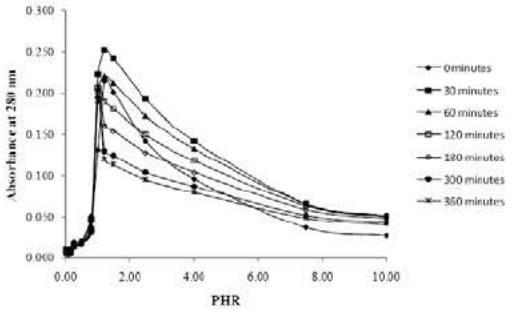


Figure 3. A_{280} Light Absorption Profile: Stability of PF4:LMWH Complexes

The effect of incubation time prior to measuring absorbance was assessed. PF4 ((b) (4) Lot number 07043) was mixed with RLD Lot 1898 at varying PHRs. (This figure is reproduced from Appendix 34 of the OIA, page 718.)

The data assessing the stability of complexes by PCS and zeta potential shows that for medium sized complexes. (This study was performed using (b) (4) lot 090243). The diameter oscillates around 150±25 for the first 2 hours and then the oscillations get smaller (140 ± 10%) around the 3 hour mark. Of note: 1) there is no data on the interassay variability, so the % of the variability that is contributed by the assay rather than the changing size of the complexes is unclear; and 2) This study was not performed with Sandoz's enoxaparin to show that the differences in complex formation over time are comparable, and 3) It is unclear whether the 3 hour time point selected is the optimal one for different PHRs.

In terms of zeta potential, a single experiment (performed on a single lot of RLD 1889 + PF4 from R&D) provided shows that the z potential varies significantly with time and PHR. However, as above, a single experiment appears to have been performed using the RLD lot 1889 and an uncharacterized lot of PF4 from R&D.

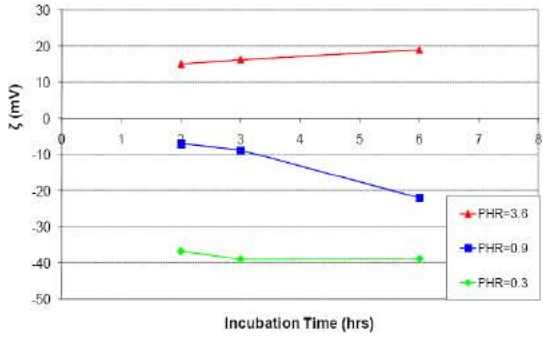


Figure 5. Zeta Potential Stability of PF4-LMWH Complexes Formed at Different PHRs.

PF4-LMWH complexes were monitored over a 6 hour time course in an early method development study. PF4 (R+D Systems Lot DQA02) was mixed with RLD Lot 1889 at varying PHRs. (This figure is reproduced from Appendix 28 of the OIA, pg 609.)

The Sponsors claim that the results from the 3 assays complement and support each other. However, that result from the results from the A280 study are opposite to the PCS and zeta potential in terms of kinetics.

Regarding question #3:"
The Agency provided the following comments:

3. *The retention time and molecular weight of the intermediate complexes formed with Sandoz Enoxaparin appear to be marginally smaller than those of the RLD (83.5kDa to 80kDa) as assessed by SEC-HLPC. T test shows=0.02(pp 428-429). Please comment as to the significance of this finding.*

The sponsor acknowledges the differences in mass but states that it is unlikely that the differences in mw observed correspond to true changes in the size of the complexes as none were evident by AUC. Sponsor states that the changes in mw are most likely related to the performance of the column. An investigation into the difference showed that within a day, using the same column the mass by SEC-HPLC of the intermediate complexes formed between PF4 and LMWH had progressively lower molecular weight. The sponsor also states that the samples were all run after a 30' incubation time and therefore the differences in size were not due to changes over time in the complexes. In future measurements S-M plans to include molecular weight standards at the beginning and end of each run.

Table 4. Molecular Weight of PF4:LMWH Intermediate Complexes Determined for RLD Lot 1889[1]

Run Number	Retention Time (min.)	Relative Retention Time (min.)	Log M_w	Molecular Weight (Da)
12Jun08 Day 3 Run 1	32.261	0.646	4.944	87,856
12Jun08 Day 3 Run 2	32.360	0.651	4.931	85,380
12Jun08 Day 3 Run 3	32.390	0.653	4.928	84,644
12Jun08 Day 3 Run 4	32.548	0.661	4.908	80,869
12Jun08 Day 3 Run 5	32.688	0.668	4.890	77,665

[1] These data are derived from the intraday repeatability study described in Appendix 18 of the OIA, Table 10, pg 373.

The response is acceptable.

Regarding Agency question #4: *We note that the recovery of enoxaparin/PF4 complexes by SEC is low. Please confirm that the percent recovery was similar*

for your product and the RLD. Please comment on whether the SEC procedure disrupts the complexes.
S/M acknowledges that recovery is very low but argues that the SEC is not intended to be quantitative.
Reviewer's comment: It can be argued that since this method is being used to characterize the size of intermediate and large complexes, and not the proportion of intermediate and large complexes, the results may be unaffected by the low recovery(~50%). *On the other hand, since it is not possible to discern what product is being lost, the results presented may be biased, particularly if ultralarge complexes are being excluded.*

Regarding Agency question #5: *Regarding your assessment of complex size by PCS:*

a. *Please submit examples of the raw readout of the PCS for your product and the RLD at the different PHRs.*

b. *Please confirm that the numbers provided correspond to the average complex size including large, intermediate and smaller complexes.*

c. *Please submit a table with the diameter of each of these for review if available.*

S-M data shows the average size of all complexes rather than the average diameter of small intermediate and large complexes. S-M argues that Photon Correlation Spectroscopy, which they use to determine complex size changes as a function of PHR, is not suitable to assess the diameter of small, medium and large complexes:

- "The raw readout from a PCS experiment is a correlogram, which displays time-dependent changes in the light scattering of particles as they move in and out of a laser path over a relatively short time duration. …
- Although PCS data can, in principle, be used to evaluate "large, intermediate and smaller complexes" as requested by FDA, PF4-LMWH complexes are not suited for such an analysis."
- In general, larger particles will move more slowly and will thus maintain high correlation function values for a longer period of time than is the case for smaller particles.….
- The reasoning is that in PCS or dynamic light scattering, each particle scatters light with an intensity that is proportional to the sixth power of its diameter (*d*). Consequently, the largest complexes will be preferentially detected over considerably smaller particles. The least transformative method of deriving size metrics from the correlograms is to calculate an average hydrodynamic diameter (or Z-average value) directly from the correlogram using the "cumulant" method of analysis (Greinacher et al. 2008).

Table 7. Hydrodynamic Diameter Values for RLD Lots (d.nm)

Sample	Protein to Heparin (Enoxaparin) Ratio (PHR)[1]											
	0.5			1.0			2.0			5.0		
RLD Lot 8998	75	80	89	5200	6100	4900	3400	3400	3700	1400	1400	1400
RLD Lot 1737	89	99	83	5000	5200	4600	2400	2500	2500	1300	1200	1200
RLD Lot 1905	92	89	95	4800	4900	4600	3400	3000	n.d.[2]	1500	1400	1400
RLD Lot 1923	75	82	78	4300	4700	4500	3500	2700	3300	1200	1300	1300

[1] These data were obtained from Table 2 of Technical Report ENX-08-0037-TR1-1 (p. 697 of OIA), and represent triplicate samples (each of which is an average of three measurements) as described in Figure 7.

[2] n.d. = not determined; correlograms did not pass suitability criteria detailed on p. 682-683 of OIA

Table 8. Hydrodynamic Diameter Values for Enoxaparin Sodium Injection Lots (d.nm)

Sample	Protein to Heparin (Enoxaparin) Ratio (PHR)[1]											
	0.5			1.0			2.0			5.0		
Enoxaparin Sodium Injection Lot 900322	81	100	94	4500	4500	4200	2700	2800	2700	1200	1200	1200
Enoxaparin Sodium Injection Lot 902392	110	78	85	4400	6200	5000	3200	3000	3300	1400	1300	1400
Enoxaparin Sodium Injection Lot 900490	85	82	80	4500	5000	4500	2800	3100	3700	1400	1400	1400
Enoxaparin Sodium Injection Lot 906559	130	150	130	4800	4400	5600	2800	2900	2800	1200	1200	1200
Enoxaparin Sodium Injection Lot 906616	95	89	89	5500	6300	5000	3500	2900	3200	1300	1400	1500
Enoxaparin Sodium Injection Lot 907811	82	98	80	6400	7200	5300	2800	3500	3000	1500	1400	1500
Enoxaparin Sodium Injection Lot 908099	99	110	120	4900	4600	4500	2800	2500	3100	1300	1300	1200
Enoxaparin Sodium Injection Lot 907966	87	78	88	5500	5400	6000	2700	2700	2500	1200	1200	1100
Enoxaparin Sodium Injection Lot 907967	95	98	92	4900	5900	5100	3400	3300	3500	1200	1300	1200

[1] These data were obtained from Table 3 of Technical Report ENX-08-0037-TR1-1 (p. 699 of OIA), and represent triplicate samples (each of which is an average of three measurements) as described in Figure 7.

Alternative analyses of PCS data have been reported, such as the plot of size distribution *vs.*number of particles as presented in Suvarna *et al.* (2007) [4] for PF4-heparin samples.

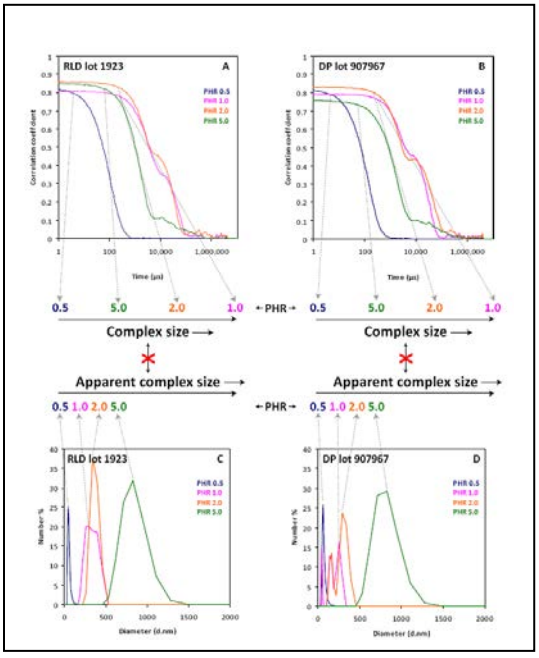


Figure 8 shows that the samples with the largest particles – i.e., those samples whose correlation coefficient takes the longest time to decay from the starting value – are atPHR 1.0 or 2.0.

Note that the rank order of complex size for all four PHRs is the same from both a visual examination of the spectrum and from the calculated Z-average values: 0.5 < 5.0 < 2.0 < 1.0. However, if the apparent complex size is obtained from the number size distribution analysis, the rank order of complex size is quite different for the four PHRs: 0.5 < 1.0 < 2.0 < 5.0.

Table 10. A Size Distribution Analysis[1] of the PCS Correlograms

Sample	PHR[2]			
	0.5	1.0	2.0	5.0
RLD Lot 1923	44	300	340	830
RLD Lot 1737	51	190	830	710
RLD Lot 8998	44	24	460	710
DP Lot 907967	59	260	300	830
DP Lot 907811	51	21	460	710
DP Lot 902392	68	300	460	830

1 As described in Section 6.3, size distribution analysis produces misleading results for PF4-LMWH samples. The complex sizes reported in this table as a function of PHR are not supported by an examination of the primary correlograms. **Note: the misleading nature of the analysis presented in Table 10 becomes evident when these data are compared with the primary correlograms (see** Figure 9, and Appendix 2).

2 For each PHR, the diameter value corresponding to the maximum histogram amplitude (as measured by number %) is listed in this Table. These values are obtained from the size distribution histograms in Figure 9, and Appendix 2. Please see text in Section 6.3 for important details concerning data interpretation.

The most questionable result in Figure 9C and Figure 9D is obtained at PHR 1.0 and 2.0, which are near PHR_{max} and show significant heterogeneity in the complexes formed. It is clear from the primary correlograms in Figure 8 – and confirmed by a cumulant analysis – that the largest particles are present at these PHR values. However, results from the histogram approach predict that the particle size for PHR 1.0 and PHR 2.0 samples would be significantly smaller than the PHR 5.0 samples. This confusing result is due to the smallest species in solution being almost invisible in the primary correlogram because of the dependence of scattering intensity on d^6, and the size distribution plot attempting to pull data from these species out of the noise in the correlogram. These factors yield two consequences: a) the resulting size distribution ends up being dominated by small particles for which there is essentially no primary data and b) the variation in size distribution results between multiple samples prepared with the same LMWH lot is extremely high. Analysis of additional RLD and Enoxaparin Sodium Injection lots (Appendix 2) confirms these consequences.

Reviewer's Comment: S-M provided raw readouts for the PCS. The data provided is in accordance with the expected profile. The use of the correlograms to calculate the mean diameter appears reasonable. By this method, the assay variability is larger than the differences between the SME and the RLD. The response is acceptable.

Regarding Agency question #6: *Regarding your assessment of complex size by A280, please clarify why PF4/Enoxaparin complexes have absorbance at 280 if PF4 has low levels of phenylalanine and tyrosine. Please clarify whether this assay reflects true absorbance or turbidity. Is the absorbance stable over time?*

Suvarna *et al* (2007) [4] have reported that addition of increasing amounts of heparin to a fixed concentration of PF4 yields an asymmetric bell-shaped curve when monitored by absorbance at 280 nm. Since PF4 indeed demonstrates a low absorbance at 280 nm, the authors propose that the assay provides a measure of light scattering which is related to the formation of ultra-large complexes. The authors confirmed this statement by measuring particle size (using photon correlation spectroscopy) for specific points on the asymmetric bell-shaped curve. Therefore, the authors concluded that "changes in the turbidity were caused by alterations in the physical composition of the PF4/heparin complexes."

Reviewer's comment: The A280 method appears to reflects turbidity and the changes in complex formation, but it is still unclear to me why the absorbance decreases with time.

Regarding Agency question #7: *Please submit a table detailing the complex charge for each PHR as assessed by z-potential.*

Table 11. Zeta-Potential Values for RLD and Enoxaparin Sodium Injection Lots Analyzed in the OIA

Sample	PHR 0.05	PHR 0.1	PHR 0.25	PHR 0.5	PHR 1.0	PHR 1.5	PHR 2.5	PHR 5.0	PHR 10.0
RLD Lot 8998 (Replicate 1)	-54.2	-56.7	-42.5	-30.6	-9.23	12.2	18.1	23.1	22.6
RLD Lot 8998 (Replicate 2)	-58.1	-48.3	-42.0	-40.3	-7.02	13.2	20.0	22.7	24.9
RLD Lot 1737 (Replicate 1)	-50.8	-47.8	-48.3	-24.7	-8.76	11.9	19.6	21.6	22.0
RLD Lot 1737 (Replicate 2)	-57.2	-50.0	-30.5	-31.0	-7.91	12.3	19.5	21.8	23.6
RLD Lot 1905 (Replicate 1)	-54.9	-53.4	-38.4	-31.5	-15.8	12.2	19.9	21.9	23.2
RLD Lot 1905 (Replicate 2)	-57.5	-48.1	-45.7	-37.8	-8.69	14.3	20.4	22.3	26.9
RLD Lot 1923 (Replicate 1)	-47.6	-57.2	-48.1	-41.6	-20.2	5.21	19.9	19.9	21.7
RLD Lot 1923 (Replicate 2)	-57.0	-57.6	-45.4	-44.0	-19.1	5.49	17.4	20.6	19.3
Enoxaparin Sodium Injection Lot 900322 (Replicate 1)	-57.1	-47.1	-43.0	-40.6	-15.4	13.3	19.6	20.3	22.1
Enoxaparin Sodium Injection Lot 900322 (Replicate 2)	-51.2	-58.1	-45.6	-26.2	-15.5	12.7	20.8	24.8	24.7
Enoxaparin Sodium Injection Lot 902392 (Replicate 1)	-54.2	-52.3	-41.1	-38.1	-10.6	5.01	n.d.[2]	18.8	21.3
Enoxaparin Sodium Injection Lot 902392 (Replicate 2)	-56.0	-55.5	-43.8	-39.1	-10.4	11.6	13.2	16.1	22.0
Enoxaparin Sodium Injection Lot 900490 (Replicate 1)	-54.0	-51.7	-45	-32.3	-10.3	13.7	20.7	21.4	22.2
Enoxaparin Sodium Injection Lot 900490 (Replicate 2)	-46.6	-47.9	-40.3	-36.1	-9.63	14.1	19.8	24.4	23.6
Enoxaparin Sodium Injection Lot 906559 (Replicate 1)	-61.7	-55.9	-41.1	-38.2	-6.93	13.5	19.2	21.9	26.5
Enoxaparin Sodium Injection Lot 906559 (Replicate 2)	-59.0	-51.2	-44.5	-31.4	-6.40	11.4	17.9	19.9	22.0
Enoxaparin Sodium Injection Lot 906616 (Replicate 1)	-55.1	-53.4	-44.3	-30.3	-10.9	12.0	20.2	22.3	21.7
Enoxaparin Sodium Injection Lot 906616 (Replicate 2)	-53.3	-48.0	-48.7	-37.1	-10.6	11.2	19.7	24.1	23.0
Enoxaparin Sodium Injection Lot 907811 (Replicate 1)	-54.9	-54.6	-38.6	-38.2	-6.03	13.4	20.7	24.0	24.0
Enoxaparin Sodium Injection Lot 907811 (Replicate 2)	-50.6	-53.2	-40.5	-35.2	-7.05	15.2	19.2	24.3	25.9
Enoxaparin Sodium Injection Lot 908099 (Replicate 1)	-52.4	-54.7	-41.9	-34.9	0.501	16.3	20.6	22.8	22.4
Enoxaparin Sodium Injection Lot 908099 (Replicate 2)	-55.8	-53.6	-34.4	-37.8	n.d.[2]	18.0	17.0	24.3	24.8
Enoxaparin Sodium Injection Lot 907966 (Replicate 1)	-52.8	-49.0	-41.7	-33.8	-9.12	15.7	19.5	25.7	26.8
Enoxaparin Sodium Injection Lot 907966 (Replicate 2)	-52.7	-49.0	-40.8	-34.7	-16.9	15.4	20.0	24.5	23.2
Enoxaparin Sodium Injection Lot 907967 (Replicate 1)	-51.9	-55.7	-47.9	-32.0	-13.5	11.8	20.6	21.7	25.2
Enoxaparin Sodium Injection Lot 907967 (Replicate 2)	-52.3	-48.9	-44.7	-27.5	-11.0	13.6	19.5	22.0	24.4

[1] PHR = PF4:LMWH ratio

[2] n.d. = Not determined. Data obtained for these measurements did not meet suitability requirements due to instrument error during the run, as explained in Appendix 29 of the OIA, pp 626-627.

<u>Reviewer's Comments</u>: The z potential at different PHR appears similar between SME and the RLD. The usefulness of this method to evaluate complex sizes appears to be marginal as changes in PHR outside a very narrow margin (0.5 to 1.5) are do not change the z potential significantly.

Regarding Agency question #8: *Please submit better copies of the gels to assess total proteins stained with colloidal blue, as the images included in this submission are hard to interpret. For example, no band is visible for the de-staining control.*

Reviewer's Comments: *The gels were provided and are acceptable.*

Regarding Agency question #9: *Please establish specifications for impurities and include them as part of your release testing.*

Proposed testing as per USP:

- (b) (4)

If FDA concurs with Sandoz' proposal to control impurities in the starting material, Sandoz will immediately adopt the draft specifications in the revised monograph for Heparin Sodium, USP and will adopt any revisions to these proposed specifications when the official monograph for Heparin Sodium, USP is issued. Additionally, Sandoz will continue to use Heparin Sodium, USP as the starting material for the manufacture of Enoxaparin Sodium Drug Substance. These controls, combined with controls already in place, assure the quality of Enoxaparin Sodium Injection Drug Product.

Reviewer's comments: *S-M proposes to test the starting material for impurities as part of their qualification for accepting a heparin lot instead of the drug product. On the one hand this would take the impurities out of release, on the other it increases the chances of detecting impurities. Please include protein content as part of your release specifications.*

Regarding Agency question #10: *Please clarify whether the in vitro studies were conducted using PBMC from a single donor. Please use additional donors to confirm that the results are representative.*

The original submission (September 2008) had data from 1 single blood donor to assess TNFa induction and cellular proliferation. The current submission has additional data from another 2 blood donors with similar results.

Briefly, PBMCs from two additional normal human donors (Donor 1529 and Donor 1546) were pre-screened for their ability to secrete TNF-α in a dose-dependent manner in response to CpG ODN or LPS stimulation. PBMCs were challenged with various concentrations of CpG ODN or LPS for 24 hrs in a humidified incubator at 37°C, 5% CO_2. The secreted TNF-α was quantified by ELISA. The EC_{50}s for TNF-α secretion in response to CpG ODN were 723 nM and 224 nM for Donors 1529 and 1546, respectively. The EC_{50}s for TNF-α secretion in response to LPS were 11.2 pg/mL and 7.7 pg/mL for Donors 1529 and 1546, respectively.

The ability of RLD and Enoxaparin Sodium Injection (DP at 1 µg/mL, 10 µg/mL and 100 µg/mL) to modulate TNF-α secretion in response to sub-optimal concentrations of CpG ODN or LPS stimulation was assessed.

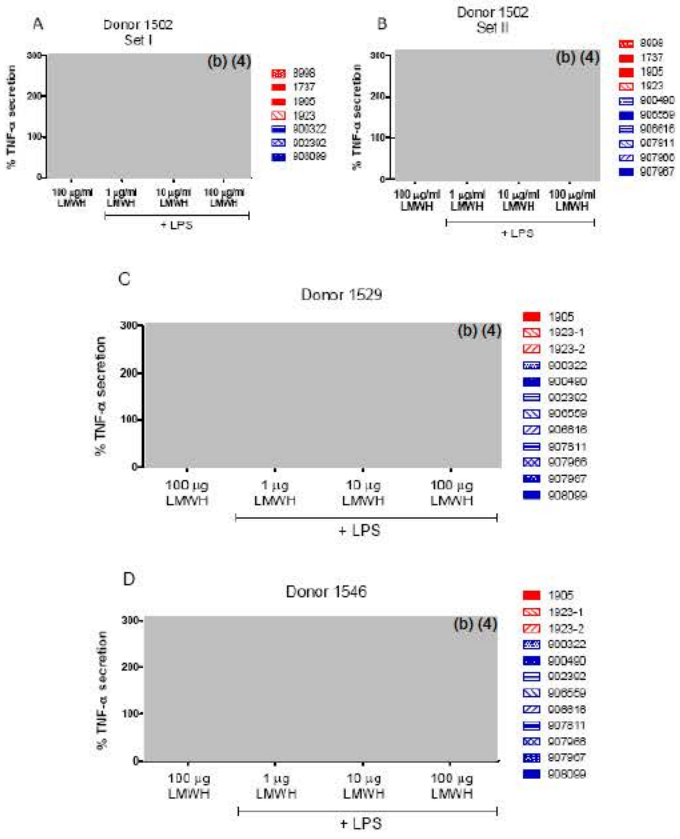


Figure 11. TNF-α secretion from Donors 1502, 1529, and 1546 PBMCs in response to LPS and LMWH

the same experiments. We conclude that the differences detected are within the experimental variability of this assay and within the variability of the RLD. This conclusion is further supported by the observation that there were no significant differences observed between either DP Lot 900322 or DP Lot 902392 and any RLD lot tested with Donor 1546. Similarly DP Lot 900322 and DP Lot 902392 showed no significant differences with any of the four RLD lots tested with Donor 1502 in the OIA.

Reviewer's comments: LMWH induced a dose dependent increase in TNFa responses to TLR agonists and to cell proliferation to recall antigens. The sponsor speculates that the negatively charged heparin may affect the binding and uptake of negatively charged CpG ODN. No differences were evident between the SME and the RLD. The data is acceptable.

Regarding Agency question #11: *Some of the lots appear to induce higher levels of TNFα production by PBMC in culture. Please comment.*

S-M retested donor PBMC (n=1) with increasing concentrations of LMWH and CpG ODN or LPS side by side. It appears that the differences noted corresponded to inter-assay variability.

Reviewer's comments:The re-test shows no differences between lots.

Regarding Agency question #12: *Thymidine uptake is highest in cells stimulated with LMWH. Is the increase in T cell proliferation antigen and/or dose dependent? Can you provide an explanation for the reduced proliferation when LPS is added to the conditions?*

The Sponsors acknowledge there is a modest dose-dependent increase in proliferation with increasing concentrations of LMWH in the presence of sub-optimal concentrations of TT Ag and CpG ODN even if LMWH do not induce proliferation in the absence of TLR agonists or antigen.

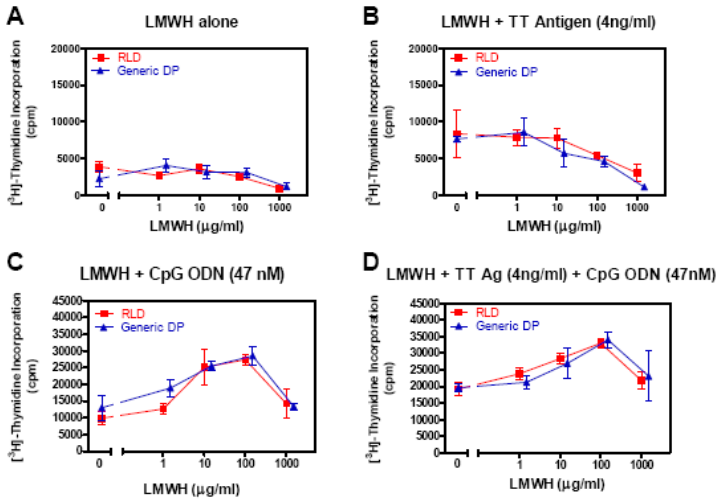


Figure 17. Effect of LMWH on T Cell Proliferation (± TT Ag and CpG ODN)

Human PBMCs were treated with 0 µg/mL, 1 µg/mL, 10 µg/mL, 100 µg/mL or 1,000 µg/mL of RLD (red) or a DP (blue; Lot 900491) for 6 days at 37°C alone (Panel A) or in the presence of a sub-optimal concentration of TT Ag (4 ng/mL; Panel B), a sub-optimal concentration of CpG ODN (47 nM; Panel C), or a combination of TT Ag and CpG ODN (Panel D). Proliferation was assessed by [^{3}H]-thymidine incorporation. The error bars represent the standard deviation (SD) of replicated measurements from one experiment. Note that the y-axis ranges are different for Panels A and B versus Panels C and D. (Data are taken from Appendix 5 of the OIA, Figure 29, pg 234.)

To our knowledge, the potentiation of CpG ODN-induced proliferation of PBMCs by LMWH has not been described in the literature. Both CpG ODN and LMWH are highly negatively-charged molecules. It is possible that heparin increases the free concentration of CpG ODNs by competing for protein binding sites that may sequester CpG ODNs. It is notable that lactoferrin, a cationic protein, has been shown to bind and inhibit the activity of CpG ODNs [8]. Moreover, heparin has been shown to negate the inhibitory activity of lactoferrin by binding lactoferrin and preventing its interaction with CpG ODNs [8]. In

Appears this way on original

…

Importantly, there was no significant difference among tested DP or RLD lots in their ability to potentiate proliferation in the presence of TT Ag and CpG ODN, as assessed with PBMCs from three healthy donors (see Figure 14).

<u>Reviewer's comment:</u> While the mechanism by which LMWH would synergize with CpG ODN to increase cell proliferation is unclear, no significant differences are evident between the product and the RLD. If it were evidence of a 2nd impurity that is not sufficient to induce cellular proliferation but can increase it when in the presence of a TLR agonists, then both products would have the similar impurities. The response is acceptable.

Regarding Agency question #13: *Regarding the in vivo studies, you have provided the antibody titers for the mice treated with LMWH in the*

presence of adjuvants. Please provide an assessment of the response to the product in the absence of LPS or CpG ODN.

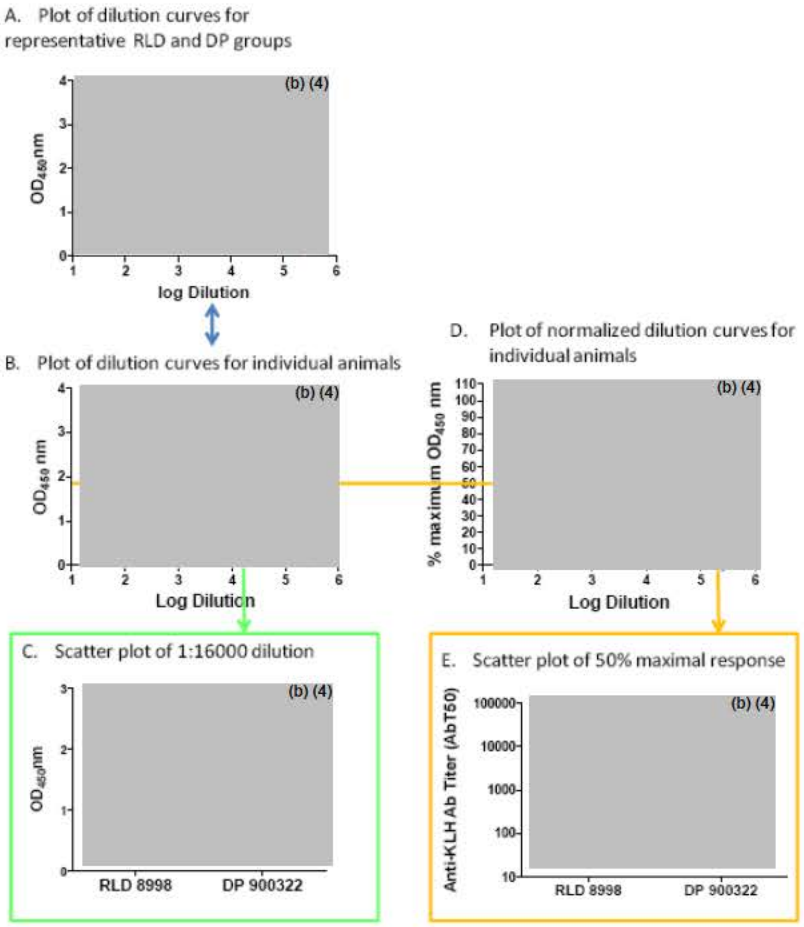


Figure 22. Derivation of the Scatterplot at a Single Dilution vs the AbT50

Representative groups of mice treated with LMWH (RLD Lot 8998 vs DP Lot 900322) are depicted. Balb/c mice (n = 12/group) were immunized S.C. on Days 0 and 14 with 50 µg KLH and 5 µg CpG ODN in the presence or absence of 100 µg RLD (red) or DP (blue), as indicated. Day 21 serum samples were serially diluted and analyzed for anti-KLH IgG antibodies by ELISA. Panel A) Dilution curves for each group representing mean OD_{450nm} values (± SD) at each dilution. Panel B) Dilution curves for each of the 12 animals per group. Panel C) Scatter

animals (n = 12/group). Bars represent the mean ± standard deviation. Data are derived and replotted from experiments described in Figure 31 of the OIA, pg 129.

<u>Reviewer's comments:</u> The product does not appear to increase the antibody titer to an unrelated antigen.

Regarding Agency question #14: *Please comment on the high variability in the antibody response. Is this due to heterogeneities in the product used to immunize the animals?*

The Sponsors claim that the high variability observed is a function of how the data was expressed and provide the following re-analysis of the data ona log scale and argue that the variability is acceptable.

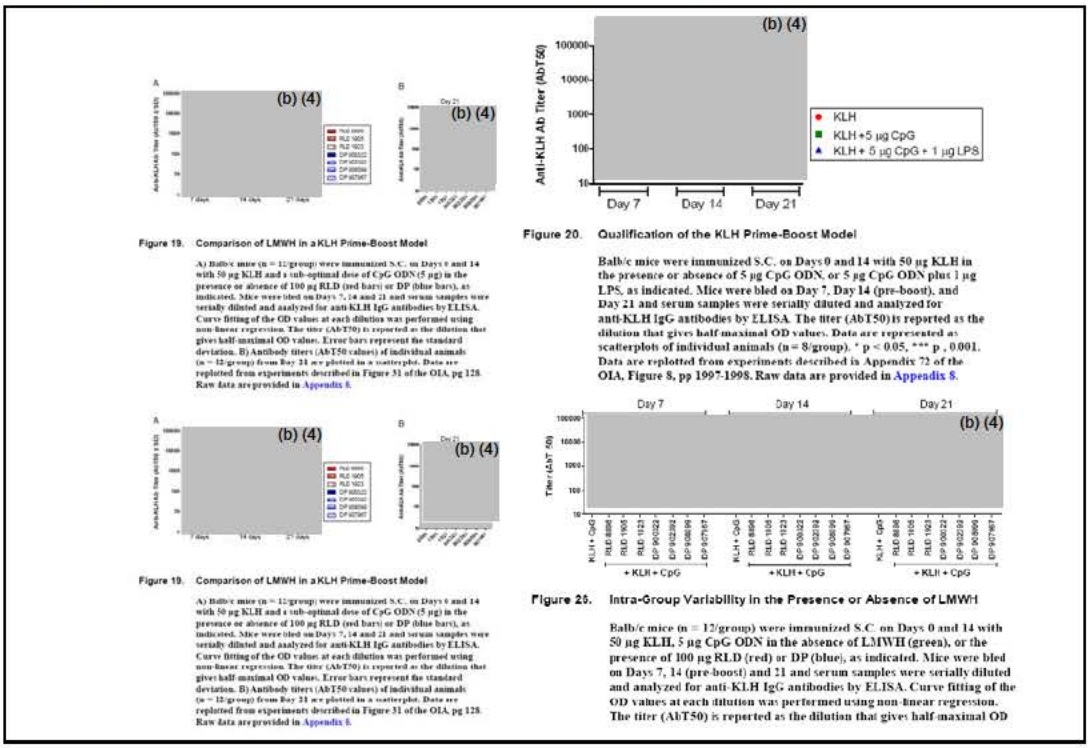


Figure 19. Comparison of LMWH in a KLH Prime-Boost Model

A) Balb/c mice (n = 12/group) were immunized S.C. on Days 0 and 14 with 50 µg KLH and a sub-optimal dose of CpG ODN (5 µg) in the presence or absence of 100 µg RLD (red bars) or DP (blue bars), as indicated. Mice were bled on Days 7, 14 and 21 and serum samples were serially diluted and analyzed for anti-KLH IgG antibodies by ELISA. Curve fitting of the OD values at each dilution was performed using non-linear regression. The titer (AbT50) is reported as the dilution that gives half-maximal OD values. Error bars represent the standard deviation. B) Antibody titers (AbT50 values) of individual animals (n = 12/group) from Day 21 are plotted in a scatterplot. Data are replotted from experiments described in Figure 31 of the OIA, pg 128. Raw data are provided in Appendix 8.

Figure 20. Qualification of the KLH Prime-Boost Model

Balb/c mice were immunized S.C. on Days 0 and 14 with 50 µg KLH in the presence or absence of 5 µg CpG ODN, or 5 µg CpG ODN plus 1 µg LPS, as indicated. Mice were bled on Day 7, Day 14 (pre-boost), and Day 21 and serum samples were serially diluted and analyzed for anti-KLH IgG antibodies by ELISA. The titer (AbT50) is reported as the dilution that gives half maximal OD values. Data are represented as scatterplots of individual animals (n = 8/group). * $p < 0.05$, *** $p < 0.001$. Data are replotted from experiments described in Appendix 72 of the OIA, Figure 8, pp 1997-1998. Raw data are provided in Appendix 8.

Figure 19. Comparison of LMWH in a KLH Prime-Boost Model

A) Balb/c mice (n = 12/group) were immunized S.C. on Days 0 and 14 with 50 µg KLH and a sub-optimal dose of CpG ODN (5 µg) in the presence or absence of 100 µg RLD (red bars) or DP (blue bars), as indicated. Mice were bled on Days 7, 14 and 21 and serum samples were serially diluted and analyzed for anti-KLH IgG antibodies by ELISA. Curve fitting of the OD values at each dilution was performed using non-linear regression. The titer (AbT50) is reported as the dilution that gives half-maximal OD values. Error bars represent the standard deviation. B) Antibody titers (AbT50 values) of individual animals (n = 12/group) from Day 21 are plotted in a scatterplot. Data are replotted from experiments described in Figure 31 of the OIA, pg 128. Raw data are provided in Appendix 8.

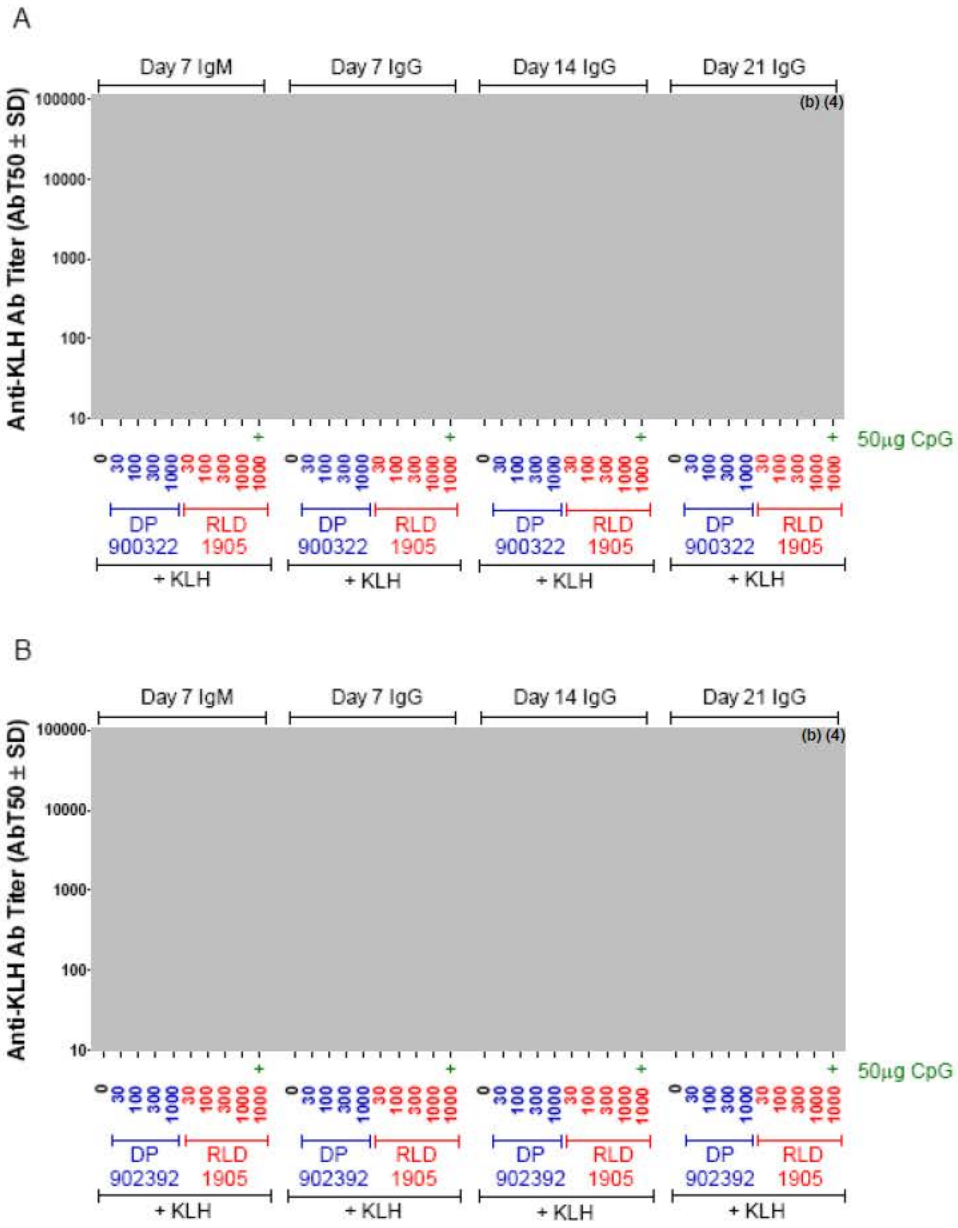
Figure 25. Intra-Group Variability in the Presence or Absence of LMWH

Balb/c mice (n = 12/group) were immunized S.C. on Days 0 and 14 with 50 µg KLH, 5 µg CpG ODN in the absence of LMWH (green), or the presence of 100 µg RLD (red) or DP (blue), as indicated. Mice were bled on Days 7, 14 (pre-boost) and 21 and serum samples were serially diluted and analyzed for anti-KLH IgG antibodies by ELISA. Curve fitting of the OD values at each dilution was performed using non-linear regression. The titer (AbT50) is reported as the dilution that gives half-maximal OD

Reviewer's comment: *The sponsor appears to have chosen a CpG ODN dose that does not increase the antibody titer non-specifically.*

Regarding Agency question #15: *Please provide a (dose dependent) assessment of the adjuvant effect of the different lots of LMWH (yours and the RLD's) in the absence of CpG ODN or LPS.*

Reviewer's comments: The sponsor provides data of several lots tested side by side with RLD where animals received KLH alone or in the presence of increasing concentrations of LMWH. The data for all 4 lots tested appears consistent with the Sponsor conclusions that there are no differences between the SM lots of enoxaparin and the RLD. Of note, administration of LMWH in animals results in the induction of antibodies even in the absence of adjuvants.



Similar data was provided for 4 different product lots.
No apparent differences between RLD and SME.

July 30, 2009

Review of an additional site for heparin source: [redacted], [redacted]

The Original Immunogenicity Amendment to ANDA 77-857, submitted September 25, 2008, evaluated the potential immunogenicity of nine lots of Enoxaparin Sodium Injection Drug Product that were derived from [redacted] This amendment provides data for three Drug Product lots (911005, 911016, & 911304) that are derived [redacted]. lots supplied by [redacted] (911304 also called 911451 is packaged in syringes).

Note: None of the lots tested were produced using heparin from this manufacturing site [redacted] makes identifying problems with any particular source very difficult.

Table 3. Enoxaparin Sodium Injection Manufacture:

[redacted]

Table 5. Heparin Sodium, USP Lot Data Presented in this Amendment

Heparin Sodium, USP (Sandoz GmbH) Lot Number	Origin of test results	(b) (4)
732007005[1]	OIA	
732007007[1]	OIA	
732007008[1]	OIA	
732007009	This amendment	
732007011	This amendment	

[1] Lot was previously tested for impurities; the data for this lot were previously submitted in the OIA

[2] (b) (4)

Criteria to choose the lots:

- The Drug Product lots include both the 100 mg/mL and 150 mg/mL formulations
- The Drug Product lots include the lowest (0.3 mL) and highest (1.0 mL) fill volumes
- The Drug Product lots were manufactured at the scale intended for use in commercial manufacture (b) (4) syringes/lot).
- The Drug Product lots are derived from "commercial scale" Drug Substance lots (manufactured at the (b) (4) scale).
- The Drug Product lots are currently designated for commercial supply (pending FDA approval of this ANDA).
- Drug Product Lot 911016 has recently been included in a stability study.

PF4: (b) (4) Lot 090243 was used for the characterization of complexes and (Momenta Lot 24002-29A was used for the in vivo studies.

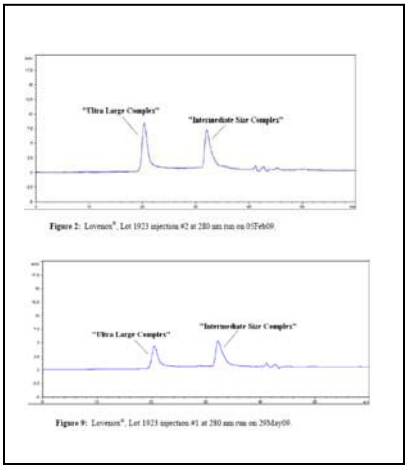
Question 1: PF4-LMWH Complex characterization:

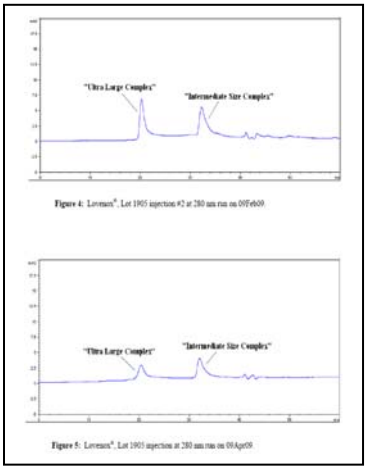
Sandoz/Momenta measured the binding of PF4 to RLD or Enoxaparin Sodium Injection and determined the size and charge of the complexes thus formed by using a series of orthogonal analytical methods as detailed above. Although there were some small differences in the absolute size estimation of the complexes between the studies performed to assess the (b) (4) material and those conducted to assess Heparin of different sources, no differences were noted between the lots that had heparin from (b) (4) and those from the RLD.

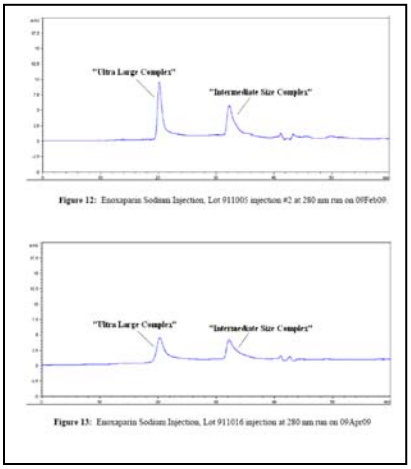
Supporting data:

To assess the avidity of the LMWH for PF4 the sponsor used Surface Plasmon Resonance. The curves and the IC50 looked indistinguishable. The interassay variability is quite4 high as previous studies had shown the RLD to have an IC50 of ~0.45, while in this study the same lots are showing a IC50 of ~0.32 ug/mL.

The SEC, which was previously shown to have very low recovery, show similar peaks. The diameter of the intermediate complexes ranged from 7.5-8.2 x10^4Da for the RLD and from 7.5-7.9 for the SME.


"Ultra Large Complex"
"Intermediate Size Complex"
"Ultra Large Complex"
"Intermediate Size Complex"


"Ultra Large Complex"
"Intermediate Size Complex"
"Ultra Large Complex"
"Intermediate Size Complex"


"Ultra Large Complex"
"Intermediate Size Complex"
"Ultra Large Complex"
"Intermediate Size Complex"

Similarly, the size of the complexes as assessed by SEC MALS at a single PHR of 0.15 were similar between the SME and the RLD. Retention time:~ 20.4 min and Mw:~ 4.5-5.5x10^7 Da for the ultra-large complexes. OF note, there is some interassay variability as comparison of the diameter obtained by SEC MALS for the same lots in this exercise and the previous one (see page 14) shows slightly larger diameters at the same PHR.

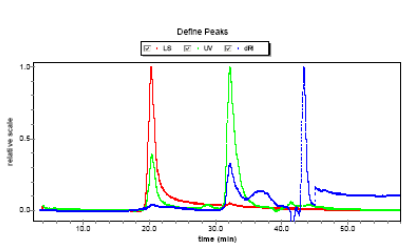


Figure 9.1 Chromatographic Profiles of Complexes formed between PF4 and Lovenox® Lot1923 (the red trace is the LS signal from the 90° detector, the green trace is the UV signal at 280nm and the blue trace is the RI signal).

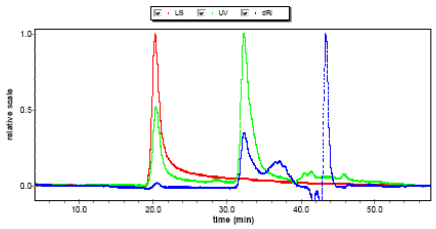


Figure 9.2 Chromatographic Profiles of Complexes formed between PF4 and Enoxaparin Sodium Injection Lot 911016 (the red trace is the LS signal from the 90° detector, the green trace is the UV signal at 280nm and the blue trace is the RI signal).

Comparison by AUC shows similar sedimentation rates for the intermediate complexes. In the previous submission the Sponsor had shown that the ultralarge complexes precipitated very fast by AUC and size could not be established.

Table 16. Complex Size by AUC: Enoxaparin Sodium Injection

Sample	Presence of ultra-large complex	$S_{20,w}$ of intermediate complexes	Relative amount of PF4 in intermediate complexes[1]
Enoxaparin Sodium Injection Lot 911005	Yes	4.03	27.8%
Enoxaparin Sodium Injection Lot 911304	Yes	4.06	25.0%
Enoxaparin Sodium Injection Lot 911016	Yes	4.03	21.5%
Admixture	Yes	4.03	27.7%
RLD_{min}	Yes	3.98	24.9%
RLD_{max}	Yes	4.08	32.7%
Acceptance criteria $(AC)_{min}$[2]	Yes	2.98	18.6%
Acceptance criteria $(AC)_{max}$[2]	Yes	5.10	40.8%

1 This value represents a ratio of fit parameters, as described in the OIA.

2 Acceptance criteria are listed in Table 8 for each analytical test.

By PCS, the PHR at which the z potential =0 was similar for all compounds tested as was the mean complex diameter at PHRs of 0.5, 1.5 and 10.

Table 18. Summary of PHR at ζ_0 for RLD, DP and Admixtures

Lot	PHR at ζ_0
RLD Lot 1905	1.3
RLD Lot 1923	1.3
RLD Lot 21041[1]	1.2
	1.2
Enoxaparin Sodium Injection Lot 911005	1.4
Enoxaparin Sodium Injection Lot 911304	1.3
Enoxaparin Sodium Injection Lot 911016	1.2
Admixture	1.4
Acceptance criteria $(AC)_{min}$[2]	0.9
Acceptance criteria $(AC)_{max}$[2]	1.6

1 RLD Lot 21041 was measured on two separate occasions; results from each experiment are fit separately.

2 Acceptance criteria are listed in Table 8 for each analytical test.

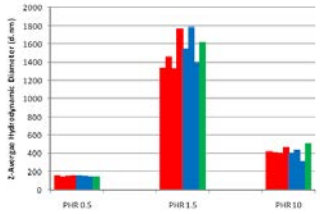


Figure 7. Particle Size Measurement

(Top) **Particle Size for three RLD lots (red), Enoxaparin Sodium Injection Lot 911005 (blue) and admixture sample (green) was measured at different PHRs. RLD Lot 21041 was measured on two separate occasions; both results are shown for each PHR.**

Of note, the diameter shown (particularly for 0.5 PHR) is about twice that shown in the data previously submitted for the same lots suggesting that the results obtained by this

Table 20. Hydrodynamic Diameter Values for Enoxaparin Sodium Injection (d.nm)

Sample	Protein to Enoxaparin (Heparin) Ratio (PHR) 0.5	1.0	2.0	5.0
Enoxaparin Sodium Injection Lot 911005	160	4400	2900	1200
Enoxaparin Sodium Injection Lot 911304	170	3800	2700	1300
Enoxaparin Sodium Injection Lot 911016	150	3800	2400	1200
Admixture	170	4200	3000	1200
RLD_{min}[1]	140	3500	2300	1100
RLD_{max}[1]	200	4700	3300	1500
Acceptance criteria $(AC)_{min}$[2]	100	2600	1700	800
Acceptance criteria $(AC)_{max}$[2]	260	5900	4100	1900

[1] RLD_{min} and RLD_{max} values are based on individual measurements determined for the RLD lots.
[2] Acceptance criteria represent (b) (4) of the minimum value measured for RLD (RLD_{min}) and (b) (4) of the maximum value measured for the RLD (RLD_{max})

method are quite variable and therefore not very sensible to small changes in complex formation. The trend in terms of diameter is maintained for the different PHRs.

No differences in A280 are noted between the RLD and the SME. The optimal ratios (PHR_{max}) of Enoxaparin Sodium Injection and PF4 to form ultra-large complexes (as measured by A_{280}) are the same as those determined for the RLD.The absorbance profiles for both RLD and Enoxaparin Sodium Injection are the same, as measured by this assay at various different PHRs.

Table 21. PHR_{max} and A_{280} Values for RLD, Enoxaparin Sodium Injection and Admixture

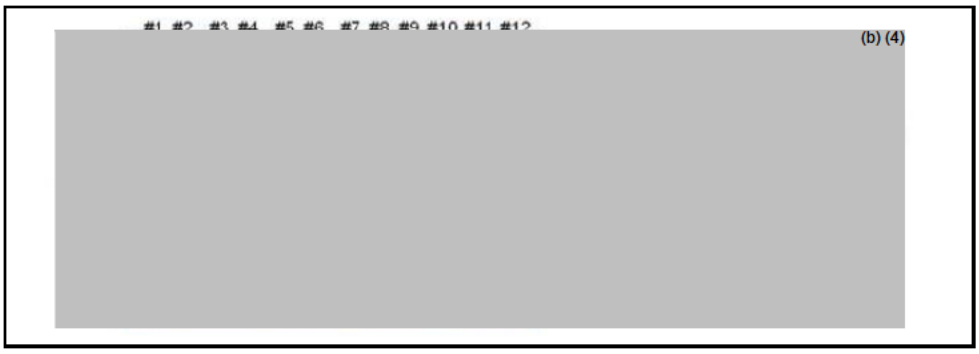
Sample	PHR_{max}	A_{280} at PHR
RLD Lot 1905	1.2	0.36
RLD Lot 1923	1.2	0.35
RLD Lot 21041	1.0	0.36
Enoxaparin Sodium Injection Lot 911005	1.2	0.36
Enoxaparin Sodium Injection Lot 911304	1.2	0.36
Enoxaparin Sodium Injection Lot 911016	1.0	0.35
Admixture	1.2	0.36
RLD_{min}	1.0	0.35

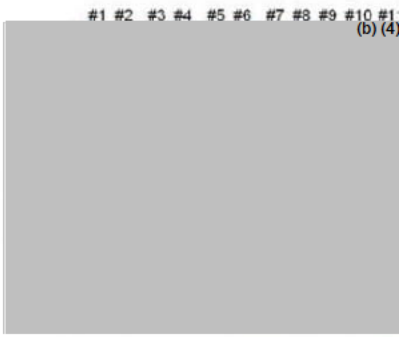
Question 2: Impurities:

The data from the evaluation of Enoxaparin Sodium Injection indicate that no individual proteins are present in Enoxaparin Sodium Injection at a level greater than (b) (4) *micrograms of protein per mL of Drug Product formulated at 100 mg/mL. Similarly, no phospholipids, triglicerides, or fatty acids (LOD:* (b) (4) *ppm) were evident by gas chromatography. No residual DNA was evident by Threshold Total DNA Assay (Spike recovery* (b) (4) *; LOD* (b) (4) *ng/150mg). Leachables were assessed by HPLC or GCMS and showed no difference between the SME and the RLD.*

Supporting data:

Protein content: Two lots of Heparin Sodium, USP (732007009 and 732007011), one lot of RLD (21041) and three lots of Enoxaparin Sodium Injection (911005, 911016 and 911304) were tested using the trichloroacetic acid precipitation method (LOD: (b) (4) ppm or (b) (4) %), the bradfor method (LOD (b) (4) %). Silver stained SDS PAGE gels (LOD: (b) (4) ng /band) loaded with 500ug) show no bands but a smear between 14- 3.5 kDa for the unfractionated heparin but no bands for the individual lots. Of note, there is a clear smear in the RLD lots that is absent in the SME lanes.

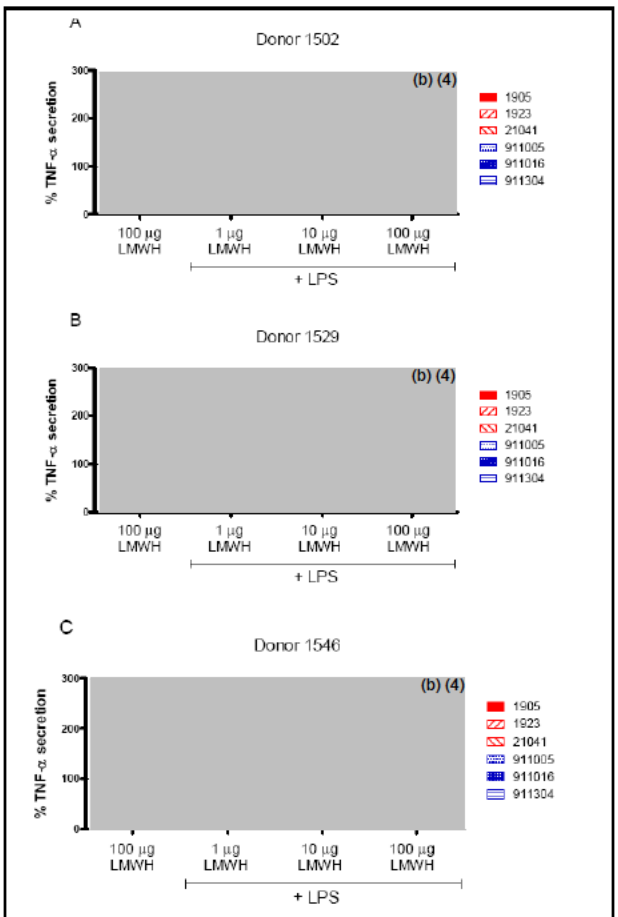




Question 3: Functional Studies:

As in previous studies the sponsors assess the immunostimulatory effect of SME by assessing TNFa induction and cell proliferation in PBMC stimulated with 1 µg/mL, 10 µg/mL and 100 µg/mL in the presence of suboptimal LPS (6.5pg/ml) or CpG ODN (). Results are shown as stimulation indexes over the same cells stimulated with CpG or LPS alone. LMWH augment the response to suboptimal doses of LPS and to a lower degree CpG ODN. No differences are evident between the SME and the RLD.

In vivo immunogenicity of LMWH was tested in a mouse model. Mice were immunized for five consecutive days with PF4:LMWH at a PHR ratio of 2:1. Mice developed an antibody response to PF4 by Day 15. All groups treated with PF4:LMWH complexes showed higher Ab response than the control group treated with PF4 alone. Note that the PHR was changed from 1:1 to 2:1 relative to the studies provided earlier.



I. **Effect of LMWH on TNF-α secretion from PBMCs stimulated with LPS**

<u>Supporting data:</u>

All in vitro studies conducted with PBMC from 3 donors.

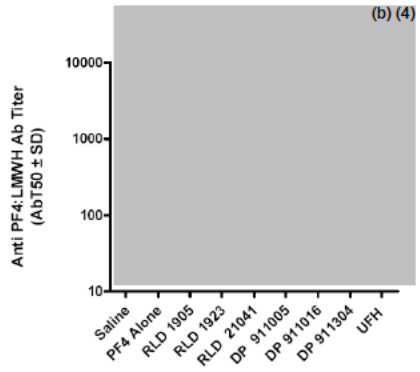
TNFa induction: The RLD and the DP on TNF induction and cell proliferation were tested at 1 µg/mL, 10 µg/mL and 100 µg/mL in the presence of suboptimal LPS (6.5pg/ml).

The readout is expressed as a percentage of TNF-α secreted in response to LPS alone. Donor 1502 PBMCs treated with LPS alone produced an average of 274.8 pg/mL, 324.1 pg/mL and 437.6 pg/mL of TNF-α in three independent experiments. Donor 1529 PBMCs treated with LPS aloneproduced an average of 169.8 pg/mL, 205.6 pg/mL and 206.1 pg/mL of TNF-α in three independent experiments. Donor 1546 PBMCs treated with LPS alone produced an average of 207.0 pg/mL,

165.9 pg/mL and 224.1 pg/mL of TNF-α in three independent experiments.
As with previous lots, addition of LMWH increases LPS induction of TNF. Previous studies suggested that LMWH improve binding to LPS binding protein. Dose dependent increase in TNFa in response to CpG ODN is less significant. Results are similar for all 3 blood donors and indistinct from those presented previously for other lots.
T cell recall response: no difference is evident between the cells stimulated with SME and RLD.

In vivo studies: Mice were immunized for five consecutive days with PF4:LMWH at a PHR ratio o f 2:1. Mice were randomly assigned to the following treatment groups: saline, hPF4 alone or PF4:LMWH complexes at a 2:1 PHR using three Lovenox ® lots or three generic Enoxaparin sodium. Ab levels were tested at day 15.

No data shown on the progression of the antibody titer, so it is not possible to tell whether the SME accelerated ab production or whether the 15 day time-point represents the maximum response.



Anti–PF4:LMWH Antibody Response

C57BL/6 mice were immunized daily by tail vein injections for 5 consecutive days with hPF4:RLD (red) or hPF4:DP (blue) complexes at a PHR ratio of 2:1, with hPF4 alone (black) or with hPF4:UFH at a 4:1 PHR (purple). DP and RLD lots tested are described in Table 34. Mice were bled on Day 15 and the serum samples were serially diluted and analyzed for anti-PF4 IgG antibodies by ELISA. Curve fitting of the OD values at each dilution was performed using non-linear regression. The titer (AbT50) is reported as the dilution that gives half-maximal OD values. Antibody titers (AbT50 values) of individual animals (n=10/group) are plotted in a scatter plot. Error bars represent the standard deviation. One-way ANOVA indicated no significant difference between any of the RLD lots and DP lots tested. The positive control group treated with PF4:UFH was significantly different from all other groups. Raw data are provided in Appendix 22.

In studies designed to compare the adjuvant effect of LMWH, three DP lots were tested in separate experiments head-to-head against a single reference lot of RLD (RLD Lot 1923) at concentrations of 0, 30, 100, 300 or 1000 µg LMWH together with KLH (50ug/mouse). No suboptimal doses opf CpG were used. Positive control used CpG at 50ug/mouse. Ab progression was monitored (day 0, 7, 14 and 21). No dose dependent increase in ab. specific responses and no differences in titer between SME and RLD for any lots at any dose.

A

Overall, the response for the material partially derived from (b) (4) *is not different from that observed for the other lots.*

Following this page, 1 page 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/

DANIELA I VERTHELYI
09/22/2009

AMY S ROSENBERG
09/29/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-857

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

MEMORANDUM

DATE: September 21, 2004

FROM: Helen N. Winkle, Director, Office of Pharmaceutical Science, CDER

TO: Florence Houn, M. D., Director, Office of Drug Evaluation III, CDER

CC: Moheb M. Nasr, Ph.D., Director, Office of New Drug Chemistry, Office of Pharmaceutical Science, CDER

Gary J. Buehler, R.Ph., Director, Office of Generic Drugs, Office of Pharmaceutical Science, CDER

SUBJECT: The appropriate regulatory pathway for ANDAs submitted for Lovenox (enoxaparin sodium injection) and other LMWHs.

TO THE ANDA RECORDS FOR: ANDA 76-684, Amphastar Pharmaceuticals
ANDA (b) (4)
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ANDA

Based on previous correspondence regarding whether Lovenox (enoxaparin sodium) ("enoxaparin") and other low molecular weight heparins (LMWHs) can be considered under 505(j) and related discussions with the Office of New Drug Chemistry (ONDC), the Office of Pharmaceutical Science (OPS) requested a scientific analysis of the question. The main emphasis of the discussion was to determine whether it was possible to demonstrate active ingredient sameness regardless of the complexities involved in characterizing the complicated chemical structure of LMWHs. This memorandum sets forth OPS's scientific conclusions on this issue.

Background

Enoxaparin is a low-molecular weight heparin (LMWH) and consists of a heterogeneous mixture of oligosaccharides. This structural heterogeneity presents unique challenges to the review of ANDAs claiming enoxaparin as the reference listed drug (RLD). Based upon these challenges, the Office of Generic Drugs (OGD) sought to determine whether it would be possible to demonstrate that the generic product contains the "same" active ingredient as the reference listed drug and, if so, how this may be achieved. As part of this undertaking OGD has scrutinized 1) relevant scientific publications regarding the characterization of LMWHs, 2) data from a citizen

petition that claims that such a demonstration of sameness would not be possible, 3) NDAs (including all supplemental applications) for this LMWH product class, and 4) proprietary data from prospective and current ANDA applicants.

This analysis concluded that it would be feasible to demonstrate active ingredient "sameness" for enoxaparin and recommended five requirements that would provide proof of "sameness". These conclusions are also applicable to other LMWH products.

1. Equivalence of physico-chemical properties
2. Equivalence of heparin starting material and mode of depolymerization
3. Equivalence in disaccharide building blocks and in sequence of major oligosaccharide species
4. Equivalence in biochemical and biological assays
5. Equivalence of in-vivo pharmacokinetic profiles

Discussion

Upon issuing this proposal for internal CDER comment, ONDC presented concerns with regard to the proposed requirements for demonstrating "sameness" in these products. ONDC's most fundamental objection was to OGD's approach for demonstrating molecule-to-molecule equivalency within the variation found in the RLD. This objection was summarized in several memos (January 9, 2004; January 12, 2004; April 18, 2004). While ONDC felt that a demonstration of molecule-to-molecule equivalency necessitates direct isolation and characterization of all components in a side-by-side, molecule-to-molecule comparison, OGD felt that this approach was both unrealistic and unnecessary, and that other approaches could demonstrate molecular equivalency.

In this context, OGD adopted an approach of providing proof of molecule-to-molecule equivalency, based upon the aggregate weight of scientific evidence. In this approach, one of the five requirements necessitates the showing of equivalence of sequence for the major oligosaccharide species, in line with ONDC's philosophy of direct isolation and characterization of all components, but we were aware that this would only be possible for a subset of oligosaccharides. Based upon the recognition that limited information would be drawn from the direct sequence comparison of a subset of oligosaccharides, additional requirements, including equivalence of disaccharide mapping and as well as four additional criteria outlined above, were proposed. OGD demonstrated in the *draft White Paper on Pharmaceutical Equivalence of LMWH* and in the *draft Enoxaparin Executive Summary*, how these five criteria comprise a weight of evidence approach, and thus show "by inference" that a generic LMWH has the required molecule-to-molecule equivalency to within the variation found in the RLD.

OGD also showed that conclusions of molecular equivalency based upon inference are not unprecedented. This approach was invoked in prior ANDA approvals of other related heterogeneous oligosaccharide products, including heparin and hetastarch. In particular, the precedent of hetastarch is significant, because hetastarch is derived via chemical hydroxyethylation (via reaction with ethylene oxide) and chemical depolymerization (acid-catalyzed) of isolated amylopectin polysaccharides (plant derived natural product). Hence,

hetastarch is in many ways analogous to enoxaparin, which is derived via chemical depolymerization (β-elimination) of heparin (animal derived natural product).

Dr. Vince H. L. Lee, Scientific Advisor to the Director of the Office of Pharmaceutical Science, has provided a thorough scientific review of this issue, including discussing the differences of opinion between OGD and ONDC. His overall conclusions, summarized in a note (July 19, 2004), were that OGD's five interrelated criteria are conceptually sound and do provide sufficient burden of proof of molecule-to-molecule equivalency. However, to further increase the confidence of the conclusions, Dr. Lee has proposed to amend requirement #3 to include MALDI-MS mapping of both partially digested (fragment mapping) and undigested oligosaccharides (chain mapping) that constitute LWMH. Criteria #3 was amended to include these requirements. Based on Dr. Lee's recommendation, the criteria for showing "sameness" in LMWH's have been changed to:

1 Equivalence of physico-chemical properties
2. Equivalence of heparin starting material and mode of depolymerization
3. Equivalence in disaccharide building blocks, fragment and chain oligosaccharide mapping, and sequence of major oligosaccharide species
4. Equivalence in biochemical and biological assays
5. Equivalence of in-vivo pharmacokinetic profiles

Over the course of discussions, ONDC raised a number of other concerns. These were addressed in the following ways:

- *ONDC suggested that approving enoxaparin would be analogous to approving a protein drug product (October 7, 2003).* Because enoxaparin is a heterogeneous mixture of oligosaccharides and not a protein drug product, this concern is not applicable.

- *Dr. Yuan-yuan Chiu, former ONDC director, suggested adding some saccharide sequencing as a requirement for determining sameness (October 10, 2003).* OGD discussed this proposal with Dr. Chiu in detail and agreed with her suggestion, amending the proposed recommendations to include this as a requirement.

- *ONDC indicated that current analytical techniques would not be capable of demonstrating "sameness" (December 7, 2003).* This was recognized and was the basis for including the non-analytical requirements in the approach for demonstrating molecular equivalency. This included equivalency of 1) heparin starting material, 2) mode of depolymerization, and 3) in vivo pharmacokinetic/ pharmacodynamic profiles.

- *ONDC also specified that the currently approved LMWH products in the US are not interchangeable (December 17, 2003).* This was acknowledged in the original proposal. OGD provided a limited comparison of enoxaparin to other FDA approved and marketed LMWHs utilizing the proposed five criteria. This analysis clearly showed that the other LMWHs would fail to meet most if not all of the five criteria proposed for "sameness" to enoxaparin, and that they would certainly not be approved by OGD as interchangeable with enoxaparin.

Conclusion

From the above scientific discussion and the information provided by Dr. Lee in his analysis, the Office of Pharmaceutical Science (OPS) has concluded that OGD's revised five criteria are sufficient to demonstrate "sameness" for enoxaparin, and that such an approach is applicable to other LMWH products. Therefore, OGD may review an ANDA for a LMWH product under section 505(j) of the Act that meets these requirements. OPS recognizes that, with improvements in the understanding of the biological and clinical properties of LMWHs and/or with advances in the analytical technologies that may be used to characterize these products, other approaches for demonstrating drug substance "sameness" under section 505(j)(2)(A)(ii)(I) of the Act may be deemed suitable as well.

Appendix I

Chronological order of significant events that relate to the general discussion of ANDAs for Lovenox (enoxaparin) and other Low Molecular Weight Heparin (LMWH) products.

August 23, 2001
The Complex Drug Substance Coordinating Committee (CDSCC) determined that it would be feasible to demonstrate, via chemical, physical, and biological tests, drug substance sameness in LMWHs. It was concluded that generic versions of LMWH products would be suitable for review and approval under section 505(j) as an ANDA. Although various criteria for accepting/approving ANDAs for LMWH products were discussed, no definitive criteria were developed and it was concluded that the criteria used in the ANDA review should be handled on a case-by-case basis.

February 19, 2003
Aventis Pharmaceuticals (Aventis) submited a citizen petition requesting that the FDA withhold approval of ANDAs for generic versions of Lovenox (enoxaparin). Aventis argues that due to the chemical heterogeneity of enoxaparin, it would not be possible to demonstrate that a generic enoxaparin product is the same as the RLD, unless 1) the generic manufacturer utilizes the same manufacturing process as the innovator, or 2) equivalence is demonstrated through comparative clinical trials. Lovenox (enoxaparin) belongs to the LMWH drug product class.

March 4, 2003
Amphastar filed ANDA 76-684 for enoxaparin, which was accepted by OGD.

(b) (4) filed ANDA (b) (4) for enoxaparin, which was accepted by OGD.

(b) (4) filed ANDA (b) (4) for enoxaparin, which was accepted by OGD. (b) (4) (b) (4) has subsequently filed two additional ANDAs (b) (4) for enoxaparin; these are simply variations in the concentration and/or packaging of the injectable drug product formulation.

October –November, 2003
OGD developed a draft "white paper" that discusses in detail the scientific and regulatory criteria (as well as the rationale) necessary for establishing drug substance sameness in ANDAs for LMWH. This document was sent to ONDC and OND for comment. Dr. Chiu suggested the necessity of adding some saccharide sequencing as a requirement. OGD discussed this proposal in detail and agreed with her suggestion. The draft "white paper" was revised on November 10, 2003, to include the following five requirements:

- Equivalence of physico-chemical properties (e.g., molecular weight distribution)
- Equivalence of heparin starting material and the mode of depolymerization
- Equivalence in disaccharide building blocks and in sequence of the major oligosaccharide species

- Equivalence of *in-vitro* biochemical and biological assays
- Equivalence of *in-vivo* pharmacokinetic parameters

October 7, 2003
In a meeting with OND and ONDC, ONDC chemists expressed some concern that approving a generic LMWH product would be analogous to approving a generic protein product. OGD pointed out that because LMWH products are a heterogeneous oligosaccharide mixture, such concerns were not relevant. Apart from this concern, OND and ONDC were in overall agreement with OGD's proposed ANDA requirements for LMWH products.

December 8, 2003
In an OPS meeting, ONDC expressed concern that current analytical techniques would be incapable of demonstrating sameness in LMWH. OGD acknowledged this and explained that this was the basis for including the non-analytical requirements in the approach for demonstrating sameness. This included equivalency of 1) heparin starting material, 2) mode of depolymerization, and 3) in vivo pharmacokinetic/pharmacodynamic profiles.

December 31, 2003
(b) (4) submited a confidential controlled correspondence to FDA, claiming that it would not be possible to demonstrate a generic LMWH product is the same as the RLD. The fundamental concepts raised in the (b) (4) controlled correspondence do not differ from those already raised in the Aventis citizen petition.

January 5, 2004
In a meeting between OGD and OPS, OPS concluded that OGD's proposed criteria would be sufficient to demonstrate sameness in LMWH products. OGD prepared a draft memo for the administrative record to explain that ONDC's concerns were considered.

January 9, 2004 and January 12, 2004
The memorandum from ONDC chemists on January 9, 2004, and the draft memorandum from ONDC on January 12, 2004, critique OGD's "white paper" and argue that the proposed criteria cannot demonstrate sameness for LMWH.

February 5, 2004
A memorandum from OND Medical Officers, Kathy M. Robie-Suh (Team Leader) and Robert Justice (Division Director) to Brian Pendleton (ORP), concludes based upon ONDC conclusions, "because enoxaparin sodium has not been sufficiently characterized at this time to allow establishing structural identity ("sameness") between Lovenox and a putative generic enoxaparin sodium using currently available methods, clinical trials are needed to establish therapeutic equivalence of a putative generic enoxaparin sodium to Lovenox".

February 12, 2004
Aventis submited a supplement to their citizen petition. The supplement does not raise new fundamental concepts that were not already put forth in the original petition.

March 30, 2004
OGD distributed a draft executive summary regarding sameness for enoxaparin. This document provided a synopsis of both the scientific and regulatory concepts that may be used to demonstrate "sameness" in ANDAs. Most significantly, the draft executive summary argued that the Agency's 1996 decision to approve an ANDA for hetastarch (a product fully analogous to enoxaparin) provides regulatory precedent for ANDAs for enoxaparin.

April 18, 2004
A draft memorandum from ONDC critiqued OGD's executive summary and argued that hetastarch is not analogous to enoxaparin, and therefore does not provide regulatory precedent for ANDAs for enoxaparin. This conclusion was based upon ONDC's claim that hetastarch is a simple polysaccharide.

July 19, 2004
In a note to Helen Winkle, Dr. Vince Lee concluded that the interrelated proposal for demonstrating "sameness" for LMWHs is scientifically sound. To further increase the confidence of the proposed approach, Dr. Lee proposes to amend requirement #3 to include MALDI-MS mapping of both partially digested (fragment mapping) and undigested oligosaccharides (chain mapping) of LMWH.

cc: ANDA 76-684
ANDA (b) (4)
ANDA
ANDA
ANDA
J. Woodcock/HF-2
S. Galson/HFD-1
J. Axelrad/HFD-5
B. Pendleton/HFD-7
A. Hussain/HFD-3
L. Yu/HFD-600
J. Korvick/HFD-180
K. M. Robie-Suh/HFD-180
D. Moore/HFD-180

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

/s/

Thomas Hinchliffe
12/22/2006 10:46:30 AM
CSO

Beth Brannan, Director
Regulatory Affairs

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2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4237
Fax +1 303 438 4600
Email:
beth.brannan@sandoz.com

SANDOZ

505(j) K2-K4 O.K
24 Oct 2005

77-857
N-000

August 26, 2005

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Original Abbreviated New Drug Application

RE: Enoxaparin Sodium Injection:
100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1.0 mL)
150 mg/mL (120 mg/0.8 mL and 150 mg/1.0 mL)
This application contains CMC, In vivo Bioequivalence data, Labeling and Sterility Assurance Data

Dear Sir or Madam:

Sandoz Inc. (Sandoz), the Applicant, is submitting herewith an abbreviated new drug application (ANDA) under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1.0 mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/1.0 mL). This filing is based upon the reference listed drug (RLD) Lovenox® (enoxaparin sodium) Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1.0 mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/1.0 mL), manufactured by Aventis Pharmaceuticals, Inc. or Sanofi-Aventis (NDA # 020164).

This application is submitted in duplicate as archival and review copies. The archival copy of this application consists of fourteen (14) volumes in blue covers. The chemistry review copy consists of twelve (12) volumes in red covers. The pharmacokinetic and bioavailability review copy consists of three (3) volumes in orange covers. Three (3) separately bound and identified copies of the method validation package are also provided.

As required under 21 CFR 314.94(d)(5) a complete and accurate copy of the technical sections of the ANDA (14 volumes in burgundy binders) has been sent to B. Belinda Collins, District Director, of the Denver District Office of FDA at Building 20 Denver Federal Center, 6th and Kipling Street, P.O. Box 25087, Denver, Colorado 80225-0087.

While this ANDA represents a duplicate of a sterile solution Drug Product, the Office of Generic Drugs (OGD) has indicated that an in vivo bioequivalence study would be necessary to obtain approval of this drug product. The in vivo study is included in Section VI of the ANDA and reinforces that our Enoxaparin Sodium Injection product is bioequivalent to the Reference Listed Drug (RLD). A waiver request for the 150mg/mL syringe is also included as part of Section VI. The complete in vivo bioequivalence study (conducted by MDS Pharma) is appended to the end of the ANDA as volumes 13 and 14 of the archival submission and volumes 2 and 3 of the pharmacokinetic/bioavailability review copies. The title of the study protocol appears below:

Protocol No. AA23230: Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Sandoz and Aventis (Lovenox®) 100 mg/mL Enoxaparin Sodium Subcutaneous Injection in Healthy Adult Volunteers under Fasting Conditions

A Diskette is included in the front cover of the pharmacokinetic and bioavailability review (orange) binders with electronic data and SAS Transport Files.

In accordance with current FDA requirements and expectations regarding content of labeling, a single CD containing an electronic copy of labeling in PDF format and MS WORD is included in the archival copy. Sandoz declares that the information on the CD is identical to the information provided in the paper copy of this ANDA.

The Exhibit Batch for this application was manufactured and fully packaged for Sandoz by Baxter Pharmaceutical Solutions LLC (Baxter) at their Bloomington, IN facility. The Drug Substance, Enoxaparin Sodium, is manufactured for Sandoz exclusively by (b) (4) located in (b) (4) In lieu of a DMF filing, complete information regarding the manufacture, characterization, release testing, and stability of Enoxaparin Sodium is provided in the ANDA as Section VIII. Sandoz commits that any changes to the process will be filed to the ANDA in an appropriate regulatory submission and, if appropriate, an amendment or supplement to support a change for the finished Drug Product will also be provided.

Sandoz has partnered with Momenta Pharmaceuticals, Inc. (Momenta) located in Cambridge, MA on this project. Momenta met with OGD regarding this product on May 20, 2003 during which time they described their methods for characterizing this complex heterogeneous Drug Product and strategy for submitting an ANDA for a generic enoxaparin sodium which was therapeutically equivalent to Lovenox®. A Briefing Book and set of presentations slides for this meeting were provided and are on file at OGD. Momenta also had a teleconference meeting with OGD on March 24, 2004, at the request of OGD. A set of presentation slides was also provided for this meeting and are on file at OGD. The characterization strategy presented in this ANDA is consistent with that which was presented to OGD at both of these prior meetings. A full description of Momenta's characterization technology is provided in Section VIII of this application.

To fulfill FDA requirements for therapeutic equivalence, the Applicant will demonstrate that its generic Enoxaparin Sodium Injection is chemically equivalent, pharmaceutically equivalent, and bioequivalent to Lovenox®. The Applicant recognizes that Lovenox® is a complex, heterogenous mixture of many different polysaccharide chains, which historically has not been well characterized. Each chain is composed of a sequence of varying disaccharide units, which have been shown to modulate over 100 different growth factors and other biological mediators involved in multiple disease states. In light of this broad potential biological and clinical activity, the Applicant considers the *entire* mixture to be the active ingredient which must be thoroughly characterized to meet FDA requirements for chemical equivalence. While current compendial and other more standard analytical tests are required, they are not sufficient to define the detailed chemical structures which comprise the active ingredients in Lovenox®.

The Applicant will present an extensive equivalence protocol which includes the more traditional elements of characterization such as conformance of UFH starting material, drug substance, and drug product with appropriate compendial requirements as well as corresponding stability studies. However, the Applicant recognizes that these alone are not sufficient to establish equivalence. Given the complexity of the mixture, any characterization protocol must account for the inherent structural diversity of the Lovenox® chains and the structurally modified components on these chains. To provide the necessary level of characterization, the Applicant presents seven Primary Characterization Methods (Section VIII.1.a.iv.4). These analytical methods provide

complementary sets of data which, when taken together, afford a comprehensive understanding of the chemical structures that define Lovenox®. Additional Confirmatory Characterization Methods (Section VIII.1.a.iv.5) will also be presented which qualify the accuracy and appropriateness of these Primary Characterization Methods.

Using these Primary Characterization Methods, the Applicant is able to discriminate enoxaparin sodium samples which are chemically equivalent and chemically non-equivalent to Lovenox®. This emphasizes that thorough characterization is essential to ensure that any approved generic enoxaparin sodium will exhibit the same clinical response in patients (efficacy and safety profile) as Lovenox®.

In summary, the Applicant presents data supporting its claim that its generic Enoxaparin Sodium Injection is pharmaceutically equivalent and bioequivalent to Lovenox®. In addition, the Applicant will present data supporting its claim that its generic Enoxaparin Sodium Injection is chemically equivalent to, and contains the same active ingredients as Lovenox®, based on the following conclusions:

1. The Applicant's generic Drug Substance and Drug Product are both chemically equivalent to a composite analysis of Lovenox®.
2. The Applicant's generic Drug Substance is chemically equivalent to the *European Pharmacopoeia* Enoxaparin sodium Certified Reference Standard, both at time of release as well as on an accelerated stability study.
3. The Applicant's generic Drug Product is chemically equivalent to Lovenox®, not only at time of release, but also on an accelerated stability study.

While all official regulatory correspondence and contact should go through Beth Brannan at Sandoz, Sandoz hereby is providing authorization for Steven Brugger (617) 395-5105 of Momenta Pharmaceuticals, Inc., Cambridge, MA and (b) (4) (b) (4) to discuss this ANDA directly with the Office of Generic Drugs.

This submission contains trade secrets and confidential information exempt from public disclosure persuant to Exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Persuant to FDA regulations Sandoz is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event of an FDA determination that all or any part of this submission may be disclosed.

Should you have any questions please contact me at (720) 810-0129 or Carmelle Lucas, Manager, Regulatory Affairs at (732) 355-4083. Our fax number is (303) 438-4600.

Sincerely,

Beth Brannan
Director, Regulatory Affairs

cc: District Office

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-857 **FIRM NAME:** SANDOZ INC.

RELATED APPLICATION(S): (b) (4)

Bio Assignments:		Micro Review
☒ BPH	☐ BCE	☒ Micro Review
☐ BST	☐ BDI	

First Generic Product Received? NO

DRUG NAME: ENOXAPARIN SODIUM
DOSAGE FORM: INJECTION, 100 MG/ML (30 MG/0.3 ML)
(40MG/0.4ML)(60 MG/0.6 ML)(80 MG/0.8 ML) AND (100 MG/1.0 ML)
150 MG/ML (120 MG/0.8 ML AND 150 MG/1.0 ML)

Random Queue: 10
Chem Team Leader: Rosencrance, Susan PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: AUGUST 26, 2005	**Received Date:** AUGUST 29, 2005
Comments: EC- 9 YES **On Cards:** YES **Therapeutic Code:** 8010500 COAGULANTS ANTI-COAGULANTS INCLUDING VITAMIN K HEPARIN	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Lanphire **Date** 10/17/05	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 24 Oct 2005

Beth Brannan
(720) 810-0129
fax (303) 438-4600

ADDITIONAL COMMENTS REGARDING THE ANDA:
Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☑
Sec. II	**Basis for Submission** **NDA# : 20-164** Ref Listed Drug: LOVENOX Firm: AVENTIS ANDA suitability petition required? NO If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: III to '618, '743 pII to 1435 2. Expiration of Patent: 2-14-2012 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use 2. Active ingredients 3. Route of administration 4. Dosage Form 5. Strength boxes of 10	☒
Sec. V	**Labeling** (Mult.Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL 2. 1 RLD label and 1 RLD container label 3. 1 side by side labeling comparison with all differences annotated and explained 4. Was a proprietary name request submitted? (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies): YES** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** Lot# 900321 BP3 Lot# 900729 Lot# 1606 **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING ON 100 MG/ML a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) ok per summary b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: NO	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation 2. Inactive ingredients as appropriate Q1/Q2	☑

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers #18557 - complete manu/characterization provided b. Type II DMF authorization letters or synthesis c. COA(s) specifications and test results from drug substance mfgr(s) d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) f. Spectra and chromatograms for reference standards and test samples g. CFN numbers 2. **Inactive Ingredients** ok a. Source of inactive ingredients identified b. Testing specifications (including identification and characterization) c. Suppliers' COA (specifications and test results) d. Applicant certificate of analysis	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification: YES 3. CFN numbers	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** ok 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 3.If sterile product: (b) (4) 4.Filter validation (if aseptic fill) 5. Reprocessing Statement ✓	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation See attached 2. In-process Controls - Specifications and data	☒
Sec. XIII	**Container** ok 1. Summary of Container/Closure System (if new resin, provide data) 2. Components Specification and Test Data (Type III DMF References) 3. Packaging Configuration and Sizes 4. Container/Closure Testing 5. Source of supply and suppliers address	☒

(b) (4)

Sec. XIV	**Controls for the Finished Dosage Form** ok 1. Testing Specifications and Data 2. Certificate of Analysis for Finished Dosage Form	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted 2. Post Approval Commitments 3. Expiration Dating Period 4. Stability Data Submitted Complete a. 3 month accelerated stability data b. Batch numbers on stability records the same as the test batch	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: ok 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	☒
Sec. XVII	**Environmental Impact Analysis Statement** yes	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) ☒	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-857 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

___ 5) Check address and contact person on letter vs. 356h. (800358 ✓ 800220

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Nov 2005 20-164

✓ 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission.

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

PIV → '435
PIII → '618 & RE '743

___ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ___yes ✓ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Gruin date 24 Oct 2005

ANDA 77-857

Sandoz, Inc.
Attention: Beth Brannan
2555 West Midway Boulevard
Broomfield, CO 80038

OCT 24 2005

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Enoxaparin Sodium Injection, 100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL prefilled syringes and 150 mg/mL, 0.8 mL and 1 mL prefilled syringes

DATE OF APPLICATION: August 26, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 29, 2005

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
(301) 827-5771

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

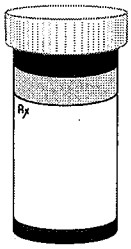
ANDA 77-857

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 24 Oct 2005
HFD-615/ACamphire, CSO _____ date 10/21/05
Word File
V:\FIRMSNZ\Sandoz\LTRS&REV\77857.ACK
F/T October 21, 2005

ANDA Acknowledgment Letter!

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Beth Brannan 720-810-0129
Sandoz Inc.
Fax: 303-438-4600

ANDA: 77-857

From: Ruby Wu
Fax: 301-827-7884 **Phone:** 301-827-7351

Number of Pages: 3 **Date:** 6/5/2006

Comments:

Labeling comments for 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: August 26, 2005 (original)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. 100 mg/mL and 150 mg/mL strengths- delete "1" appearing with "mL". (100 mg/mL and 150 mg/mL)

   b. The RLD supplement approved on March 7, 2005 (NDA 20-164/S-063) provides for revision of the graduation statements for Lovenox® 120 mg and 150 mg strengths from "Each 0.025 mL graduation equals 3.75 mg enoxaparin sodium injection." to "Each 0.02 mL graduation equals 3 mg enoxaparin sodium injection." Please update your labels and labeling to be in accord.

   c. 60 mg/0.6 mL strength only: In the HOW SUPPLIED section of the insert labeling, the syringe label color for the 60 mg/0.6 mL strength is described as "orange". The label and labeling submitted in the August 26, 2005 submission may be mistaken as yellow/gold. We encourage you to choose another shade of orange.

   d. The syringe labels and peel lid labeling are blurry and difficulty to read. Please ensure that the final printed labels and labeling are true to color, size and clarity.

2. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. On page 3137 of your original submission, you stated: "A clear label containing graduated markings is applied to the 60, 80, 100, 120, and 150 mg strengths." Please submit the label with the graduated markings for our review. If possible, please mail us samples of the syringe with the syringe label and graduated markings to facilitate our review.

   b. Include the net quantity on your labels.

   c. Include the route of administration on your labels.

3. PEEL LID LABELING (One syringe)

   Refer to GENERAL COMMENTS

4. CARTON LABELING (10 syringes)

   Directions for use: Please confirm if the directions and explanations of the activation of the safety system are true for your product.

5. INSERT

   a. GENERAL COMMENTS

      i. We note that you reference the "W.H.O. Second International Low Molecular Weight Heparin

Reference Standard" throughout your insert, whereas the RLD references the "W.H.O. First International Low Molecular Weight Heparin Reference Standard". Please explain.

ii. Please note that USAN names are common nouns and should be treated as such in a text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.

b. CLINICAL PHARMACOLOGY, Clinical Trials

i. Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, third paragraph, fifth sentence-revise to read "Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery."

ii. Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE), second paragraph-revise the ninth and tenth sentences to read "Enoxaparin sodium injection or standard heparin therapy was administered for a minimum of 5 days. Enoxaparin sodium injection was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism."

iii. CONTRAINDICATIONS, second paragraph: delete (b) (4).

c. DOSAGE AND ADMINISTRATION, title of the table: "...<30 mL/minute)" [add a space between "30" and "mL"]

Please revise your labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2alG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Beth Brannan
Director, Regulatory Affairs

Sandoz
US Generics
Development
Broomfield, CO
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446
Phone 303 438 4237
Fax 303 438 4600
E-mail beth.brannan
@sandoz.com

SANDOZ

FEDERAL EXPRESS

Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

7/7/06
Change in patent cert for '618 + '743. PIII → PIV. Both expire 12/14/12. Awaiting RR.
DH.

June 22, 2006

RE: ANDA 77-857 Enoxaparin Sodium Injection:
100 mg/ml (30 mg/0.3 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml, and 100 mg/1.0 ml)
150 mg/ml (120 mg/0.8 ml and 150 mg/1.0 ml)
Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc is hereby submitting an amendment to its unapproved Abbreviated New Drug Application for ANDA 77-857 Enoxaparin Sodium Injection, 100 mg/ml and 150 mg/ml in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our original ANDA application dated August 26, 2005, Section III (Patent Certification Statement).

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent Certification for Sanofi Aventis' U.S. Patent Nos 5,389,618 and RE 38,743. In support of this revision, we are enclosing a signed Patent Certification Statement. Concurrent with this amendment we are providing Notice to the Patent Holder per 21 CFR 314.95(a) and (c).

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Beth Brannan, Director
Regulatory Affairs

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

ORIG AMENDMENT
N AF

JUL 0 6 2006

RE: ANDA 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Amendment – Response to Facsimile of June 5, 2006

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your fax correspondence dated June 5, 2006. The labeling deficiencies have been addressed and are summarized below:

1. GENERAL COMMENTS

a. For the 100 mg and 150 mg strengths, we have deleted the "1" appearing with "mL" so they now read 100 mg/mL and 150 mg/mL.

b. We have updated the graduation statements on our labeling for the 120 mg and 150 mg strengths to read "Each 0.02 mL graduation equals 3 mg enoxaparin sodium injection."

c. The orange color for the 60 mg/0.6 mL strength was poorly represented in our original submission. The final printed label will clearly be orange. Please reference the attached paper copies which more closely match the final print color.

RECEIVED
JUL 0 7 2006
OGD / CDER

d. We are providing a new electronic CD that includes legible copies of our container labels. In addition, we are providing one hard copy of our labels for reference purposes.

2. **SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)**

a. At this time we do not have samples of the syringe or label with graduated markings. Per a telephone conversation between Caryn McCullough (Sandoz) and Ruby Wu (FDA) on June 28, 2006, this is acceptable. If these are needed in the future, please let us know.

To clarify, the label is clear with graduated markings on the label itself. This label will be applied to the graduated prefilled syringe (60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL strengths). A drawing of the label was submitted with the original application and is provided again for reference purposes. Please note we are providing two separate labels, one for the 100 mg/mL strengths and one for the 150 mg/mL strengths.

b. Net quantities (e.g. 0.3 mL syringe) have been added to the syringe labels.

c. We have added the route of administration, "For Subcutaneous Injection," to the syringe labels.

3. **PEEL LID LABELING (One Syringe)**

a. We have incorporated the changes listed under General Comments.

4. **CARTON LABELING (10 Syringes)**

We hereby confirm that the directions and explanations of the activation of the safety system are true for our product. Please note that we use the same safety system as the innovator.

5. **INSERT**

a. GENERAL COMMENTS

i. We reference the W.H.O. Second International Low Molecular Weight Heparin Reference Standard" throughout the insert, whereas the RLD references the "W.H.O. First International Low Molecular Weight Heparin Reference Standard." The Second International Standard is the current standard from the USP. The First International Standard is no longer available.

SANDOZ

ii. We have changed the USAN names to lower case where applicable throughout the package insert.

b. CLINICAL PHARMACOLOGY, Clinical Trials

i. Part of the text under "Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery" was inadvertently omitted. This text has been added.

ii. Part of the text under "Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE)" was inadvertently omitted. This text has been added.

iii. As requested, we deleted "[redacted] (b) (4)" from the CONTRAINDICATIONS section.

c. DOSAGE AND ADMINISTRATION: We have added a space between "30" and "mL" in the title of the table.

Enclosed is an electronic CD containing the revised insert and container labels in PDF format. Since we are submitting our labeling in electronic format, we are providing only one copy in hard copy form for reference purposes. Also included on the CD are the insert in Word format, the side-by-side comparison of our proposed labeling compared to our last submission, and the syringe graduation labels in PDF format.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

Enclosures

BB/ckm

MAJOR AMENDMENT

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 11 2006

APPLICANT: Sandoz Inc. TEL: 303-438-4237

ATTN: Beth Brannan FAX: 303-438-4600

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 26, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Enoxaparin Sodium, 100 mg/mL and 150 mg/mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry comments provided in this communication.

Following this page, 2 pages withheld in full - (b)(4)

cc: ANDA 77-857 Original
ANDA 77-857 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-600/SLee/ 7/5/06
HFD-600/ARaw/ 7/5/06
HFD-640/NYa/6/26/06 7/5/06
HFD-640/THinchliffe/Y.Kong for THinchliffe 7/7/06

F/T by /rad6/28/06

V:\FIRMSNZ\Sandoz\ltrs&rev\77857rev1.doc

TYPE OF LETTER: NOT APPROVABLE - MAJOR

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

ORIG AMENDMENT
N|AC

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MAJOR AMENDMENT

August 31, 2006

RE: **ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)**

Major Amendment - Response to FDA Telefax Dated July 10, 2006
Chemistry, Manufacturing and Control Items Addressed

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your fax correspondence dated July 10, 2006. The items noted in this deficiency fax have been addressed. Please refer to Questions 1a–1j, and 2 below for details of our response. Also, as stated in this correspondence, Sandoz notes and acknowledges that review of the remainder of this application is deferred until submission of additional active ingredient information has been provided.

Reference is also made to a meeting with OGD on August 4, 2006. As requested in this meeting, we are providing additional integration and method validation data. Please reference our response to Questions 3 and 4 below for additional detail and data.

SANDOZ

Also, per our meeting with OGD on August 4, 2006, we have included additional information to increase drug product commercial scale, and we have added (b) (4) as a Drug Substance release testing site. Details of these changes are provided below under items 5 and 6.

At the request of OGD, we are including two compact discs (CDs), presenting word documents of the enclosed material in this amendment as well as Section VIII.1.a.iv of our original ANDA 77-857. These CDs represent a true and complete copy of the hard copy material. Please note, however, that the medium itself is not a product of a validated computer system.

The deficiency questions, and the follow-up discussions at our August 4, 2006 meeting, suggest that a less rigorous set of characterization analytics and approach may be considered acceptable to demonstrate sameness to the RLD. For this reason, we would like to briefly summarize our position.

Background

Characterization criteria for DS to demonstrate sameness should focus on the key molecular properties of the oligosaccharides that comprise Lovenox®, the RLD – including chain composition, distribution and sequence – as these properties are strongly dictated by both the UFH starting material and multiple quality attributes of the manufacturing process. Thus, our enclosed responses to the questions focus primarily on our characterization approach to demonstrate equivalence to the RLD, and our plans to put appropriate controls in place for both UFH starting material and our manufacturing process to ensure that we will reproducibly manufacture an equivalent version of the RLD, at commercial scale, on a routine basis.

API Characterization Requirements: Demonstrate Sameness

Based on our understanding of existing FDA policies, the preferred approach to demonstrate sameness of a generic to the RLD is to characterize any active, or potentially active ingredient, prevalent at ≥ 0.1%. While the dominant clinical use of Lovenox® has been as an anti-coagulant, we have demonstrated in ANDA 77-857 that < (b) (4)% of the total composition is directly responsible for this pharmacological activity. As both composition and sequence of an oligosaccharide chain dictate its protein binding affinity (which leads to its potential physiological effects in man), one must consider the more than (b) (4) unique oligosaccharide sequences in the mixture, ranging from 4mer to 40mer in length, as the active ingredient of the RLD. In addition to describing those oligosaccharides in larger abundance, it is also important to describe the oligosaccharides in smaller abundance, which in aggregate, represent a significant portion (~20%) of the total mixture. Any characterization approach must achieve a level of resolution which adequately describes the molecular properties of these oligosaccharides, fully capturing the macro- and microheterogeneity of the RLD.

SANDOZ

It is critically important that one utilize appropriate analytical techniques, with sufficient analytical rigor, to fully understand the molecular properties of oligosaccharides. Many analytical techniques can be used to measure certain molecular properties, however, each has its own limitations when dealing with complex, heterogeneous mixture products. An example of this is presented in our response to Question 1b. One must utilize some form of "data integration approach" to account for these analytical limitations.

In our approach presented in ANDA 77-857, it is a combination of (1) the rigor of our individual analytical techniques and (2) the integration of the derived data sets which allows us to thoroughly characterize the RLD mixture. This enables us to achieve the resolution required to accurately describe the molecular properties, and concurrently map them to the oligosaccharide chains (describing the location, distribution and/or abundance of these biologically active structures). Utilizing this integration approach, we have demonstrated that our Enoxaparin Sodium contains the same levels and distribution of molecular properties, and in the same context (sequence) as found in the RLD. We have also demonstrated that our Enoxaparin Sodium does not contain any new oligosaccharide properties which we have not observed in the RLD. We consider this level of resolution an absolute necessity to ensure that our Enoxaparin Sodium does not contain any differences in molecular properties from the RLD, which could potentially impact physiological parameters and clinical outcomes in patients. We will discuss our integration approach in more detail in our response to Question 3.

Manufacturing Process Control

Early on in development, it became apparent that we would not be able to (b) (4) [redacted] We will discuss this in more detail in our response to Question 1j (Attachment 9).

SANDOZ

Response to Deficiency Questions Received July 10, 2006:

(b) (4)

ANDA 77-857, is reviewed. *(See Attachment 2)*

Question 1c: (b) (4) These data are provided for the RLD and our generic Enoxaparin Sodium. *(See Attachment 3)*

(b) (4)

discussed. *(See Attachment 5)*

(b) (4)

observed for the RLD. *(See Attachment 7)*

(b) (4)

Following this page, 1 page withheld in full - (b)(4)

SANDOZ

A summary of the documents provided in Attachment 14 is provided in the table below. The documents are placed in order of the section identified in the table, which is also the section where these documents were originally located in the our original ANDA.

Changes from Original Submission		
Section	**Description**	**Change**
VII.2.a	Exhibit Batch Composition Statement	New exhibit batch size presented
VII.2.b	Proposed Production Batch Composition Statement	Increased commercial production batch sizes proposed
XI.1.c	Comparison of Exhibit Batch to Commercial Process	Comparison of original exhibit batches, new exhibit batches, and commercial batches presented
XIV.2	Testing Specifications and Data (COA)	Certificates of Analysis for new exhibit batches

2. Addition of (b) (4) as a Drug Substance release testing site

(b) (4) Inc. has been qualified as a Drug Substance release testing site. *(See Attachment 15 for supporting information.)*

In summary, we recognize the importance of FDA's decision on pending generic enoxaparin applications as we expect it will have a significant impact on the criteria and level of analytical standards which will be required by FDA for future complex generics. We appreciated the opportunity to discuss our ANDA and approach to FDA's questions on our application at our meeting on August 4, 2006. We welcome ongoing discussions and dialogue with FDA as we address these critical issues relating to establishing an acceptable regulatory pathway for generic enoxaparin sodium.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Beth Brannan
Director, Regulatory Affairs

Enclosures: Attachments 1 - 15
Compact Disc #1 (Word Document of this Amendment)
Compact Disc #2 (Word Document of Section VIII.1.a.iv of ANDA 77-857)

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT
PAPER & ELECTRONIC

ORIG AMENDMENT
N AB

September 7, 2006

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device)

Bio Amendment – Electronic Copy of Data From Original Submission

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL, (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a request by OGD to provide an electronic copy of the bio study data and include the eight tables now requested by FDA. A CD is provided containing this data. No new data is included, this CD represents an electronic version of the original submission.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Beth Brannan
Director, Regulatory Affairs

Enclosure: Disc

RECEIVED
SEP 08 2006
OGD / CDER

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd,
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

10/2/06
Notice of PIV cert on patents '618 & '743 sent 6/22/06. Rec'd 6/28/06. Litigation filed on both patents 8/4/06. JL.

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP.

SEP 8 2006

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Documentation of Notification/Receipt of Notice and Documentation of Litigation

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

In accordance with 21 CFR 314.95(b), Sandoz wishes to inform you that Patent Certification Notice to the Patent owner and to the NDA Holder of Patent Nos. 5,389,618 and RE 38,743, as required by Section 505(j)(2)(B)(i) and (ii) of the Act, was given on June 22, 2006.

Sandoz also certifies that the notification to the Patent owner and to the NDA Holder met th content requirements under 21 CFR 314.95 (c)

In accordance with 21 CRF 314.95(e), documentation of receipt (June 26th) by each person provided the notice is provided in **Attachment 1**.

RECEIVED
SEP 11 2006
OGD / CDER

SANDOZ

DOCUMENTATION OF LITIGATION

In accordance with Section 505(j)(4)(B)(iii), Sandoz Inc. certifies that it has been notified of being subject to a lawsuit by Aventis Pharma S.A. and Aventis Pharmaceuticals, Inc. within the prescribed 45-day time frame, for U.S. Patent Nos. 5,389,618 and RE 38,743. A suit was filed August 4, 2006. The Civil Docket for Case # is: 3:06-cv-03671-MLC-TJB. A copy of this complaint is provided in **Attachment 2**.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

Enclosures

BB/jep

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
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Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

ORIG AMENDMENT
N1/AC

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT

RECEIVED
OCT 06 2006
OGD / CDER

October 5, 2006

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Amendment - Response to OGD/FDA Teleconference on September 21, 2006 Chemistry, Manufacturing and Control Items Addressed

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our teleconference with Drs. Raw and Lee on September 21, 2006.

The focus of this teleconference was on our quantitative chain mapping analysis using (b) (4) (b) (4) which we proposed in our formal response to deficiency questions raised in your fax correspondence on July 10, 2006. In the teleconference, FDA requested that we provide two additional data sets, as outlined below.

- (b) (4)
-

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

SANDOZ

In conclusion, based on the proposed equivalence criteria established using four lots of Lovenox®, Enoxaparin Sodium Exhibit Batch 0503X043 is judged to be equivalent to the RLD.

We appreciate the opportunity to discuss our ANDA and approach to equivalence with the Agency, and welcome ongoing discussions and dialogue as we address these critical issues relating to establishing an acceptable regulatory pathway for generic enoxaparin sodium.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope.

Sincerely,

SANDOZ INC.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB:ckm

Record of Telephone Conversation

The following was communicated and followed up via fax:

Please provide a description of analytical procedure for the quantitative chain mapping (e.g., column, mobile phase, detector).

(b) (4)

Although the applicant has demonstrated the (b) (4)

With regard to (b) (4)

This should be included in the submission.

With regard to the in-process control for (b) (4)

specification during release testing. Please explain and justify this discrepancy.

Date:
10/24/06

ANDA Number:
77-857

Product Name:
Enoxaparin

Firm Name:
Sandoz

Firm Representative:
Beth Brannan (Sandoz)
Jennifer Smith (Momenta)
(b) (6) (Momenta)
John Bishop (Momenta)
Zach Shriver (Momenta)
Steve Brugger (Momenta)
(b) (6) (Momenta)

Phone Number:

FDA Representative:
Thomas Hinchliffe
Andre Raw
Naiqi Ya
Lawrence Lee

Signatures:

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

/s/

Thomas Hinchliffe
10/30/2006 01:04:15 PM
PHARMACIST

Sau Lee
10/30/2006 03:13:11 PM
INTERDISCIPLINARY

Andre Raw
11/27/2006 01:29:07 PM
CHEMIST

Naiqi Ya
11/27/2006 01:35:13 PM
CHEMIST

BIOEQUIVALENCY AMENDMENT

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Sandoz Inc. TEL: 303-438-4237

ATTN: Beth Brannan FAX: 303-438-4600

FROM: Steven Mazzella PROJECT MANAGER: (301) 827-5847

Dear Madam::

This facsimile is in reference to the bioequivalency data submitted on August 26, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Enoxaparin Sodium, 100 mg/mL and 150 mg/mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-857 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Enoxaparin Sodium Injection, 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) 150 mg/mL (120 mg/0.8 mL and 150 mg/mL)

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified and additional information is requested:

1. You have stated in the Bioanalytical Method validation CTD format Tables (Anti-Xa and Anti-IIa) that the selectivity has failed to meet acceptance criteria. Please clarify.

2. Please submit a complete report of pre-study assay method validation data including long-term stability data for Anti-Xa and Anti-IIa in frozen plasma samples for a storage period equivalent to the maximum freezer storage duration of the actual study samples. Stability data for processed and unprocessed samples in refrigerator, on benchtop or autosampler, if applicable, freeze thaw stability and stock solution stability data should also be submitted.

3. Please provide a complete list of reassay samples, with original and repeat values (including subject number, period, type of treatment, blood sampling times), and reasons for the reassays including reasons for selecting the final reported values.

4. Please submit all raw numerical data for the anti-Xa and anti-lla assays.

5. Please submit any correlation coefficients for the calibration curves.

6. Please submit all dilution QCs used in the analysis and repeat analysis of actual samples, with dilution magnitude and assay values included.

7. Please confirm that the actual sampling times were used for calculating the pharmacodynamic parameter concentrations.

8. Please submit the certificate of analysis for the test and reference lots used in the study. The certificate of analysis should include assay results of anti-Xa activity, anti-IIa activity and anti-Xa/anti-IIa ratio.

9. Please provide the start and finish dates for the sample analyses of the BE study.

10. Please provide the standard operating procedures (SOPs) describing how the chromogenic assays of anti-factor Xa and anti-factor IIa are conducted.

Note: It would be helpful for the DBE if the response to the above deficiencies was submitted electronically in MSWord format in addition to the hard copy.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
10/27/2006 08:56:57 PM
Signing for Dale P. Conner

Telephone Fax

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (301-827-7351)

TO: Sandoz, Inc.

TEL:303-438-4237

ATTN: Beth Brannan

FAX: 303-438-4600

FROM: Ruby Wu

Dear Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for 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 (Prefilled Single Dose Syringes with Automatic Safety Device).

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-857

Date of Submissions: July 6, 2006 (amendment)

Applicant's Name: Sandoz, Inc.

Established Name: 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Graduated markings for 60, 80, and 100 mg strengths: revise "Graduation 0.025 mL" to read "Each Graduation = 2.5 mg (0.025 mL)"
   b. Graduated markings for 120 and 150 mg strengths: revise "Graduation=3 mg (0.02 mL)" to read "Each Graduation = 3 mg (0.02 mL)" [spacing]

2. PEEL LID LABELING (One syringe)

   150 mg/mL strength only- delete "1" appearing with "mL" (i.e., 150 mg/mL)

3. CARTON LABELING (10 syringes)

   Satisfactory in final print.

4. INSERT

   GENERAL COMMENT: 100 mg/mL and 150 mg/mL strengths- delete "1" appearing with "mL" (100 mg/mL and 150 mg/mL)

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
11/7/2006 04:02:40 PM
Lillie Golson for Wm. Peter Rickman

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

N/AC

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

November 9, 2006

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Telephone Amendment - Response to OGD/FDA Teleconference on October 24, 2006 and Follow up Fax Correspondence dated October 30, 2006
Chemistry, Manufacturing and Control Items Addressed

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our teleconference with the Office of Generic Drugs on October 24, 2006, and your follow up fax correspondence dated October 30, 2006. The items noted in this deficiency fax have been addressed. Please refer to Questions 1-5 (summarized below) in the following pages, with supporting data in the attachments.

Question 1: *Please provide a description of the analytical procedure for the quantitative chain mapping (e.g., column, mobile phase, detector).*

- Experimental conditions for the quantitative Chain Mapping by (b) (4) are provided in **Attachment 1**. These include instrument setup and specifications, sample running conditions, and the data analysis procedure used to obtain quantitative information.

Following this page, 1 page withheld in full - (b)(4)

SANDOZ

Question 4: *With regard to* (b) (4) *This should be included in the submission.*

- We have provided a summary report of the (b) (4) method validation report from (b) (4) (see **Attachment 3**).

Question 5: *With regard to the in-process control for* (b) (4) *Please explain and justify this discrepancy.*

- The discussion held during our October 24, 2006 teleconference on the specification limits for the Drug Product in-process (b) (4) and justification for the limits is summarized in **Attachment 4**.

We appreciate the opportunity to discuss our ANDA and approach to equivalence with the Agency, and welcome ongoing discussions and dialogue as we address these critical issues relating to establishing an acceptable regulatory pathway for generic enoxaparin sodium.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan
Director, Regulatory Affairs

Enclosures:
Attachment 1: Experimental conditions for the quantitative Chain Mapping by (b) (4)
Attachment 2: Updated (b) (4)
Attachment 3: Summary report of the (b) (4) method validation report
Attachment 4: Justification of limits for Drug Product in-process (b) (4)

TELEPHONE CONFERENCE FAX

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Sandoz Inc. TEL: 303-438-4237

ATTN: Beth Brannan FAX: 303-438-4600

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 26, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Enoxaparin Sodium, 100 mg/mL and 150 mg/mL.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten calendar days. If you have questions regarding these deficiencies please contact the Project Manager, Thomas Hinchliffe at (301) 827-5771. Please submit documentation by fax to the attention of the Project Manager a t301-461-8062. Please also submit official hard copies of any faxed documentation to the Document Room.

Question from FDA for ANDA 77-857

1. We note that you have provided quantitative chain mapping data by (b) (4) demonstrating that one production batch of your proposed generic enoxaparin drug substance falls within the Lovenox equivalence criteria. However, to demonstrate that your manufacturing process can reproducibly generate enoxaparin material that is the "same" as the RLD, please provide data on three production batches of your proposed generic enoxaparin, demonstrating that these fall within the Lovenox equivalence criteria.

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

/s/

Thomas Hinchliffe
11/15/2006 10:23:46 AM
PHARMACIST

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

ORIGINAL

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N / AB

November 17, 2006

RE: ANDA 77-857: Enoxaparin Sodium Injection, 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/mL and 150/mL (120 mg/0.8 mL & 150 mg/mL)

Bioequivalency Amendment – Response to FDA Correspondence Dated 10/30/06

NOV 2 0 2006
OGD/ODER

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for 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 in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your letter telefaxed to us on October 30, 2006. The items noted in this deficiency fax have been addressed. Please refer to our response to your deficiencies in the following pages, with supporting data in the attachments 1-8. This bio submission is contained in 5 volumes.

Please note, for convenience purposes, we have provided a CD containing a Word version of this cover letter and PDF versions of this cover letter, the 356h form and Attachments 1-6. Attachments 7 and 8 are provided only in hard copy form.

FDA Deficiency #1

You have stated in the Bioanalytical Method validation CTD format Tables (Anti-Xa and Anti-IIa) that the selectivity has failed to meet acceptance criteria. Please clarify.

Response:

The selectivity failed to meet acceptance criteria stated in (b) (4) SOP (b) (4)

SANDOZ

-Acceptance criteria:

The precision and accuracy of at least 80% (8 out of 10) of the individual human plasma matrix lots tested must be within ±25% at the LLQC and ±20% at the HQC. These plasma lots are used to prepare the appropriate dilutions.

-Results:

For Anti-Xa; Of the 10 lots of human plasma tested, none met acceptance criteria at both the LLQC and HQC levels. All 10 individual human plasma lots tested as blank (i.e., when prepared with no analyte - 0 IU/mL) and generated anti-Xa values below the LLOQ of the method. Five out of ten (5/10) and 2/10 have acceptable recovery at the LLQC and HQC level, respectively.

For Anti-IIa; Of the 10 lots tested, 50% (5 out of 10) of the individual human plasma lots met acceptance criteria at both the LLQC and HQC levels (less than 80% of the lots). All 10 individual human plasma lots tested as blank (i.e., when prepared with no analyte - 0 IU/mL) and generated anti-IIa values below the LLOQ of the method. Nine out of ten (9/10) and 6/10 have acceptable recovery at the LLQC and HQC level, respectively.

-Impact assessment on the data:

(b) (4) acknowledges that there is a human plasma matrix lot-to-lot variation when introducing LMWH at the LLOQ and HQC levels as demonstrated in the selectivity evaluations assessed in the method validations for both anti-IIa and anti-Xa chromogenic methods. Both of these methods only measure the free form of LMWH in human plasma matrix.

In this study, as the same subject received each of the two investigational products (reference product and generic product) in a cross-over design, the effects of human plasma matrix interference is obviated since the relative anti-Xa and anti-IIa profiles of the two investigational products are compared within a single subject. Selectivity would be of greater concern if treatments were compared between independent groups of subjects or if absolute values for anti-Xa and anti-IIa activities were compared between individual subjects.

FDA Deficiency #2

Please submit a complete report of pre-study assay method validation data including long-term stability data for Anti-Xa and Anti-IIa in frozen plasma samples for a storage period equivalent to the maximum freezer storage duration of the actual study samples. Stability data for processed and unprocessed samples in refrigerator, on benchtop or autosampler, if applicable, freeze thaw stability and stock solution stability data should also be submitted.

SANDOZ

Response:

The complete validation report for LMWH anti-Xa and anti-IIa activity assays, including stability and dilution integrity studies for each method is Provided in **Attachment 1**.

FDA Deficiency #3

Please provide a complete list of reassay samples, with original and repeat values (including subject number, period, type of treatment, blood sampling times), and reasons for the reassays including reasons for selecting the final reported values.

Response:

The list of re-assay samples was included in the final report for each of the methods (anti-Xa: Volume 2 of 2, Appendix 16.4, Appendix B, Table 8, Pages 728-729; anti-IIa: Volume 2 of 2, Appendix 16.4, Appendix A, Table 8, Page 659) with subject number, period, sampling timepoints, reason for repeat and rational for final value reported (vc; no valid initial results, therefore repeat is the only valid value).

Revised tables, which include treatment assignment, original and repeat values, and reason for re-assay are provided in **Attachment 2**.

FDA Deficiency #4

Please submit all raw numerical data for the anti-Xa and anti-IIa assays.

Response:

Hard copies of raw data for all assays related to sample analysis for each method are provided. **Attachment 7** contains the hard copy data relating to anti-Xa assays. **Attachment 8** contains the hard copy data relating to anti-IIa assays. These hard copies are a true and exact copy of the original raw data from MDSPS Project Number AA23230_02/FXa and AA23230_FIIa (MDS Pharma Services Project No. AA23230). They include the (b) (4) (b) (4) map, Softmax Pro printout, and (b) (4) regression for data calculation.

FDA Deficiency #5

Please submit any correlation coefficients for the calibration curves.

Response:

Correlation coefficients for the calibration curves for each method are included. Refer to Table 9 provided in **Attachment 3**.

SANDOZ

FDA Deficiency #6

Please submit all dilution QCs used in the analysis and repeat analysis of actual samples, with dilution magnitude and assay values included.

Response:

Dilution QCs (DHQC) were added to any batch (plate) that included diluted samples (b) (4) (b) (4). The DHQC, which was prepared on the day of the assay, was generated in (b) (4) is designed to cover (b) (4) dilutions due to space limitations on the plate, in order to run complete subject profiles on a single plate. Dilution QCs were not used for batch acceptance but for the acceptance of the dilutions in the batch; if both replicates of the dilution QC failed, those samples covered by the DHQC would be rejected. Refer to Table 10 provided in **Attachment 4** for the anti-Xa method. Samples for anti-IIa analysis were not diluted.

FDA Deficiency #7

Please confirm that the actual sampling times were used for calculating the pharmacodynamic parameter concentrations.

Response:

All blood samples were assumed to been taken at the nominal times, unless the actual sampling times exceeded the deviation windows outlined below. The following deviation windows were permitted:

Nominal Time	Reporting Standard
0.0 - 0.5 h	+/- 30 seconds
>0.5 - 2.0 h	+/- 60 seconds
>2.0 - 8.0 h	+/- 2 minutes
>8.0 - 24 h	+/- 5 minutes
>24 - 36 h	+/- 10 minutes

These times were adjusted in the anti-factor IIa, anti-factor Xa (chromogenic assay) and enoxaparin anti-factor Xa (Heptest® assay) data sets used for pharmacodynamic and statistical analyses to reflect the actual times (accurate to within ±0.01 hour) at which the samples were obtained.

FDA Deficiency #8

Please submit the certificate of analysis for the test and reference lots used in the study. The certificate of analysis should include assay results of anti-Xa activity, anti-IIa activity and anti-Xa/anti-IIa ratio.

SANDOZ

Response:

The certificates of analysis for the test and reference lot used in the study are included in **Attachment 5**.

FDA Deficiency #9

Please provide the start and finish dates for the sample analyses of the BE study.

Response:

For Anti-Xa: The start date of sample analysis is 05 Jul 2005 and end date 26 Jul 2005.
For Anti-IIa: The start date of sample analysis is 05 Jul 2005 and the end date is 29 Jul 2005.
These dates are listed in the summary of batches tables included in the final report for each of the methods (anti-Xa: Volume 2 of 2, Appendix 16.4, Appendix B, Table 2, Pages 662-664; anti-IIa: Volume 2 of 2, Appendix 16.4, Appendix A, Table 2, Pages 590-593).

FDA Deficiency #10

Please provide the standard operating procedures (SOPs) describing how the chromogenic assays of anti-factor Xa and anti-factor IIa are conducted.

Response:

Both method SOP's and respective versions are included in **Attachment 6**.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope.

Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Sandoz Inc.

Beth Brannan
Director, Regulatory Affairs

/jep

Enclosures

ORIGINAL

Beth Brannan, Director
Regulatory Affairs

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Fax +1 303 438-4600
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Beth.Brannan@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

ORIG AMENDMENT
N/A

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

November 29, 2006

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Telephone Amendment - Response to OGD/FDA Fax Correspondence dated 11/14/06
Chemistry, Manufacturing and Control Items Addressed

RECEIVED
NOV 30 2006
OGD / CDER

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the Telephone Conference Fax from the Office of Generic Drugs on November 14, 2006. The items noted in this deficiency fax have been addressed and are summarized below.

FDA Question:

We note that you have provided quantitative chain mapping data by (b) (4)

Response:

In our August 31, 2006 and October 23, 2006 Amendments to ANDA 77-857, we provided Chain Mapping by (b) (4) data on our Enoxaparin Sodium Exhibit Batch (Lot 0503X043).

In response to the Agency's most recent request, we are also providing Chain Mapping by (b) (4) data for two additional lots of our Enoxaparin Sodium Drug Substance: Lot 0602X963 and Lot 0602X113. The data from all three lots are presented in **Table 1** (enclosed), and are compared to the RLD using the equivalence ranges we outlined in our October 23, 2006 Amendment.

These data confirm that the three lots are equivalent to the RLD, even given the limited sample of four Lovenox® lots used to set the equivalence ranges. All of the (b) (4) chain compositions measured by this method are present within our three Enoxaparin Sodium Drug Substance lots, at a level that is consistent with the observed variability in the four batches of the RLD. Additional related substances (i.e., chain compositions) observed in our Enoxaparin Sodium Drug Substance are also present at comparable levels found in the RLD.

As previously stated, we fully agree that quantitative mapping of chains, including the distribution of molecular properties, is critical to demonstrating equivalence to the RLD. To overcome the analytical limitations presented by this complex mixture, we used an integration of multiple analytical methods to provide the required quantitative chain mapping data as well as the required data on all other molecular properties of the Enoxaparin Sodium mixture necessary for an adequate assessment of chemical equivalence. Using the (b) (4) Primary Characterization methods presented in ANDA 77-857, we developed equivalence criteria based on two critical parameters: (1) characterization of 30-40 batches of Lovenox® to at least partially capture the variability of the innovator product and (2) development of science-based ranges based on the implementation of rigorous analytical methods, including measuring and understanding analytical variability. With this approach, accurate and detailed comparison of Enoxaparin Sodium to the RLD is possible.

Based on our previous discussions with the Agency, we understood that the characterization approach presented in our ANDA was acceptable and that the requirement for additional quantitative chain mapping data was necessary only to confirm our demonstration of equivalence. Therefore, we have provided this information in our response. We believe that (b) (4) can not be used as a primary characterization test to judge the "sameness" of Enoxaparin Sodium lots, but rather should be viewed as a secondary, confirmatory tests (similar to those confirmatory tests provided in our original ANDA submission and subsequent amendments).

In conclusion, we have provided quantitative chain mapping data by (b) (4) for three production batches of our Enoxaparin Sodium Drug Substance. These data – consistent with the data and conclusions from the (b) (4) Primary Characterization datasets presented in our original ANDA submission and subsequent amendments – confirm that our Enoxaparin Sodium Drug Substance is equivalent to the RLD. These data further demonstrate that our manufacturing process can reproducibly generate enoxaparin material that is equivalent to the RLD.

We appreciate the opportunity to discuss our ANDA and approach to equivalence with the Agency, and welcome ongoing discussions and dialogue as we address these critical issues relating to establishing an acceptable regulatory pathway for generic enoxaparin sodium.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Sandoz Inc.

Beth Brannan
Director, Regulatory Affairs

BB:imc
Enclosures

Following this page, 2 pages withheld in full -(b)(4)

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

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OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

NOV 29 2006

RE: ANDA 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Amendment – Response to Facsimile of November 8, 2006

RECEIVED
NOV 30 2006
OGD / CDER

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your fax correspondence dated November 8, 2006. The labeling deficiencies have been addressed and are summarized below:

1. SYRINGE LABEL

We have revised the graduation markings. The 60, 80, and 100 mg strengths read "Each Gradulation = 2.5 mg (0.025 mL)" and the 120 and 150 mg strengths read "Each Graduation = 3 mg (0.02 mL)"

2. PEEL LID LABELING

For the 150 mg strength, we have deleted the "1" appearing with "mL" so it now reads 150 mg/mL.

3. INSERT

References to the 100 mg and 150 mg strengths have been revised. We have deleted the "1" appearing with "mL" so they now read 100 mg/mL and 150 mg/mL.

SANDOZ

Please note that Sandoz has also updated the labeling format. In accord with 21 CFR Part 201.1(g) we have incorporated our corporate headquarter address on the labeling. Therefore, the address changed from Broomfield, CO to Princeton, NJ.

Enclosed is an electronic CD containing the revised insert in PDF and Word format. Since we are submitting our labeling in electronic format, we are not providing labeling in hard copy form. Also included on the CD are the side-by-side comparison of our proposed labeling compared to our last submission, the syringe graduation labels in PDF format, and the peel lid labeling for the 150 mg/mL strength in PDF format.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

Enclosures

BB/ckm

Telephone Fax

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (301-827-7351)

TO: Sandoz, Inc.

TEL:303-438-4237

ATTN: Beth Brannan

FAX: 303-438-4600

FROM: Ruby Wu

Dear Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for 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 (Prefilled Single Dose Syringes with Automatic Safety Device).

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	77-857
Date of Submissions:	November 29, 2006 (amendment)
Applicant's Name:	Sandoz, Inc.
Established Name:	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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.
   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)

   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT

   Satisfactory in draft.

Please submit your insert labeling in final print electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
12/21/2006 04:52:17 PM
Lillie Golson for Wm. Peter Rickman

Thursday, December 21, 2006

Memo

To:
Elizabeth Dickinson, Associate Chief Counsel, OCC/FDA

From:
Keith Webber, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER

Re:
ANDA 76-684 (Amphastar) and ANDA 77-857 (Sandoz) for Enoxaparin Sodium Injection

Dear Ms. Dickinson,

The Office of Generic Drugs (OGD), the Office of New Drug Quality Assessment (ONDQA), and the Office of Pharmaceutical Science (OPS) have been working on the problem of what data is needed to demonstrate pharmaceutical equivalence (PE) between different low molecular weight heparins for a number of years. After extensive discussion with representative from OGD and ONDQA, Helen Winkle (Director, OPS) issued a memo on September 21, 2004 (Attachment A) outlining the criteria that sponsors must meet in order to establish PE. These criteria include:

1. Equivalence of physico-chemical properties
2. Equivalence of heparin starting material and mode of depolymerization
3. Equivalence in disaccharide building blocks and in sequence of major oligosaccharide species
4. Equivalence in biochemical and biological assays
5. Equivalence of in-vivo pharmacokinetic profiles

OGD communicated these criteria to manufacturers and reviewed the associated data submitted by Amphastar and Sandoz. This information was presented to representatives of OPS, OGD, ONDQA, Office of Regulatory Policy, Office of New Drugs, and the Office of Chief Counsel on November 9th, 2006 (Minutes-Attachment B). Questions posed to the OGD at this meeting were adequately addressed (refer to Minutes).

Over the years of discussing LMWHs, the difficulty of *producing* pharmaceutically equivalent products and *demonstrating* their equivalence has been a major theme. This is appropriate because there is agreement that demonstrating pharmaceutical equivalence for complex drug substances, such as enoxaparin, is not an easy task. However, "difficult" is not the same as "impossible" and we need to base our regulatory decisions on the science and data available. Although the manufacturing process can significantly affect

the resultant product's characteristics, this means that one must maintain an appropriate level of control over the manufacturing process, NOT that there can't be more than one way to make a given product. Likewise, when establishing equivalence between two complex products, one must set criteria that are meaningful within the context of the variability of the reference listed drug.

A broad array of complementary criteria were included in the assessments of these products, including evaluation of 1) the starting material, 2) the method of active pharmaceutical ingredient (API) preparation, 3) the general physicochemical properties of the intact API, 4) the disaccharide components of the API, 5) the distribution and sequence of API oligosaccharide fragments, 6) biochemical assays, 7) in vitro biological activity, and 8) in vivo biological activity.

In conclusion, it is my belief that Amphastar and Sandoz have met the scientifically sound criteria established for determining pharmaceutical equivalence and bioequivalence of their products to the reference listed drug.

Attachments A and B

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

/s/

Thomas Hinchliffe
12/22/2006 10:40:36 AM
CSO

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
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SANDOZ

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OVERNIGHT DELIVERY

ORIG AMENDMENT
AS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

UNSOLICITED AMENDMENT

(MICROBIOLOGY)

December 28, 2006

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Unsolicited Amendment – Additional Filling Line (Filling Line (b) (4) Building (b) (4) Microbiology Information Included

Dear Mr. Buehler:

Sandoz Inc. (Sandoz), is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act and with accordance with 21 CFR Part 314.96.

This amendment provides information on a second filling line, Line (b) (4) in Building (b) (4), at Baxter's manufacturing site as an additional line for the manufacture of Enoxaparin Sodium Injection, in addition to Baxter's filling Line (b) (4) in Building (b) (4) that was described as the manufacturing site in our original application.

Baxter's filling Line (b) (4) in Building (b) (4) was recently approved for the commercial manufacture of a biologic product. It was inspected by CBER June 26 – 30th, 2006, and found acceptable by inspectors Rebecca Olin and Sean Byrd from Rockville, MD.

The batch sizes for Enoxaparin to be manufactured on Line (b) (4) are the same as those described in our August 31, 2006, amendment to this application. In addition, the components and composition of the drug product and the manufacturing process are identical to that provided in our original submission.

In support for this additional filling line, we are providing the following information/documents that relate specifically to Filling Line # (b) (4) n Building (b) (4)

Attachment 1 - Facility Drawings
Attachment 2 - Material, Component, and Product Flow Diagrams
Attachment 3 - Information on sterilization of equipment
Attachment 4 - Media Fill Information
Attachment 5 - Written Procedures

For informational purposes, we would like to inform you that information corresponding to our currently filed Filling Line # (b) (4) Building (b) (4), can be found in Section XXII.2.(a), (b), (c), (d) and (j) of our original application for Filling Line # (b) (4) Bldg. (b) (4):

Should you have any questions please contact me at (303) 483-4237. Our fax number is (303) 438-4600.

Sincerely,

Beth Brannan
Director, Regulatory Affairs

/jep

Enclosures

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

Patent not in OB as of 2/2/07
I. Margand 2/2/07

OVERNIGHT DELIVERY

ORIGINAL

XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

January 3, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our Patent Amendment dated June 22, 2006, Section III (Patent Certification Statement), which included a Paragraph IV Certification Statement with respect to Aventis Pharma's Patent #s 5,389,618 and RE 38,743.

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505 (j) (2) (A) (vii) (IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent Certification to provide an additional Paragraph IV Certification for Aventis Pharma's Patent # 7,157,445. In support of this revision, we are enclosing a signed Patent Certification Statement. Concurrent with this amendment we are providing Notice to the Patent Holder per 21 CFR 314.95 (a) and (c).

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 0 3 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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SANDOZ

OVERNIGHT DELIVERY

ORIGINAL
XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

January 4, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our Patent Amendment dated June 22, 2006, Section III (Patent Certification Statement), which included a Paragraph IV Certification Statement with respect to Aventis Pharma's Patent #s 5,389,618 and RE 38,743.

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505 (j) (2) (A) (vii) (IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent Certification to provide an additional Paragraph IV Certification for Aventis Pharma's Patent # 7,157,445. In support of this revision, we are enclosing a signed Patent Certification Statement. Concurrent with this amendment we are providing Notice to the Patent Holder per 21 CFR 314.95 (a) and (c).

Sincerely,

Patent not in OB as of 2/2/07
I. Margand 2/2/07

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 04 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
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SANDOZ

ORIGINAL

Patent not in OB as of 2/2/07
I. Margand 2/2/07

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

January 5, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our Patent Amendment dated June 22, 2006, Section III (Patent Certification Statement), which included a Paragraph IV Certification Statement with respect to Aventis Pharma's Patent #s 5,389,618 and RE 38,743.

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505 (j) (2) (A) (vii) (IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent Certification to provide an additional Paragraph IV Certification for Aventis Pharma's Patent # 7,157,445. In support of this revision, we are enclosing a signed Patent Certification Statement. Concurrent with this amendment we are providing Notice to the Patent Holder per 21 CFR 314.95 (a) and (c).

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 05 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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2555 W. Midway Blvd.
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Fax +1 303 438-4600
Email: Beth.Brannan@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

GENERAL CORRESPONDENCE

ORIGINAL
MC

January 5, 2007

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Dear Mr. Buehler:

Sandoz Inc. (Sandoz), is hereby submitting a communication to its unapproved Abbreviated New Drug Application 77-857 for 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR Part 314.96.

On behalf of Andreas Rummelt, CEO of Sandoz International, and Craig Wheeler, CEO of Momenta, Sandoz is submitting correspondence to its Enoxaparin Sodium Injection ANDA # 77-857. A copy of this correspondence is provided as Attachment A.

Should you have any questions please contact me at (303) 483-4237. Our fax number is (303) 438-4600.

Sincerely,

Beth Brannan

Beth Brannan
Director, Regulatory Affairs

BB/imc

Attachment

RECEIVED
JAN 0 8 2007
CGD / CDER

cc: Janet Woodcock, MD, Deputy Commissioner for Operations
Murray Lumpkin, MD, Deputy Commissioner for International Programs
Steven Galson, MD, Director, Center for Drug Evaluation and Research
Helen Winkle, Director, Office of Pharmaceutical Science

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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ORIGINAL

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

Patent not in OB as of 2/2/07
L Margand 2/2/07

January 8, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 0 8 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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OVERNIGHT DELIVERY

Patent not in OB as of 2/2/07
I. Margand 2/2/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

January 9, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

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Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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OVERNIGHT DELIVERY

Gary Buehler, Director
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Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

Patent not in OB as of 2/2/07
I. Margand 2/2/07

January 10, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 10 2007
OGD / CDER

Enclosures
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Beth Brannan, Director
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SANDOZ

OVERNIGHT DELIVERY

Patent not listed in OB as of 8/6/07. BB

PATENT AMENDMENT

XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

January 11, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 11 2007
OGD / CDER

Enclosures
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Beth Brannan, Director
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SANDOZ

Patent not in OB as of 2/2/07
I. Margand 2/2/07

OVERNIGHT DELIVERY

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

January 12, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

RECEIVED
JAN 12 2007
OGD / CDER

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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2555 W. Midway Blvd.
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Broomfield, CO 80038-0446

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Fax +1 303 438-4600
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SANDOZ

ORIGINAL

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

ORIG AMENDMENT
N-000-XP

January 16, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Patent not in OB as of 2/2/07
I. Margand 2/2/07

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 16 2007
CDD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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Fax +1 303 438-4600
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Beth.Brannan@sandoz.com

SANDOZ

Patent not in OB as of 2/2/07
I. Margand 2/2/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

January 17, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 17 2007
OGD / CDER

Enclosures
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Beth Brannan, Director
Regulatory Affairs

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SANDOZ

Patent not in OB as of 2/2/07
I. Margand 2/2/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

January 18, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 18 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

ORIGINAL

ORIG AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

N-000-XP

Patent not in OB as of 2/2/07
I. Margand 2/2/07

January 19, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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JAN 19 2007
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Beth Brannan, Director
Regulatory Affairs

Enclosures
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Gary Buehler, Director
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PATENT AMENDMENT

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January 22, 2007

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
JAN 22 2007
OGD / CDER

AII-1

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Beth Brannan, Director
Regulatory Affairs

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Patent not in OB as of 2/2/07
I. Margand 2/2/07

Gary Buehler, Director
Office of Generic Drugs
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Metro Park North 2, Room 150
7500 Standish Place
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PATENT AMENDMENT

XP

January 23, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505 (j) (2) (A) (vii) (IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent Certification to provide an additional Paragraph IV Certification for Aventis Pharma's Patent # 7,157,445. In support of this revision, we are enclosing a signed Patent Certification Statement. Concurrent with this amendment we are providing Notice to the Patent Holder per 21 CFR 314.95 (a) and (c).

Sincerely,

Sandoz Inc.

RECEIVED
JAN 2 3 2007
OGD / CDER

Beth Brannan, Director
Regulatory Affairs

SANDOZ

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Patent not in OB as of 2/2/07
I. Margand 2/2/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

January 24, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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Sincerely,

RECEIVED
JAN 24 2007
OGD / CDER

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

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ORIGINAL

XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

Patent not in OB as of 2/2/07
I. Margand 2/2/07

January 25, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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RECEIVED
JAN 25 2007
OGD / CDER

Sincerely,

Sandoz Inc.

Beth M Bra

Beth Brannan, Director
Regulatory Affairs

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Patent not in OB as of 2/2/07
I. Margand 2/2/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

January 26, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

RECEIVED
JAN 26 2007
OGD / CDER

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

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Patent not in OB as of 2/2/07
I. Margand 2/2/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

January 29, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

RECEIVED
JAN 29 2007
OGD / CDER

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

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Patent not listed in OB as of 4/20/07.

Gary Buehler, Director
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Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

January 30, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

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Beth Brannan, Director
Regulatory Affairs

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Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

Patent not listed in OB as of 4/20/07.

January 31, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

RECEIVED
JAN 31 2007
OGD / CDER

Sandoz Inc.

Beth Brannan, Director
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Fax +1 303 438-4600
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Beth.Brannan@sandoz.com

Patent not listed in OB as of 4/20/07. JM.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP.

February 1, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

SANDOZ

Beth Brannan, Director
Regulatory Affairs

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Patent not listed in OB as of 4/20/07 GM.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

February 2, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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Sincerely,

RECEIVED
FEB 0 2 2007
OGD / CDER

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

Beth Brannan, Director
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Patent not listed in OB as of 4/20/07. FM.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

February 5, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 05 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
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Patent not listed in OB as of 4/20/07. JL.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

February 6, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 06 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
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Fax +1 303 438-4600
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Beth.Brannan@sandoz.com

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Patent not listed in OB as of 4/20/07.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

February 7, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 07 2007
OGD / CDER

Enclosures
BB/imc

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ORIGINAL Patent not listed in OB as of 4/20/07.

PATENT AMENDMENT

XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

February 8, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

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In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505 (j) (2) (A) (vii) (IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent Certification to provide an additional Paragraph IV Certification for Aventis Pharma's Patent # 7,157,445. In support of this revision, we are enclosing a signed Patent Certification Statement. Concurrent with this amendment we are providing Notice to the Patent Holder per 21 CFR 314.95 (a) and (c).

Sincerely,

Sandoz Inc.

RECEIVED
FEB 0 8 2007
OGD / CDER

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

Patent not listed in OB as of 4/20/07. JP.

PATENT AMENDMENT

XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

February 9, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 09 2007
OGD / CDER

Enclosures
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Beth Brannan, Director
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SANDOZ

Patent not listed in OB as of 4/20/07. JM

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

February 12, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 12 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

ORIGINAL Patent not listed in OB as of 4/20/07.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

February 13, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 13 2007
OGD / CDER

Enclosures
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Beth Brannan, Director
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Patent not listed in OB as of 4/20/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP.

February 14, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

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FEB 14 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
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SANDOZ

ORIGINAL

XP

PATENT AMENDMENT

Patent not listed in OB as of 4/20/07.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

February 15, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

RECEIVED
FEB 15 2007
OGD / CDER

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/imc

Beth Brannan, Director
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Beth.Brannan@sandoz.com

SANDOZ

Patent not listed in OB as of 4/20/07.

PATENT AMENDMENT

XP.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

February 16, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

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Sincerely,

Sandoz Inc.

RECEIVED
FEB 16 2007
OGD / CDER

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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Broomfield, CO 80038-0446

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SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

FEB 2 0 2007

ORIG AMENDMENT
N-AE

RE: ANDA 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Amendment – Response to Facsimile of December 22, 2006

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for 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 (Prefilled Single Dose Syringes with Automatic Safety Device) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your fax correspondence dated December 22, 2006. We acknowledge that the syringe, peel lid, and carton labeling are satisfactory in final print and the insert is satisfactory in draft.

Enclosed is an electronic CD containing the insert in final print. Since we are submitting our labeling in electronic format (PDF), we are not providing labeling in hard copy form.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 2 1 2007
OGD / CDER

Enclosures
BB/ckm

Beth Brannan, Director
Regulatory Affairs

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Broomfield, CO 80038-0446

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Fax +1 303 438-4600
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Beth.Brannan@sandoz.com

SANDOZ

ORIGINAL

Patent not listed in OB as of 4/20/07. GM.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

February 20, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 20 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
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SANDOZ

ORIGINAL

Patent not listed in OB as of 4/20/07.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

February 21, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 21 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

ORIGINAL

Patent not listed in OB as of 4/20/07. BM.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

XP

February 22, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 2 2 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

Patent not listed in OB as of 4/20/07

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

February 23, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/imc

RECEIVED
FEB 23 2007
OGD / CDER

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

ORIGINAL

Patent not listed in OB as of 4/20/07.

PATENT AMENDMENT

XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

February 26, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our Patent Amendment dated June 22, 2006, Section III (Patent Certification Statement), which included a Paragraph IV Certification Statement with respect to Aventis Pharma's Patent #s 5,389,618 and RE 38,743.

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505 (j) (2) (A) (vii) (IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent Certification to provide an additional Paragraph IV Certification for Aventis Pharma's Patent # 7,157,445. In support of this revision, we are enclosing a signed Patent Certification Statement. Concurrent with this amendment we are providing Notice to the Patent Holder per 21 CFR 314.95 (a) and (c).

Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 26 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
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Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

ORIG AMENDMENT
N-AF

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT - LABELING

FEB 2 7 2007

RE: ANDA 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Telephone Amendment – Labeling

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for 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 (Prefilled Single Dose Syringes with Automatic Safety Device) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our Labeling Amendment filed on February 20, 2007, and a telephone conversation between Ruby Wu (FDA) and Beth Brannan (Sandoz) on February 26, 2007. In response to this call, we are providing a CD that contains a text-based PDF file of our package insert in final print.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 2 8 2007
OGD / CDER

Enclosures
BB/ckm

Beth Brannan, Director
Regulatory Affairs

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Beth.Brannan@sandoz.com

SANDOZ

Patent not listed in OB as of 4/20/07. GR.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

February 27, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 27 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

Patent not listed in OB as of 4/20/07.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

February 28, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

BBran

Beth Brannan, Director
Regulatory Affairs

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Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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Beth.Brannan@sandoz.com

SANDOZ

Patent not listed in OB as of 4/20/07. JM

PATENT AMENDMENT

N/XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

March 1, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

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Sincerely,

Sandoz Inc.

BBran

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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SANDOZ

Patent not listed in OB as of 4/20/07. JM.

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

N/XP

March 2, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

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MAR 0 2 2007
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Enclosures
BB/imc

Beth Brannan, Director
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Beth.Brannan@sandoz.com

SANDOZ

Patent not listed in OB as of 4/20/07. GM.

PATENT AMENDMENT

N/xP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

March 5, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan/gp

Beth Brannan, Director
Regulatory Affairs

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Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

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Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

Patent not listed in OB as of 4/20/07. BB.

PATENT AMENDMENT

N/XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

March 6, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan/gp

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/imc

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MAR 06 2007
OGD / CDER

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
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Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

Patent not listed in OB as of 4/20/07.

PATENT AMENDMENT

N/kP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

March 7, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

RECEIVED
MAR 07 2007
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Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
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Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

Patent not listed in OB as of 4/20/07. JL,

PATENT AMENDMENT

XP

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

March 8, 2007

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
MAR 0 8 2007
OGD / CDER

Enclosures
BB/imc

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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Beth.Brannan@sandoz.com

SANDOZ

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

March 9, 2007

PATENT AMENDMENT

N/xP

Patent not listed in OB as of 4/20/07. JH.

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Revised Patent Certification

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Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
MAR 09 2007
OGD / CDER

Enclosures
BB/imc

Record of Telephone Conversation

1. The following comment was sent on 3/13/07 and discussed today:

We note that in your (b) (4) analysis of enoxaparin, that you have assigned an (b) (4) Therefore we request that you provide an explanation for these reported differences.

Firm will Provide a written response.

2. The following comment was sent 3/8/07 and discussed today:

The specification for the level of the (b) (4) should be (b) (4) Alternatively, as these (b) (4), the applicant can provide comparative data showing that the levels of the (b) (4) these (b) (4) the levels found in Lovenox.

Firm will Provide a written response.

Date:
3/16/07

ANDA Number:
77-857

Product Name:
Enoxaparin

Firm Name:
Sandoz

Firm Representative:
Beth Brannan - Sandoz RA
John Bishop - Momenta
Jennifer Smith - Momenta
Zach Shriver - Momenta
(b) (6) –Momenta
omenta

Phone Number:
1-866 (b) (4)
passcode

FDA Representative:
Naiqi Ya
Larry Lee
Andre Raw
Thomas Hinchliffe

Signatures:

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

/s/

Thomas Hinchliffe
3/16/2007 03:02:02 PM
CSO

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (301-594-0320)

TO: Beth Brannan		**FROM:** Bonnie McNeal
Sandoz Inc.		Microbiology Project Manager
PHONE: 303-438-4237		**PHONE:** (301) 827-0530
FAX: 303-438-4600		**FAX:** (301) 827-5911

Total number of pages, excluding this cover sheet: **4**

Date: March 19, 2007

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 77-857. The submissions reviewed were submitted on August 26, 2005, August 31, 2006 and December 28, 2006. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Bonnie McNeal or Mark Anderson.

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

Please clearly identify your amendment to this facsimile as “RESPONSE TO MICROBIOLOGY DEFICIENCIES”. The “RESPONSE TO MICROBIOLOGY DEFICIENCIES” should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs

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

/s/

Lynne Ensor
3/19/2007 07:41:25 AM

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
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SANDOZ

OVERNIGHT DELIVERY

ORIG AMENDMENT
N|AC

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT

March 23, 2007

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Amendment - Response to OGD/FDA TeleConference on March 9, 2007; TeleConference Fax on March 13, 2007; and TeleConference on March 16, 2007 Chemistry, Manufacturing and Control Items Addressed

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the Telephone Conference on March 9, 2007, the Telephone Conference Fax received from the Office of Generic Drugs on March 13, 2007, and the subsequent Telephone Conference on March 16, 2007. The two items noted in these communications have been addressed in Attachments 1 and 2 and are summarized below.

Question 1: (b) (4) Limits for (b) (4)

We propose to (b) (4) the limit for (b) (4) to (b) (4)%. In addition, we present the results from our planned analyses of ten batches of unfractionated heparin. The (b) (4) in all ten batches tested was below the limit of detection (less than (b) (4)%).

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SANDOZ

Question 2: Explain Reported Differences in (b) (4) (b) (4):

(b) (4)

We have implemented appropriate control of our heparin starting material, including identification and quantification of the building blocks to ensure the reproducible production of Enoxaparin Sodium, in a commercial manufacturing environment, which is equivalent to the RLD

We appreciate the opportunity to discuss with the Agency our approach to (1) demonstrating pharmaceutical equivalence to Lovenox® and (2) controlling our manufacturing process (unfractionated heparin starting material and critical process parameters) to ensure routine product quality in a commercial manufacturing environment. We welcome ongoing discussions and dialogue as we address these critical issues relating to establishing an acceptable regulatory pathway for generic enoxaparin sodium.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

BB:ckm

Attachment 1: Revised Limits for (b) (4)
Attachment 2: (b) (4)
Attachment 3:
Attachment 4:
Attachment 5:
Attachment 6:

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MAR 2 6 2007

TELEPHONE AMENDMENT

N/AC

RE: ANDA 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Telephone Amendment – Providing cGMP and Debarment Statements

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for 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 (Prefilled Single Dose Syringes with Automatic Safety Device) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone conversation between Tom Hinchliffe (FDA) and Beth Brannan (Sandoz) on March 23, 2007. In response to this call, we are providing a cGMP Compliance Certification and Debarment Statement from Momenta Pharmaceuticals.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan, Director
Regulatory Affairs

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MAR 2 7 2007
CDD / CDER

Enclosures
BB/ckm

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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Tel +1 303 438-4237
Fax +1 303 438-4600
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Beth.Brannan@sandoz.com

SANDOZ

ORIG AMENDMENT
N-000-AS

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

Response to Microbiology Deficiencies

June 8, 2007

RE: **ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)**

Minor Amendment - Response to Microbiology Deficiency letter dated March 19, 2007

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your letter dated March 19, 2007. A response to your deficiencies is provided below:

A. Microbiology Deficiencies:

1. **FDA Comment:**

We acknowledge the provided [redacted] (b) (4) in the subject drug. However, please provide evidence of [redacted] (b) (4)

Sandoz Response:

Please refer to the DMF response in **Attachment 1**.

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Following this page, 7 pages withheld in full - (b)(4)

Sandoz Response:

We acknowledge your comment regarding the [redacted] (b) (4)

2. **FDA Comment:**

With regard to organization of this submission, we note that the ANDA is comprised of entire volumes of information not subdivided to facilitate retrieval of specific information and/or documents by the reviewer. For future submissions, please consider using labeled tabs and page numbers to separate subsections and documents with the ANDA and ANDA amendments. Furthermore, if referring to a document in another ANDA section, please include the page number of its location. For expediency of review, the best case scenario is to include all sterility assurance information in the Sterility Assurance Section XXII.

Sandoz Comment:

We note and acknowledge your comments.

3. **FDA Comment:**

We note that the submission relies very heavily on SOPs and reports to describe the [redacted] (b) (4) processes rather than providing the pertinent information in the narrative. It should be noted that often qualification reports and SOPs do not sufficiently describe the production parameters and acceptance criteria, so these cannot be relied upon for this information. In the future, we would recommend that the pertinent information such as the sterilization process parameters and acceptance criteria be summarized in the narrative.

Sandoz Comment:

We note and acknowledge your comments.

For convenience purposes, we have provided a copy of the deficiency letter in **Attachment 11**.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope.

Sincerely,

SANDOZ INC.

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB:jep

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (301-594-0320)

TO: Beth Brannan, Director, Regulatory Affairs		**FROM:** Mark Anderson
Sandoz Inc.		Microbiology Project Manager
PHONE: 303-438-4237		**PHONE:** (301) 827-0530
FAX: 303-438-4600		**FAX:** (301) 827-5911

Total number of pages, excluding this cover sheet: **1**

Date: July 16, 2007

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 78-857 for Enoxaparin Sodium Injection. The submission reviewed was submitted on June 8, 2007. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Bonnie McNeal or Mark Anderson.

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA: 77-857 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Enoxaparin Sodium Injection

A. Microbiology Deficiencies:

1. DMF (b) (4) has been recently reviewed and was found deficient. The DMF holder has been notified.

2. DMF (b) (4) indicates that there are (b) (4) of components for Enoxaparin Sodium Injection in ANDA 77-857.

3. In regard to the (b) (4) .

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs

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

/s/

Lynne Ensor
7/16/2007 03:07:46 PM

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

N-000-AC

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

UNSOLICITED AMENDMENT
(Electronic Submission)

SEP 19 2007

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Unsolicited Amendment - Chemistry, Manufacturing and Control Information

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

We are also providing the information in this amendment on compact disc (CD). This CD represents a true and complete copy of the hard copy material. Please note, however, that the medium itself is not a product of a validated computer system.

Sandoz and Momenta have begun preparations for the launch of the Enoxaparin Injection product. As part of this effort we are submitting the following information:

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1. We have identified an alternate source of Heparin Sodium, USP, starting material. We are proposing to add [redacted] (b) (4) as an alternate source of Heparin Sodium, USP. Please see Appendix A for the supportive information.
2. As previously described in our application (Aug 31, 2006 Amendment question # 1j) a [redacted] (b) (4) drug substance (DS) process was proposed as the scaled up manufacturing process. Appendix B provides further information and data for the [redacted] (b) (4) batch size.
3. Two compositional analysis methods have been revised. The source of the [redacted] (b) (4) used in these methods has also changed. Details of these changes are provided in Appendix C.
4. As described in our August 31, 2006 amendment, equivalence criteria for additional lots of Lovenox were to be evaluated, and the equivalence criteria would be updated. Appendix D provides further information for the equivalence criteria update.
5. The method for [redacted] (b) (4) has been revised based on experience gained performing this method. Appendix E provides further details for this revision.
6. The method for [redacted] (b) (4) testing of Drug Substance has been revised to harmonize it with the method used for Drug Product. Appendix F provides further details for this revision.
7. A new contract lab for drug substance release testing is being proposed. Appendix G provides the details for [redacted] (b) (4) They will be performing the [redacted] (b) (4) assay for the DS.
8. A revised drug product stability protocol is provided in Appendix H. The [redacted] (b) (4) [redacted] (b) (4) has been deleted.
9. Specifications for Drug Substance and Drug Product have been updated to the current USP. Please refer to Appendix I for the revised specifications.
10. Updated ongoing stability is being provided for the Drug Substance (Appendix J) and Drug Product (Appendix K).

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Beth Brannan
Director, Regulatory Affairs

Enclosures

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

Response to Microbiology Deficiencies

ORIG AMENDMENT
NJ/AS

OCT 2 6 2007

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Minor Amendment - Response to Microbiology Deficiency letter dated July 16, 2007

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your letter dated July 16, 2007. A response to your deficiencies is provided below:

A. Microbiology Deficiencies:

1. **FDA Comment:**

DMF (b) (4) has been recently reviewed and found deficient. The DMF holder has been notified.

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OCT 29 2007

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SANDOZ

Sandoz Response:

[redacted] which was provided in Attachment 8 of the response to microbiology deficiences submitted on June 8, 2007. However, we are providing this SOP again in **Attachment 2.**

ADDITIONAL INFORMATION:

In a recent ANDA amendment (Unsolicited Amendment [Appendix F], submitted September 19, 2007), we informed you that the [redacted] method for testing Enoxaparin Sodium (Drug Substance) had also been changed to a [redacted] method. This change was implemented to harmonize [redacted] testing of Drug Substance with testing of Drug Product, and to avoid the [redacted] that is occasionally observed in the [redacted] method.

A [redacted] method is now employed to perform [redacted] testing of Drug Product and Drug Substance. The Drug Product method was submitted to FDA previously (Response to Microbiological Deficiencies [Attachment 8], submitted June 8, 2007). We are now providing the Drug Substance method in **Attachment 3** with the corresponding method validation report in **Attachment 4.**

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope.

Sincerely,

SANDOZ INC.

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB:jep

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-857

Sandoz, Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
255 W. Midway Blvd.
Broomfield, CO 80038

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 26, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Enoxaparin Sodium Injection, 100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL prefilled syringes and 150 mg/mL, 0.8 mL and 1 mL prefilled syringes.

Reference is also made to your amendments dated August 31, October 5, November 9, and November 29, 2006; and March 23, March 26, and September 19, 2007.

We have reviewed this ANDA and have determined that the ANDA is not approvable because the application does not adequately address the potential for immunogenicity of the drug product. We recommend that Sandoz/Momenta contact this office to schedule a meeting to address what additional information should be provided to adequately address this concern.

The file on this ANDA is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this ANDA. Your amendment should respond to all the deficiencies listed. Partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered as MINOR AMENDMENT and should be so designated in your cover letter.

If you have substantial disagreement with our reasons for not approving this ANDA, you may request an opportunity for a

hearing. If you have any questions, please contact Thomas Hinchliffe, PharmD at (301) 827-5771.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Gary Buehler

11/5/2007 11:36:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-857

Sandoz, Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
2555 W. Midway Blvd.
Broomfield, CO 80038

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 26, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Enoxaparin Sodium Injection, 100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL prefilled syringes and 150 mg/mL, 0.8 mL and 1 mL prefilled syringes.

This letter is in follow-up to the November 5, 2007 communication issued by our office in which we raised certain concerns regarding immunogenicity of enoxaparin that must be addressed in your ANDA.

The current analytical methods, which provide information regarding the characterization of the active ingredient, that are included in the Sandoz/Momenta ANDA may not fully predict biological properties of complex drug products, such as enoxaparin, derived from biological sources. FDA is particularly concerned with product and process derived impurities that may modify the biological activity or enhance the immunogenicity of your product. Understanding the potential for your product to elicit an immune response is critical, since low molecular weight heparins are associated with a serious immune-driven adverse event, heparin induced thrombocytopenia (HIT). Impurities can interact either with the product or with the host immune system in ways that alter outcome. Thus, for products that have the potential for immunologic adverse events and certainly for products with known immunologic adverse events, the contribution of impurities needs to be carefully considered.

Below are items you need to address as part of your ANDA, together with some suggested approaches to addressing these issues. Other approaches may also be acceptable. Although these approaches may resolve uncertainty regarding immunogenicity for your product and preclude the need for a clinical immunogenicity study, we will need to review the resulting data before we can determine whether our concerns have been adequately addressed. We recommend that you provide protocols for the Agency to review. You may also contact the Agency to discuss the specifics of your planned work or if you have additional questions before initiating these studies.

1. Studies assessing the interaction of Enoxaparin with PF4

   HIT is mediated by antibodies to the PF4-heparin complex. Although Sandoz/Momenta used sophisticated approaches to show the sameness of its active ingredient to that in Lovenox, the presence of impurities may affect the interaction of enoxaparin with PF4. Please compare the ability of your product with that of the innovator product to bind to and form complexes with the chemokine PF4, and characterize the size and charge of the resulting complexes. Please include in your studies product lots that are newly released as well as those that are close to expiry date.

2. Studies to assess differences in impurities and their potential affect on immunogenicity

   Studies have shown that low levels of innate immune agonists can act synergistically to activate the innate immune system. Consequently, it is important to understand the amount and nature of potential product contaminants relative to those in the innovator product.

   a. Please quantify the level of protein impurities utilizing a highly sensitive method.

   b. Please characterize any protein impurities present in your product as compared to the innovator product. These studies should have a high sensitivity and be capable of comparing patterns of protein impurities. This could be achieved using discriminating 2D gels, HPLC, or immunoassays. Data from sensitive assays that demonstrate a similar pattern of impurities would support the contention that the generic product is similar with regard to impurity content. Data demonstrating the extent

of impurity removal during the manufacturing process could also be of value.

c. Please provide information on process removal of nucleic acids and lipids. Significant residual materials may require further comparative characterization.

d. Impurities leaching from container closure systems can potentially contribute to the immunogenicity of products. Please assess differences in leachables arising from the syringes used by the generic and innovator products and determine whether they affect immunogenicity, or provide a rationale for why such studies are not needed. Please include in your studies product lots that are newly released as well as those that are close to expiry date, as leachables may be most apparent in older lots of product.

3. Functional studies to assess differences in impurities and their potential affect on immunogenicity:

The following studies may contribute to the understanding of any potential immunogenic properties of your product as compared to the innovator product, and provide useful information to assist in the review of your ANDA. Depending on the outcomes of the above studies, this functional evaluation of potentially immunogenic properties may influence the agency action on the ANDA.

i) Development of an in vitro assay to compare the immunomodulatory (adjuvant-like) effect of the generic and innovator products. For example, assays could be used to assess the immune responses elicited by an antigen in the presence and absence of generic or innovator low molecular weight heparins to examine whether they affect immune responses similarly. The addition of suboptimal levels of innate immune agonists such as LPS or CpG ODN to the system may be useful in amplifying any immunomodulatory effect of the product.

ii) Development of an animal model to determine whether the products, alone or in complex with PF4, are similarly immunogenic in vivo. While animal models do not necessarily predict immunogenicity in humans, differences in the immune response would signal that

the two molecules are regarded as different by the immune system.

We stand ready to discuss the specifics of these and any other studies you may propose to respond to the Agency's concern. Please direct your questions on these to Thomas Hinchliffe, PharmD, Project Manager, Office of Generic Drugs at 301-827-5771 or, alternatively, Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs at 240-276-9310.

Sincerely,

{See appended electronic signature page}

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Gary Buehler

12/4/2007 05:16:46 PM

Telephone Conversation Memorandum

ANDA: 77-857

DRUG: Enoxaparin

FIRM:

Attendees: Sandoz Inc.

Beth Brannan, Director, Regulatory Affairs
Kalpana Rao Vanam, Vice President, Regulatory Affairs
Jeff Bauer, Head of Business Development
Bernhard Hampl, Chief Executive Officer

Attendees: Momenta Pharmaceuticals, Inc.

Ganesh Venkataraman, Senior Vice President Research and Chief Scientific Officer
John Bishop, Senior Vice President, Pharmaceutical Sciences
Kei Kishimoto, Senior Director, Disease Biology
Gerard Riedel, Vice President, Regulatory Affairs

FDA PERSONS INVOLVED:

Andre Raw, OGD
Sau (Larry) Lee, OGD
Florence Fang, Director, Div of Chem II, OGD
Richard Adams, Deputy Director, Div of Chem II,OGD
Naiqi Ya, OGD
Cecelia Parise, OGD
Thomas Hinchliffe, OGD
Keith Webber, Deputy Director, OPS
Steven Kozlowski, Director, OBP
Amy Rosenberg, OBP
Elizabeth Shores, OBP
Daniela Verthelyi, OBP

DATE: January 9, 2008 – 11am est

Conversation:

FDA Question (FDA Letter Dated 12/04/07)	Subsection	Requested clarification
Studies assessing the nteraction with PF4	1.	**Background:** This question includes the following sentence: "Please include in your studies product lots that are newly released as well as those close to expiry date." **Sandoz' query:** Does the term "product lots" refer to Sandoz' drug product lots, the innovator's drug product lots, or both? The term "product lots" refers to both. Please use Sandoz lots that are newly released as well as those close to expiry date. We understand that obtaining such lots for the innovator product may be hard, however using lots with very different expiry dates would be recommended.
2. Studies to assess differences n impurities and their potential effect on immunogenicity	2c.	**Background:** This question includes the following sentence: "Please provide information on process removal of nucleic acids and lipids". **Sandoz' query:** For the requested lipid studies, are there specific types of lipids that are of particular interest to FDA? Please select polar and non polar lipids that are likely to be present in the intestinal mucosa. Cholesterol, phospholipids and triglycerides should be considered.
	2d.	**Background:** This question includes the following sentence: "Please assess differences in leachables arising from the syringes used by the generic and innovator products and determine whether they affect immunogenicity, or provide a rationale for why such studies are not needed." Sandoz believes it can demonstrate that the container/closure used in its generic product is identical to that of the innovator product. **Sandoz' query:** Does FDA consider the Sandoz' use of a container/closure that s identical to that used by the innovator to be sufficient rationale for not performing the requested studies? The studies are not necessary if all components of the container closure system (including the glass, the syringe barrel, the manufacturer, the rubber stopper etc.) are **the same** as those

		on the innovator.
3. Functional studies to assess differences in impurities and their potential effect on mmunogenicity	3.	**Background:** This question includes the following sentence: “Depending on the outcomes of the above studies, this functional evaluation of potentially immunogenic properties may influence the agency action on the ANDA”. Sandoz currently interprets FDA’s statement to mean that: Sandoz should first generate responses to questions 1 and 2. If the data generated to address questions 1&2 indicate that the mpurity profiles of Sandoz’ and innovator’s are equivalent, Sandoz should not include the studies requested in question 3 n its complete response. **Sandoz’ query:** Does FDA concur with Sandoz’ interpretation? The FDA position is that Sandoz needs to provide robust data definitively demonstrating that the impurities present in enoxaparin are quanitatively and qualitatively the same as in the innovator product. The functional studies are suggested as a means to reduce any uncertainties in the impurity evaluation and to assess the immunogenic potential effect of any impurities present in your product as compared to the innovator product.

Additional discussion during the meeting:

- Regarding Q4 we stressed that the functional studies were an additional tool that was provided to the sponsor to reduce uncertainties relating to impurities when contemplating whether clinical trials would be necessary.
- Sandoz proposed to send us a draft of proposed studies and hold a face to face. Dr Raw and Dr Verthelyi stressed that it would be important to see some preliminary data on impurities with the research plan so we could make an informed decision as to the adequacy of the plan.
- FDA stated that the format of the response would be decided after receiving and evaluating the package.

Sandoz Inc.
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Princeton, NJ 08540
Telephone: 609.627.8882
Telefax: 609.395.2792
Cell: 516.304.8780
Email : kalpana.rao@sandoz.com

FDA Teleconference minutes

Meeting: Enoxaparin ANDA 77-857
Meeting Attendees: Sandoz Inc. (Sponsor)
Momenta Pharmaceuticals, Inc. (on behalf of Sponsor)
Food and Drug Administration

Meeting Date / Time: January 9, 2008 / 11:00 am – 12:00 pm EST

Meeting Minutes Date: January 10, 2008

Meeting Location: N/A

Meeting Goals To clarify several statements in FDA's letter (dated December 4, 2007) concerning FDA's requests for immunogenicity-related analyses

Attendees: Sandoz Inc.

Beth Brannan, Director, Regulatory Affairs
Kalpana Rao Vanam, Vice President, Regulatory Affairs
Jeff Bauer, Head of Business Development
Bernhard Hampl, Chief Executive Officer

Attendees: Momenta Pharmaceuticals, Inc.

Ganesh Venkataraman, Senior Vice President Research and Chief Scientific Officer
John Bishop, Senior Vice President, Pharmaceutical Sciences
Kei Kishimoto, Senior Director, Disease Biology
Gerard Riedel, Vice President, Regulatory Affairs

Attendees: FDA *(please add any attendee's name that we may have missed)*

Andre Raw, OGD
Sau (Larry) Lee, OGD
Florence Fang, Director, Div of Chem II, OGD
Richard Adams, Deputy Director, Div of Chem II,OGD
Naiqi Ya, OGD
Cecelia Parise, OGD
Thomas Hinchliffe, OGD
Keith Webber, Deputy Director, OPS
Steven Kozlowski, Director, OBP
Amy Rosenberg, OBP
Elizabeth Shores, OBP
Daniela Verthelyi, OBP

Reference materials

Letter (December 4, 2007) from FDA to Sandoz Inc. (Attachment 1)

E-mail (December 20, 2007) from Sandoz Inc. to FDA requesting teleconference. (Attachment 2)

Meeting Summary

I. FDA responses to clarifications requested by Sandoz:

FDA Question (FDA Letter Dated 12/04/07)	Sub section	Requested clarification (from Sandoz e-mail to FDA, dated December 20, 2007)	FDA's response
1. Studies assessing the interaction with PF4	n/a	**Background:** This question includes the following sentence: "Please include in your studies product lots that are newly released as well as those close to expiry date." **Sandoz' query:** Does the term "product lots" refer to Sandoz' drug product lots, the innovator's drug product lots, or both?	The term "product lots" refers to both Sandoz' and innovator's lots. Sandoz' product lots should include lots that are newly released as well as those close to expiry date. FDA understands that it is difficult to obtain innovator product lots close to expiry date. In its analyses, Sandoz should include innovator product lots with different expiry dates.
2. Studies to assess differences in impurities and their potential effect on immunogenicity	2c.	**Background:** This question includes the following sentence: "Please provide information on process removal of nucleic acids and lipids". **Sandoz' query:** For the requested lipid studies, are there specific types of lipids that are of particular interest to FDA?	Sandoz should assess the presence of both polar and non-polar lipids that are typical components of the intestinal mucosa. Sandoz should specifically assess the presence of cholesterol, phospholipids and tryglycerides.
	2d.	**Background:** This question includes the following sentence: "Please assess differences in leachables arising from the syringes used by the generic and innovator products and determine whether they affect immunogenicity, or provide a rationale for why such studies are not needed." Sandoz believes it can demonstrate that the container/closure used in its generic product is identical to that of the innovator product. **Sandoz' query:** Does FDA consider the Sandoz' use of a container/closure that is identical to that used by the innovator to be sufficient rationale for not performing the requested studies?	If all product-contact components of Sandoz' container closure system are identical to those of the innovator product, then the requested studies are not necessary.
3. Functional studies to assess differences in impurities and their potential effect on immunogenicity	n/a	**Background:** This question includes the following sentence: "Depending on the outcomes of the above studies, this functional evaluation of potentially immunogenic properties may influence the agency action on the ANDA". Sandoz currently interprets FDA's statement to mean that: Sandoz should first generate responses to questions 1 and 2. If the data generated to address questions 1 & 2 indicate that the impurity profiles of Sandoz' and innovator's products are equivalent, Sandoz should	FDA requires robust data to determine whether the impurity profile of Sandoz' product is the same, quantitatively and qualitatively, as the impurity profile of the innovator's product. FDA expects that it will be very difficult to demonstrate that a generic product's impurity profile is exactly the same as that of an innovator's product. Consequently, FDA has suggested

		not include the studies requested in question 3 in its complete response. **Sandoz' query:** Does FDA concur with Sandoz' interpretation?	the experimental analyses in question 3, to provide an alternative way for Sandoz to assess the potential immunogenicity of its product, in comparison to the innovator's product. These studies will inform the Agency in its decision as to whether clinical studies will be necessary to license the product.

II. Next steps

- Sandoz/Momenta informed FDA that the information from this teleconference will be incorporated into the detailed analytical plan (in preparation) to address all requests listed in FDA's letter of December 4, 2007. This detailed plan will be submitted to FDA for its review, revision (if necessary) and endorsement. Sandoz proposed a face-to-face meeting with FDA as an efficient means to obtain alignment with FDA regarding the analytical plan.

- Following FDA's endorsement of the final analytical plan, Sandoz/Momenta will perform all analyses and submit the data as an ANDA amendment.

- FDA requested (and Sandoz/Momenta agreed to include) preliminary data with the detailed analytical plan that will be submitted for FDA's review. FDA explained that these data provide information that helps to define the appropriate context for FDA's review of the proposed plan.

- FDA requested (and Sandoz/Momenta agreed to provide) a draft summary of this teleconference so that FDA could confirm that Sandoz' understanding of its responses is accurate.

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

/s/

Thomas Hinchliffe

7/2/2009 01:21:14 PM

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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P.O. Box 446
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Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT

ORIG AMENDMENT
IJ/AA

February 13, 2008

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Gratuitous Amendment – Withdrawal of Alternate Source (b) (4) of Heparin Sodium

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the Unsolicited Amendment we filed September 19, 2007. In this amendment, we requested approval of an alternate source (b) (4) for our heparin sodium in addition to making several chemistry, manufacturing and control changes. We would now like to request withdrawal of this alternate source (b) (4) for our heparin sodium without prejudice to future filings. The other chemistry, manufacturing and control changes mentioned in our 9/19/07 amendment, however, still apply.

This information is submitted for your review. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

BBrannan

Beth Brannan, Director
Regulatory Affairs

RECEIVED
FEB 14 2008
OGD

Enclosures
BB/jep

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

ORIG AMENDMENT
N-000-AC

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT

RECEIVED
FEB 28 2008
OGD

February 27, 2008

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Amendment – Interim Response to FDA letter of December 4, 2007

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your letter of December 4, 2007 requesting Sandoz to address concerns regarding immunogenicity of enoxaparin in our ANDA. In our follow-up telephone conference with FDA on January 9, it was also requested that Sandoz submit any preliminary data available in response to the immunogenicity questions raised by FDA in the December 4, 2007 letter.

In response, Sandoz/Momenta have proposed a plan to address the FDA concerns regarding immunogenicity for enoxaparin. Scientists at Momenta Pharmaceuticals, our partner company, have spent several months developing new analytical methods and generating preliminary data, both of which are now ready for FDA's review. For each of the 3 areas of concern we have provided proposed test methods and evaluation criteria. We have also provided a list of the drug product samples planned for analysis. Newly released lots as well as those close to expiry, for both Lovenox and the Sandoz product, will be included in our evaluation. Preliminary data is also included where available. The proposed responses for each of FDA's 3 areas of issue are described below:

SANDOZ

1) Studies assessing the interaction of Enoxaparin with PF4

FDA Request: *HIT is mediated by antibodies to the PF4-heparin complex. Although Sandoz/Momenta used sophisticated approaches to show the sameness of its active ingredient to that in Lovenox, the presence of impurities may affect the interaction of enoxaparin with PF4. Please compare the ability of your product with that of the innovator product to bind to and form complexes with the chemokine PF4, and characterize the size and charge of the resulting complexes. Please include in your studies product lots that are newly released as well as those that are close to expiry date.*

Sandoz Response: Sandoz/Momenta propose to conduct the following 5 studies to assess the interaction of PF4 with Enoxaparin. The following preliminary data are available in the attached report

Method	RLD	Generic	UFH
PF4: Binding by SPR:	X	X	X
PF4: Enoxaparin Complex Size by SEC-UV.	X	X	
PF4: Enoxaparin Complex Size by SEC-MAL:			
PF4: Enoxaparin Complex Size by AUC			X
PF4: Enoxaparin Complex Charge by Zeta Potential	X	X	X

Data from 4 lots of Lovenox and 3 lots of Sandoz Enoxaparin Sodium will be tested for each method and provided in our final report.

Further detail for our proposal to assess the interaction of Enoxaparin with PF4 is provided in Section 9, pages 13-29 of the attached report.

2) Studies to assess differences in impurities and their potential effect on immunogenicity

Studies have shown that low levels of innate immune agonists can act synergistically to activate the innate immune system. Consequently, it is important to understand the amount and nature of potential product contaminants relative to those in the innovator product.

a) FDA Request: *Please quantify the level of protein impurities utilizing a highly sensitive method.*

Sandoz Response: Sandoz/Momenta propose to conduct the following 2 studies to assess the levels of protein impurities. The following preliminary data are available in the attached report

Method	RLD	Generic	UFH
Measurement of Total Protein USP/TCA	X	X	X
Measurement of Individual protein: SDS-PAGE	X	X	X

SANDOZ

b.) FDA Request: *Please characterize any protein impurities in your product as compared to the innovator product. These studies should have a high sensitivity and be capable of comparing patterns of protein impurities. This could be achieved using discriminating 2D gels, HPLC, or immunoassays. Data from sensitive assays that demonstrate a similar pattern of impurities would support the contention that the generic product is similar with regard to impurity content. Data demonstrating the extent of impurity removal during the manufacturing process could also be of value.*

Sandoz Response: Preliminary data from the evaluation of the RLD as well as Enoxaparin Sodium indicate that there is no detectable individual protein impurity at a level > (b) (4) ppm. Additionally, preliminary data from the evaluation of UFH in Section 11 show no individual protein impurity > (b) (4) ppm exists in the UFH starting material. If this observation is maintained after analysis of the proposed UFH and Enoxaparin Sodium samples, further evaluation will not be performed.

c) FDA Request: *Please provide information on process removal of nucleic acids and lipids. Significant residual materials may require further comparative characterization.*

Sandoz Response: Sandoz/Momenta propose to conduct the following 4 studies to measure the levels of lipids and nucleic acids. The following preliminary data are available in the attached report.

Method	RLD	Generic	UFH
Cholesterol and Triglyceride Detection by GC-MS	X	X	X
Phospholipid Measurement by LC-MS	X	X	X
Fatty Acid Measurement by GC-MS	X	X	X
Measurement of DNA Impurities	X	X	X

If observations in the preliminary data for lipids and nucleic acids (i.e. levels below the defined thresholds for both Enoxaparin and UHF) continue through the assessment of the completed proposed protocol, no additional process removal studies will be done (based on the thresholds proposed for both lipids, (b) (4) ppm for individual species, and nucleic acids, < (b) (4) ng/dose).

d) FDA Request: *Impurities leaching from container closure systems can potentially contribute to the immunogenicity of products. Please assess differences in leachables arising form the syringes used by the generic and innovator products and determine whether they affect immunogenicity, or provide a rationale for why such studies are not needed. Please include in your studies product lots that are newly released as well as those that are close to expiry date, as leachables may be most apparent in older lots of product.*

Sandoz Response: Container closure system impurities will be evaluated by extractables and leachables studies as described in Section 14

SANDOZ

3) Functional studies to assess differences in impurities and their potential affect on immunogenicity.

The following studies may contribute to the understanding of any potential immunogenic properties of your product as compared to the innovator product, and provide useful information to assist in the review of your ANDA. Depending on the outcomes of the above studies, this functional evaluation of potentially immunogenic properties may influence the agency action on the ANDA.

i) ***FDA Request*** *- Development of an in vitro assay to compare the immunomodulatory (adjuvant-like) effect of the generic and innovator products. For example, assays could be used to assess the immune responses elicited by an antigen in the presence and absence of generic or innovator low molecular weight heparins to examine whether they affect immune responses similarly. The addition of suboptimal levels of innate immune agonists such as LPS or CpG ODN to the system may be helpful in amplifying any immunomodulatory effect of the product.*

Sandoz Response: Sandoz/Momenta propose to conduct the following 3 studies to compare the immunomodulatory properties of Enoxaparin Sodium and the RLD. The following preliminary data are available in the attached report.

Method	RLD	Generic	UFH
(b) (4)	X	X	
Effects on Primary Human PBMCs	X	X	
Effects on Antigen-Specific T cell Recall Responses	X	X	

ii) ***FDA Request-*** *Development of an animal model to determine whether the products, alone or in complex with PF4, are similarly immunogenic in vivo. While animal models do not necessarily predict immunogenicity in human, differences in the immune response would signal that the two molecules are regarded as different by the immune system*

Sandoz Response: Sandoz/Momenta propose to evaluate the potential immunogenicity of Enoxaparin Sodium and the RLD by the Murine Immunogenicity Study. The following preliminary data are available in the attached report.

Method	RLD	Generic	UFH
Murine Immunogenicity Study	X	X	

For each proposed study in the attached report, the following information is provided:

SANDOZ

- methods to be used
- preliminary data generated to date
- samples to be analyzed
- acceptance criteria

Sandoz/Momenta would like to obtain the concurrence of FDA in regards to our proposed studies that are intended to address the FDA concerns identified in its December 4, 2007 letter. We would propose a meeting or a telephone conference to be held at your convenience.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope.

Sincerely,

SANDOZ INC.

BBrannon for KRV

Kalpana Rao Vanam
VP, Regulatory Affairs

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2008-0201**	
TO *(Division/Office)* OBP - Office of Biotechnology Products; Thru: Marilyn Welschenbach			**FROM:** Thomas Hinchliffe	
DATE: 3/4/2008	**IND NO.**	**ANDA NO.** 77857	**TYPE OF DOCUMENT** Original	**DATE OF DOCUMENT** 2/27/2008,
NAME OF DRUG Enoxaparin Sodium		**PRIORITY CONSIDERATION** 30 days	**CLASSIFICATION OF DRUG** Rx	**DESIRED COMPLETION DATE** 4/3/2008

NAME OF FIRM Sandoz,Inc.

REASON FOR REQUEST

I. GENERAL

- ✆ NEW PROTOCOL
- ✆ PROGRESS REPORT
- ✆ NEW CORRESPONDENCE
- ✆ DRUG ADVERTISING
- ✆ ADVERSE REACTION REPORT
- ✆ MANUFACTURING CHANGE/ADDITION
- ✆ MEETING PLANNED BY _____
- ✆ PRE NDA MEETING
- ✆ END OF PHASE II MEETING
- ✆ RESUBMISSION
- ✆ SAFETY/EFFICACY
- ✆ PAPER NDA
- ✆ CONTROL SUPPLEMENT
- ✆ RESPONSE TO DEFICPENCY LETTER
- ✆ FINAL PRINTED LABELING
- ✆ LABELING REVISION
- ✆ ORIGINAL NEW CORRESPONDENCE
- ✆ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW ✆ END QF PHASE II MEETING ✆ CONTROLLED STUDI ES ✆ PROTOCOL REVIEW ✆ OTHER	✆ CHEMISTRY ✆ PHARMACOLOGY ✆ BIOPHARMACEUTICS ✆ OTHER

III.BIOPHARMACEUTICS

- DISSOLUTION
- PROTOCOL-- BIOPHARMACEUTICS
- IN--VIVO WAIVER REQUEST
- DEFICIENCY LETTER RESPONSE
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

IV.DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- _SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS

Here is the official Consult request for this Enoxaparin ANDA. OGD requests review of the Immunogenicity data submitted

The Submission is located in the EDR: \\Cdsesub1\nonectd\N77857\N_000\2008-02-27

Please cc Thomas Hinchliffe, HFD-617 (thomas.hinchliffe@fda.hhs.gov) and Benjamin Danso, HFD-617 (benjamin.danso@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER Thomas Hinchliffe	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

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

/s/

Thomas Hinchliffe
3/4/2008 11:36:15 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-857

Sandoz, Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
255 W. Midway Blvd.
Broomfield, CO 80038

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 26, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Enoxaparin Sodium Injection, 100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL prefilled syringes and 150 mg/mL, 0.8 mL and 1 mL prefilled syringes.

Reference is made to your amendment dated February 27, 2008.

This material consists of our preliminary responses to your questions. However, please note that lack of details and adequate validation of the proposed methods preclude definitive answers. The advice given above is offered as comments by the Agency and is not meant to convey any commitments by the Agency to Sandoz, Inc..

Question #1: Regarding the ability of your product to form complexes with PF4 and the characterization of such complexes: The overall approach proposed to assess the avidity of Enoxaparin for PF4 using SPR and the characterization of the complexes appears acceptable. However:

- The size and charge of the HIT complexes are governed by the ratio of the reactants. Please compare the size and charge profiles resulting from tests in which different ratios of Enoxaparin:PF4 or RLD:PF4 are compared.
- Please identify all the peaks in the HPLC profile. There are some apparent differences in the HPLC profile of Enoxaparin and the RLD, particularly around the (b) (4) and (b) (4) minute marks (Figure 4) that should be explained.

- Please perform a co-mixture analysis to ensure that the Enoxaparin and RLD profiles are similar.
- Please establish that the optimal ratios of Enoxaparin and PF4 to form ultra-large HIT complexes is comparable to that of the RLD.

Please justify the number of lots that you plan to use in your studies and provide a rationale for the lots that you have selected. The lots selected should be representative of product and its lot to lot variability. Please include at least 3 lots each of freshly manufactured, mid-cycle and close to expiry product. This comment applies for all the studies planned.

Question#2: Regarding potential impurities that may be present in your product:
Overall the Agency agrees with the approach proposed in section 14.1, 2 &3. However, we have the following requests for information:

- Please confirm that your turbidimetry assay SOP leads to the precipitation of all proteins regardless of charge and size.
- Please confirm the total protein content results obtained by visual turbidimetry using an orthogonal method of recognized higher sensitivity, as a sensitivity level of (b) (4) is not sufficient to ensure the absence of protein impurities.
- For assessing specific protein impurities, please develop a method of higher sensitivity. This could be SDS PAGE gels coupled with a stain that has higher sensitivity (1-5 ng/band are preferred). Please include for reference the MW for the main bands identified.
- Please establish the impact of product on the sensitivity of your assays. In particular establish whether the negatively charged heparin interferes with nucleic acid detection/quantification assays.

Question#3: Regarding the adequacy of the functional studies planned, the strategies proposed to explore whether the immune system views Enoxaparin and the RLD similarly are overall acceptable. However, we have the following requests:

- In assays using human PF4, please determine the effect of the endogenous PF4 on the sensitivity and specificity of the assay.
- If the cell line (b) (4) is not sensitive to low levels of impurities, then please consider an alternative line.

- While measuring TNFα and IL-6 is reflective of a potential mechanism of increase immunogenicity, their output by the chosen cell line (b) (4) may not be the most sensitive to the presence of low levels of impurities.
- Please fully describe and justify the experimental design for the in vivo studies. Daily administration of antigen may result in the induction of strong immune responses (not optimal for detecting small changes in immunogenicity) or tolerance. Please carefully establish a method for assessing the response in vivo to the antigen that does not elicit maximal responses or tolerance in the mice.

Additional comments:

Please submit data on the source and quality of the PF4 used in your assays.

Please direct your questions on these to Thomas Hinchliffe, PharmD, Project Manager, Office of Generic Drugs at 240-276-8536.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Gary Buehler

4/28/2008 03:42:25 PM

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

OVERNIGHT DELIVERY

ORIG AMENDMENT
N-AE

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

CMC TELEPHONE AMENDMENT

June 2, 2008

RE: ANDA 77-857 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

CMC Telephone Amendment – Testing for Heparin Contaminants

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for 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 (Prefilled Single Dose Syringes with Automatic Safety Device) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone conversation between Tom Hinchliffe (FDA) and Beth Brannan (Sandoz) on April 18, 2008. During this conversation, Mr. Hinchliffe requested Sandoz conduct testing of all unfractionated heparin (UFH) lots used to manufacture batches of Enoxaparin Sodium Injection intended for commercial distribution. Mr. Hinchliffe asked that Sandoz provide results from the two tests specified on their web site: the Proton NMR method and the Capillary Electrophoresis method.

In response to this request, we are providing results for the requested tests. Enclosed is a report entitled "CMC Amendment: UFH Contaminant Analysis" that identifies the lots that were tested and provides analytical data for each lot tested using both methods. The report concludes OSCS was not detected in any UFH lot.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

SANDOZ

Document	ANDA 77-857
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Deficiency Response	**cmc** folder UFH contaminant analysis.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

A Sherwood for

Beth Brannan, Director
Regulatory Affairs

Enclosures
BB/jep

Beth Brannan, Director
Regulatory Affairs

Sandoz Inc.
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Fax +1 303 438-4600
Email:
Beth.Brannan@sandoz.com

SANDOZ

ORIG AMENDMENT

N-000-AF
N-000-XR

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT AND EXCLUSIVITY CERTIFICATION

(Electronic Submission)

RECEIVED
JUN 16 2008
OGD

June 13, 2008

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Labeling Amendment and Exclusivity Certification – Updates to Physician Insert and Exclusivity Statement

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

We have revised our labeling to be consistent with the reference listed drug (Lovenox® Injection, NDA 20-164, Sanofi-Aventis, approved May 16, 2007). This update also includes changing the format of our physician insert to PLR format.

Enclosed you will find our insert in final print (true size) as well as in enlarged PDF, Word and SPL format. Also enclosed is a PDF file containing a side-by-side comparison of our new proposed insert versus the revised Lovenox insert, as well as the RLD insert in PDF format.

In addition, Sandoz has identified a new exclusivity associated with the reference listed drug. All information in regard to exclusivity code I-533, Acute ST-Segment Elevation Myocardial Infarction (STEMI), has been carved out. A revised Exclusivity Certification is provided.

SANDOZ

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Folder	Document	File Name
ANDA 77-857	Cover Letter (scanned)	*cover.pdf*
	FDA Form 356h (scanned)	*356h.pdf*
other		
	Revised Exclusivity Certification (scanned)	*exclusivity.pdf*
labeling		
	Package insert – True Size	*final print.pdf*
	Package insert in enlarged PDF format	*enlarged.pdf*
	Package insert in MS Word format	*Insert 04-08.doc*
	Side by Side comparison versus RLD	*side by side.pdf*
	RLD Insert (Lovenox) approved 5/16/07	*rld 051607.pdf*
spl	Revised insert in SPL format	*enoxaparin.xml*

We are also providing hard copies of our cover letter, FDA form 356h, and revised Exclusivity Certification with original signatures.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

BBrannan

Beth Brannan
Director, Regulatory Affairs

Enclosures

BB:ckm

Meeting Minutes

Meeting Date: July 31, 2008 **Time:** 2:30 pm **Location:** Telephone

ANDA and Drug Name: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Type of meeting: Teleconference

Minutes Recorder: Thomas Hinchliffe, Project Manager, OGD

FDA Attendees:

Steven Kozlowski, OBP
Daniela Verthelyi, OBP

Andre Raw, OGD
Sau Lee, OGD
Naiqi Ya, OGD
David Skanchy, OGD

Industry Attendees:

Sandoz Inc.:

Kalpana Rao Vanam, Vice President of Regulatory Affairs
Beth Brannan, Director of Regulatory Affairs
Jean Pederson, Sr. Associate, Regulatory Affairs

Momenta attendees:

Ganesh Venkataraman, Senior Vice President Research and Chief Scientific Officer
Kei Kishimoto, Vice President, Disease Biology
Tanmoy Ganguly, Associate Director, Disease Biology
Birgit Schultes, Director, Disease Biology
Gerard Riedel, Vice President, Regulatory Affairs

Meeting Objectives:

To discuss Sandoz questions rose in their July 15, 2008 email, See below discussion for copy of email and FDA response.

Attention **Via E-mail**
Tom Hinchliffe, Project Manager
Food and Drug Administration
Office of Generic Drugs

E-mail thomas.hinchliffe@fda hhs.gov
Number of pages 4 including cover page

Date July 15, 2008

Concerning **ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)**

REQUEST FOR A TELECONFERENCE

Dear Tom:

Reference is made to our deficiency letter dated December 5, 2007, regarding immunogenicity of Enoxaparin.

During a May 15, 2008 teleconference among FDA/Sandoz/Momenta, FDA responded to Sandoz/Momenta's proposal to study the immunogenicity of PF4:LMWH complexes in a murine model (deficiency item #3)
.
FDA commented:

- *"Sandoz/Momenta may wish to consider an alternative/additional approach…*
- *One alternative approach would use a model antigen and a more traditional immunization protocol. Such an approach would assess whether impurities in Enoxaparin Sodium Injection enhance the antibody response to the model antigen."*

FDA acknowledged that the use of Enoxaparin Sodium Injection in such a model may generate negative results. **FDA suggested that Sandoz/Momenta could generate a proposal for such an approach for FDA's review.**

Sandoz/Momenta have conducted pilot studies of the use of CpG oligonucleotides (ODN) as an adjuvant to boost antibody responses to model antigens. The design of the pilot studies is based on published studies (Klinman et al., Use of CpG oligonucleotides as immune adjuvants, Immunol. Rev., 2004, 199: 201-216).

Based upon the results of these pilot studies (see following page), Sandoz/Momenta propose to conduct the following studies and report the results in the complete response to FDA's immunogenicity questions. However, prior to conducting these studies, Sandoz would like to discuss the details of this proposal with FDA.

Murine Model Proposal		
Topic	Notes	Request to FDA

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/

Thomas Hinchliffe

8/11/2008 01:44:54 PM

Beth Brannan, Director
Regulatory Affairs

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SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

NEW CORRESP
N/XP

SEP 16 2008

RE: ANDA 77-857: Enoxaparin Sodium Injection: 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device

Patent Amendment – Summary Judgment of Unenforceability is Granted

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 100 mg/mL (30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/mL) and 150 mg/mL (120 mg/0.8 mL and 150 mg/mL) Pre-filled Single Dose Syringes with Automatic Safety Device in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our patent amendment filed September 8, 2006. In this amendment, we informed you of being subject to a lawsuit by Aventis Pharma S.A. and Aventis Pharmaceuticals, Inc. within the prescribed 45-day time frame, for U.S. Patent Nos. 5,389,618 and RE 38,743. There were two cases that applied to this lawsuit:

1.) California case CV-07-2558 (previously known as case CV-06-3671, which was a New Jersey case that was later transferred to California and given the number CV-07-2558).

2.) California case CV-06-4858.

Sandoz Inc. would like to inform you that Aventis's complaint for infringement of U.S. Patent No. 5,389,618 and RE 38,743 was dismissed and final judgment entered. A copy of the Orders Granting Defendant's Motion of Summary Judgment of Unenforceability are provided on the enclosed CD.

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This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Folder: ANDA 77-857
356h.pdf
cover.pdf
Summary Judgment CV-06_4858
Summary Judgment CV_07_2558

This information is submitted for your review.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

BBrannan

Beth Brannan, Director
Regulatory Affairs

Enclosures

BB/jep

Beth Brannan, Director
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OVERNIGHT DELIVERY

Gary Buehler, Director
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Center for Drug Evaluation and Research
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Rockville, MD 20855

UNSOLICITED AMENDMENT
(Electronic Submission)

ORIG AMENDMENT

SEP 23 2008

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Unsolicited Amendment - Chemistry, Manufacturing and Control Information
DMF Type II, No. 18557, Heparin Sodium Updates

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Sandoz Inc. would like to inform you of changes that have been made to DMF Type II No. 18557 for Heparin Sodium that is referenced in our application. Details of these changes are provided below.

Sandoz GmbH, (b) (4) Austria, holder of DMF Type II, No. 18557, for Heparin Sodium, our currently filed site used for manufacturing the purified starting material, Heparin Sodium, has amended its DMF 18557 to include the following site as an additional source of crude starting material Heparin Sodium (b) (4):

(b) (4)

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Sandoz GmbH has also added identity tests A, B and C to their drug substance release criterion to be in compliance with recent USP requirements. In addition, they have added a specification for "OSCA (over-sulphated chondroitin sulphate) NMT (b) (4)%" and "other glycosaminoglycans NMT (b) (4)%" using their already filed method.

Lastly, Sandoz GmbH has (b) (4) for purified starting material heparin sodium (b) (4).

Sandoz GmbH amended its DMF on September 19, 2008, to include the above referenced changes. Enclosed is a copy of their amendment cover letters, for your reference, which provide further details of these changes.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Folder: ANDA 77-857
356h.pdf
cover.pdf
DMF_covers.pdf

This information is submitted for your review.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope. Should you have any questions please contact me at (303) 438-4237.

Sincerely,

Beth Brannan
Director, Regulatory Affairs

/jep

Enclosures

Beth Brannan, Director
Regulatory Affairs

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OVERNIGHT DELIVERY

Gary Buehler, Director
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Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT

(electronic submission)

N-000-AF

SEP 23 2008

RE: ANDA 77-857 Enoxaparin Sodium Injection
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)
and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Gratuitous Amendment – Labeling

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to an email from Ruby Wu (FDA) to Caryn McCullough (Sandoz) on July 25, 2008, informing us of an update to the reference listed drug labeling (RLD) that was posted on the Drugs@FDA website. In response to this update, Sandoz has revised our insert in accordance with the RLD labeling (Lovenox®, sanofi-aventis, approved 7/16/2008).

Enclosed you will find our revised package insert in final print (true size). In addition, we are providing our insert in SPL, enlarged PDF, and Word format, as well as the RLD insert in PDF format. Also provided are side-by-side comparisons of our proposed insert versus the RLD and versus our last submission.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

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Folder	Document	File Name
ANDA 77-857	Cover Letter (scanned)	*cover.pdf*
	FDA Form 356h (scanned)	*356h.pdf*
labeling		
	Revised insert – True Size	*fpl insert.pdf*
	Revised insert in enlarged PDF format	*enlarged pi.pdf*
	Revised insert in MS Word format	*pi word.doc*
	Side by Side comparison versus last filed	*sidexside v last filed.pdf*
	Side by Side comparison versus RLD	*sidexside v rld.pdf*
	RLD insert (Lovenox®, approved 7/25/08)	*rld insert 071608.pdf*
spl	Revised insert in SPL format	*enoxaparin-sodium.xml*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

Enclosures

BB/ckm

Beth Brannan, Director
Regulatory Affairs

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96-1

SANDOZ

OVERNIGHT DELIVERY

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AMENDMENT

ORIG AMENDMENT

N/A

SEP 25 2008

RE: ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)

Amendment – Immunogenicity Data Provided
Response to letters dated November 5, 2007, December 4, 2007, & April 28, 2008

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 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 (Pre-filled Single Dose Syringes with Automatic Safety Device) in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your letter dated November 5, 2007 and to your follow up letters dated December 4, 2007 and April 28, 2008.

In your correspondence dated November 5, 2007, it was stated that Sandoz ANDA 77-857 for Enoxaparin Sodium Injection was determined to be not approvable because our application did not adequately address the potential for immunogenicity of the drug product. At that time, it was recommended that Sandoz/Momenta contact your office to schedule a meeting to address what additional information should be provided to adequately address this concern.

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SEP 26 2008

OGD

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In your correspondence dated December 4, 2007, it was stated that the current analytical methods, which provide information regarding the characterization of the active ingredient, that are included in the Sandoz/Momenta ANDA may not fully predict biological properties of complex drug products, such as enoxaparin, derived from biological sources and that you are particularly concerned with product and process derived impurities that may modify the biological activity or enhance the immunogenicity of our product. You also stated that understanding the potential for our product to elicit an immune response is critical, since low molecular weight heparins are associated with a serious immune-driven adverse event, heparin induced thrombocytopenia 9HIT), and that impurities can interact either with the product or with the host immune system in ways that alter outcome. Thus, for products that have the potential for immunologic adverse events and certainly for products with known immunologic events, the contribution of impurities needs to be carefully considered.

In your correspondence dated December 4, 2007, you also asked that several items be addressed as part of our ANDA, and provided suggested approaches to addressing these issues. You also recommended that we provide protocols for Agency review.

In subsequent telephone conversations and correspondence to and from your office, including your letters dated November 5, 2007 and December 4, 2007, and our amendment filed February 27, 2008, a plan on how Sandoz could address the potential for immunogenicity of its drug product was agreed upon by FDA and Sandoz. A chronology of correspondence between FDA and Sandoz concerning this amendment is located in Section 3.5 of the immunogenicity report provided on the enclosed CD.

Thus, in this amendment, we would like to provide a response to the comments raised in your letter of December 4, 2007, that adequately addresses your concerns about the potential for immunogenicity of our drug product::

1. **FDA Comment**

Studies assessing the interaction of Enoxaparin with PF4: HIS is mediated by antibodies to the PF4-heparin complex. Although Sandoz/Momenta used sophisticated approaches to show the sameness of its active ingredient to that in Lovenox, the presence of impurities may affect the interaction of enoxaparin with PF4. Please compare the ability of your product with that of the innovator product to bind to and form complexes with the chemokine PF4, and characterize the size and charge of the resulting complexes. Please include in your studies product lots that are newly released as well as those that are close to expiry date.

Sandoz Response: Sandoz/Momenta measured PF4 binding and determined the physiochemical characteristics of the resulting complexes for nine lots of Enoxaparin Sodium Injection as well as four lots of RLD. The Enoxaparin Sodium Injection lots were selected to provide a broad representation of manufacturing experience; RLD lots were selected to provide appropriate comparators and to estimate the lot-to-lot variability of the RLD. In addition, Sandoz/Momenta completed the same analysis on three admixtures

created by mixing lots of Enoxaparin Sodium Injection with Lovenox. The results demonstrate that Enoxaparin Sodium Injection and the RLD form the same complexes upon binding to PF4. Please refer to our immunogenicity report that is provided on the enclosed CD for a summary of the data and discussion of our results.

2. **FDA Comment**

Studies to assess differences in impurities and their potential affect on immunogenicity: Studies have shown that low levels of innate immune agonists can act synergistically to activate the innate immune system. Consequently, it is important to understand the amount and nature of potential product contaminants relative to those in the innovator product.

a. **Please quantify the level of protein impurities utilizing a highly sensitive method.**

b. **Please characterize any protein impurities present in your product as compared to the innovator product. These studies should have a high sensitivity and be capable of comparing patterns of protein impurities. This could be achieved using discriminating 2D gels, HPLC, or immunoassays. Data from sensitive assays that demonstrate a similar pattern of impurities would support the contention that the generic product is similar with regard to impurity content. Data demonstrating the extent of impurity removal during the manufacturing process could also be of value.**

c. **Please provide information on process removal of nucleic acids and lipids. Significant residual materials may require further comparative characterization.**

d. **Impurities leaching from container closure systems can potentially contribute to the immunogenicity of products. Please assess differences in leachables arising from the syringes used by the generic and innovator products and determine whether they affect immunogenicity, or provide a rationale for why such studies are not needed. Please include in your studies product lots that are newly released as well as those that are close to expiry date, as leachables may be most apparent in older lots of product.**

Sandoz Response: To address parts a, b and c of your request, Sandoz/Momenta measured protein, lipid and nucleic acid impurities in nine lots of enoxaparin Sodium Injection and two lots of RLD. These lots represented various dates of manufacture and/or expiry. Additionally, Sandoz/Momenta performed the same analyses on twelve lots of Unfractionated Heparin USP starting material.

To address part d, we assessed differences in leachables arising from the syringes used by the generic and innovator products to determine whether they affected immunogenicity. These studies included product lots that were newly released as well as those that were close to expiry date.

Methodologies have been developed and executed to assess for differences in impurity profiles between Enoxaparin Sodium Injection and RLD due to proteins, lipids, nucleic acids, and leachables from container closure system. Based on these executed studies, the impurities profile for Enoxaparin Sodium Injection is confirmed to fall within the variability observed with the RLD to the limits identified for these respective methods. Pease refer to our immunogenicity report that is provided on the enclosed CD for a summary of the, protocol used for testing, data and discussion of our results.

3. FDA Comment

Functional studies to assess differences in impurities and their potential affect on immunogenicity: The following studies may contribute to the understanding of any potential immunogenicity properties of your product as compared to the innovator product, and provide useful information to assist in the review of your ANDA. Depending on the outcomes of the above studies, this functional evaluation of potentially immunogenic properties may influence the agency action of the ANDA.

i) Development of an in vitro assay to compare the immunomodulatory (adjuvant-like) effect of the generic and innovator products. For example, assays could be used to assess the immune responses elicited by an antigen in the presence and absence of generic or innovator low molecular weight heparins to examine whether they affect immune responses similarly. The addition of suboptimal levels of innate immune agonists such as LPS or CpG ODN to the system may be useful in amplifying any immunomodulatory effect of the product.

ii) Development of an animal model to determine whether the products, alone or in complex with PF4, are similarly immunogenic in vivo. While animal models do not necessarily predict immunogenicity in humans, differences in the immune response would signal that the two molecules are regarded as different by the immune system.

Sandoz Response: Sandoz/Momenta has conducted studies *in vitro* to evaluate the immunomodulatory properties of potential contaminants in nine lots of Enoxaparin Sodium Injection and four lots of the RLD. Assays were performed to assess the effect of the DP and the RLD on TNF-α secretion in human primary PBMC. The effects of the DP and the RLD on antigen-specific T cell responses were evaluated in human primary PBMC. As a result, we can conclude that there are no substantive differences in the activities of any of the tested lots of DP or RLD with respect to their immunomodulating effects on TNF-α secretion or on antigen-specific T cell proliferation, even in the presence of sub-optimal concentrations of LPS or CpG ODN.

Sandoz/Momenta conducted a comprehensive set of studies to evaluate the effects of potential contaminants in Enoxaparin Sodium Injection and RLD on an antibody response to a model antigen. Three RLD lots and four Enoxaparin Sodium Injection lots were used

SANDOZ

in this study. In summary, we can conclude that Enoxaparin Sodium Injection and RLD are equivalent with respect to any immunomodulatory effects in vivo.

Please refer to our immunogenicity report that is provided on the enclosed CD for a summary of our protocols, methodologies, data and a discussion of our results.

This information is submitted for your review.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Folder: ANDA 77-857
356h.pdf
cover.pdf
Immunogenicity_Report.pdf

This information is submitted for your review.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Beth Brannan

Beth Brannan, Director
Regulatory Affairs

Enclosures

BB/jep

Telephone Conversation Memorandum

ANDA: 77-857

DRUG: Enoxaparin

FIRM: Sandoz

PERSONS INVOLVED: Andre Raw, Larry Lee, Naiqi Ya, Tom Hinchliffe

PHONE NUMBER: 303-386-5534

DATE: 10/16/08

Conversation:

- Please provide a complete heparin pediqree supply chain from (b) (4) and subsequently used to manufacture enoxaparin lots used to demonstrate both sameness as well as perform the recent studies for immunogenicity and how you control them. Please also update DMF with this and amend ANDA to inform of DMF update.

- Please provide data to show that the Scale marks on the Pre-filled syringes are correct.

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

/s/

Thomas Hinchliffe
10/17/2008 12:15:03 PM

Jean Pederson, Senior Associate
Regulatory Affairs

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Center for Drug Evaluation and Research
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Rockville, MD 20855

AMENDMENT

(electronic submission)

N/AC

November 20, 2008

NEW CORRESP

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Amendment –Withdrawal of Heparin Source [redacted] (b) (4)

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

We would like to inform you of a change that has been made to DMF Type II No 18557, Heparin Sodium, which is referenced in our application.

The DMF holder, Sandoz GmbH, [redacted] (b) (4) Austria, filed an amendment to its DMF on November 19, 2008, to withdraw [redacted] (b) (4) [redacted] (b) (4) as a supplier of crude heparin for the the commercial manufacture of Heparin Sodium USP purified starting material. This request is made without prejudice to future filings. For your reference, copies of the amendment cover letters are attached.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

NOV 2 1 2008

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Document	ANDA 77-857
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder attachments.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Pederson

Jean Pederson, Senior Associate
Regulatory Affairs

Enclosures

JP/ckm

Jean Pederson, Senior Associate
Regulatory Affairs

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SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
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Metro Park North 2, Room 150
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Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

ORIG AMENDMENT
N
AA

November 21, 2008

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Telephone Amendment –Data to Support Accuracy of the Syringe Graduated Scale

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone conversation between FDA (Tom Hinchliffe, Andre Raw, Sau Larry Lee, and Naiqi Ya) and Sandoz (Beth Brannan) on October 21, 2008. In this call, the labeling reviewer requested data which support the accuracy of the graduated scale on our prefilled syringe.

Please note, information regarding clarification of our (b) (4) Heparin sources was also requested in this conversation and will be provided in a separate amendment.

Sandoz has conducted development and validation studies to ensure the graduated scale label is accurately placed and yields the intended dose of Enoxaparin Sodium Injection. Provided on the enclosed CD is a report detailing the development, verification, and placement of the graduated scale label that is applied to our prefilled syringes (60 mg, 80 mg, 100 mg, 120 mg, and 150 mg). The Label Placement Validation Summary Report and Pharmaceutical Development Reports for the syringe graduation study and evaluation of the graduation label are also provided.

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NOV 24 2008
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This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	ANDA 77-857
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	labeling folder graduated label report.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Pederson

Jean Pederson, Senior Associate
Regulatory Affairs

Enclosures

JP/ckm

Jean Pederson, Manager
Regulatory Affairs

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Fax +1 303 438-4600
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SANDOZ

OVERNIGHT DELIVERY

ORIG AMENDMENT

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Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

N-000-AC

DEC 12 2008

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Telephone Amendment – Clarification of (b) (4) Heparin Sources

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone conversation between FDA (Tom Hinchliffe, Andre Raw, Sau Larry Lee, and Naiqi Ya) and Sandoz (Beth Brannan) on October 21, 2008. In this call, the following information was requested regarding clarification of our (b) (4) Heparin sources:

a. Clarification of the Sandoz sources of (b) (4) material and how it relates to the processing of Heparin.

b. Identification of the (b) (4) source(s) for each lot of Heparin and Enoxaparin Sodium that Sandoz filed to its application.

c. Information regarding Sandoz testing that would confirm that the material from all (b) (4) sources is the same and results in the "same" Enoxaparin drug substance.

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SANDOZ

A report describing Sandoz Heparin sources, including processing and testing, sources used to manufacture batches of Heparin Sodium, Enoxaparin Sodium drug substance, and Enoxaparin Sodium Injection drug product, and chemical equivalence of Enoxaparin Sodium Injection drug substance lots is provided in the CMC folder of the enclosed CD.

Please note that data supporting the accuracy of the graduated scale on our prefilled syringe was also requested in the telephone conversation referenced above. This information was provided in an amendment filed on November 21, 2008.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder report.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Pederson

Jean Pederson, Manager
Regulatory Affairs

Enclosures

JP/ckm

Meeting Minutes

MEETING DATE: December 22, 2008 **TIME:** 2:00 pm
LOCATION: MPNIV, Conference Room A

DRUG NAME: Enoxaparin Sodium Injection
ANDA 76-684 (Amphastar) and ANDA 77-857 (Sandoz)

TYPE OF MEETING: OGD Internal

MEETING RECORDER: Theresa Liu

OGD Participants
Robert West (Meeting Chair), Deputy Director, Office of Generic Drugs
Lawrence Yu, Director for Science, Office of Generic Drugs
Naiqi Ya, Team Leader, Office of Generic Drugs
Andre Raw, Chemist, Office of Generic Drugs
Sau Lee, Chemical Engineer, Office of Generic Drugs
David Read, Regulatory Counsel, Office of Generic Drugs
Theresa Liu, Regulatory Review Officer, Office of Generic Drugs

MEETING OBJECTIVES:
The objectives of the meeting were to discuss: 1) the Office of Generic Drugs (OGD) definition for the starting material (heparin sodium) for enoxaparin and 2) the OGD Letter to Amphastar regarding (b) (4) on the approvability of Amphastar's application (ANDA 76-684) for enoxaparin sodium injection.

MINUTES/DISCUSSION/DECISIONS REACHED:

Discussion Points

- Dr. Yu raised a question on whether heparin sodium used to manufacture enoxaparin sodium should be treated as a starting material or critical intermediate.

  Dr. Raw explained how heparin sodium could be viewed as a critical intermediate based upon the manufacturing process used to produce heparin sodium. Nevertheless, he stated that both the terms "starting material" and "critical intermediate" could be used interchangeably (b) (4)

  Dr. Ya stressed that the term "starting material" has always been used in all the ANDA reviews of enoxaparin, deficiency letters to generic sponsors, various

memoranda, and presentations to the Office of New Drug Quality Assessment (ONDQA), the Office of Biotechnology Products (OBP), and the Director for the Center for Drug Evaluation and Research (CDER) (Dr. Woodcock). He stated that OGD never used the term "critical intermediate" to describe heparin sodium used to manufacture enoxaparin sodium.

Dr. Lee stated that from a review perspective, there was not enough scientific reason to support the replacement of the term "starting material" with the term "critical intermediate."

- Dr Yu raised a question on whether the OGD Letter to Amphastar should contain information regarding (b) (4) (b) (4).

  Dr. Ya stated that the Office of Compliance (OC) should communicate (b) (4) ssues directly with Amphastar.

  Mr. West indicated that the statement regarding the possibility that Amphastar may need to submit a (b) (4)

  Mr. West and Dr. Ya made reference to issues related to (b) (4)

Conclusions

- There was an agreement among participants that OGD should continue to use the term "starting material" to describe heparin sodium used to manufacture enoxaparin sodium.
- There was an agreement that changes might be necessary to avoid statement(s) related to (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/

Robert L. West
1/30/2009 07:54:40 AM
Deputy Director, Office of Generic Drugs

Jean Pederson,
Manager, Regulatory Affairs

Sandoz Inc.
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Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

SANDOZ

77-857

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MC

January 20, 2009

RE: Attached List of Applications

Dear Mr. Buehler:

Sandoz Inc. wishes to provide you with New Correspondence announcing a change in the responsible agent for the attached list of product applications.

Effective November 17, 2008, the contact name for this application was changed from Beth Brannan to Jean Domenico, who can be reached at (303) 438-4242. The agent address did not change. Reference is made to a telephone conversation between Tom Hinchliff (FDA) and Jean Pederson (Sandoz) on November 20, 2008. Per Tom, a 356h is not required to be submitted, and that a cover letter with the attached list of products is all that is needed, plus one CD and a copy of the letter for each application. Therefore, one copy of this letter is enclosed for each ANDA provided on the list. Also enclosed is one CD containing a copy of this entire submission.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico,
Manager, Regulatory Affairs

RECEIVED
JAN 21 2009
OGD

Enclosures: List of Applications

JP/sc

Jean Domenico, Manager
Regulatory Affairs

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OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

ORIG AMENDMENT

N/AC

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MAR 0 2 2009
OGD

FEB 27 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Telephone Amendment –Response to FDA Correspondence Dated 1/29/09

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to correspondence received from Tom Hinchliffe (FDA) via telefax to Jean Domenico on January 29, 2009. In response to this correspondence, we are providing the following information:

1. **FDA Request:**
   Please provide a detailed description of the (b) (4)
   Please explain how the

   Sandoz Response:
   A complete response is provided in Section 2 (pages 6-22) of the attached report.

Following this page, 1 page withheld in full - (b)(4)

SANDOZ

5. **FDA Request:**
Data associated with (b) (4): Recently, Sandoz withdrew (b) (4) (b) (4) from its ANDA, as a supplier of Heparin (b) (4) (b) (4) Consequently, OGD informed Sandoz/Momenta that data derived from materials that include the use of Heparin (b) (4) supplied by (b) (4) would not be used to support the approval of the current ANDA application. OGD has conducted its internal review of the consequences of removing the data; currently OGD does not see a problem doing so. OGD requested Sandoz/Momenta to conduct its own assessment and inform OGD if this assessment identifies any data gaps in the ANDA.

Sandoz Response:
A complete response is provided in Section 5 (pages 36-40) of the attached report.

6. **FDA Request:**
Selection of (b) (4) suppliers: OGD requested additional information from Sandoz GmbH regarding how it selected/qualified its (b) (4) suppliers of Heparin (b) (4)

Sandoz Response:
A complete response is provided in Section 6 (pages 41-42) of the attached report.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder report.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

SANDOZ INC.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures
JD/ckm

Jean Domenico, Manager
Regulatory Affairs

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SANDOZ

OVERNIGHT DELIVERY

DRUG AMENDMENT
N-AA

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

UNSOLOCITED AMENDMENT

(electronic submission)

MAR 2 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Unsolicited Amendment – Change to the Drug Substance Manufacturing Process and Residual Solvents Update

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

This amendment presents information concerning the following:

- Changes to the drug substance manufacturing process
  - ✓ A change in the (b) (4) of the manufacturing process for Enoxaparin Sodium.
  - ✓ A change in specifications for (b) (4) (b) (4) of the manufacturing process for Enoxaparin Sodium.
- Compliance with USP general chapter <467> for residual solvents

Complete details of these changes are provided in the attachment located in the cmc folder on the enclosed CD.

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OGD

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder attachment.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Telephone Conversation Memorandum

ANDA: **77-857**

DRUG: Enoxaparin

FIRM: Sandoz

Sandoz Inc. - USA
Kalpana Rao Vanam, VP, Regulatory Affairs
Srinivasa Rao, Director, Regulatory Affairs
Jean Pederson, Manager, Regulatory Affairs

Momenta
Ganesh Venkataraman, Senior VP Research/Chief Scientific Officer
John Bishop, Senior VP, Pharmaceutical Sciences
James Anderson, Senior Director, Analytical Development
Kei Kishimoto, Vice President, Disease Biology
Zachary Shriver, Senior Director, Analytics
Jennifer Smith, Senior Director, QA/QC
Gerard Riedel, Vice President, Regulatory Affairs

FDA PERSONS INVOLVED:

Amy Rosenberg, OBP
Daniela Verthelyi, OBP
Andre Raw, OGD
Sau Lee, OGD
Florence Fang, OGD
Richard Adams, OGD
Naiqi Ya, OGD

PHONE NUMBER: (b) (4) **Meeting Number:** (b) (4)

DATE: Friday, March 6, 2009 – 11am est

Conversation:

Regarding question #1:" .. does FDA consider the data analyses and acceptance criteria described in this amendment to sufficiently address FDA's requests"
The Agency provided the following comments:

1 *Regarding the PF4 source:*

   a. *Your studies show that the individual lots of PF4 used have differences in the percent of monomer, dimer, trimer and tetramer. Please comment on how these differences impact on the analytical and functional studies performed to characterize the PF4-heparin complexes.*

   b. *After qualifying the* (b) (4) *PF4,* (b) (4) *PF4 was used for certain studies. Please clarify the source of PF4 that was used for each study and confirm that all the PF4 used was similarly qualified.*

   c. *Please confirm that the same lot of PF4 was used in all head to head studies.*

2 *With reference to your assessment of complex formation, please comment on the stability of the complexes formed. The work of Suvarna et al. suggests that the size of complexes may change over time.*

3 *The retention time and molecular weight of the intermediate complexes formed with Sandoz Enoxaparin appear to be marginally smaller than those of the RLD (83.5kDa to 80kDa) as assessed by SEC-HLPC. T test shows=0.02(pp 428-429). Please comment as to the significance of this finding.*

4 *We note that the recovery of enoxaparin/PF4 complexes by SEC is low. Please comment on whether the SEC procedure disrupts the complexes. Please confirm that the percent recovery was similar for your product and the RLD.*

5 *Regarding your assessment of complex size by PCS:*

   a. *Please submit examples of the raw readout of the PCS for your product and the RLD at the different PHRs.*

   b. *Please confirm that the numbers provided correspond to the average complex size including large, intermediate and smaller complexes.*

c. *Please submit a table with the diameter of each of these for review if available.*

6 *Regarding your assessment of complex size by A280, please clarify why PF4/Enoxaparin complexes have absorbance at 280 if PF4 has low levels of phenylalanine and tyrosine. Please clarify whether this assay reflects true absorbance or turbidity. Is the absorbance stable over time?*

7 *Please submit a table detailing the complex charge for each PHR as assessed by z-potential.*

8 *Please submit better copies of the gels to assess total proteins stained with colloidal blue, as the images included in this submission are hard to interpret. For example, no band is visible for the de-staining control.*

9 *Please establish specifications for impurities and include them as part of your release testing.*

10 *Please clarify whether the in vitro studies were conducted using PBMC from a single donor. Please use additional donors to confirm that the results are representative.*

11 *Some of the lots appear to induce higher levels of TNF production by PBMC in culture. Please comment.*

12 *Thymidine uptake is highest in cells stimulated with LMWH. Is the increase in T cell proliferation antigen and/or dose dependent? Can you provide an explanation for the reduced proliferation when LPS is added to the conditions?*

13 *Regarding the in vivo studies, you have provided the antibody titers for the mice treated with LMWH in the presence of adjuvants. Please provide an assessment of the response to the product in the absence of LPS or CpG ODN.*

14 *Please comment on the high variability in the antibody response. Is this due to heterogeneities in the product used to immunize the animals?*

15 *Please provide a (dose dependent) assessment of the adjuvant effect of the different lots of LMWH (yours and the RLD's) in the absence of CpG ODN or LPS.*

FDA will fax a list of the comments/questions to the sponsor.

Regarding question#2, Does the Agency agree with Sandoz/Momenta's proposal to perform the all the previously agreed upon set of tests to assess the presence of impurities and relative risk of increased immunogenicity except for the in vivo study to assess antibody production on only 1 lot to qualify a new source of UFH?

No. The Agency stated that at least 3 lots would be needed to assess the product from the new source. Regarding the need to repeat the in vivo studies to assess antibody responses to the product, the Agency stated that, as currently designed, the study to assess the development of antibodies in vivo was uninformative due to the extremely high variability within treatment groups. The reviewers expressed concern that the assay could indicate previously unappreciated heterogeneity in the product. The SOP for the in vivo testing was discussed at length. The sponsor was encouraged to develop a more sensitive method to assess the rate and magnitude of the antibody response to the product.

The sponsor agreed to perform the immunogenicity studies on 3 lots of current material and 1 of expired product to assess the new source of UFH.

Regarding Question #3 was not discussed.

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P.O. Box 446
Broomfield, CO 80038 0446
Tel +1 303 438 4237
Fax +1 303 438 4600
Email: Jean.Domenico@sandoz.com

FDA Teleconference minutes

Meeting:	Enoxaparin ANDA 77-857
Meeting Attendees:	Sandoz Inc. (Sponsor) Momenta Pharmaceuticals, Inc. (on behalf of Sponsor) Food and Drug Administration
Meeting Date / Time:	March 6, 2009 / 11:00 am -12:00 pm EST
Meeting Minutes Date:	March 11, 2009
Meeting Location:	N/A
Meeting Goals	To clarify several topics related to immunogenicity testing

Attendees: Sandoz Inc.	Jean Domenico, Manager, Regulatory Affairs Kalpana Rao Vanam, Vice President, Regulatory Affairs Srinivasa S. Rao, Director, Regulatory Affairs
Attendees: Momenta Pharmaceuticals, Inc.	Ganesh Venkataraman, Senior Vice President Research and CSO John Bishop, Senior Vice President, Pharmaceutical Sciences James Anderson, Vice President, Analytical Development Kei Kishimoto, Vice President, Disease Biology Zachary Shriver, Consultant Jennifer Smith, Senior Director, QA/QC Gerard Riedel, Vice President, Regulatory Affairs
Attendees: FDA	Amy Rosenberg, Office of Biotechnology Products Daniela Verthelyi, Office of Biotechnology Products Andre Raw, Office of Generic Drugs Sau Lee, Office of Generic Drugs Naiqi Ya, Office of Generic Drugs Florence Fang, OGD Richard Adams, OGD Thomas Hinchliffe, Project Manager, Office of Generic Drugs

Reference materials

Attachment 1: Correspondence (telefax) from FDA to Sandoz (March 9, 2009)
Attachment 2: Correspondence (email) from Sandoz to FDA (March 5, 2009)

Meeting Summary

1. FDA comments/questions for Sandoz/Momenta

FDA stated that, before FDA responded to Sandoz' list of questions, FDA wanted to discuss several topics associated with its ongoing review of the immunogenicity amendment submitted to ANDA 77-857 (September 27, 2008). Dr Verthelyi (OBP) led the discussion of the following topics, which are organized according to the list of questions that FDA sent to Sandoz after the teleconference (attachment 1):

FDA request		Reference: Amendment Section	Comments during the teleconference	
#	Request [reproduced from attachment 1]		FDA	Sandoz/Momenta
1a	Your studies show that the individual lots of PF4 used have differences in the amounts of monomer, dimer, trimer and tetramer. Please comment on how these differences impact on the analytical and functional studies performed to characterize the PF4-heparin complexes.	4.4		*Detailed information to be provided in an upcoming written response to this request.*
1b	After qualifying the (b) (4) PF4, (b) (4) PF4 was used for certain studies. Please clarify the source of PF4 that was used for each study and confirm that all the PF4 used was similarly qualified.	5, 8.1		*Detailed information to be provided in an upcoming written response to this request.* The amount of PF4 required was larger that the amount available in any single, commercially available lot. Lots were screened for suitability of use for the intended assay and were consistently used within an assay for all sample comparisons.
1c	Please confirm that the same lot of PF4 was used in all head to head studies.	5, 8.1		*Detailed information to be provided in an upcoming written response to this request.* The same lot of PF4 was used in all head-to-head studies presented in section 5. Several PF4 lots were used in the studies presented in section 8.1. Within each head to head experiment, the same PF4 lot was used for all samples. Specific lot details will be provided in the written response to this request
2	With reference to your assessment of complex formation, please comment on the stability of the complexes formed. The work of Suvarna et al. suggests that the size of complexes may change over time.	5		*Detailed information to be provided in an upcoming written response to this request.*
3	The retention time and molecular weight of the intermediate complexes formed with Sandoz Enoxaparin appear to be marginally smaller than those of the RLD (83.5 kDa to 80 kDa) as assessed by SEC-HPLC. T test shows = 0.02 (pp 428-429). Please comment as to the significance of this finding.	5.2	What is the functional significance of the differences observed between different samples in this assay?	*Detailed information to be provided in an upcoming written response to this request.*

FDA request		Reference: Amendment Section	Comments during the teleconference	
#	Request [reproduced from attachment 1]		FDA	Sandoz/Momenta
4	We note that the recovery of enoxaparin/PF4 complexes by SEC is low. Please comment on whether the SEC procedure disrupts the complexes. Please confirm that the percent recovery was similar for your product and the RLD.	5.2		*Detailed information to be provided in an upcoming written response to this request.* SEC-UV is not intended to be a quantitative assay, rather intended to accurately and precisely measure the MW of the "intermediate complex"; other methods in Section 5 measure quantity of complexes. Recovery is low because of the disparate charge densities of the complexes. (PF4 is positively charged, enoxaparin is negatively charged.) The recovery was similar between enoxaparin and the RLD
5a	Regarding your assessment of complex size by PCS: Please submit samples of the raw readout of the PCS for your product and the RLD at the different PHRs.	5.6		
5b	Regarding your assessment of complex size by PCS: Plese confirm that the numbers provided correspond to the average complex size including large, intermediate and smaller complexes.			*Detailed information to be provided in an upcoming written response to this request.*
5c	Regarding your assessment of complex size by PCS: Please submit a table with the diameter of each of these for review if available.		The requested data may provide insight into the observations associated with lot ------559	
6	Regarding your assessment of complex size by A280, please clarify why PF4/enoxaparin complexes have absorbance at 280 nm if PF4 has low levels of phenylalanine and tyrosine. Please clarify whether this assay reflects true absorbance or turbidity. Is the absorbance stable over time?	5.7		*Detailed information to be provided in an upcoming written response to this request.* PF4 does absorb at A280, but absorbance is low due to the low levels of aromatic aa in PF4. There is a turbidometric component of the A280 measurement in this assay
7	Please submit a table detailing the complex charge for each PHR as assessed by z-potential.	5.5	Provide a table with the data used to generate the graphs in figures 5 and 6 of the amendment	*Detailed information to be provided in an upcoming written response to this request.*
8	Plese submit better copies of the gels to assess total proteins stained with colloidal blue, as the images included in this submission are hard to interpret. For example, no band is visible for the de-staining control.	6.2		*Detailed information to be provided in an upcoming written response to this request.* Post-meeting clarification for FDA: Sandoz/Momenta use silver stained gels, not colloidal-blue stained gels.
9	Please establish specifications for impurities and include them as part of your release testing.	6		*Detailed information to be provided in an upcoming written response to this request.*

FDA request		Reference: Amendment Section	Comments during the teleconference	
#	Request [reproduced from attachment 1]		FDA	Sandoz/Momenta
10	Please clarify whether the in vitro studies were conducted using PBMC from a single donor. Please use additional donors to confirm that the results are representative.	7		*Detailed information to be provided in an upcoming written response to this request.* PBMCs from a single donor were used for the head-to-head experiments presented in section 7.1. Similarly, PBMCs from a single donor were used in the experiments presented in section 7.2
11	Some of the lots appear to induce higher levels of TNF-alfa product by PBMC in culture. Please comment.	7.1	Comment on the lot-to-lot variability observed in the assay.	*Detailed information to be provided in an upcoming written response to this request.* Each DP lot was tested at three concentrations in three independent experiments. Within any given experiment there was minor lot-to-lot variability in the assay. However no particular RLD or DP lot was consistently high or low at any of the three dilutions across the three experiments. The head-to-head comparison was performed by taking the grand mean of eighteen data points at each dilution (six values for each of the three independent experiments). No significant difference was observed among the DP and RLD lots as assessed by two way ANOVA.
12	Thymidine update is highest in cells stimulated with LMWH. Is the increase in T cell proliferation antigen and/or dose dependent? Can you provide an explanation for the reduced proliferation when LPS is added to the conditions?	7.2		*Detailed information to be provided in an upcoming written response to this request.* The observation that LPS attenuates T cell proliferation is consistent with literature reports (e.g. Wyant et al., Infect Immunity, 1999, 67: 1338-1346; Molloy et al, Proc Natl Acad USA, 1990, 87: 973-977; Yaqub et al, 2003, Med Sci Monit, 2003, 9: BR120-126). There was no significant difference among tested DP or RLD lots in their ability to further decrease T cell proliferation in the presence of LPS or further increase proliferation in the presence of CpG ODN.
13	Regarding the in vivo studies, you have provided the antibody titers for the mice treated with LMWH in the presence of adjuvants. Please provide an assessment of the response to the product in the absence of LPS or CpG ODN.	8.2		*Detailed information to be provided in an upcoming written response to this request.*
		8.2	Provide any available data for the antibody titers generated when no adjuvant was included in the immunizations	*Detailed information to be provided in an upcoming written response to this request.* Data are available in the method development studies - e.g. Figures 7 and 8 in report ENX-08-0040-MDR (Appendix 72, pg 1984). In addition, all head-to-head studies presented in section 8.2 included a control group immunized with KLH in the absence of CpG ODN.

FDA request		Reference: Amendment Section	Comments during the teleconference	
#	Request [reproduced from attachment 1]		FDA	Sandoz/Momenta
14	Please comment on the high variability in the antibody response. Is this due to heterogeneities in the product used to immunize the animals?	8.1, 8.2	The intragroup variability of antibody titers is so high that it compromises the ability of these assays to discriminate differences between groups. As currrently presented, the Sponsor's two in vivo models do not allow FDA to make definitive conclusions. The Sponsor may wish to explore several approaches, including: • Provide an acceptable explanation that addresses the observed intragroup variability. • Consider modifications to the current method (or consider alternative methods/models) to enable data to be used for comparing inter-group results. [e.g. prime/boost approach]	*Detailed information to be provided in an upcoming written response to this request.*
15	Please provide a (dose dependent) assessment of the adjuvant effect of the different lots of LMWH (yours and the RLD's) in the absence of CpG ODN or LPS.	8.2		*Detailed information to be provided in an upcoming written response to this request.*

Notes:
Dr. Vethelyi noted that, in general, the Sponsor's use of orthogonal methods to conduct the biophysical characterization of PF4: LMWH complexes was a good approach.

II. FDA responses to Sandoz/Momenta questions of February 24, 2009:

FDA subsequently responded to the questions submitted by Sandoz/Momenta in advance of the teleconference:

Topics for FDA teleconference (February 25, 2009)			
Topic	**Notes on Sandoz/Momenta question**	**Requests to FDA**	**FDA Response**
1. **Immunogenicity Amendment [ANDA 77-857] (syringe) September 25, 2008**	**Background:** On January 30, 2009, OGD representatives informed Sandoz/Momenta that an additional immunogenicity study would be requested for syringe drug product that included (in its manufacturing history) Heparin Sodium (b) (4) supplied by (b) (4). Sandoz/Momenta have developed a proposal for FDA's consideration (See topic 2). *This proposal assumes that the studies previously developed in collaboration with FDA for the September 2008 immunogenicity amendment remain relevant for this request.* The September 2008 immunogenicity amendment resulted from an extensive collaborative effort between FDA, Sandoz and Momenta during 2008, to achieve prior agreement on the design and scope of studies that respond to FDA's requests: • January 9, 2008 teleconference (to clarify FDA requests for immunogenicity information) • May 15, 2008 teleconference (to provide FDA comments to Sandoz/Momenta's proposed response, filed February 26, 2008) • July 31, 2008 teleconference (to provide FDA comments to Sandoz/Momenta's proposal for an additional in vivo immunogenicity model) This amendment specifically supports the syringe presentations of Enoxaparin Sodium Injection.	On the basis of the review that FDA has conducted todate, does FDA consider the data analyses and acceptance criteria described in this amendment to sufficiently address FDA's requests? Would FDA please provide an update as to the status of its review of this amendment?	**See table in Section I.**

Topics for FDA teleconference (February 25, 2009)

Topic	Notes on Sandoz/Momenta question	Requests to FDA	FDA Response
2. [redacted]: **FDA request for additional immunogenicity study [ANDA 77-857] (syringe)**	**Background:** On January 30, 2009, OGD representatives informed Sandoz/Momenta that an additional immunogenicity study would be requested for syringe drug product that included (in its manufacturing history) Heparin Sodium, [redacted], supplied by [redacted]. Sandoz/Momenta have developed a proposal for FDA's consideration that is described below. *This proposal assumes that the studies previously developed in collaboration with FDA for the September 2008 immunogenicity amendment remain relevant for this request.* **Proposal:** Sandoz/Momenta propose to perform immunogenicity testing [redacted] with the appropriate manufacturing history, as a confirmatory study. Sandoz/Momenta propose to perform all the immunogenicity testing that was performed for the September 2008 ANDA amendment except for [redacted] Consequently, for this drug product lot, the potential immunomodulatory activity of any impurity will be assessed in: • [redacted] • [redacted] **Timeline:** Sandoz/Momenta estimate that the immunogenicity information described above can be provided to FDA by the end of March, 2009. **Rationale:** Heparin Sodium, USP (the starting material for manufacture of Enoxaparin Sodium) that is manufactured using [redacted] has the same impurity profile, the same quality attributes (including the same saccharide composition) as other Heparin Sodium, USP lots derived from other [redacted] suppliers: • Impurity profile: Three (of the twelve) Heparin Sodium, USP lots that were analyzed in the September 25th amendment were [redacted]. These three lots had the same impurity profile as the other nine lots and met all Sandoz acceptance criteria for Heparin Sodium, USP starting material. [reference: Immunogenicity amendment to ANDA 77 857, filed September 25, 2008] • Critical quality attributes: Sandoz has defined the critical quality attributes of Enoxaparin Sodium Drug Substance (DS) that are required to demonstrate equivalence to the RLD. Sandoz has also defined the critical quality attributes (e.g. saccharide composition) that are required in the Heparin Sodium, USP starting material that is used to manufacture DS. Heparin Sodium, USP lots [redacted] have the same critical quality attributes (including saccharide composition) as other Heparin Sodium, USP lots that are derived from materials that do not include material supplied by [redacted]. Moreover, DS lots derived from material supplied by [redacted] have the same critical quality attributes as other DS lots that are derived from materials that do not include material supplied by [redacted] [reference: CMC amendment to ANDA 77 857, filed December 12, 2008]	Does FDA concur with Sandoz' proposal?	**It is not possible to definitively respond to this question until the Sponsor addresses FDA's queries that were listed in this meeting [see Section I].** **In the context of FDA's queries and comments in the previous section, the Sponsor should not assess the in vivo immunogenicity of PF4:LMWH complexes using the method described in the September 2008 amendment.** **Additionally, FDA typically requests sponsors to provide data from three lots, to establish the data are reproducibly observed.**

The Agency expressed concern that the assay could indicate previously unappreciated heterogeneity in the product. The FDA encouraged the development of a more sensitive method to assess the rate and magnitude of the antibody response to the product in vivo.

Topics for FDA teleconference (February 25, 2009)

Topic	Notes on Sandoz/Momenta question	Requests to FDA	FDA Response
3. **PROPOSED Immunogenicity Amendment [ANDA 78-660] (vial) Proposal filed November 20, 2008**	*The vial proposal (filed November 20, 2008) assumes that the studies previously developed in collaboration with FDA for the September 2008 syringe immunogenicity amendment remain relevant for this dosage form of Enoxaparin Sodium Injection.* The vial dosage form of Enoxaparin Sodium Injection differs from the syringe dosage form in the following ways: • Contain/closure system • Concentration of Enoxaparin Sodium in the drug product • Inclusion of 1.5%benzyl alcohol as a preservative in the drug product **Timeline:** Sandoz/Momenta estimate that the vial immunogenicity amendment can be provided to FDA by the end of the second quarter, 2009.	Does FDA concur with Sandoz/ Momenta's proposal?	**It is not possible to definitively respond to this question until the Sponsor addresses FDA's queries that were listed in this meeting [see Section I].** **FDA will probably agree with the Sponsor's proposal for the** (b) (4) **It may be possible for the Sponsor to just perform the** (b) (4)

III. Next steps

FDA: provide comments/questions discussed at the meeting by email to sponsor; **[Transmitted March 9, 2009]**
Sandoz/Momenta: submit teleconference summary to FDA for review and confirmation **[Transmitted March 11, 2009]**
Sandoz/Momenta: prepare responses to FDA requests and request clarifications, if necessary

TELEPHONE CONFERENCE FAX

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sandoz Inc.

TEL: 303-438-4242

ATTN: Jean Domenico

FAX: 303-438-4600

FROM: Thomas Hinchliffe

FDA CONTACT PHONE: (240) 276-8536

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 26, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Enoxaparin Sodium, 100 mg/mL and 150 mg/mL.

If you have questions regarding these comments please contact the Project Manager, Thomas Hinchliffe at (240) 276-8536. Please submit official hard copies to the Document Room in electronic if possible. Please submit documentation of submission of the Amendment by fax to the attention of the Project Manager at 240-276-8582.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-857 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Enoxaparin Sodium Injection, 100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL prefilled syringes and 150 mg/mL, 0.8 mL and 1 mL prefilled syringes

Request for additional information:

1 *Regarding the PF4 source:*

   a. *Your studies show that the individual lots of PF4 used have differences in the percent of monomer, dimer, trimer and tetramer. Please comment on how these differences impact on the analytical and functional studies performed to characterize the PF4-heparin complexes.*

   b. *After qualifying the* [redacted] (b) (4) *PF4,* [redacted] (b) (4) *PF4 was used for certain studies. Please clarify the source of PF4 that was used for each study and confirm that all the PF4 used was similarly qualified.*

   c. *Please confirm that the same lot of PF4 was used in all head to head studies.*

2 *With reference to your assessment of complex formation, please comment on the stability of the complexes formed. The work of Suvarna et al. suggests that the size of complexes may change over time.*

3 *The retention time and molecular weight of the intermediate complexes formed with Sandoz Enoxaparin appear to be marginally smaller than those of the RLD (83.5kDa to 80kDa) as assessed by SEC-HLPC. T test shows=0.02(pp 428-429). Please comment as to the significance of this finding.*

4 *We note that the recovery of enoxaparin/PF4 complexes by SEC is low. Please comment on whether the SEC procedure disrupts the complexes. Please confirm that the percent recovery was similar for your product and the RLD.*

5 *Regarding your assessment of complex size by PCS:*

   a. *Please submit examples of the raw readout of the PCS for your product and the RLD at the different PHRs.*

   b. *Please confirm that the numbers provided correspond to the average complex size including large, intermediate and smaller complexes.*

   c. *Please submit a table with the diameter of each of these for review if available.*

6 *Regarding your assessment of complex size by A280, please clarify why PF4/Enoxaparin complexes have absorbance at 280 if PF4 has low levels of phenylalanine and tyrosine. Please clarify whether this assay reflects true absorbance or turbidity. Is the absorbance stable over time?*

7 *Please submit a table detailing the complex charge for each PHR as assessed by z-potential.*

8 *Please submit better copies of the gels to assess total proteins stained with colloidal blue, as the images included in this submission are hard to interpret. For example, no band is visible for the de-staining control.*

9 *Please establish specifications for impurities and include them as part of your release testing.*

10 *Please clarify whether the in vitro studies were conducted using PBMC from a single donor. Please use additional donors to confirm that the results are representative.*

11 *Some of the lots appear to induce higher levels of TNF□ production by PBMC in culture. Please comment.*

12 *Thymidine uptake is highest in cells stimulated with LMWH. Is the increase in T cell proliferation antigen and/or dose dependent? Can you provide an explanation for the reduced proliferation when LPS is added to the conditions?*

13 *Regarding the in vivo studies, you have provided the antibody titers for the mice treated with LMWH in the presence of adjuvants. Please provide an assessment of the response to the product in the absence of LPS or CpG ODN.*

14 *Please comment on the high variability in the antibody response. Is this due to heterogeneities in the product used to immunize the animals?*

15 *Please provide a (dose dependent) assessment of the adjuvant effect of the different lots of LMWH (yours and the RLD's) in the absence of CpG ODN or LPS.*

Jean Domenico
Manager, Regualtory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038 0446

Tel +1 303 438 4242
Fax +1 303 438 4600
Internet: jean.domenico@sandoz.com

Sent Via E-mail

Attention: Thomas Hinchliffe, PharmD
LCDR, U.S. Public Health Service
Project Manager
Office of Generic Drugs
Food and Drug Administration
HFD-617, Rm E230, MPN2
240-276-8536

E-mail Address: thomas.hinchliffe@fda.hhs.gov

Date: March 5, 2009

Concerning: ANDA 77-857: Enoxaparin
Questions for FDA Teleconference

Dear Tom,

Following you will find details regarding the teleconference that we have scheduled for Wednesday, February 25, 2009, with your reviewing division, OBP and representatives from Sandoz and Momenta. The list of teleconference attendees as well as the list of questions that we would like discussed during the teleconference are presented below, as well as details of the teleconference itself.

Date of TC: Friday, March 6, 2009
Time: 11:00 a.m EST
Dial In Number: (b) (4) (US)
Meeting Number: (b) (4)

Representing Sandoz Inc. will be:
Jean Domenico, Manager, Regulatory Affairs
Kalpana Rao Venam, Vice President

Representing Momenta will be:
Ganesh Venkataraman, Senior Vice President Research and Chief Scientific Officer
John Bishop, Senior Vice President, Pharmaceutical Sciences
James Anderson, Senior Director, Analytical Development
Kei Kishimoto, Vice President, Disease Biology
Zachary Shriver, Senior Director, Analytics
Jennifer Smith, Senior Director, QA/QC
Gerard Riedel, Vice President, Regulatory Affairs

Topics for FDA teleconference (February 25, 2009)		
Topic	**Notes**	**Request to FDA**
1. **Immunogenicity Amendment [ANDA 77-857] (syringe) September 25, 2008**	**Background:** On January 30, 2009, OGD representatives informed Sandoz/Momenta that an additional immunogenicity study would be requested for syringe drug product that included (in its manufacturing history) Heparin Sodium (b) (4) supplied by (b) (4). Sandoz/Momenta have developed a proposal for FDA's consideration (See topic 2). ***This proposal assumes that the studies previously developed in collaboration with FDA for the September 2008 immunogenicity amendment remain relevant for this request.*** The September 2008 immunogenicity amendment resulted from an extensive collaborative effort between FDA, Sandoz and Momenta during 2008, to achieve prior agreement on the design and scope of studies that respond to FDA's requests: • January 9, 2008 teleconference (to clarify FDA requests for immunogenicity information) • May 15, 2008 teleconference (to provide FDA comments to Sandoz/Momenta's proposed response, filed February 26, 2008) • July 31, 2008 teleconference (to provide FDA comments to Sandoz/Momenta's proposal for an additional in vivo immunogenicity model) This amendment specifically supports the syringe presentations of Enoxaparin Sodium Injection.	On the basis of the review that FDA has conducted to date, does FDA consider the data analyses and acceptance criteria described in this amendment to sufficiently address FDA's requests? Would FDA please provide an update as to the status of its review of this amendment?
2. (b) (4) **FDA request for additional immunogenicity study [ANDA 77-857] (syringe)**	**Background:** On January 30, 2009, OGD representatives informed Sandoz/Momenta that an additional immunogenicity study would be requested for syringe drug product that included (in its manufacturing history) Heparin Sodium, (b) (4) supplied by (b) (4) Sandoz/Momenta have developed a proposal for FDA's consideration that is described below. ***This proposal assumes that the studies previously developed in collaboration with FDA for the September 2008 immunogenicity amendment remain relevant for this request.***	Does FDA concur with Sandoz' proposal?

2. (b) (4) **FDA request for additional immunogenicity study [ANDA 77-857] (syringe)** (Continued)	**Proposal:** Sandoz/Momenta propose to perform immunogenicity testing (b) (4) (b) (4) with the appropriate manufacturing history, as a confirmatory study. Sandoz/Momenta propose to perform all the immunogenicity testing that was performed for the September 2008 ANDA amendment, except for (b) (4)). Consequently, for this drug product lot, the potential immunomodulatory activity of any impurity will be assessed in: • (b) (4) • **Timeline:** Sandoz/Momenta estimate that the immunogenicity information described above can be provided to FDA by the end of March, 2009. **Rationale:** Heparin Sodium, USP (the starting material for manufacture of Enoxaparin Sodium) that is manufactured (b) (4) (b) (4) has the same impurity profile, the same quality attributes (including the same saccharide composition) as other Heparin Sodium, USP lots derived from other (b) (4) suppliers: • Impurity profile: Three (of the twelve) Heparin Sodium, USP lots that were analyzed in the September 25th amendment were (b) (4) These three lots had the same impurity profile as the other nine lots and met all Sandoz acceptance criteria for Heparin Sodium, USP starting material. [reference: Immunogenicity amendment to ANDA 77-857, filed September 25, 2008] Critical quality attributes: Sandoz has defined the critical quality attributes of Enoxaparin Sodium Drug Substance (DS) that are required to demonstrate equivalence to the RLD. Sandoz has also defined the critical quality attributes (e.g. saccharide composition) that are required in the Heparin Sodium, USP starting material that is used to manufacture DS. Heparin Sodium, USP lots (b) (4) have the same critical quality attributes (including saccharide composition) as other Heparin Sodium, USP lots that are derived from materials that do not include material supplied by (b) (4). Moreover, DS lots derived from material supplied by (b) (4) have the same critical quality attributes as other DS lots that are derived from materials that do not include material supplied by (b) (4). [reference: CMC amendment to ANDA 77-857, filed December 12, 2008]

3. **PROPOSED Immunogenicity Amendment [ANDA 78-660] (vial) Proposal filed November 20, 2008**	***The vial proposal (filed November 20, 2008) assumes that the studies previously developed in collaboration with FDA for the September 2008 syringe immunogenicity amendment remain relevant for this dosage form of Enoxaparin Sodium Injection.*** The vial dosage form of Enoxaparin Sodium Injection differs from the syringe dosage form in the following ways: • Contain/closure system • Concentration of Enoxaparin Sodium in the drug product • Inclusion of 1.5%benzyl alcohol as a preservative in the drug product **Timeline:** Sandoz/Momenta estimate that the vial immunogenicity amendment can be provided to FDA by the end of the second quarter, 2009.	Does FDA concur with Sandoz/ Momenta's proposal?

If you should have any questions or comments, please don't hesitate to contact me at (303) 438-4242.

Sincerely,

Sandoz Inc.

Jean Domenico, Manager
Regulatory Affairs

/jep

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/s/

Thomas Hinchliffe

3/16/2009 02:24:25 PM

Telephone Conversation Memorandum

ANDA: 77-857

DRUG: Enoxaparin

FIRM: Sandoz

Kalpana Rao Vanam, VP, Regulatory Affairs
Jean Pederson, Manager, Regulatory Affairs

FDA PERSONS INVOLVED:

Andre Raw; Sau Lee; Naiqi Ya; Tom Hinchliffe

PHONE NUMBER: (b) (4)

DATE: Tuesday, April 28, 2009 – 11am est

Conversation:

1. Sandoz needs clarification:
   With regards to question 10 from the March teleconference: *Please clarify whether the in vitro studies were conducted using PBMC from a single donor. Please use additional donors to confirm that the results are representative.*

   Will the use of 3 additional donors would be sufficient to confirm the in vitro studies?

   OGD Response:
   Appears to be sufficient but OGD asked Sandoz to provide this question to them in writing and they would forward on to OBP. OGD does not know how long it will take OBP to respond.

2. FDA acknowledged Sandoz has always used (b) (4) (b) (4) in its heparin USP lots used for making enoxaparin.

   OGD would like Sandoz to provide sameness and impurity data on enoxaparin sodium manufactured by using a (b) (4) One lot of data are required from (b) (4) source, and the following information from (b) (4) lot should be provided:

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/s/

Thomas Hinchliffe

5/29/2009 11:35:01 AM

Jean Domenico, Manager
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4242
Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

ORIG AMENDMENT
N/AC

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

MAY 21 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Telephone Amendment – Response to Questions Raised in 3/6/09 Teleconference

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to our Immunogenicity Amendment dated September 25, 2008. Reference is also made to a follow-up teleconference between FDA, Sandoz, and Momenta on March 6, 2009. In this teleconference, FDA's queries associated with the Immunogenicity Amendment were reviewed, and several questions were raised. Our detailed response to these questions is provided in the enclosed report. For reference purposes, we are also providing a copy of our original Immunogenicity Report that was submitted in September, 2008.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

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MAY 22 2009
OGD

Document	ANDA 77-857
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder *telephone amendment.pdf* *original rpt 092508.pdf*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

ASherwood for

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

SANDOZ

Jean Domenico, Manager
Regulatory Affairs

Sandoz Inc.
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Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

ORIG AMENDMENT
N-AA

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

UNSOLICITED AMENDMENT

(electronic submission)

JUN 19 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Unsolicited Amendment – CMC: Updates to Heparin Sodium DMF #18557 and Submission of Current Contract Manufacturing/Testing Site List

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

This amendment presents information concerning the following:

- An update to Heparin Sodium DMF #18557
- An update to the Contracting Manufacturing/Testing Site List.

RECEIVED
JUN 22 2009
OGD

Complete details of these changes are provided below:

1.) Update to Sandoz GmbH DMF 18557 [Heparin Sodium, USP]

Reference is made to a telephone amendment to ANDA 77-857, dated February 27, 2009. In this amendment, Sandoz responded to FDA's request to provide information regarding the heparin (b) (4) (e.g., the manufacturing process, facilitites, controls, batch

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records and certificates of analysis). In this amendment, Sandoz stated, "Due to its confidential nature, this information will be mailed directly to Thomas Hinchliffe, Project Manager, FDA by the [redacted] (b) (4)." Since that time, the data packages have been mailed to Mr. Hinchliffe directly on the following dates from the following [redacted] (b) (4):

[redacted] (b) (4)

Attached for your reference is a copy of the cover letters for each of these data packages that were sent to Mr. Hinchliffe's attention as "Miscellaneous Correspondence – Heparin Response to Item #4 in Fax dated 1/29/09".

Reference is also made to a telephone message from Thomas Hinchliffe (FDA) to Jean Domenico (Sandoz) on May 11, 2009. In his message, Mr. Hinchliffe stated he would like Sandoz GmbH to update its DMF # 18557 for Heparin Sodium to include a Letter of Authorization from [redacted] (b) (4) authorizing FDA to review the data packages that were submitted by [redacted] (b) (4) as noted above. In response to this request, Sandoz GmbH updated its DMF #18557 on June 9, 2009, to include Letters of Authorization from [redacted] (b) (4) Enclosed is a copy of the cover letter that was sent to Sandoz GmbH's DMF 18557 on June 9, 2009, as well as a copy of [redacted] (b) (4) letter of authorization.

2.) Contracting Manufacturing/Testing Sites

Sandoz would also like to take this opportunity to update its application with a current, all-encompassing list of contract manufacturing/testing sites. These are not new sites; rather, Sandoz is providing FDA with one list that includes all sites and functions.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	ANDA 77-857
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder attachment.pdf (bookmarked)

SANDOZ

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Jean Domenico
Manager, Regulatory Affairs

Sandoz Inc.
2555 West Midway Boulevard
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Fax: 303-438-34600
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SANDOZ

ORIG AMENDMENT

OVERNIGHT DELIVERY

N-000-AC

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

N-000-MC

TELEPHONE AMENDMENT

AND

FORMAL MEETING REQUEST

June 25, 2009

RE: **ANDA 77-857: 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 (Pre-filled Single Dose Syringes with Automatic Safety Device)**

Telephone Amendment Response to FDA Questions Raised April 28, 2009 and Formal Meeting Request (Type C)

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its pending Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a teleconference between Sandoz and FDA on April 28, 2009. During this teleconference, four questions were raised by FDA. This amendment specifically responds to FDA's request #3 from this teleconference where FDA asked for data relating to the (b) (4) manufacture of Enoxaparin Sodium. Sandoz' response to this request #3 is provided in Attachment #1, entitled "Telephone Amendment: Additional (b) (4) Information". Sandoz will submit a response to FDA's three other requests (#1, #2 and #4) in a subsequent ANDA Amendment.

In parallel, Sandoz requests a meeting (Type C), via teleconference or face-to-face, that would include senior level representatives from OGD and the Office of Compliance. The purpose of this proposed meeting would be to discuss Sandoz' current controls for testing (b) (4) present results of Sandoz' recent (b) (4) investigation and discuss current analytical standards for detecting and controlling (b) (4)

Adequate information to assess the potential utility of this meeting is provided below.

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JUN 26 2009
OGD

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SANDOZ

We hope you will carefully consider our request for a meeting. If you need any additional information or have any questions, please don't hesitate to contact me at (303) 438-4242.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder (b) (4) eport.pdf (bookmarked)

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs, Sandoz Inc.

Enclosure: Telephone Amendment: Additional (b) (4) Information

SANDOZ

Jean Domenico, Manager
Regulatory Affairs

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OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

July 1, 2009

N-000-AC

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Telephone Amendment – Response to January 30, 2009 Teleconference Request
(b) (4) Immunogenicity Data Provided

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a teleconference between FDA, Sandoz, and Momenta on January 30, 2009, and to our telephone amendment dated February 27, 2009, in response to the questions discussed in this teleconference. In that amendment, we informed you that the immunogenicity data for qualifying (b) (4) as an alternative Heparin Sodium, (b) (4) supplier (FDA Request #2) would be submitted once they became available.

Reference is also made to a teleconference between FDA, Sandoz, and Momenta on March 6, 2009, in which FDA provided additional guidance regarding immunogenicity data for qualifying (b) (4). This amendment provides the immunogenicity data that FDA has requested for qualifying (b) (4) and reflects the guidance that FDA has provided.

SANDOZ

For your reference, the table below summarizes the immunogenicity data we have submitted in our application to date and identifies the suppliers of Heparin Sodium (b) (4) which were represented in the data.

Amendment Date	
9/25/08	Original Immunogenicity Amendment This amendment responds to FDA's original request for data to assess the potential immunogenicity of the Drug Product. Drug Product lots tested in this amendment were derived (in part) from Heparin Sodium (b) (4) supplied by (b) (4): (b) (4)
5/21/09	Immunogenicity Telephone Amendment This amendment responds to FDA's questions from a March 6, 2009 teleconference, relating to data submitted in 9/25/08 amendment. Drug Product lots tested in this amendment were derived (in part) from Heparin Sodium (b) (4) supplied by (b) (4): (b) (4)
7/1/09	Telephone Amendment This amendment responds to FDA's request for immunogenicity data to qualify (b) (4) as a supplier of Heparin Sodium (b) (4) Drug Product lots tested in this amendment were derived (in part) from Heparin Sodium (b) (4) supplied by (b) (4): (b) (4)

SANDOZ

The analyses and data presented in this amendment, as well as our past amendments, demonstrate that Enoxaparin Sodium Injection and the RLD are equivalent with respect to the potential for immunogenicity of the Drug Product.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder *amendment.pdf*

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico/ckm

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Jean Domenico, Manager
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4242
Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

SD-108

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

August 6, 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Telephone Amendment – Response to Questions Raised in 4/28/09 Teleconference

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a teleconference between FDA and Sandoz on April 28, 2009, in which four questions were raised by FDA. Reference is also made to our amendment dated June 25, 2009, in which we responded to question #3 from this teleconference. We are now providing a response to the three other requests (questions 1, 2, and 4), listed below.

Question 1
FDA acknowledged Sandoz has always used [redacted] (b) (4) in its heparin USP lots used for making enoxaparin.

OGD would like Sandoz to provide sameness and impurity data on enoxaparin sodium manufactured by using a [redacted] (b) (4) One lot of data is required from [redacted] (b) (4) source, and the following information from [redacted] (b) (4) lot should be provided:

- Data for the 7 primary characterization tests.
- Quantitative chain mapping by GPC-mass-spectroscopy.
- Protein and DNA Impurity results

Note: Development data is acceptable to provide if it's available.

SANDOZ

Question 2

OGD stated (b) (4) [redacted] Sandoz informed OGD that this assessment has already been done and no gaps were found and that this information was communicated to them in an amendment (dated 2/27/09) that we filed to our application.

Question 4

(b) (4) [redacted]

Our detailed responses to these questions are provided in the enclosed report.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder *amendment.pdf*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

TELEPHONE CONFERENCE - MINOR FAX

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sandoz Inc. TEL: 303-438-4242

ATTN: Jean Domenico, Manager, Regulatory Affairs FAX: 303-438-4600

FROM: Thomas Hinchliffe FDA CONTACT PHONE: (240) 276-8536

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 26, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Enoxaparin Sodium, 100 mg/mL and 150 mg/mL.

Attached are 3 pages of deficiencies.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Thomas Hinchliffe at (240) 276-8536. Please submit documentation by fax to the attention of the Project Manager at 240-276-8582. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 77-857 APPLICANT: Sandoz, Inc.
DRUG PRODUCT: Enoxaparin Sodium, 100 mg/mL and 150 mg/mL

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Thomas Hinchliffe at (240) 276-8536. Please submit documentation by fax to the attention of the Project Manager at 240-276-8582. Please also submit official hard copies of any faxed documentation to the Document Room.

- (b) (4)

- Please ensure that enoxaparin sodium lots will comply with the proposed USP requirements for enoxaparin sodium when the proposed USP monograph for enoxaparin sodium becomes official.

- Please ensure that enoxaparin sodium injection lots will comply with the USP proposed requirements for enoxaparin sodium injection when the proposed USP monograph for enoxaparin sodium injection becomes official.

- (b) (4)

- With regard to your stability data in the Amendments submitted September 19, 2007 and February 24, 2009, please provide explanations or justifications on why (b) (4)

- Please provide updated long-term stability data for enoxaparin sodium batches that were not manufactured by using (b) (4)
  enoxaparin sodium batch being tested.

- Please provide updated long-term stability data for enoxaparin sodium injection batches that were not manufactured by using (b) (4) .

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

NAIQI YA
09/14/2009
for Florence S. Fang

Jean Domenico, Manager
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4242
Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT - LABELING

(electronic submission)

ORIG-1/SD-109

September 18, 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Gratuitous Amendment – Updated Labeling

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

The physician insert labeling for this product has been revised according to the Drugs@FDA website. In response to this update, Sandoz has revised our insert in accordance with the RLD labeling (Lovenox®, Sanofi-Aventis, approved 7/23/09).

Enclosed you will find our revised package insert in final print (true size). In addition, we are providing our insert in SPL, enlarged PDF, and Word format, as well as the RLD insert in PDF format. Also provided are side-by-side comparisons of our proposed insert versus the RLD and versus our last submission.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

SANDOZ

Folder	Document	File Name
ANDA 77-857	Cover Letter (scanned)	*cover.pdf*
	FDA Form 356h (scanned)	*356h.pdf*
labeling		
	Final Print Package Insert (True Size)	*fpl insert.pdf*
	Package Insert in enlarged PDF format	*enlarged pi.pdf*
	Package Insert in MS Word format	*pi word.doc*
	Side by Side comparison versus last filed	*sidebyside v last filed.pdf*
	Side by Side comparison versus RLD	*sidebyside v rld.pdf*
	RLD insert (Lovenox®, approved 7/23/09)	*rld insert 072309.pdf*
spl	Revised insert in SPL format	*741c994d... .xml*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Jean Domenico, Manager
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
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Tel +1 303 438-4242
Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

ORIG-1/ SD-110

September 30, 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Telephone Amendment – Response to FDA Letter Dated 9/14/09

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your letter dated September 14, 2009. In response to your questions, we are providing the following information:

- (b) (4)
- Confirmation enoxaparin sodium drug substance will comply with proposed USP requirements

SANDOZ

- Confirmation enoxaparin sodium injection will comply with proposed USP requirements
- Confirmation [redacted] (b) (4)
- Explanation of [redacted] (b) (4)
- Updated long-term stability batches for enoxaparin sodium drug substance
- Updated long-term stability batches for enoxaparin sodium injection

Our detailed response to these issues is enclosed.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder *amendment.pdf*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Jean Domenico, Manager
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4242
Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

UNSOLICITED AMENDMENT

(electronic submission)

SD-111

October 7, 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Unsolicited Amendment – Notification of Updates to DMF 18557 (Heparin Sodium)

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

We would like to inform you of the following updates that were made to DMF Type II Number 18557 for Heparin Sodium, which is referenced in our application. The DMF holder is Sandoz GmbH. (b) (4) Austria.

1. September 25, 2009: The DMF holder filed a DMF amendment in response to deficiencies identified in a letter from FDA dated September 14, 2009. For your reference, a copy of the complete amendment is attached.

2. October 7, 2009: The DMF holder filed a DMF amendment to submit documents requested during their pre-approval inspection for Heparin Sodium at Sandoz GmbH in Austria, which took place from July 6-10, 2009. For your reference, a copy of the complete amendment is attached.

SANDOZ

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	356h.pdf
Sandoz cover letter (scanned)	cover.pdf
	cmc folder *dmf updates.pdf*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Telephone Fax

ANDA 77-857

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8952)

TO: Sandoz, Inc. TEL:303-438-4242

ATTN: Jean Domenico FAX: 303-438-4600

FROM: Ruby Wu

Dear Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Enoxaparin Sodium Injection USP, 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 (Prefilled Single Dose Syringes with Automatic Safety Device).

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	77-857
Date of Submissions:	September 18, 2009 (amendment)
Applicant's Name:	Sandoz, Inc.
Established Name:	Enoxaparin Sodium Injection USP, 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 (Prefilled Single Dose Syringes with Automatic Safety Device)

Labeling Deficiencies:

1. SYRINGE LABEL (Prefilled syringe: 30 mg/0.3 mL, 40 mg/0.4 mL; Graduated prefilled syringe: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL and 150 mg/mL)

   a. Syringe Labels: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. Graduated markings for 60, 80, and 100 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

   c. Graduated markings for 120 and 150 mg strengths: Satisfactory in final print as submitted in the November 29, 2006 amendment.

2. PEEL LID LABELING (One syringe)

   a. 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, and 120 mg/0.8 mL: Satisfactory in final print as submitted in the July 6, 2006 amendment.

   b. 150 mg/mL: Satisfactory in final print as submitted in the November 29, 2006 amendment.

3. CARTON LABELING (10 syringes)
   Satisfactory in final print as submitted in the July 6, 2006 amendment.

4. INSERT
   You have chosen to carve-out information pertaining to the indication protected by exclusivity I-533. Please make the following revisions:
   a. 6.1: Revise the third paragraph to read (b) (4)

   b. 12.2: Upon further consideration, please delete (b) (4)

   c. 12.3: Upon further consideration, please delete ' (b) (4)

(b) (4)

."

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

LILLIE D GOLSON
10/15/2009
for Wm. Peter Rickman

Jean Domenico, Director
Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4242
Fax +1 303 438-4600
Email:
jean.domenico@sandoz.com

SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT - LABELING

(electronic submission)

OCT 2 1 2009

SD # 112

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Labeling Amendment – Response to FDA Letter Dated 10/15/09

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your letter dated October 15, 2009. In response to this letter, we are providing the following information:

1. **SYRINGE LABEL:**
   We acknowledge that the syringe labels and graduated markings for the 100 mg/mL and 150 mg /mL concentrations are satisfactory in final print.

2. **PEEL LID LABELING:**
   We acknowledge that the peel lid labeling for the 100 mg/mL and 150 mg /mL concentrations are satisfactory in final print.

3. **CARTON LABELING:**
   We acknowledge that the carton labeling is satisfactory in final print.

RECEIVED

OCT 2 2 2009

OGD

4. **INSERT:**
   In regard to the indication protected by exclusivity I-533, we have made the following revisions:
   a. We revised the third paragraph in section 6.1 as requested.
   b. We deleted the requested text in section 12.2.
   c. We deleted the requested text in section 12.3.

Enclosed you will find our revised package insert in final print (true size). In addition, we are providing our insert in SPL, enlarged PDF, and Word format, as well as a side-by-side comparison of our proposed insert versus our last submission.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Folder	Document	File Name
ANDA 77-857	Cover Letter (scanned)	*cover.pdf*
	FDA Form 356h (scanned)	*356h.pdf*
labeling		
	Final Print Package Insert (True Size)	*fpl insert.pdf*
	Package Insert in enlarged PDF format	*enlarged pi.pdf*
	Package Insert in MS Word format	*pi word.doc*
	Side by Side comparison versus last filed	*sidebyside v last filed.pdf*
spl	Revised insert in SPL format	*741c994d... .xml*

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures
JD/ckm

Telephone Conversation Memorandum

ANDA: 77-857

DRUG: Enoxaparin

FIRM: Sandoz

Jean Pederson, Manager, Regulatory Affairs
Marcy Macdonald, Director, Regulatory Affairs
Joe Carrado, Vice President, Regulatory Affairs

FDA PERSONS INVOLVED:

Andre Raw; Sau Lee; Naiqi Ya; Tom Hinchliffe

DATE: November 4, 2009 – 1pm;
Follow-up - November 5, 2009
Follow-up – November 16, 2009
Follow-up – November 19, 2009

Conversation:

November 4, 2009:

FDA asked Sandoz:

1.) [redacted] (b) (4) Would like to see this commitment submitted to Sandoz GmbH DMF for Heparin USP.

2.) In the recent amendment, Sandoz indicated that they would follow the current USP monograph for Heparin, USP when published. FDA said the [redacted] (b) (4) This change should be referenced in the DMF update. FDA was open to Sandoz discussing a proposed specification if there was a concern about acceptability of the proposed specification.

FDA confirmed the [redacted] (b) (4) specifications were acceptable.

3.) To submit a copy of [redacted] (b) (4) will also need to be filed to Sandoz GmbH Heparin USP DMF.

Follow-up - November 5, 2009:

Sandoz proposed a [redacted] (b) (4) n Heparin Sodium, USP that was used for the manufacture of enoxaparin sodium. The following options were discussed:

a.) Sandoz may be allowed to have a [redacted] (b) (4) test for enoxaparin sodium drug substance or drug product.

b.) Add a specification of [redacted] (b) (4) method as an alternate method to the USP proposed method. Sandoz would have to submit comparability results (alternate vs USP method).

FDA would like [redacted] (b) (4) They said the DMF could contain the exact package they already reviewed

and this would be fine. They said filing this DMF would not hold up anything because the information had already been reviewed. The (b) (4) information.

Sandoz would be required to submit the USP comparative information to the application if FDA approved application after December 1st. Sandoz should submit the USP comparison information to the application for enoxaparin sodium drug substance and finished dosage form as soon as it becomes available. FDA recommended Sandoz to submit the amendment prior to December 1st if the data are available before then.

Sandoz indicated that the (b) (4) would be provided as soon as it became available.

Follow- up - November 19, 2009:

FDA asked Sandoz to:

- Provide updated control procedure for Heparin Sodium, USP that complies with the current USP monograph for Heparin Sodium
- Provide updated COAs of representative Heparin Sodium, USP batches
- Provide updated stability testing, based upon the current USP for heparin sodium

Sandoz Inc.
2555 West Midway Boulevard
Broomfield, CO 80020
Telephone: 303.438.4242
Telefax: 303.438.4600
Cell: 303.243.2418
Email : jean.domenico@sandoz.com

Teleconference Minutes

Product: Enoxaparin Sodium Injection
ANDAs 77-857

Attendees: Sandoz Inc.
FDA, Office of Generic Drugs

Teleconference Date: November 4, 2009, Noon MDT

Regarding: FDA Request for Information

Attendees: Sandoz Inc.

Jean Domenico, Manager, Regulatory Affairs
Marcy Macdonald, Director, Regulatory Affairs
Joe Carrado, Vice President, Regulatory Affairs

Attendees: FDA, OGD

Thomas (Tom) Hinchliffe, Project Manager, OGD
Andre Raw, OGD
Naigi Ya, OGD
Sau (Larry) Lee, OGD

Tom Hinchliffe called and left Sandoz (Jean Domenico) a message letting her know he would like to call back at Noon MDT, along with several FDA officials, to discuss questions they had in regard to Sandoz ANDA 77-857 for Enoxaparin Sodium for Injection.

During the call, FDA had three requests:

4.) (b) (4) would be reported to FDA. They would like to see this commitment submitted to Sandoz GmbH DMF for Heparin USP.

5.) In our recent amendment, we indicated we would follow the current USP monograph for Heparin, USP when published. FDA said the (b) (4)

(b) (4). This change should be referenced in the DMF update. FDA was open to Sandoz discussing a proposed specification if there was a concern about acceptability of the proposed specification.

FDA did confirm the (b) (4) (b) (4) specifications were acceptable.

6.) Please submit a copy of (b) (4) will also need to be filed to Sandoz GmbH Heparin USP DMF.

A summary of other items discussed:

- Sandoz confirmed for FDA that its (b) (4) that were submitted to them were filed to Sandoz GmbH DMF.
- A question was raised as to the difference between the (b) (4)
- Sandoz asked if the immunogenicity study review by the OBP was complete. FDA said it was still under review, but that question #2 noted above was in response to OBP's review.
- Sandoz informed FDA that the immunogenicity study for the vial application was complete and asked if it was submitted at this time, if it would hold up review and/or approval of Sandoz syringe application. FDA said it should not hold up the review of the Sandoz syringe application.
- Sandoz asked if answering the above questions would close out the CMC portion of the application. This was not confirmed by FDA.
- Sandoz asked if the inspections that were currently taking place at Momenta, Baxter, etc. would hold up approval of Sandoz application. FDA said they did not know.

FDA asked that we respond to the above listed questions in a telephone amendment to the application.

11/05/09 – Follow up Conversation with FDA

Attendees: Sandoz Inc.

Jean Domenico, Manager, Regulatory Affairs

Attendees: FDA, OGD

Andre Raw, OGD
Sau (Larry) Lee, OGD

2.) In a follow up conversation between Andre Raw and Larry Lee and Jean Domenico, where Jean proposed a (b) (4) [redacted]. Based on this information, Sandoz was given the following options:

a.) Sandoz may be allowed to have a (b) (4) [redacted] release test for enoxaparin sodium drug substance or drug product.

b.) Add a specification of (b) (4) [redacted] method as an alternate method to the USP proposed method. However, Sandoz would have to submit comparability results (alternate vs USP method).

3.) Jean explained to Andre and Larry that the information (b) (4) [redacted] were sent directly to Tom Hinchliff with reference to the Sandoz DMF and ANDA. Jean also explained this was done due to the fact that (b) (4) [redacted]

(b) (4) to amend Sandoz DMF with the complete data package.

4.) Larry and Andre were asked if Sandoz would be required to submit the USP comparative information to the application if FDA approved application after December 1st. The answer was "yes", Sandoz should submit the USP comparison information to the application for enoxaparin sodium drug substance and finished dosage form as soon as it becomes available. FDA recommended Sandoz to submit the amendment prior to December 1st if the data are available before then.

5.) Larry and Andre were informed the (b) (4)

11/05/09 – Follow up Conversation with FDA

Attendees: Sandoz Inc.

Jean Domenico, Manager, Regulatory Affairs

Attendees: FDA, OGD

Sau (Larry) Lee, OGD
Naigi Ya, OGD

FDA (Larry and Naigi) contacted Jean in response to the direction that was given to Sandoz for the (b) (4) (noted in item #2 above). Naiqi explained that the (b) (4) DMF. They said the DMF could contain the exact package they already reviewed and this would be fine. They said filing this DMF would not hold up anything because the information had already been reviewed. So, the (b) (4) information.

Following this page, 1 page withheld in full - (b)(4)

obligated to provide copies of all amendments / supplements / all other documentation submitted to the application if requested by the application owner. FDA said Color component manufacturer's do submit information to them under confidentiality, however, this information has to be included in the ANDA and that they have no means to keep this information from the application holder if it is requested at a later date. FDA did say that minimal data is provided to them from the Color Manufacturers in order to get the application accepted for filing, but DMF's for these color components are typically available where more technical information can be reviewed. FDA did say that they have seen documentation / data submitted to applications under a confidential nature, but in reality, the data are not confidential because the application holders have the right to that information if / when requested.

If (b) (4) wants to keep its (b) (4) technical package completely confidential, they will have to file their own DMF.

FDA was informed the (b) (4) would be providing the technical packages directly to the Sandoz GmbH DMF. FDA confirmed the packages should be sent directly to the document control room and NOT to Tom Hinchcliff. However, they did say we need to notify Tom when all data packages have been filed to the Sandoz DMF and should also update our ANDA with this information so that DMF packages.

11/19/09 – Follow up Message left by FDA

Attendees: Sandoz Inc.

Jean Domenico, Manager, Regulatory Affairs

Attendees: FDA, OGD

Tom Hinchliffe, OGD

The following items were discussed:

- Provide updated control procedure for Heparin Sodium, USP that complies with the current USP monograph for Heparin Sodium
- Provide updated COAs of representative Heparin Sodium, USP batches
- Provide updated stability testing, based upon the current USP for heparin sodium

Minutes by Jean Domenico

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

THOMAS O HINCHLIFFE
12/01/2009

Jean Domenico, Manager
Regulatory Affairs

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OVERNIGHT DELIVERY

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Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

UNSOLICITED AMENDMENT

(electronic submission)

December 1, 2009

SD #114

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Unsolicited Amendment – Notification of Amendments to Sandoz GmbH DMF No. 18557 for Heparin Sodium, USP, Updates to Enoxaparin USP Monographs, and Response to FDA Telephone Requests for Information

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an unsolicited amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

In this amendment, Sandoz Inc. would like to notify you of the availability of certain information recently submitted to DMF 18557, as well as provide additional information that has recently been requested by FDA:

1.) Amendments to Sandoz GmbH DMF No. 18557 for Heparin Sodium, USP

Recently, Sandoz GmbH filed two amendments to DMF 18557:

a.) DMF Amendment (filed 11/18/09) included the following information:

- Updated Heparin Sodium, USP Control Procedure and COA's to demonstrate that Sandoz GmbH is compliant with the new USP monograph for Heparin Sodium, USP that went into effect October 1, 2009.

- Information on the method [redacted] (b) (4)

- Response to the following questions raised in a teleconference between Sandoz Inc. (Jean Domenico) and FDA (Larry Lee, Naiqi Ya and Andre Raw) on November 4th, 2009:

  i) [redacted] (b) (4) would be reported to FDA."

  ii) [redacted] (b) (4)

  iii) "Please submit a copy of [redacted] (b) (4)

  Please note that Sandoz GmbH responded to items i. and iii. above in its DMF Amendment of November 18, 2009. Specifically: in response to FDA request (i), [redacted] (b) (4) committed to report to FDA any change made to its manufacturing process; and in response to FDA request (iii) [redacted] (b) (4)

  Additionally, Sandoz Inc. responds to FDA request (ii) in this amendment as a result of a follow-up conversation on November 16, 2009, between Sandoz Inc. (Jean Domenico) and FDA (Larry Lee, Naiqi Ya and Tom Hinchliffe) which resulted in the following agreement regarding that response:

  I. Sandoz GmbH will maintain its proposed specification of [redacted] (b) (4) [redacted] (b) (4) in Heparin Sodium, USP.

  II. Sandoz Inc. will add [redacted] (b) (4). Sandoz provides relevant information and data to support this new specification in Section 6 below. The test will be performed by Momenta Pharmaceuticals, Inc.

For your convenience, a complete copy of this DMF amendment is provided in Attachment 1.

b.) DMF Amendment (December 1, 2009) included the following information:

- Stability Protocol – to support the new USP monograph for Heparin Sodium, USP that went into effect October 1, 2009.

- Stability Commitment - to support the new USP monograph for Heparin Sodium, USP that went into effect October 1, 2009.

During a telephone conversation on November 19, 2009, between Sandoz Inc. (Jean Domenico) and FDA (Tom Hinchliffe), FDA requested the following information to be provided by Sandoz GmbH when updating its DMF to comply with the USP monograph for Heparin Sodium, USP:

i. Revised Control Procedure
ii. COAs
iii. Stability Protocol
iv. Stability Commitment

During this telephone conversation, Mr. Hinchliffe was informed that Sandoz GmbH had already filed an amendment on November 18, 2009, in which updates to the current USP monograph, effective October 1, 2009, for Heparin Sodium were already reported (as noted in Section 1a above). However, that DMF amendment did not include a stability protocol or stability commitment. Therefore, in response to FDA's request, Sandoz GmbH submitted a subsequent DMF amendment that included the stability protocol and stability commitement for Heparin Sodium, USP.

Additionally, Sandoz GmbH also included the following information:

- Confirmation that (b) (4) packages to DMF 18557, in response to an FDA request via a teleconference between Sandoz Inc. (Jean Domenico) and FDA (Larry Lee, Naiqi Ya and Andre Raw) on November 5th, 2009, which was a follow up to a teleconference that took place on November 4th, 2009.

A complete copy of this DMF amendment is provided in Attachment 2 for your convenience.

2.) Revised Control Procedure for Heparin Sodium, USP

Attachment 3 presents the updated specification for Heparin Sodium, USP that is used (b) (4) comply with the revised USP monograph for Heparin Sodium, USP that went into effect October 1, 2009.

3.) OSCS Testing Commitment Update:

The current USP monograph revises the tests used to control oversulfated chondroitin sulfate (OSCS) contamination in Heparin Sodium, USP. Because Sandoz has revised its testing procedures to comply with the revised USP requirements, Sandoz has also revised a testing commitment previously submitted to ANDA 77-857, to align the testing commitment with current USP requirements and methods.

In an amendment to ANDA 77-857, filed June 2, 2008, Sandoz described two (b) (4) In that ANDA amendment, Sandoz described the results of testing with those two methods, and made the following commitment to FDA:

(b) (4)

At this time, Sandoz updates this testing commitment as follows:

(b) (4)

4.) Revised control procedure for Enoxaparin Sodium, USP

Attachment 4 presents the updated release specifications for Enoxaparin Sodium, USP. The specifications for release of Enoxaparin Sodium, USP have been amended to meet the new USP monograph for Enoxaparin Sodium that went into effect December 1, 2009.

Stability Commitment: Sandoz will incorporate the new USP testing requirements into its ongoing stability program for Enoxaparin Sodium, USP. The stability protocol will be submitted in our annual report post-approval.

5.) Revised control procedure for Enoxaparin Sodium Injection, USP

Attachment 5 presents the updated release specifications for Enoxaparin Sodium Injection, USP. The specifications for release of Enoxaparin Sodium Injection, USP have been amended to meet the new USP monograph for Enoxaparin Sodium Injection that went into effect December 1, 2009.

Stability Commitment: Sandoz will incorporate the new USP testing requirements into its ongoing stability program for Enoxaparin Sodium Injection, USP. The stability protocol will be submitted in our annual report post-approval.

6.) Addition of (b) (4) Test for Enoxaparin Sodium Injection, USP

In response to FDA's request during a teleconference between Sandoz Inc. (Jean Domenico) and FDA (Larry Lee, Naiqi Ya and Andre Raw) on November 4th, 2009, and in a following teleconference on November 16, 2009, Sandoz has added a (b) (4)

As endorsed by FDA during the teleconference on November 16th, Sandoz has set a (b) (4) for this specification.

(b) (4)

[redacted] (b) (4)
are presented in Attachment 8.

7.) Updated "Outside Testing Site" List

Finally, Sandoz includes an updated "Outside Testing Site" list in Attachment 9. The list was revised to add Momenta as a testing site for drug product.

This submission is in electronic format. One CD is provided that includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	*356h.pdf*
Sandoz cover letter (scanned)	*cover.pdf*
	cmc folder *attachments.pdf* Attachment 1 – Sandoz GmbH DMF II No 18557 for Heparin Sodium, USP Amendment (dated 11/18/09) Attachment 2 – Sandoz GmbH DMF II No 18557 for Heparin Sodium, USP Amendment (dated 12/1/09) Attachment 3 - [redacted] (b) (4) Heparin Sodium USP Specifications Attachment 4 – [redacted] Enoxaparin Sodium USP Specifications Attachment 5 – Enoxaparin Sodium for Injection Specifications Attachment 6 – Method TP-276 Attachment 7 – Validation Report for TP-276 Attachment 8 – Representative data from TP-276 Attachment 9 – Outside Testing Site List

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Marcy Macdonald, Director
Regulatory Affairs

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Rockville, MD 20855

AMENDMENT - LABELING

(electronic submission)

ORIG-1/SD-115

DEC 30 2009

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Labeling Amendment – Response to FDA Communication Dated 12/24/2009

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to email correspondence from FDA (Ruby Wu) to Sandoz (Caryn McCullough) on December 24, 2009 in which a revised physician insert for the reference listed drug, Lovenox® was forwarded to Sandoz. In response, we are providing our revised package insert in final print (true size). In addition, we are providing our insert in SPL format, enlarged PDF, and Word format, as well as side-by-side comparisons of our proposed insert versus the reference listed drug insert and our last filed insert.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

RECEIVED

DEC 31 2009

OGD

SANDOZ

Folder	Document	File Name
ANDA 77-857	Cover Letter (scanned)	*cover.pdf*
	FDA Form 356h (scanned)	*356h.pdf*
Labeling		
	Final Print Package Insert (True Size)	*fpl insert.pdf*
	Package Insert in enlarged PDF format	*enlarged pi.pdf*
	Package Insert in MS Word format	*pi word.doc*
	Side by Side comparison versus RLD	*Sidebyside v rld.pdf*
	Side by Side comparison versus last filed	*sidebyside v last filed.pdf*
	Revised insert in SPL format	spl

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Marcy Macdonald

Marcy Macdonald, Director
Regulatory Affairs

Enclosures
MM/pln

Jean Domenico, Manager
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SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
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Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

SD-116

January 13, 2010

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Telephone Amendment – Clarification of Outside Testing Facility ((b) (4))

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone message from Tom Hinchliffe (FDA) to Jean Domenico (Sandoz) on January 13, 2010. Mr. Hinchliffe requested that Sandoz clarify what testing is currently performed by its outside testing facility, (b) (4) in (b) (4) and what testing they have done in the past in support for Sandoz Enoxaparin Sodium Injection application.

We would like to inform you that (b) (4) is not one of our primary or back-up testing facilities for enoxaparin sodium drug substance or finished drug product. (b) (4) can be used by Baxter, our finished drug product manufacturer, as a back-up testing facility for the annual confirmation testing of the syringe barrel and stopper components used to package our enoxaparin sodium finished drug product.

SANDOZ

Sandoz would also like to confirm that (b) (4) has not been used as an outside lab for any testing on the active drug substance, finished drug product, or components used in the manufacturing of Enoxaparin.

(b) (4) is only qualified as a back-up test site for annual testing of syringe barrels and stoppers. However, Baxter has confirmed they have not been used on any of its annual component testing of the syringe barrels and stoppers performed in 2005 through 2009. Consequently, (b) (4) has not participated in any testing in support for any drug product lot presented in Sandoz application 77-857 nor in any of the drug product lots that are currently planned for commercial distribution.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	*356h.pdf*
Sandoz cover letter (scanned)	*cover.pdf*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

SANDOZ

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Gary Buehler, Director
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Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

(electronic submission)

ORIG-1/SD-117

January 28, 2010

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Telephone Amendment – Response to Questions Raised in 01/27/10 Teleconference

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a teleconference between FDA and Sandoz on January 27, 2010, in which FDA requested additional information. In response for these requests, we are providing the following information:

1.) **FDA Request:**

Does Sandoz / Momenta have data available on the RLD product, Lovenox®, to support and justify its specification of (b) (4)

[redacted]

observed in Lovenox®.

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

SANDOZ

Document	ANDA 77-857
356h form (scanned)	*356h.pdf*
Sandoz cover letter (scanned)	*cover.pdf*
(b) (4) Memorandum USP Correlation Study Drug Substance Specifications	cmc folder *Attachment 1.pdf* *Attachment 2.pdf* *Attachment 3.pdf*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures
JD/ckm

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SANDOZ

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

General Correspondence

March 15, 2010

GI-1, SD #118

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

General Correspondence

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to an e-mail correspondence from Joseph Carrado (Sandoz) to Tom Hinchliffe (FDA) on March 09, 2010. As stated in this correspondence, authorization is hereby given for Mr. [redacted] (b) (4) Esq, to speak to FDA on behalf of Sandoz concerning the above-referenced enoxaparin application.

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Document	**ANDA 77-857**
356h form (scanned)	*356h.pdf*
Sandoz cover letter (scanned)	*cover.pdf*

SANDOZ

Please incorporate this information into ANDA 77-857.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures
JD/ckm

SANDOZ

Jean Domenico, Manager
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OVERNIGHT DELIVERY

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7500 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT - LABELING

(electronic submission)

APR 2 8 2010

RE: ANDA 77-857 Enoxaparin Sodium Injection
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)
and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)
Gratuitous Amendment – Updated Labeling

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

The physician insert labeling for this product has been revised to include information on Exclusivity Code I-533 which will be expiring May 16, 2010. Sandoz labeling previously did not include information pertaining to Exclusivity Code I-533, ST-segment Elevation Myocardial Infarction (STEMI). Since this exclusivity expires soon, we have revised our insert to include all text related to STEMI. However, Sandoz will not use this labeling until after the exclusivity has expired. If Sandoz should get approval of its application prior to May 16, 2010, we will withdraw this labeling amendment and use our currently filed labeling that does not include the STEMI indication information.

Enclosed you will find our revised package insert in final print (true size). In addition, we are providing our insert in enlarged PDF and Word format. Also provided are side-by-side comparisons of our proposed insert versus the currently approved RLD and versus our last submission. We will submit our insert in SPL format upon approval of our application.

SANDOZ

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a Letter of Non-Repudiation Agreement was submitted by Sandoz on November 30, 2007.

Folder	Document	File Name
ANDA 77-857	Cover Letter (scanned)	*cover.pdf*
	FDA Form 356h (scanned)	*356h.pdf*
labeling		
	Final Print Package Insert (True Size)	*fpl insert.pdf*
	Package Insert in enlarged PDF format	*pi enlarged.pdf*
	Package Insert in MS Word format	*pi word.doc*
	Side by Side comparison versus last filed	*sidebyside v last filed.pdf*
	Side by Side comparison versus RLD	*sidebyside v rld.pdf*

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Jean Domenico

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Jean Domenico, Manager
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ESG DELIVERY

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
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GRATUITOUS AMENDMENT

(electronic submission)

May 26, 2010

RE: ANDA 77-857 Enoxaparin Sodium Injection
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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

Gratuitous CMC Amendment – (b) (4)

Dear Dr. Webber:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 77-857 for Enoxaparin Sodium Injection 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) and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone conversation between Tom Hinchliffe (FDA) and Jean Domenico (Sandoz) on May 25, 2010. Mr. Hinchliffe informed Ms. Domenico that one of Sandoz outside testing facilities, (b) (4), has changed its name to (b) (4) (b) (4) and moved to a new physical location that has not yet been inspected.

In light of this information, Sandoz has decided to remove (b) (4) from ANDA 77-857 . A revised list of Sandoz's contract manufacturing/testing sites is provided. In the future, if Sandoz decides to use (b) (4), Sandoz will update ANDA 77-857 accordingly.

This submission is in electronic format and includes the content described below.

Document	**ANDA 77-857**
356h form (scanned)	*356h.pdf*
Sandoz cover letter (scanned)	*cover.pdf*
List of Contract Testing Facilities	*outsidelabs.pdf*

This information is submitted for your review and approval.

Sincerely,

Sandoz Inc.

Digitally signed by Domenico Jean
DN: cn=Domenico Jean, ou=people, GX, serialNumber=405645, dc=com, novartis
Date: 2010.05.26 14:56:10 -06'00'

Jean Domenico, Manager
Regulatory Affairs

Enclosures

JD/ckm

Date: July 20, 2010

From: Keith O. Webber, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER

To: ANDA 77-857

Subject: Assessment of June 29, 2009, Office of Biotechnology Products' Review regarding immunogenicity data submitted by Sandoz

In a review dated June 29, 2009, the Office of Biotechnology Products (OBP) concludes that data submitted by Sandoz do not indicate that Sandoz's generic enoxaparin would be more immunogenic than the reference listed drug (RLD), Lovenox. Sandoz's data compare its generic exoxaparin to Lovenox with regard to: (a) the ability of enoxaparin to form complexes with PF4, (b) the presence of impurities that could stimulate the immune system directly, (c) activation of human PBMC, and (d) the induction of antibodies to the product in mice. Accordingly, OBP's review recommends approval of Sandoz's generic enoxaparin.

Nonetheless, OBP expresses reservations about its recommendation based on five concerns that, in OBP's judgment, may limit the interpretation of Sandoz's data. Such concerns are not atypical in a thorough review. I have reviewed OBP's concerns and conclude that they do not call into question the approvability of Sandoz's generic enoxaparin product or warrant additional studies. I address below each of the items identified in OBP's review (June 29, 2009, OBP Review, "Recommendations," at 1-2).

First, OBP comments that the enoxaparin used in the studies is made from Heparin Sodium USP, which is manufactured (or purified) from (b) (4) (b) (4) (which OBP refers to as crude heparin). OBP indicates that the (b) (4) " The concern is that there may be differences in impurities between Heparin Sodium (b) (4) that could affect immunogenicity. To address this concern, Sandoz was asked to provide scientific data to demonstrate that the use of (b) (4) (b) (4) does not affect the quality of Heparin Sodium USP and hence the quality of the resulting enoxaparin sodium. Specifically, Sandoz provided the following information:

- (b) (4)

[1] In addition to the reasons set forth in the text, this issue is also not a concern because Sandoz GmbH retains samples of Heparin Sodium (b) (4) and it has ensured traceability back to the crude supplier. See July 20, 2009, Memorandum from Sau L. Lee, Douglas Campbell, Kevin Foley, subject: Summary of Pre-approval Inspection for Sandoz GmbH, Austria.

(b) (4) directly in the production of enoxaparin sodium.

- The enoxaparin batches, which were manufactured by using (b) (4) materials, were found to be chemically equivalent based upon the five criteria for sameness.

For details regarding the above information, please refer to Dr. Lee's CMC review #3. Furthermore, it should be noted that the reason for using more (b) (4) requirements to ensure the continuous production of Heparin Sodium USP. Such a practice is common in the manufacture of Heparin Sodium USP.

Second, OBP comments that, "[s]everal lots of the RLD showed impurities that were evident in the silver stained SDS-PAGE gels (polyacrylamide gel electrophoretograms). These were no[t] present in the lots of enoxaparin from Sandoz-Moment[a] that were submitted for evaluation. While we presume that the absence of impurities is better in terms of product immunogenicity, their potential impact quenching an immune response has not been formally investigated." (June 29, 2009, OBP Review at 2). The concern with regard to the effect that impurities may have on the immunogenicity of enoxaparin products is primarily related to protein impurities. Sandoz's generic enoxaparin was shown to have comparably low levels of protein impurities as compared to the levels present in Lovenox. However, OBP noted that a few lots of the RLD (Lovenox) showed a smear on the SDS-PAGE gels that appears not to be of protein origin.[2] Such a smear was not observed in Sandoz's enoxaparin products. Lower impurity levels are generally considered to be of lower risk from an immunogenicity perspective. Although there is still a remote possibility that these non-protein impurities may have an immunosuppressive effect, the in vitro functional assays and animal studies that were conducted by Sandoz do not show any evidence of such an immunosuppressive effect. Accordingly, I do not believe any additional studies are indicated to further ascertain immunosuppressive effect.

Third, OBP recommends that Sandoz be requested to commit to characterize the level of protein as part of the release specifications using validated acceptable methods for every lot of enoxaparin product or to demonstrate that any protein present in their starting material is cleared in excess by their manufacturing process. Sandoz has addressed this issue by committing to characterize the level of protein as part of the release specifications using validated acceptable methods for every lot of enoxaparin product and has incorporated a validated protein assay and acceptable specifications into the enoxaparin lot release testing criteria.

[2] See June 29, 2009, OBP review, at 4. According to Sandoz, the smear observed in the RLD is generally consistent with the response observed for (b) (4) in the SDS-PAGE method. See Amendment to ANDA 77-857 dated Sept 25, 2008.

Fourth, OBP comments that the methods utilized to characterize the PF4--enoxaparin complexes have individual weaknesses that hinder the interpretation of the data. OBP nevertheless found that comprehensive analysis of the data do not suggest that complexes formed by PF4 and Sandoz's enoxaparin differ significantly from those formed with Lovenox. I, like the reviewer, acknowledge that there might be individual weaknesses to the tests; however, in light of the fact that the weaknesses are not overlapping and there has been comprehensive data analysis, I conclude that the tests and findings are scientifically appropriate and adequate.

Fifth, OBP comments that "Similarity in the observed responses (between innovator and generic products) reduces the risk of unexpected immune responses, but does not fully ensure that the risk of developing an immune response to the product will be equivalent in patients." This statement warrants some additional context, as it is important to recognize that no amount of in vitro, in vivo, or clinical testing would provide absolute certainty of clinical equivalence between two products. In the case of enoxaparin, a comparative clinical study would not necessarily be expected to be more sensitive to meaningful differences between the generic enoxaparin product and Lovenox.[3]

Overall, I find, as did OBP, that Sandoz's assessment of immunogenicity is scientifically appropriate and adequately addresses the issue of immunogenicity. It is scientifically reasonable, based on the comprehensive data submitted, to conclude that Sandoz' generic enoxaparin would be no more immunogenic than Lovenox.

[3] For example, a double blind clinical study showed that the rate of deep-vein thrombosis after orthopedic surgery was equivalent for two LMWHs: enoxaparin and tinzaparin. See Planes, A. et al. (1999), "Prevention of Deep Vein Thrombosis after Hip Replacement: Comparison between Two Low-Molecular Heparins, Tinzaparin and Enoxaparin," *Thrombosis and Haemostasis* 81: 22-25. However, despite such evidence of equivalence of clinical effectiveness, enoxaparin and tinzaparin would not be considered to have the same active ingredient, given that, among other characteristics, they: (1) are manufactured via different modes of depolymerization (i.e., enoxaparin is manufactured by chemical alkaline β-elimination, and tinzaparin is manufactured via enzymatic β-elimination.); (2) have different anti-IIa/anti-Xa ratios (for tinzaparin, the anti-IIa/anti-Xa ratio varies between 1.5 and 2.5, and for enoxaparin this ratio varies between 3.3 and 5.3); (3) have different proportions of sulfated and non-sulfated $\Delta^{4,5}$ – uronate structures at the non-reducing end of the oligosaccharide chains. (This is because in the mode of depolymerization by enzymatic β-elimination, cleavage takes place exclusively in heparin polysaccharide chains at sites where the disaccharide unit has the 2-O-sulfoiduronic acid structure, whereas in the mode of depolymerization by chemical (alkaline) β-elimination, cleavage occurs without preference for the presence or absence of a 2-O-sulfo group in the iduronic acid structure. See Linhardt, R.J., Gunay, N.S. (1999), "Production and Chemical Processing of Low Molecular Weight Heparin," Semin Thromb Hemost 25 S3:10.); and have different pharmacokinetics Eriksson, B.I. et.al., (1995), "A comparative study of three low-molecular weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers," *Thrombosis and Haemostasis* 73: 398-401.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

THOMAS O HINCHLIFFE
07/20/2010

KEITH O WEBBER
07/20/2010

Date: July 20, 2010

To: Helen N. Winkle, Director, Office of Pharmaceutical Science (OPS), Center for Drug Evaluation and Research (CDER)

From: Keith O. Webber, Ph.D., Deputy Director, OPS, CDER

Subject: Active ingredient sameness for enoxaparin sodium and FDA's request for immunogenicity data

Attachment: Dr. Janet Woodcock's draft memo on enoxaparin generics

This memorandum addresses two issues. First, I am making the final decision regarding a scientific disagreement between two offices within the Center for Drug Evaluation and Research's (CDER's) Office of Pharmaceutical Science (OPS) -- the Office of New Drug Quality Assessment (ONDQA) and the Office of Generic Drugs (OGD). Second, I am deciding what immunogenicity data are scientifically appropriate to approve an ANDA for enoxaparin sodium injection.

The crux of the scientific disagreement involves the type of information that would be sufficient in an abbreviated new drug application (ANDA) to show that the generic drug product contains the same active ingredient (enoxaparin sodium or "enoxaparin") as that of the reference listed drug (RLD) – Lovenox (enoxaparin sodium injection). Specifically, the scientific disagreement focuses on whether the five criteria developed by OGD are sufficient to determine active ingredient sameness for enoxaparin. ONDQA's view is that complete characterization, including sequence elucidation and molecule-to-molecule comparison is necessary to make such a determination.

I have carefully considered the differing views of OGD and ONDQA in reaching my conclusion that OGD's approach is a scientifically robust and valid approach for determining and demonstrating enoxaparin sameness for purposes of ANDA approval. This decision is based on discussions at meetings held on, among other dates, September 25, 2007, and October 2, 2007; consultation with Agency experts in chemistry, biochemistry, and immunology; and review of associated documentation regarding the issue of enoxaparin sameness, including the Sanofi Aventis (Aventis) citizen petition (submitted by the RLD sponsor), the chemistry reviews by Dr. Sau Lee, the memoranda reflecting the differing views of OGD and ONDQA scientists, and numerous other scientific documents.

I have further concluded that *in vitro* and *in vivo* assays of the type requested by FDA in 2007 provide sufficient assurance that the risk of immunogenicity due to potential impurities in a generic enoxaparin will not be greater than that of the RLD, Lovenox.

The first part of this memorandum focuses on resolution of the scientific disagreement. The second part of this memorandum addresses FDA's request that ANDA applicants for enoxaparin sodium injection provide immunogenicity data.

PART I: ACTIVE INGREDIENT SAMENESS

A. Lovenox and Enoxaparin

Lovenox is indicated for serious medical conditions, such as prophylaxis of deep vein thrombosis (DVT) in certain surgeries or in patients with severely restricted mobility during acute illness, and inpatient and outpatient treatment of acute DVT under certain circumstances.[1]

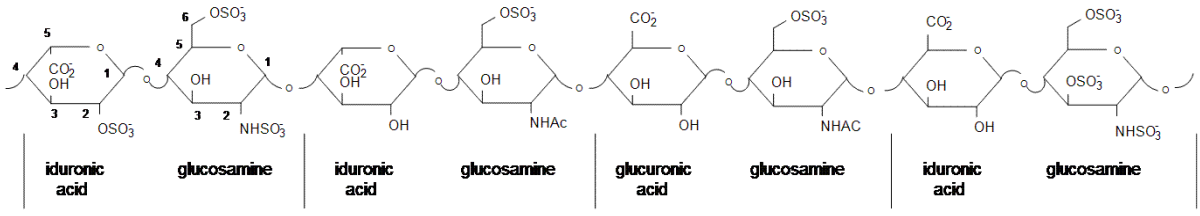
Lovenox contains the active ingredient enoxaparin sodium and is commonly referred to as a low molecular weight heparin (LMWH) because it is prepared by depolymerizing the parent compound, heparin sodium, to obtain smaller oligosaccharides with a lower average molecular weight.[2] Enoxaparin is prepared by alkaline depolymerization of the benzyl ester of heparin derived from porcine intestinal mucosa. Enoxaparin shares characteristics of the basic structure of heparin sodium.[3] Similar to heparin sodium, enoxaparin is a heterogeneous mixture of oligosaccharides composed of a diverse array of disaccharide units assembled in chains of varying length and disaccharide sequence.[4]

In addition, enoxaparin has unique chemical modifications at the terminal ends of the oligosaccharide chains, such as the Δ-4,5-uronate structure and 1,6-anhydro ring structure

[1] See product labeling for Lovenox (enoxaparin sodium injection), NDA 20-164; Revised December 23, 2009 for a complete description of clinical indications; available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

[2] Because LMWH chains are shorter than the parent heparin chains, the term "oligosaccharide(s)" is generally used in connection with the term LMWH and the term "polysaccharide(s)" is generally used in connection with the term heparin.

[3] Disaccharide repeating units present in heparin are shown below. These repeating units are composed of glucosamine and an uronic acid (either iduronic or glucuronic acid) with the linkage sequence: $[(1\rightarrow4)\ \alpha\text{-D-glucosaminyl} - (1\rightarrow4)\ \beta\text{-D-hexuronosyl}]_n$.



[4] Each disaccharide unit is comprised of a 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. 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.

at the non-reducing and reducing ends, respectively.[5] These unique features 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 is not present in heparin sodium.

The diversity of enoxaparin sodium comes from 1) polydispersity[7] of the chain length, 2) the diversity of the disaccharide units and the corresponding distribution of disaccharide unit sequences in oligosaccharide chains, and 3) the diversity of modified terminal end disaccharide units in the oligosaccharide chains.[8]

Both heparin and enoxaparin act by inhibiting enzymes (Factor Xa & Factor IIa) in the blood clotting cascade;[9, 10] however, enoxaparin sodium has a distinctly different ratio of anti-Xa and anti-IIa activities from heparin. The molecular basis for factor Xa inhibition (anti-Xa) and factor IIa inhibition (anti-IIa) is mediated by the AT-III binding pentasaccharide sequence present in heparin sodium and LMWHs, including enoxaparin.[11] The biochemical inhibitory effect on factor Xa and factor IIa in the coagulation cascade accounts for the most thoroughly understood pharmacological basis by which LMWHs (including enoxaparin) and heparins function as anticoagulants. 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.[12]

B. Standard for Active Ingredient Sameness

My evaluation of the scientific disagreement between the two offices takes into account the appropriate standard for active ingredient sameness for purposes of ANDA approval

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[5] The description section of the current Lovenox Injection product labeling (NDA 20-164; Dec 23, 2009) reads in part: Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain.

[6] Linhardt, R.J., Gunay, N.S. (1999), "Production and Chemical Processing of Low Molecular Weight Heparin," *Semin. Thromb. Hemost.* 25 S3:5-16.

[7] Polydispersity is a measure of the distribution of molecular weights in a given polymer.

[8] For background on the diversity of enoxaparin refer to e.g., chemistry review by Dr. Sau Lee (Executive Summary); November 29, 2006, Enoxaparin Executive Summary; and July 27, 2006, Pharmaceutical Equivalence of Low Molecular Weight Heparins.

[9] 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).

[10] 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.

[11] See chemistry review by Dr. Lee (Executive Summary); November 29, 2006, Enoxaparin Executive Summary; and July 27, 2006, Pharmaceutical Equivalence of Low Molecular Weight Heparins for additional details regarding this mechanism of action.

[12] Hirsh, J., Warkentin, T.E., Shaughnessy, S.G., Anand, S.S., Halperin, J.L., Raschke, R., Granger, C., Ohman, E.M., Dalen, J.E. (2001), "Heparin and Low-Molecular Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety," *Chest* 119:64S-94S.

under the Federal Food, Drug, and Cosmetic Act (the Act) and implementing regulations. I have included a summary below.

An ANDA must contain information to show that the active ingredient of the generic drug product is the "same" as that of the listed drug.[13] The Agency must approve an ANDA referencing a listed drug that has only one active ingredient unless, among other things, the ANDA contains insufficient information to show that the active ingredient is the same as that of the listed drug.[14] There are parallel FDA regulations implementing these statutory provisions.[15]

FDA regulations also provide that an ANDA is suitable for consideration and approval if the generic drug product is the same as the reference listed drug.[16] Specifically, the regulations states that the term "same as" means, among other things, "identical in active ingredient(s)." FDA further clarified in the preamble to the final rule its intent to adopt a flexible approach and stated that it would "consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity."[17] FDA further stated that, in most cases, the standards for identity are prescribed in the *U.S. Pharmacopeia* (USP), although we might "prescribe additional standards that are material to the ingredient's sameness."[18] In the case of enoxaparin, there is a USP monograph and there are additional standards that are material to enoxaparin's sameness.

In approaching this disagreement, I am also relying on the U.S. Court of Appeals for the District of Columbia's decision in *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998), which squarely addressed the issue of active ingredient sameness within the meaning of the above statutory and regulatory provisions. The *Serono* decision upheld as reasonable the Agency's interpretation of the statutory requirement for active ingredient "sameness," as well as the Agency's interpretation of the word "identical" in the regulations.[19] The Court of Appeals concluded that the statute does not require the term "same as" to be defined as "complete chemical identity," noting that the statute does not describe the type of information an ANDA applicant must submit, nor the type of information upon which the Agency may rely.[20] This statutory requirement, as noted in *Serono*, grants the Agency broad discretion in making active ingredient sameness determinations, particularly when the Agency considers the "kind of drug at issue" in making such determinations.[21]

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[13] 505(j)(2)(A)(ii)(I) of the Act.
[14] Section 505(j)(4)(C)(i) of the Act.
[15] 21 CFR 314.94(a)(5)(i) and 314.127(a)(3).
[16] 21 CFR 314.92(a)(1).
[17] See 57 Fed. Reg. 17950, at 17958-17959 (April 28, 1992) (FDA specifically rejected in the preamble to the final rule a requirement that active ingredients "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics and solid state forms of the drug have not been altered.")
[18] 57 Fed. Reg. at 1759.
[19] *Serono*, at 1321.
[20] *Serono*, at 1319.
[21] *Serono*, at 1319.

C. History of Scientific Disagreement

Active ingredient sameness is one of the primary issues underlying several ANDAs for enoxaparin sodium injection under review by OGD. This is also the primary issue raised by a citizen petition submitted by Aventis and related supplements and comments submitted to the Agency's docket.[22] The regulatory history of enoxaparin reflects the complexity of the scientific issues involved. Subsequent to submission of the first ANDA for enoxaparin sodium injection, OGD developed five criteria for assessing sameness of the active ingredient enoxaparin through a process that involved extensive scientific discussions within CDER. As with many complicated scientific issues, differences in scientific opinion arose concerning the appropriate approach for assessing enoxaparin sameness. Some scientists in CDER's ONDQA expressed the view, although they have not reviewed the ANDAs for enoxaparin,[23] that a showing of sameness for the active ingredient enoxaparin can only be assessed by complete characterization, including sequence elucidation in a molecule-to-molecule comparison.

In 2004, this disagreement between ONDQA and OGD scientists was brought to Helen Winkle, Director of OPS. She agreed with OGD scientists, decided that generic versions of Lovenox could be reviewed as ANDAs, and documented her reasoning in a memorandum dated September 21, 2004. In 2007, in light of the continuing difference of opinion between ONDQA and OGD scientists, the issue was brought to Dr. Steven Galson (Director of CDER at the time) in the context of the review of the first ANDA submitted for enoxaparin sodium injection (i.e., Amphastar's ANDA and its showing of enoxaparin sameness).[24] Because Dr. Galson left the Agency prior to documenting a

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[22] Docket No. 2003-P-0273.

[23] Since ONDQA does not have primary responsibility for reviewing ANDAs, the fact that ONDQA has not reviewed the ANDAs for enoxaparin is not atypical.

[24] Dr. Galson gave both offices an opportunity to present their views during briefings held for him on April 27, 2007 and July 19, 2007, and through (among other means) memoranda setting forth their respective positions. (A timeline of major events leading up to that point is set forth in the May 9, 2007, OGD and September 21, 2004, OPS memoranda.)
Supporting documentation includes:

(1) May 3, 2007, ONDQA memo with the following attachments: April 27, 2007 ONDQA slides, January 12, 2004 ONDQA memo (subject: Commentary on the January 5, 2004 Memorandum From OGD regarding Lovenox (enoxaparin sodium injection) ("enoxaparin") and other LMWHs) and January 9, 2004, ONDQA memo (subject: Comments regarding the OGD white paper (Draft) for pharmaceutical equivalency of Low Molecular Weight Heparin), January 24, 2007, European Medicines Agency concept paper, April 18, 2004, ONDQA memo (subject: Comments on OGD's Enoxaparin Executive Summary), July 19, 2004, Dr. Vincent Lee's report, and August 30, 2004, ONDQA Comments on Dr. Lee's Report on Enoxaparin;
(2) May 9, 2007, OGD memo (subject: Response to Dr. Nasr's Concerns Dated May 3, 2007 Regarding the Recommendations for Approval of Generic Enoxaparin Sodium) with the following attachments: July 13, 2004, Andre Shrake email (subject: Hetastarch and Low Molecular Weight Heparin), September 21, 2004, OPS memo (subject: the appropriate regulatory pathway for ANDAs submitted for Lovenox (enoxaparin sodium injection) and other LMWHs); October 21, 2004, Division of Gastrointestinal and Coagulation Drug Products memo (subject: Generics of Lovenox (enoxaparin sodium) and other low molecular weight heparins (LMWH)), November 9, 2006, FDA internal meeting minutes (Enoxaparin Sodium Injection ANDAs), November 29, 2006, OGD memo (subject:

resolution of the scientific disagreement, Dr. Janet Woodcock – then the Acting Director of CDER – was asked to resolve the issue. Dr. Woodcock agreed with OGD scientists, concluding at the time that Amphastar had submitted sufficient information to show sameness of the enoxaparin active ingredient.[25] I attach Dr. Woodcock's draft memorandum, which reflects her thinking at the time and was prepared prior to sending the November 2, 2007, letter to Amphastar informing the company that no further documentation of active ingredient sameness was necessary. (Dr. Woodcock's draft memorandum also addresses her initial determination regarding impurities and immunogenicity, which is discussed in Part II of this memorandum).[26]

D. Final Assessment of Differing Views of OGD and ONDQA

After Dr. Woodcock's initial determination, I have undertaken a thorough and independent review of these scientific issues, including the differing views of OGD and ONDQA. Since both OGD and ONDQA fall within OPS, I am resolving the disagreement between the two offices as part of my duties as Deputy Director of OPS. I summarize below my views on the strength and relevance of the scientific perspectives of each office, and final resolution of the scientific disagreement.

Summary of OGD's and ONDQA's Positions

OGD's view is that satisfaction of the following five criteria[27] together is sufficient to demonstrate active ingredient sameness for enoxaparin:

- Equivalence of physicochemical properties,

Enoxaparin Executive Summary), July 27, 2006, OGD memo (subject: Pharmaceutical Equivalence of Low Molecular Weight Heparins).

Because scientific views and available information may change over time, conclusions and information in later documents may supersede those in earlier ones.

[25] Subsequently, however, FDA learned that the manufacturer of heparin sodium USP for enoxaparin initially identified in Amphastar's ANDA (b) (4) the heparin sodium USP. Based on facts and circumstances surrounding Amphastar's heparin sodium USP (b) (4) and its ANDA, FDA determined that the submitted data had been confounded and that certain tests to demonstrate enoxaparin sameness and address immunogenicity needed to be repeated. It is also important to use a manufacturer of heparin sodium USP that has been inspected by FDA to ensure that current good manufacturing practice (CGMP) is being met. The Agency cannot approve Amphastar's ANDA until it meets the requirements for ANDA approval.

[26] Drafts of Agency memoranda are ordinarily not included as references to documents in the administrative record of the Agency's decision. Here, however, Dr. Woodcock's draft memorandum served as the basis for the Agency's initial view that sameness of active ingredient could be satisfied by the five criteria, and that more information about immunogenicity should be requested. At the time, no final Agency action on any particular ANDA for enoxaparin sodium injection was being taken. Dr. Woodcock later decided that she would no longer participate in the enoxaparin ANDA reviews, and therefore did not make the final Agency decision on those matters. I am including her draft memorandum in these unusual circumstances to show the analysis supporting the Agency's letter to Amphastar on November 2, 2007, and the letters issued soon after to all pending ANDA applicants for enoxaparin sodium injection to address immunogenicity.

[27] Equivalence for the above criteria is based upon qualitative and/or quantitative comparisons of the generic drug product's enoxaparin and multiple batches of Lovenox's enoxaparin and takes into account the batch-to-batch variability and sampling of Lovenox, and analytical test variability.

- Equivalence of heparin source material and mode of depolymerization,
- Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species,
- Equivalence in biochemical and biological assays,
- Equivalence of *in vivo* pharmacodynamic profile.

OGD has presented its rationale for establishing these five criteria as sufficient for assessing sameness for enoxaparin on, among other dates, October 2, 2007. OGD also has prepared several memoranda with varying degrees of detail on the underlying principles of the five criteria.[28] OGD maintains that its approach is supported by science, and is consistent with relevant law and previous ANDA approvals for heparin and hetastarch.

ONDQA has argued in its memoranda that none of these criteria, either individually or combined, are adequate to ensure enoxaparin sameness.[29] The essence of ONDQA's argument is that it is impossible to demonstrate active ingredient sameness for enoxaparin sodium because it is a mixture of a variety of oligosaccharides that have not been fully characterized and it is unknown which aspects of the mixture contribute to the activity of the drug product. According to ONDQA, a demonstration of active ingredient sameness for enoxaparin sodium requires a complete characterization of the oligosaccharides, including sequence elucidation in a molecule-to-molecule comparison. ONDQA states that the five criteria are insufficient to prove "molecular sameness" and it is not appropriate to demonstrate sameness by "inference."[30] ONDQA also states that OGD's approach is not consistent with applicable law and FDA policy.[31] ONDQA also distinguishes previous ANDA approvals for hetastarch, and comments on the relative complexity of enoxaparin compared to proteins.[32]

<u>My Final Assessment of the Differing Views of OGD and ONDQA</u>

I find that satisfaction of the five criteria developed by OGD results in a robust and rigorous demonstration of enoxaparin sameness, within the meaning of the term "same" in the applicable statutes and regulations for ANDA approval. I summarize below the type of data captured by these five criteria and their relevance for demonstrating sameness of the active ingredient enoxaparin. The following summary of the five criteria is not intended to capture, or be a substitute for, the extensive information submitted by ANDA applicants, supporting FDA-generated documentation, or the assessment of enoxaparin sameness by OGD as reflected in their ANDA reviews.

1. Equivalence of physicochemical properties.

[28] See also, e.g., November 29, 2006, Enoxaparin Executive Summary, and July 27, 2006, Pharmaceutical Equivalence of Low Molecular Weight Heparins.
[29] See footnote 24.
[30] May 3, 2007, ONDQA memo, at 2.
[31] May 3, 2007, ONDQA memo, at 2; January 4, 2004, ONDQA memo, at 6.
[32] May 3, 2007, ONDQA memo, at 1-2; and April 18, 2004, ONDQA memo, at 1-2

An important aspect of demonstrating enoxaparin sameness between the generic drug product's enoxaparin and Lovenox's enoxaparin is equivalence in overall chemical composition using many different methods, including nuclear magnetic resonance, ultraviolet specific absorbance, sodium content, molar ratio of sulfate to carboxylate, and molecular weight distribution via size exclusion chromatography. Equivalence in chain length distribution can be demonstrated using, among other techniques, chain mapping, which provides a panoramic view of the distribution of chains in the basic backbone of enoxaparin.[33] This technique demonstrates that the extent of cleavage of porcine heparin sodium is the same as Lovenox's enoxaparin, and is done by comparing qualitatively and quantitatively the peaks present in the chromatographs and/or mass spectra of the generic enoxaparin lots to those of Lovenox lots. This analysis provides a robust assessment of the average molecular weight and molecular weight distribution of the generic product's enoxaparin and Lovenox's enoxaparin and their equivalence. Equivalence in these physicochemical properties, including chain mapping, establishes equivalence in broad, but nonetheless important, aspects of the structural characteristics of enoxaparin.

2. Equivalence of heparin source material and mode of depolymerization.

A second important aspect of demonstrating enoxaparin sameness between the generic drug product's enoxaparin and Lovenox's enoxaparin is equivalence of heparin source material (i.e., heparin that is derived from porcine intestinal mucosa and that meets USP monograph standards for Heparin Sodium USP). It is important that the source material be analyzed according to methods and specifications described in the USP monograph for heparin sodium as well as additional controls. The molecular diversity of natural disaccharide building block sequences within heparin results from its biosynthetic pathway. Thus, the same heparin source material, for the purposes of manufacturing enoxaparin, will be expected to have at least a similar distribution of natural disaccharide building block sequences (within the context of its variability). In addition, it is important that the quality of heparin source material be controlled, at minimum, according to methods and specifications described in the USP monograph for heparin sodium.

It is also important that there be equivalence in mode of depolymerization (i.e., alkaline β-elimination of the benzyl ester of heparin). It is important that critical process parameters be identified and controlled during each critical manufacturing step. During the depolymerization of the parent heparin polysaccharide chains into enoxaparin oligosaccharide chains, there is no rearrangement of the sequences of "natural" disaccharide building blocks in heparin. Hence, the distribution of sequences of disaccharide units in enoxaparin is a result of the (1) sequences found "naturally" in heparin and (2) site(s) where the cleavage reaction occurs in the parent heparin chains. This mode of depolymerization also has the effect of introducing a modified disaccharide

[33] Mourier, P.A.J., Viskov, C. (2004), "Chromatographic Analysis and Sequencing Approach of Heparin Oligosaccharides Using Cetyltrimethylammonium Dynamically Coated Stationary Phases," *Analytical Biochemistry* 332:299-313 Thanawiroon, C., Rice, K.G., Toida, T., Linhardt, R.J. (2004), "Liquid Chromatography/Mass Spectrometry Sequencing Approach for Highly Sulfated Heparin Derived Oligosaccharides," *The Journal of Biological Chemistry*, 279: 2608-261

unit having a $\Delta^{4,5}$ uronate structure at the non-reducing end of the chain where cleavage occurs. From this criterion, together with physicochemical equivalence, it can be concluded that two enoxaparins are at least similar with respect to (1) the distribution of sequences of disaccharide units in the oligosaccharide chains, and (2) the diversity of the modified disaccharide units at the terminal end of the oligosaccharide chains.[34]

3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species.

A third important aspect of demonstrating enoxaparin sameness between the generic drug product's enoxaparin and Lovenox's enoxaparin is equivalence in disaccharide building block composition. This shows that the generic product's enoxaparin uses the same "natural" disaccharide units and in the same quantitative levels to assemble the distribution of sequences of oligosaccharide chains, and that it has the same identity and quantitative levels of modified disaccharide building blocks at the terminal ends (including the 1,6 anhydro ring content within the level specified in the Lovenox product labeling, i.e., 15-25% and the USP monograph for enoxaparin). Applicants have included in their ANDAs qualitative and quantitative fragment mapping as part of their demonstration of equivalence to Lovenox's enoxaparin. Fragment mapping represents a signature of recurring oligosaccharide sequences unique to enoxaparin and thus provides global information on the relative arrangement of sequences within the enoxaparin structure. These data are intended to indicate that there are no global differences in the distribution of disaccharide sequences between the generic product's and Lovenox's enoxaparin. ANDA applicants also have submitted information on equivalence by sequencing a subset of the oligosaccharide species (i.e., tetrasaccharides, hexasaccharides) which, by virtue of being the result of the most cleavage reactions of the precursor heparin oligosaccharide chains, are those oligosaccharides whose sequence identities are most dependent on the chemical selectivity of depolymerization. They also have provided additional information on the discriminatory power of these methods to detect subtle differences in the molecular structures of oligosaccharides comprising enoxaparin.

4. Equivalence in biochemical and biological assays.

A fourth important aspect of demonstrating enoxaparin sameness between the generic drug product's enoxaparin and Lovenox's enoxaparin is equivalence of biochemical properties for certain markers of anticoagulant activity, such as anti-factor Xa and anti-factor IIa activity. This criterion is part of the USP monograph specifications for enoxaparin sodium. Heptest and aPTT clotting times can be used for equivalence in biological assays for in-vitro anticoagulant activity.

5. Equivalence in *in vivo* pharmacodynamic profiles.

[34] Linhardt RJ, Gunay NS. Production and chemical processing of low molecular weight heparin. Semin Thromb Hemost. 1999;25 Suppl 3:5-16.

A fifth important aspect of demonstrating enoxaparin sameness between the generic drug product's enoxaparin and Lovenox's enoxaparin is equivalence in *in-vivo* pharmacodynamic profiles using, for example, anti-factor Xa activity, anti-factor IIa activity, and pharmacodynamic parameters for Heptest and aPPT clotting time. It is well established that the different LMWH products approved in the United States have different pharmacodynamic profiles based on their *in vivo* anti-Xa and anti-IIa profiles, so this information provides additional evidence of enoxaparin sameness.

* * *

By virtue of satisfying all five criteria described above, the standards for identity described in the USP for enoxaparin and additional standards material to enoxaparin's sameness are met. I find that the five criteria together are based on scientific experience, expertise and knowledge of enoxaparin such that they can be used to adequately assess important properties of enoxaparin and its structure, including: (1) the polydispersity of chain lengths, (2) the diversity of disaccharide units and corresponding distribution of sequences of disaccharide units in the oligosaccharide chains, and (3) the diversity of modified terminal end disaccharide units in the oligosaccharide chains.

I find that a product that has satisfied the above five criteria will have demonstrated that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin is equivalent. (The term "molecular diversity" refers to the heterogeneity of oligosaccharides). Equivalent molecular diversity demonstrates sameness for enoxaparin. The five criteria ensure that that the generic drug product's enoxaparin will have the same active ingredient components as those of Lovenox's enoxaparin (within the context of its variability) even though the contribution of each component has not been fully elucidated. Therefore, the pharmacological activity of the active ingredient of the generic enoxaparin product and that of Lovenox can be expected to be the same.

I acknowledge, as do both OGD and ONDQA scientists in their respective memoranda, that there may be unique challenges to pinpointing the pharmacological activity of enoxaparin; however, such challenges do not preclude a finding of active ingredient sameness for enoxaparin. Dr. Vince Lee, former Scientific Advisor to the Director of OPS, also acknowledged the unique challenges to pinpointing the pharmacological activity of enoxaparin when he conducted a thorough scientific review of the difference in opinion between the two offices in 2004. Dr. Lee also concluded (with one recommendation which has been incorporated) that OGD's approach was appropriate for assessing enoxaparin sameness.[35]

Although ONDQA asserts that Dr. Lee did not provide any specific recommendations for pinpointing what Dr. Lee refers to as the "hot spot" in enoxaparin,[36] the five criteria for enoxaparin have implicitly taken into account the "hot spots" that are important for the pharmacological activity of enoxaparin. As explained above, the five criteria for

[35] Dr. Vince Lee's July 19, 2004, report.
[36] May 3, 2007, ONDQA memo. (Dr. Vince Lee uses the term "hot spot" to refer to the domain on the complex molecule where the pharmacological activity resides).

demonstrating sameness ensure that a generic product's enoxaparin will possess an equivalent molecular diversity of oligosaccharide species to those present in Lovenox's enoxaparin. As a result, the generic enoxaparin will have the same pharmacological activity as Lovenox's enoxaparin, including the biochemically relevant AT-III binding pentasaccharide sequence motif that is known to contribute significantly to the anticoagulant activity of enoxaparin.[37, 38]

I also disagree with ONDQA's assertion that OGD's approach is inconsistent with relevant law and deviates from FDA policy. ONDQA states that a demonstration of equivalence, per FDA policy, can only be achieved by confirming directly that the polysaccharide moieties in LMWH of the generic drug product are the same as in the RLD without any chemical or enzymatic treatment or modification.[39]

Depending on the kind of drug at issue, there may be different ways to show active ingredient sameness. While it is true that, under OGD's approach, all the individual constituents of the generic product's active ingredient have not been characterized and compared to the individual constituents of Lovenox's active ingredient through sequence elucidation in a molecule-to-molecule comparison, it is not necessary to perform this level of analysis for enoxaparin.[40] Findings (and demonstrations) of active ingredient sameness are made on a case-by-case basis taking into account the specific drug at issue. In the case of enoxaparin, OGD's five criteria together are based on scientific experience, expertise and knowledge of enoxaparin such that they can adequately be used to assess important properties of enoxaparin and its structure. OGD's approach ensures that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent; and, therefore, the pharmacological activity of the active ingredients can be expected to be the same. I find that OGD's approach ensures that the generic drug product and Lovenox have same active ingredient, within the meaning of the term "same" in the statute and regulations for ANDA approvals.

Further, there is no FDA policy that prohibits chemical or enzymatic treatment or modification in the demonstration of equivalence. I also note that, under OGD's approach, enoxaparin sameness is established by methods that involve chemical or enzymatic treatments as well as those that do not, such as compositional analysis by Nuclear Magnetic Resonance (NMR), Ultra Violet (UV) spectroscopy, molecular weight

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[37] Hirsh J., Warkentin T.E., Shaughnessy S.G., Anand S.S., Halperin J.L., Raschke R., Granger C., Ohman E.M., Dalen J.E. (2001), "Heparin and Low-Molecular Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety," *Chest* 119 64S-94S.

[38] Dr. Vince Lee also refers in his July 19, 2004, report to three points that need to be addressed in the event OGD's approach is adopted (i.e., the degree of permitted variability, weight of each criterion, and the degree of experimental verification). I note that these issues have been presented to me and others in the context of the presentations, and chemistry reviews. I find the resolution of each issue to be scientifically reasonable and appropriate.

[39] May 3, 2007, ONDQA memo, at 2; January 4, 2004, ONDQA memo, at 6.

[40] It is noteworthy in this regard that the individual constituents of Lovenox's enoxaparin have not been compared from batch to batch. Instead, the Lovenox manufacturer relies on the consistency of the source material and the manufacturing process to generate the same product batch to batch.

distribution determinations by size exclusion chromatography, and chain mapping by high-resolution liquid chromatography and/or mass spectroscopy.

I also find that OGD's approach is consistent with previous ANDA approvals. ONDQA distinguishes, and OGD cites, hetastarch as precedent for potential ANDA approvals of enoxaparin.[41] Both OGD and ONDQA provide their views on the complexity of hetastarch relative to enoxaparin. I do not find it necessary to address the question of whether hetastarch is more or less complex than enoxaparin as each active ingredient sameness inquiry should be made in the context of the drug at issue. OGD also cites previous ANDA approvals of heparin as precedent. Hetastarch and heparin can be cited as precedent for potential enoxaparin ANDA approvals insofar as they stand for the proposition that the Agency has not required complete characterization, including sequence elucidation in a molecule-to-molecule comparison, to assess active ingredient sameness for those ANDA approvals.

Although ONDQA cites "CDER policy" on conjugated estrogens as precedent for requiring complete chemical characterizations to establish active ingredient sameness, the comparison is misplaced.[42] In the case of conjugated estrogens (Premarin), CDER decided that it could not make a finding of active ingredient sameness for synthetic versions of Premarin because the active ingredient had not been adequately characterized. CDER's conclusion, however, did not preclude a finding of active ingredient sameness if, for example, the active ingredient were derived from the same natural source as the RLD.

Finally, both OGD and ONDQA comment on the complexity of enoxaparin compared to proteins.[43] The extent to which this decision on enoxaparin serves as a precedent for future decisions on protein products should be addressed. Enoxaparin is a polysaccharide, a very different type of macromolecule than a protein. For example, proteins are processed and presented to the recipient's immune system in the context of HLA molecules. HLA molecules are extremely polymorphic and add an additional layer of complexity to protein immunogenicity. Also, generally speaking, the complexity of protein products is greater than that of enoxaparin. This greater complexity is manifest in the entropic component of a protein's secondary and tertiary structure in addition to the complexity of primary sequence and functionally significant posttranslational modifications. In other words, most proteins are large linear molecules that are only therapeutically active when folded into a unique three dimensional structure. The structure and biological activity of proteins are often quite sensitive to minor changes in the manufacturing process and formulation such that small changes in the manufacturing conditions may result in structural modifications that affect their function, stability and immunogenicity. In addition, trace levels of both organic and inorganic impurities can interact with a protein, inducing changes in its conformation and activity.

[41] May 9, 2007, OGD memo, at 8; May 3, 2007, ONDQA memo, at 3; April 18, 2004, ONDQA memo, at 1.
[42] April 18, 2004, ONDA memo, at 2; and August 30, 2004.
[43] May 3, 2007, ONDQA memo, at 1-2; May 9, 2007, OGD memo, at 3.

The structural characteristics of enoxaparin required for activity are much less complex and more stable than those of most proteins. This is evidenced by the fact that no significant higher order structure has been found for either heparin or enoxaparin. Furthermore, the structure and biological activity of a complex protein would be destroyed if subjected to the manufacturing conditions used to produce enoxaparin. Taken together, these facts justify focusing on the covalent structural characteristics of the components of enoxaparin for assessing sameness.

In summary, although there is heterogeneity within the individual oligosaccharide species in enoxaparin, the robustness of the product's biological activity and lack of significant higher-order structure makes it scientifically reasonable to rely on the five criteria that include *in vitro* and *in vivo* characterization for demonstrating enoxaparin sameness.

PART II: IMPURITIES AND IMMUNOGENICITY

At the time Dr. Woodcock initially determined, in the Fall of 2007, that an ANDA applicant could demonstrate enoxaparin sameness by satisfying the five criteria developed by OGD, she also determined that additional information was necessary to demonstrate that *impurities* in the proposed products would not result in greater immunogenic effects relative to the reference listed drug. I attach for reference her draft memorandum, which reflects her thinking at the time and was prepared prior to sending the November 2, 2007, letter to Amphastar informing the company that the ANDA did not adequately address the potential for immunogenicity of the product. Shortly thereafter, OGD sent letters to all ANDA applicants for enoxaparin sodium injection asking them to address the potential for immunogenicity of their respective products.

Every NDA and ANDA applicant is required to provide information on the drug substance and the drug product as part of the chemistry, manufacturing, and controls section of its application.[44] ANDA applicants are also required to assure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity.[45]

A small percentage of patients treated with either heparin sodium or enoxaparin experience an adverse event known as heparin-induced thrombocytopenia (HIT). It is the major immune-mediated adverse event resulting from enoxaparin therapy. In the clinical trials supporting the approval of Lovenox, it occurred in 1.3% of patients receiving Lovenox, 1.2% of patients receiving heparin sodium, and 0.7% of patients receiving placebo.[46] However, subsequent reports in the literature indicate that the risk of HIT is

[44] 21 CFR 314.94(a)(9) referencing 314.50(d)(1).
[45] Section 505(j)(4) of the Act, and 21 CFR 314.127(a)(1).
[46] See "Warnings and Precautions" section of Lovenox product labeling, NDA 20-164; Revised December 23, 2009.

~0.2% for patients treated with enoxaparin and 2-3% for patients treated with heparin sodium.[47,48] HIT is often life-threatening and can be fatal.

In a memorandum dated August 8, 2007, OGD concluded that, based on what was known about the physical and chemical characteristics of enoxaparin in the generic Amphastar product and Lovenox, the same immune response would result for these products and thus an indistinguishable rate of HIT would occur. The OGD scientists, Drs. Takahara and Raw, based their conclusion on literature reports indicating that binding of LMWH oligosaccharides to platelet factor 4 (PF4), which is believed to be the initiating event in triggering HIT, is based primarily on a sequence-independent oligosaccharide interaction with PF4 that is dependent on chain length and charge density. Because of the sameness of the active ingredient, they concluded that no differences in immunogenicity between Lovenox and generic product should occur and no additional testing to assess immunogenicity was needed.

Dr. Woodcock, however, determined in consultation with the Office of Biotechnology Products that there was not sufficient information upon which to conclude that the product's level of purity was adequate for approval. As described in her draft memorandum, generation of an immune response, including an unwanted immune response, is a complex phenomenon, the molecular and cellular basis of which has only recently begun to be elucidated. Long-term empirical experience with vaccination and studies of other immune responses have demonstrated that minor changes in the antigen, or the presence of other molecules associated with, or simply co-administered with, the antigen can result in changes in the immune response. In this regard, HIT is believed to result from an immune response generated against a heparin-PF4 complex rather than heparin alone, and impurities in the LMWH product, including aggregates of impurities and the active ingredient, might be important in determining whether or not an immune response occurs or magnitude of that response. For this reason, she requested that immunologists in OPS's Office of Biotechnology Products be consulted regarding the potential for residual impurities to impact the immunogenicity of enoxaparin and provide suggestions for addressing this concern. Dr. Woodcock also indicated in her draft memorandum that she was not able to predict whether—even after the additional studies were conducted—further studies would be needed to allay immunogenicity concerns. She indicated that it would depend on the findings, and it was possible that immunogenicity would have to be tested in clinical studies.

Upon consultation, the Office of Biotechnology Products evaluated the issue regarding the potential for differential immunogenicity between the RLD and the generic enoxaparin due to impurities and identified a number of uncertainties that needed to be resolved in order to address this concern. The Office of Biotechnology Products decided that certain assessments could help address these uncertainties, including a comparative assessment of the products for residual proteins, nucleic acids, and lipids; evaluating the

[47] Martel, N., Lee, J. Wells, P.S. (2005), "Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular weight heparin thromboprophylaxis: a meta analysis," Blood, . Vol. 106, 2710-2715.
[48] Arepally, G.M. and Ortel, T.L (2010), "Heparin-Induced Thrombocytopenia," Ann. Rev. of Med. 61: 77-90.

characteristics of the complexes formed between enoxaparin and PF4; and assessing the product impurities that may leach from the container-closure system.

This additional information was requested of Amphastar at a face-to-face meeting on November 18, 2007 (and in writing on November 21, 2007) and of Sandoz in a letter dated December 4, 2007. The sponsors were also asked to develop an *in vitro* assay system to evaluate the ability of impurities in the product to act as an immunostimulatory adjuvants and an *in vivo* assay to compare the immunogenicity of the RLD and their product, alone and when complexed with PF4. Other applicants were also asked to provide this information.

Amphastar originally responded to the information request by submitting an amendment to its ANDA on February 18, 2008. Sandoz originally responded to the requested information in a September 25, 2008 amendment to its ANDA. Both applicants submitted additional information in response to Agency comments.

The Office of Biotechnology Products has concluded, based on its knowledge and expertise in the field of immunology and review of sponsor data comparing generic enoxaparin and Lovenox with regard to: a) the ability of enoxaparin to form complexes with PF4, b) the presence of impurities that could stimulate the immune system directly, c) activation of human PBMC by the generic, and d) the induction of antibodies to the product in mice, that it is possible to show that there is no indication that generic enoxaparin would be more immunogenic than the RLD, Lovenox.

I have independently reviewed Dr. Woodcock's initial determination that immunogenicity data should be requested. I believe that pending ANDA applicants for enoxaparin sodium injection should be asked to address the risk of immunogenicity because it is known to occur in patients receiving this product.[49] I also find that *in vitro* and *in vivo* assays requested by FDA in 2007 are scientifically appropriate, and that this assessment can provide scientifically appropriate assurance that the risk of immunogenicity due to potential impurities in a generic enoxaparin will not be greater than that of the RLD, Lovenox. In the case of enoxaparin, a comparative clinical study would not necessarily be expected to be more sensitive to meaningful differences between the generic enoxaparin product and Lovenox.[50]

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[49] Furthermore, when the RLD manufacturer proposes to change its heparin sodium supplier or its manufacturing process, it should consider the potential risks to patient safety, including those associated with immunogenicity. However, I believe that in some cases the immunogenicity concerns may be addressed without immunological testing. The extent to which empirical immunogenicity testing will be needed may depend on factors such as: the individual applicant's understanding of the relationship among the manufacturing process, input materials, and the variability in product quality; the characteristics of the specific drug at issue; and the current state of science and technology.

[50] For example, a double blind clinical study showed that the rate of deep-vein thrombosis after orthopedic surgery was equivalent for two LMWHs: enoxaparin and tinzaparin. See Planes, A. et al. (1999), "Prevention of Deep Vein Thrombosis after Hip Replacement: Comparison between Two Low-Molecular Heparins, Tinzaparin and Enoxaparin," *Thrombosis and Haemostasis* 81: 22-25. However, despite such evidence of equivalence of clinical effectiveness, enoxaparin and tinzaparin would not be considered to have the same active ingredient, given that, among other characteristics, they: (1) are manufactured via different modes of depolymerization (i.e., enoxaparin is manufactured by chemical alkaline β-elimination,

CONCLUSION

In conclusion, and after considering all available information, I find that the five criteria established by OGD are sufficient for demonstrating sameness between two enoxaparins. I further conclude that the *in vitro* and *in vivo* assays recommended by the Office of Biotechnology Products are needed to provide sufficient assurance that the risk of immunogenicity due to potential impurities in a generic enoxaparin will not be greater than that of the RLD, Lovenox. Provided the requirements for ANDA approval are met, including those relating to active ingredient sameness and impurities, generic enoxaparin products can be expected to perform the same as Lovenox, and they can be expected to have the same safety and effectiveness profile.

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and tinzaparin is manufactured via enzymatic β̃-elimination.); (2) have different anti-IIa/anti-Xa ratios (for tinzaparin, the anti-IIa/anti-Xa ratio varies between 1.5 and 2.5, and for enoxaparin this ratio varies between 3.3 and 5.3); (3) have different proportions of sulfated and non-sulfated $\Delta^{4,5}$ –uronate structures at the non-reducing end of the oligosaccharide chains. (This is because in the mode of depolymerization by enzymatic β-elimination, cleavage takes place exclusively in heparin polysaccharide chains at sites where the disaccharide unit has the 2-O-sulfoiduronic acid structure, whereas in the mode of depolymerization by chemical (alkaline) β-elimination, cleavage occurs without preference for the presence or absence of a 2-O-sulfo group in the iduronic acid structure. See Linhardt, R.J., Gunay, N.S. (1999), "Production and Chemical Processing of Low Molecular Weight Heparin," Semin Thromb Hemost 25 S3:10.); and have different pharmacokinetics Eriksson, B.I. et.al., (1995), "A comparative study of three low-molecular weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers," *Thrombosis and Haemostasis* 73: 398-401.

Attachment

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
(b) (4)	ORIG-1	(b) (4)	ENOXAPARIN SODIUM
	ORIG-1		ENOXAPARIN SODIUM
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	ORIG-1		ENOXAPARIN SODIUM
ANDA-78660	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM
(b) (4)	ORIG-1	(b) (4)	ENOXAPARIN SODIUM
	ORIG-1		ENOXAPARIN SODIUM
ANDA-76684	ORIG-1	AMPHASTAR PHARMACEUTICAL INC	ENOXAPARIN SODIUM

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/s/

THOMAS O HINCHLIFFE
07/20/2010

KEITH O WEBBER
07/20/2010

Date: July 23, 2009

From: Keith O. Webber, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER

To: Sandoz Inc. (Sandoz) Abbreviated New Drug Application (ANDA 77-857)

This memorandum is intended to provide a summary of the Office of Generic Drug's (OGD's) approval of Sandoz's ANDA for enoxaparin sodium injection (ANDA 77-857). In August 2005, Sandoz submitted its ANDA, which references the listed drug, Lovenox (enoxaparin sodium injection). Sanofi-Aventis (Aventis) is the sponsor of the new drug application for Lovenox (NDA 20-164). OGD has concluded that Sandoz's ANDA for enoxaparin sodium injection meets the requirements for ANDA approval, including those regarding active ingredient sameness and purity of the proposed drug.

Enoxaparin sodium injection is a low molecular weight heparin (LMWH) and contains the active ingredient enoxaparin sodium ("enoxaparin"). Enoxaparin consists of a complex mixture of oligosaccharides. The structural heterogeneity of enoxaparin presents unique challenges to the review of ANDAs for enoxaparin sodium injection.

A finding of "sameness" of the proposed drug's active ingredient and that of the reference listed drug is a fundamental requirement for ANDA approval. After the submission of the first ANDA for enoxaparin sodium injection, OGD developed five criteria for assessing sameness of enoxaparin through a process that involved extensive scientific discussions within CDER over a period of several years. As with many complicated scientific issues, differences in scientific opinion arose regarding the appropriate approach for assessing sameness of the active ingredient enoxaparin. Some scientists in CDER's Office of New Drug Quality Assessment (ONDQA) believed that a showing of active ingredient sameness for enoxaparin can only be assessed by complete characterization, including sequence elucidation in a molecule-to-molecule comparison. In the Fall of 2007, Dr. Woodcock had preliminarily concluded that OGD's approach was appropriate for demonstrating active ingredient sameness. In my capacity as the Deputy Director of the Office of Pharmaceutical Science (OPS), I ultimately made the final decision regarding the disagreement, concluding that OGD's five criteria provided a scientifically robust and valid approach for assessing and demonstrating enoxaparin sameness. (See July 20, 2010, Memorandum from Keith O. Webber, Deputy Director of OPS to Helen N. Winkle, Director of OPS, subject: Active ingredient sameness for enoxaparin sodium and FDA's request for immunogenicity data).

The issue of active ingredient sameness is also the subject of a citizen petition submitted by Aventis in February 2003 and related supplements and comments (See Docket No. 2003-P-0273). The Agency is issuing a response to Aventis's citizen petition, which has been reviewed by the relevant components of the Agency.

In the Fall of 2007, Dr. Woodcock decided that ANDA applicants for enoxaparin sodium injection, including Sandoz, should be asked to submit additional information regarding the impurity profile of their proposed drug to address immunogenicity. She requested that

immunologists in the Office of Biotechnology Products (OBP) be consulted to determine which types of information would need to be submitted to address the issue. She indicated that she was not able to predict whether, even after these studies were done, further studies would be needed to allay immunogenicity concerns, and it would depend upon the findings.

OGD sent letters asking Sandoz for the information requested by OBP (e.g., studies assessing the interaction of enoxaparin with PF4, studies characterizing differences in impurities, and functional studies to assess differences in impurities and their potential effect on immunogenicity (including those involving an animal model)). (See December 4, 2007, letter). Sandoz has submitted that information and OBP has determined that the data does not indicate that Sandoz's generic enoxaparin sodium product would be more immunogenic than Lovenox. (See June 29, 2009, OBP review for ANDA 77-857, and July 20, 2010, Memorandum from Keith O. Webber, Ph.D., Deputy Director, OPS, CDER to Helen N. Winkle, Director OPS, CDER, subject: Active ingredient sameness for enoxaparin sodium and FDA's request for immunogenicity data; July 20, 2010, Memorandum from Keith O. Webber, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER, subject: Assessment of June 29, 2009, Office of Biotechnology Product's Review regarding immunogenicity data submitted by Sandoz).

The Office of Compliance has closely evaluated the compliance status of the facilities involved in the manufacture of Sandoz's generic enoxaparin sodium product, including the facilities that manufacture the heparin source material (heparin sodium) from which the active ingredient (enoxaparin sodium) is made. The Office of Compliance has determined they are in substantial compliance with CGMP and are acceptable. (See July 22, 2010, Memorandum from Carmelo Rosa and Harry Schwirk through Douglas Stearn to Deborah Autor, subject: Compliance Status of Heparin Sodium Suppliers for Sandoz's Enoxaparin ANDA, 77-857).

The Agency also has evaluated allegations regarding disparate treatment of another ANDA applicant relative to Sandoz, and has found them to lack merit. Those allegations have been considered to ensure the Agency applies the most current scientific knowledge and information to ensure equitable treatment of similarly situated applications and sponsors based on relevant facts. (See e.g., July 23, 2010, Memorandum from Jane A. Axelrad, Director of the Office of Regulatory Policy, CDER, Keith O. Webber, Deputy Director, Office of Pharmaceutical Science, CDER, and Douglas Stearn, Assistant Director Office of Compliance, subject Amphastar's allegations regarding unfair treatment with respect to its ANDA for enoxaparin sodium injection).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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

/s/

THOMAS O HINCHLIFFE
07/23/2010

KEITH O WEBBER
07/23/2010

OGD APPROVAL ROUTING SUMMARY

ANDA # 077857 Applicant Sandoz, Inc.
Drug Enoxaparin Injection Strength(s) 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/mL), and 150 mg/mL (120 mg/0.8 mL, 150 mg/mL)

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 7 January 2010 Initials MHS	Date 7/20/10 Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = Lovenox NDA# 20-164
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☒ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.

Comments: ANDA submitted on 8/29/2005, BOS=Lovenox Injection NDA 20-164, PII to '435, PIII to '618 and 'RE743. ANDA ack for filing on 8/29/2005(LO dated 10/24/2005), strengths accepted are 100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL pfs and 150 mg/mL, 0.8 mL and 1 mL pfs. Patent amendment submitted on 6/23/2006-Sandoz amends from PIII to PIV on the '618 and 'RE743. Patent Amendment submitted on 9/11/2006-RR from Sanofi Aventis in Bridgewater, NJ, notice also sent via DHL to Sanofi Aventis in Paris France with notice delivered on 6/26/2006 signed and dated 6/26/2006, suit filed in the D of NJ on 8/4/2006 for infringement of the 'RE743, CA #06-CV-3671. On 1/3/2007 the sponsor submitted a PIV cert to the '445 patent(not a listed patent), Sandoz continued to provide serial certifications to this patent through 3/9/2007. On 6/16/2008 the firm provided a revised exclusivity statement which communicated their intent to omit claims related to the I-533 exclusivity. Patent amendment submitted on 9/17/2008-Sandoz informs the Agency that CA 06-3671 from the D of NJ was transferred to CA and assigned case # 07-2558, Sandoz provided copies of signed court orders dated 8/28/2008 in which Sandoz Motion for Summary Judgment of Unenforceability was granted and final judgment with prejudice in favor of Sandoz was entered, these orders applied to CA #07-2558 and 06-4858 both in the D of CA, Central District. OGD notes that the orders entered by the DC of CA were dated after the Judgement was entered by the CAFC in Sanofi v. Amphastar and TEVA in which the court entered the order on 5/14/2008. The mandate associated with the CAFC ruling was issued on 10/2/2008 which finalized the order. This issuance of the mandate served as a trigger of 180 day exclusivity. Minimally the issuance of the Mandate triggered the 180 day exclusivity of Amphastar which is associated with the '618 patent.

Remaining patent issues: does the issuance of the mandate trigger exclusivity for both the '618 and RE743 patents(did the court rule on both patents) or does OGD need to draft a memo which explains our position regarding 180 day exclusivity for reissued patents.

Update 1/21/2010-in the CP response OCC has included a footnote which answers the question posed above. The outcome being the issuance of the Mandate triggered 180 day exclusivity for both the '618 and RE743 patents. This exclusivity expired on 3/31/2009.

2. **Project Manager**, Thomas Hinchliffe Team 10 Review Support Branch	Date 1/5/09 Initials TOH	Date 1/5/09 Initials TOH

Original Rec'd date 08/29/2005
Date Acceptable for Filing 08/29/2005
Patent Certification (type) III then to IV
Date Patent/Exclus.expires 2/14/2012
Citizens' Petition/Legal Case Yes ☒ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☒ No ☐
(If yes, prepare Draft Press Release, Email

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status _____
Date of Office Bio Review 12/28/2006
Date of Labeling Approv. Sum _____
Labeling Acceptable Email Rec'd Yes ☒ No ☐
Labeling Acceptable Email filed Yes ☒ No ☐
Date of Sterility Assur. App. 02/04/2008
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☒ No ☐

it to Cecelia Parise)

Acceptable Bio reviews tabbed Yes ☐ No ☒ Modified-release dosage form: Yes ☐ No ☒
Bio Review Filed Electronically: Yes ☒ No ☐ Interim Dissol. Specs in AP Ltr: Yes ☐
Suitability Petition/Pediatric Waiver Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer: Labeling Team Leader:
Date_____ Date7/20/10
Name/Initials_____ Name/Initials rlw/for

Comments:
Final-printed labeling (FPL) found acceptable for approval 5/5/10, as endorsed via eMail dated 7/19/10 from R.Wu (copy filed to DARRTS).

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 13Jan10
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: Edits made to approval letter.

5. Div. Dir./Deputy Dir. Date1/11/10
Chemistry Div. II Initials FF

Comments:Chemistry review to be revised to add PIV information and EA status.

CMC ok.

6. Frank Holcombe **First Generics Only** Date 7/20/10
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
The CMC review of this ANDA has been coordinated by OGD's Science Team headed by Dr. Lawrence Yu, Ph.D.

First-generic CMC review completed by F. Holcombe, Ph.D. on 2/24/10.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Lovenox Injection, 100 mg/mL and 150 mg/mL
Sanofi Aventis US, LLC NDA 20-164

8. Peter Rickman Date 7/20/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments: Microbiology/Sterility Assurance found acceptable for approval (Microbiology Review #2) 2/4/08.

Final-printed labeling (FPL) found acceptable for approval 5/5/10, as endorsed 7/19/10.

Pharmacokinetic/pharmacodynamic studies (fasting) on the 100 mg/mL strength to assess in-vivo pharmacodynamic markers anti-factor Xa, anti-factor IIa, Heptest and aPTT, with anti-factorXa being the primary endpoint - found acceptable. Drug products are "Q&Q" to the RLD. Waivers granted to both strengths under 21 CFR 320.22(b)(1). Office-level bio endorsed 10/26/06, 12/28/06 and 7/9/10.

CMC found acceptable for approval. Documentation of CMC reviews provided in DARRTS.

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☒ No☐
Press Release Acceptable ☐
Comments: Acceptable EES dated 7/15/10 (Verified 7/20/10). No "OAI" Alerts noted.

Refer to summary provided above by M.Shimer for the legal/regulatory basis of approval of this ANDA.

Issuance of Citizen Petition response to be coordinated with issuance of approval letter.

There is no 180-day generic drug exclusivity associated with this drug product; it has expired.

This ANDA is recommended for approval.

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments: for Keith Webber, Ph.D.
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Thomas Hinchliffe Team 10 Date7/23/10
Review Support Branch Initials TOH
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
7/23/10Date notified of approval by phone 7/23/10Date approval letter faxed

FDA Notification:
7/23/10Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/23/10Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020164 Product 005 in the OB_Rx list.

<>

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020164	005	5389618	Feb 14, 2012	Y	Y	U - 545	
N020164	005	RE38743	Feb 14, 2012	Y	Y	U - 545	

<>

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N020164	005	I - 533	May 16, 2010

Additional information:

1. **Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).**
2. **Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.**
3. ****** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.**

View a list of all patent use codes
View a list of all exclusivity codes
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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through June, 2010
Patent and Generic Drug Product Data Last Updated: July 22, 2010

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-77857	ORIG-1	SANDOZ INC	ENOXAPARIN SODIUM

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/s/

THOMAS O HINCHLIFFE
07/23/2010