CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-051

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals Products, Inc.

Approval Date: June 20, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter	
Labeling	X
Labeling Review	X
Medical Review	
Chemistry Review	
Pharmacology / Toxicology Review	
Statistical Review	
Microbiology Review	
Clinical Pharmacology / Biopharmaceutics Review	
Administrative and Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-051

Aventis Pharmaceuticals, Inc.
Attention: Shaler G. Smith, III, Ph.D.
Global Drug Regulatory Director and Liaison
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

Dear Dr. Shaler:

Please refer to your supplemental new drug application dated December 19, 2002, received December 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium injection).

We acknowledge receipt of your submissions dated April 16 and 18, May 9 and June 5, 2003.

This "Changes Being Effected" supplemental new drug application provides for the addition of an automatic safety device to all presentations of Lovenox® pre-filled syringes.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with minor editorial revisions listed below.

Include the manufacturing information on the Lovenox multiple-dose vial in the **HOW SUPPLIED** section at your next printing of the package insert.

All previous revisions as reflected in the most recently approved labeling, specifically Supplement S-043 approved January 23, 2003, must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

The final printed labeling (FPL) must be identical, and include the minor editorial revision indicated, to the text for the package insert submitted December 19, 2002, carton labels submitted December 19, 2002, immediate container labels for the 30 mg, 80 mg, 100 mg, 120 mg and 150 mg strength prefilled syringes submitted December 19, 2002, and immediate container labeling for the 40 mg and 60 mg strength prefilled syringes submitted June 5, 2003. This revision is terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission

should be designated "FPL for approved supplement NDA 20-164/S-051." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
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/

Joyce Korvick
6/20/03 02:21:13 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

APPROVED DRAFT LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

LABELING REVIEWS

Division of Gastrointestinal and Coagulation Drug Products (DGICDP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SLR-051

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Inc.

Materials Reviewed: Package Insert (PI)
Container labeling

Submission Date:	December 19, 2002
Receipt Date:	December 20, 2002
Amendment Date:	April 16, 2003
Receipt Date:	April 22, 2003
Amendment Date:	April 18, 2003
Receipt Date:	April 21, 2003
Amendment Date:	May 9, 2003
Receipt Date:	May 12, 2003
Amendment Date:	June 5, 2003
Receipt Date:	June 6, 2003

Background and Summary

Background: Lovenox is a low molecular weight heparin (LMWH) which was approved March 29, 1993, for the following indications:

- 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;
- 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;
- prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin;
- the inpatient treatment of acute DVT with or without PE when administered in conjunction with warfarin sodium; and
- the outpatient treatment of acute DVT without PE when administered in conjunction with warfarin sodium.

The most recent approved labeling for the Lovenox PI and for the immediate container, blister labeling and carton labeling for the Lovenox 300 mg/3.0 mL multiple-dose vial was submitted on September 20, 2002 (received September 23, 2002) to SCM-043 (approved on draft

January 23, 2003). The most recent approved labeling for the immediate containers, blister labeling and carton labeling for Lovenox syringes was submitted on May 23, 2001 (received May 24, 2001) to SCF-030 (acknowledge and retained on June 19, 2001). The most recent approved labeling for the 30 mg/0.3 mg ampule was submitted on May 31, 2000 to the annual report Y-007 (received June 12, 2000).

Supplement S-051 was submitted by Aventis to comply with the Occupational Safety and Health Administrations's (OSHA) Needlestick Safety and Prevention Act (Public Law 106-430) dated November 6, 2000, and the Department of Labor, Occupational Safety and Health Administration (OSHA) regulations (29 CFR Part 1910 [Docket No. H370A] RIN 1218-AB85 Final Rule entitled, "Occupational Exposure to Bloodborne Pathogens; Needlestick and Other Sharps Injuries" dated January 18, 2001.

The sponsor referenced Becton Dickinson's Device Master File (DMF) 501 in support of the automatic safety device proposed for use with the Lovenox prefilled syringes. A consult was sent to the Center for Devices and Radiological Health (CDRH) on March 18, 2003, requesting review of the revised labeling. On April 16, 2003 (received April 22, 2003), the DMF holder, Becton Dickinson (BD) submitted a clarification to S-051 that the DMF file (DMF-501) referenced in S-051 for the BD HYPAK™ for the Prefillable Syringe System is identical to the DMF (MHF 454) reviewed by CDRH.

A consult review by CDRH for NDA 20-164/S-051 was completed April 17, 2003. From the CDRH perspective, the addition of the safety feature raises no issues of safety and effectiveness and the labeling in this supplement is consistent with the Device Master File (see Memorandum from Patricia Cricenti, Branch Chief, General Hospital Devices Branch (GHDB), Division of Anesthesiology, General Hospital Infection Control and Dental Devices (DAGID) dated April 17, 2003).

The sponsor submitted a general correspondence to Supplement 051 on April 18, 2003, agreeing to revise the color of the "40 mg/0.4 mL" and the "60 mg/0.6 mL" foil backing and syringe labeling to reflex blue letters in yellow and orange boxes, respectively, at the next printing. On May 9, 2003, the sponsor submitted revised copies of the 40mg/0.4 mL and the 60 mg/0.6 mL pre-filled syringe immediate container label and the 40mg/0.4 mL and 60 mg/mL prefilled syringe foil backing.

On May 16, 2003, Diane Moore, RPM, called Shaler G. Smith III, Director and Regulatory Liaison at Adventis Pharmaceuticals, Inc., to advise the sponsor that the labeling for the 50mg/0.6 mL foil backing submitted on May 9, 2003, was inconsistent with previous versions of the labeling and requested clarification as to which version the sponsor desired. Specifically, in the 60mg/0.6 mL foil backing, the third sentence in the second column that reads "Each 0.025mL graduation equals 2.5 mg enoxaparin sodium injection" was deleted in the labeling submitted May 9, 2003, (received May 12, 2003) and ——— was added ——— in the first column. In the 40mg/0.4 mL foil backing, ——— was added ——— ———in the first column. On June 5, 2003 (received June 6, 2003) the sponsor submitted

revised foil backing labeling and syringe labeling for the 40mg/0.4 mL and 60 mg/mL pre-filled syringes.

Review

I. PACKAGE INSERT

The PI to S-051 submitted on December 19, 2002, received December 20, 2002 (identified as "50066809") was compared to the draft labeling to SCM-043 (submitted September 20, 2002; received September 23, 2002) approved on draft January 23, 2003 (no identifier). The PIs are identical except for the following:

A. **DESCRIPTION** section

The sponsor has not included the following revisions to the **DESCRIPTION** section of the PI that were made in S-043, submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003:

1. The sponsor has not added the term "aqueous" following the term "sterile" in the first paragraph, first sentence that reads "Lovenox Injection is a sterile, aqueous solution containing enoxaparin sodium, a low molecular weight heparin." as revised in the approved labeling to S-043.

2. In the second paragraph, first sentence that reads, "Lovenox Injection is available in two concentrations: **1. 100mg per mL of Water for Injection,**" the sponsor has not included the period following the number "1" and has not deleted the phrase, "of Water for Injection" so that the sentence reads "Lovenox Injection is available in two concentrations: **1. 100 mg per mL**" as revised in the PI labeling to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

3. In the second paragraph, the sixth line, the sponsor has not added "*Multiple-Dose Vials* 300 mg/3.0 mL" to the list of available syringes and ampules as revised in the PI labeling to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

4. In the fourth paragraph, first line that reads, "**2. 150 mg per mL of Water for Injection,**" the sponsor has not added the period after the number "2" and has not deleted the phrase "**of Water for Injection.**" as revised in the PI labeling for S-043.

5. In the sixth paragraph, first sentence that begins, "The solutions are preservative-free . . ." the sponsor has not deleted the term "solutions" and has not added the phrase, "Lovenox prefilled syringes, graduated prefilled syringes, and ampules" so that the sentence reads, "The Lovenox prefilled syringes, graduated prefilled syringes, and ampules are preservative-free and intended for use only as a single-dose injection." as

revised in the PI labeling in S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2002.

6. The sponsor has not added the second sentence in the sixth paragraph that reads, "The multiple-dose vial contains 15 mg/1.0 mL benzyl alcohol as a preservative." that was added in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

7. In the sixth paragraph, the sponsor has not deleted the third sentence that reads, "Nitrogen is used in the headspace to inhibit oxidation." that was deleted in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

8. In the seventh paragraph, the first sentence that begins, "Enoxaparin is obtained by . . ," the sponsor has not added the term "sodium" after "Enoxaparin" so that the sentence reads, "Enoxaparin sodium is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa." as was added in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

9. In the seventh paragraph, the third sentence that begins, "The drug is the sodium . . ." The term "drug" has not been added before the term "substance" so that the sentence reads, "The drug substance is the sodium salt." as in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

The above revisions (I.A. 1.-9.) were made to the PI in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The revisions should be included in the PI to SLR-051.

B. **CONTRAINDICATIONS** section

In the second paragraph, first sentence that begins, "Patients with known hypersensitivity . . ." the sponsor has not added the phrase, "or any of its constituents" so that the sentence reads, "Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection or any of its constituents." as revised in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

The addition of the phrase "or any of its constituents" in the second paragraph, first sentence was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

C. **WARNINGS** section:

The sponsor has not added the **Miscellaneous** subsection following the **Prosthetic Heart Valves** subsection in the **WARNINGS** section that was added to the PI in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The Paragraph reads as follows:

> "**Miscellaneous:** Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS, Pregnancy**)."

The addition of the Miscellaneous subsection following the Prosthetic Heart Valves subsection of the WARNINGS section of the PI was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

D. **PRECAUTIONS** section

The sponsor has not added the paragraph following the **Pregnancy** subsection, *Non-teratogenic Effects* subsection in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The Paragraph reads as follows:

> "Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see **WARNINGS, Miscellaneous**)."

The addition of the paragraph regarding "Gasping Syndrome" at the end of the PRECAUTIONS section, Pregnancy *Non-teratogenic Effects* subsection of the PI was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

E. **DOSAGE AND ADMINISTRATION** section

1. In the third paragraph, first sentence that begins, "**1. 100 mg/mL Concentration**: 30 mg/0.3 mL ampules, . . ." the sponsor has not added the period following the number "1" and has not added "300 mg/3.0 mL multiple-dose vials" at the end of the first item. Item 1. should read as follows:

   > "**1. 100 mg/mL Concentration**: 30 mg/0.3 mL ampules, 30 mg/0.3 ml and 40 mg/0.4 mL prefilled single-dose syringes, 60 mg/0.6 mL, 80 mg/0.8 ml, and 100 mg/1 ml prefilled, graduated, single- dose syringes, 300 mg/3.0 ml multiple-dose vials."

The addition of the period after the number "1" and the phrase "300 mg/3.0 mL multiple-dose vials" in the DOSAGE AND ADMINISTRATION section were made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The additions should be included in the PI to SLR-051.

2. In the fourth paragraph that begins, "2 150 mg/mL Concentration . . ." ." the sponsor has not added the period following the number "2." Item 1. should read as follows:

   "2. 150 mg/mL Concentration: 120 mg/0.8 mL and 150 mg/1mL prefilled, graduated, single-dose syringes."

   The addition of the period after the number "2" in the DOSAGE AND ADMINISTRATION section was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

3. In the **Administration** subsection, second paragraph, the sponsor has not revised the first sentence that reads as follows:

   "When using Lovenox Injection ampules to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended."

   To:

   "The use of a tuberculin syringe or equivalent is recommended when using Lovenox ampules or multiple-dose vials to assure withdrawal of the appropriate volume of drug."

   This revision was made in SCM-043 submitted September 20, 2002 (received September 13, 2002) and approved January 23, 2003. The revision should be included in the PI to SLR-051.

4. *Subcutaneous Injection Technique* sub-subsection, of the **Administration** subsection

   a. In the first paragraph, the sponsor has deleted the sixth and seventh sentences that read as follows:

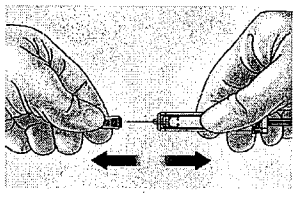
      " An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device."

Since the sponsor is discontinuing the EasyInjector™ product, the deletion of these two sentences is acceptable.

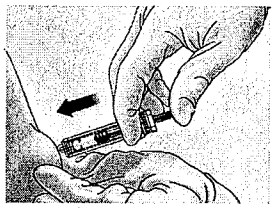
b. In the first paragraph, following the fifth sentence that begins "To minimize bruising, . . ." the sponsor has added the following section to describe the use of the needle safety system to shield needle after injection (based on manufacturer's device labeling):

"Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

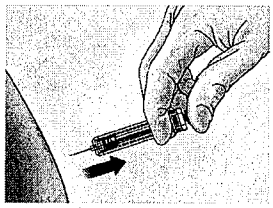
- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



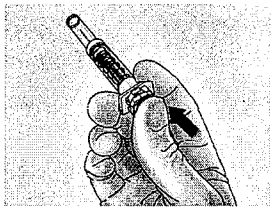
- Inject using standard technique, pushing the plunger to the bottom of the syringe.



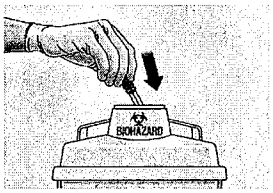
- Remove the syringe from the injection site keeping your finger on the plunger rod.



- 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.



- 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."

This addition is acceptable per Dr. Ruyi He, Medical Officer, in a verbal comment to Diane Moore, RPM on April 18, 2003.

F. **HOW SUPPLIED** section

1. The sponsor has not included the following revisions that were made in SCM-043, submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003:

   a. In the table entitled, "100 mg/mL Concentration":

   b. In the fourth column, first row, the sponsor has not deleted the term "syringe."

   c. In the first column, fifth row, the sponsor has not added the title, "**Multiple-Dose Vial**. 300 mg/3.0 mL."

   d. In the second column, fifth row, the sponsor has not added "30,000 IU."

   e. In the third column, fifth row, the sponsor has not added "1 vial."

   f. In the fourth column, fifth row, the sponsor has not added the term "Red."

g. In the fifth column, fifth row, the sponsor has not added "0626-03."

2. In the footnotes to the table entitled, "100 mg/mL Concentration" the sponsor has not added the footnote that reads, "[4] Each Lovenox multiple-dose vial contains 15 mg/1.0 mL of benzyl alcohol as a preservative." as in the PI labeling to SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

3. In the first paragraph after the table entitled, "150 mg/mL Concentration," the sponsor has not revised the phrase, "Store at Controlled Room Temperature 15-25°C (59-77°F) [see USP]" to "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]." as revised in the PI labeling in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

   The above revisions (I.F.1.-3.) were made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The revisions should be included in the PI to SLR-051.

4. In the table entitled, "100 mg/mL Concentration," the sponsor has added additional lines between the rows to separate the30 mg/0.3 mL Prefilled Syringes from the 40 mg/0.4 mL Prefilled Syringes and the 60 mg/0.6 mL, 80 mg/0.8 mL and100 mg/1 mL Graduated Prefilled Syringes

   This makes the table clearer. The revisions are editorial and acceptable.

5. After the second sentence of the first paragraph following the second table entitled "150 mg/mL Concentration," that reads "**Keep out of the reach of children**," the sponsor has revised the manufacturing information for Lovenox from:

   "Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
   Lovenox Injection ampules manufactured in England.
   Lovenox multiple-dose vial manufactured for Aventis Pharmaceuticals products Inc. by DSM Pharmaceuticals, Inc. Greenville, NC 27835.
   Aventis Pharmaceuticals Products Inc.
   BRIDGEWATER, NJ 08807
   © 2002 Aventis Pharmaceuticals Inc.
   Prescribing information as of XXXX"

   to:

   "Lovenox Injection prefilled and graduated prefilled syringes manufactured by:
   Aventis Pharma Specialties

94700 Maisons-Alfort
France.
And
Aventis Pharma
Boulevard Industriel
76580 Le Trait
France
Lovenox Injection ampules manufactured by:
Aventis Pharma LTD
Dagenham Essex RM 10 7XS
United Kingdom.

Aventis Pharmaceuticals, Inc.
Bridgewater, NJ 08807

Prescribing information as of September 2002"

The revisions are editorial and acceptable, however, the sponsor should be requested to include the manufacturing information on the Lovenox multiple-dose vial in the HOW SUPPLIED section of the PI at the next printing.

II. IMMEDIATE CONTAINER LABEL

A. All Prefilled Syringe Device Dosage Strengths Labels:

The following prefilled syringe device labels in SLR-051 (submitted December 19, 2002; received December 20, 2002) were compared to the respective prefilled syringe labels in the Final Printed Labeling (FPL) to SCF-030 (submitted May 23, 2001; received May 24, 2001; acknowledged and retained on June 19, 2001). (See chart below for identification and lot numbers):

IMMEDIATE CONTAINER LABELING CHART

Labeling Item	**SLR-051 identification number**	**SCF-030 Approved labeling identification number**	**Lot number added to SLR-051 labeling**
30mg/0.3 mL Pre-filled Syringe immediate container label	50067912	50062330	512106A
40mg/0.4 mL Pre-filled Syringe immediate	50067913	50057403	512107A

container label			
60mg/0.6 mL Pre-filled Syringe immediate container label	50067914	50057404	512140A
80mg/0.8 mL Pre-filled Syringe immediate container label	50067915	50057405	512145A
100mg/1 mL Pre-filled Syringe immediate container label	50067916	50057406	512143A
120mg/0.8 mL Pre-filled Syringe immediate container label	50067917	50058603	512188A
150mg/1.0 mL Pre-filled Syringe immediate container label	50062650	50062331	512191A

The sponsor made the following revisions to all of the above syringe immediate container labels in the December 19, 2002, submission:

1. The sponsor revised the tradename "**LOVENOX®** (enoxaparin sodium) Injection" to **LOVENOX®** (*enoxaparin sodium injection*)."

   Note: The numbers "120" and "150" after the tradename "Lovenox" for the 120 mg and 150 mg dosage strengths were deleted.

   The revisions are editorial and acceptable.

2. The sponsor added the phrase "Rx ONLY" to the top right corner.

   The addition is acceptable.

3. The sponsor revised the sponsor information from "Aventis Pharmaceuticals Products Inc." to "Mfd for: **Aventis Pharmaceuticals Inc."**

   The revision is editorial and acceptable.

4. The identification numbers for each dosage strength was revised (see above chart entitled "IMMEDIATE CONTAINER LABELING CHART").

   The revisions are editorial and acceptable.

5. The lot number for each dosage strength has been added to the left side of the label (see above chart entitled "IMMEDIATE CONTAINER LABELING CHART").

   The additions are acceptable.

B. 30mg/0.3 mL Pre-filled Syringe Immediate Container Label

In the section immediately following the trademark "Lovenox® (*enoxaparin sodium injection*)" the following revision was made to the 30mg/0.3 mL dosage strength:

The sponsor added the phrase "[100mg/mL]" to the phrase that reads "30 mg/0.3 mL" so that the phrase reads "30mg/0.3mL [100mg/mL]."

The addition clarifies the 30 mg/0.3 mL dosage strength. The revision is acceptable.

C. 4mg/0.4 mL Pre-filled Syringe Immediate Container Label

The following revisions were made to the 40mg/0.4 mL dosage strength prefilled syringe:

1. In the section immediately following the trademark "Lovenox® (*enoxaparin sodium injection*)" the sponsor added the phrase "[100mg/mL]" to the phrase that reads "40 mg/0.4 mL" so that the phrase reads "40mg/0.4mL [100mg/mL]."

   The addition clarifies the 40mg/0.4 mL dosage strength. The revision is acceptable.

2. The sponsor revised the color from black numbers inside a yellow rectangular box to —— letters in a yellow rectangular box.

   This is not acceptable. The letters are difficult to distinguish.
   The sponsor submitted a general correspondence to Supplement 051 on April 18, 2003 agreeing to revise the color of the "40 mg/0.4 mL" and the "60 mg/0.6 mL" the syringe label and foil backing to reflex blue at the next printing. On May 9, 2003, the sponsor submitted revised mock-up labeling for the 40 mg/0.4 mL syringe label. The 40 mg/0.4 mL prefilled syringe label submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the label submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067913). The sponsor revised the color from the —— letters in a yellow rectangular box to reflex blue letters in a yellow rectangular box. The reflex blue color gives an acceptable contrast for the 40 mg/0.4 mL prefilled syringe label. This proposed revision is acceptable. Because the labeling was a mock-up representation, the lot number was not included. This is acceptable.

On June 5, 2003, (received June 6, 2003), the sponsor submitted revised labeling for the 40mg/0.4 mL and 60 mg/0.6 mL foil backing and syringe labeling. The syringe label for the 40mg/0.4 mL submitted on June 5, 2003 (received June 6, 2003; no identifier number) is identical to the 40mg/0.4 mL syringe label submitted to S-051 on May 9, 2003 (received May 12, 2003; no identifier number). The label submitted on June 5, 2003 (received June 6, 20003; no identifier number) is acceptable.

D. 60mg/0.6 mL Pre-filled Syringe Immediate Container Label

The following revisions were made to the 60mg/0.6 mL Pre-filled Syringe Label dosage strength:

1. In the section immediately following the trademark "Lovenox® (*enoxaparin sodium injection*)" the sponsor added the phrase "[100mg/mL]" to the phrase that read "60 mg/0.6 mL" so that the phrase reads "60mg/0.6mL [100mg/mL]."

   The addition clarifies the dosage strength. The revision is acceptable.

2. The sponsor revised the color from black numbers inside an orange rectangular box to ——— letters in an orange rectangular box.

   This is not acceptable. The numbers are difficult to distinguish.
   The sponsor submitted a general correspondence to Supplement 051 on April 18, 2003 agreeing to revise the color of the "40 mg/0.4 mL" and the "60 mg/0.6 mL" syringe label and foil backing to reflex blue at the next printing. On May 9, 2003, the sponsor submitted revised mock-up labeling for the 60 mg/0.6 mL syringe label. The 60 mg/0.6 mL prefilled syringe label submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the label submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067914). The sponsor revised the color from the ——— letters in an orange rectangular box to reflex blue letters in an orange rectangular box. The reflex blue color gives an acceptable contrast for the 60 mg/0.6 mL prefilled syringe label. The proposed revision is acceptable. Because the labeling was a mock-up representation, the lot number was not included. This is acceptable.

   On June 5, 2003, (received June 6, 2003), the sponsor submitted revised labeling for the 40mg/0.4 mL and 60 mg/0.6 mL foil backing and syringe labeling. The syringe label for the 60mg/0.6 mL submitted on June 5, 2003 (received June 6, 2003; no identifier number) is identical to the 60mg/0.6 mL syringe label submitted to S-051 on May 9, 2003 (received May 12, 2003; no identifier number). The label submitted on June 5, 2003 (received June 6, 20003; no identifier number) is acceptable.

E. 80mg/0.8 mL Pre-filled Syringe Immediate Container Label

The following revisions were made to the 80mg/0.8 mL Pre-filled Syringe Label dosage strength:

In the section immediately following the trademark "Lovenox® (*enoxaparin sodium injection*)" the sponsor added the phrase "[100mg/mL]" to the phrase that reads "80 mg/0.8 mL" so that the phrase reads "80mg/0.8mL [100mg/mL]."

The addition clarifies the dosage strength. The revision is acceptable.

F. 120mg/0.8 mL Prefilled Syringe Immediate Container Label

The following revisions were made to the 120mg/0.8 mL Pre-filled Syringe Label dosage strength:

1. The sponsor revised the tradename "LOVENOX 120 (enoxaparin sodium) Inj." to "LOVENOX (enoxaparin sodium injection)".

   The revision is editorial and acceptable.

2. In the section immediately following the trademark "Lovenox® (*enoxaparin sodium injection*)" the sponsor added the phrase "[150mg/mL]" to the phrase that reads "120 mg/0.8 mL" so that the phrase reads "120mg/0.8mL [150mg/mL]."

   The addition clarifies the dosage strength. The revision is acceptable.

G. 150mg/1 mL Prefilled Syringe Immediate Container Label

The following revisions were made to the 150mg/1 mL Pre-filled Syringe Label dosage strength:

The sponsor revised the tradename "LOVENOX® 150 (enoxaparin sodium) Inj." to "LOVENOX (enoxaparin sodium injection)."

The revision is editorial and acceptable.

III. BLISTER LABELING

A. Prefilled Syringe Blisterfoil Labeling

The following prefilled Syringe Blister backing labeling in SLR-051 (submitted December 19, 2002; received December 20, 2002) was compared to the prefilled Syringe

Blister Labeling in the FPL to SCF-030 (submitted May 23, 2001; received May 24, 2001; acknowledged and retained on June 19, 2001):

BLISTER LABELING CHART

Labeling Item	**SLR-051 identification number**	**SCF-030 Approved labeling identification number**	NDC number	Lot number **added to SLR-051 labeling**
30mg/0.3 mL Prefilled syringe blister backing labeling	50067137	50062182	NDC 0075-0624-30	512115A
40mg/0.4 mL Prefilled syringe blister backing labeling	50067138	50062015	NDC 0075-0620-40	512116A
60mg/0.6 mL Prefilled syringe blister backing labeling	50067139	50062018	NDC 0075-0621-60	512140A
80mg/0.8 mL Prefilled syringe blister backing labeling	50067140	50062021	NDC 0075-0622-80	512145A
100mg/1 mL Prefilled syringe blister backing labeling	50067141	50062024	NDC 0075-0623-00	512146A
120mg/0.8 mL Prefilled syringe blister backing labeling	50067142	50062030	NDC 0075-2912-01	512188A
150mg/1 mL Prefilled syringe blister backing labeling	50067143	50062034	NDC 0075-2915-01	512189A

The sponsor made the following revisions to all of the above syringe blisterfoil labeling in the December 19, 2002 submission (received December 20, 2003):

1. The NDC number (see above chart for specific NDC numbers for each strength) was moved from the top of the third column to the top of the first column (following the Lovenox tradename) of the blisterfoil labeling.

   The revision is editorial and acceptable.

2. In the first column, in the first and second lines, the sponsor revised the tradename from "**LOVENOX®** (enoxaparin sodium) Injection' to "**LOVENOX®** (*enoxaparin sodium injection*)."

   Note: The numbers "120" and "150" after the tradename "Lovenox" for the 120 mg and 150 mg dosage strengths were deleted.

   The revisions are editorial and acceptable.

3. The sponsor moved the phrase "**Rx ONLY**" from the bottom of the second column after the "Store at Controlled Room Temperature" section to the middle of the first column after the "XXmg/YYmL [100mg/mL]" phrase for each strength syringe. (see above chart titled "BLISTER LABELING CHART" for each dosage strength). Herein, the "Y.Y" denotes the syringe amount for each respective syringe size (i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL) and "XX" denotes the amount of enoxaparin sodium in each respective syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg and 150mg, respectively).

   The revision is acceptable.

4. The sponsor added the following three phrases below the "**Rx ONLY**" addition in the left column of the blisterfoil labeling:

   "Single Dose Syringe with Automatic Safety Device; One Y.Y mL syringe; For Subcutaneous Injection." (Where "Y.Y" denotes the syringe amount for each respective syringe size, i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL for the 30mg, 40mg, 60mg, 80mg, 100mg, 120mg and 150mg, respectively.)

   The additions clarify the number of syringes, type of injection and note the automatic safety device. The additions are acceptable.

5. The sponsor revised the first sentence in the second column that reads "Each Y.Y mL contains XX mg of enoxaparin sodium in Water for Injection. See insert for directions." to read as follows:

   > "Each LOVENOX® Syringe contains XX mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection."

   Herein, the "Y.Y" denotes the syringe amount for each respective syringe size (i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL) and "XX" denotes the amount of enoxaparin sodium in each respective syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg and 150mg, respectively).

   The revisions are acceptable.

6. In the third column, the sponsor deleted the phrase "1 Single Dose Prefilled Syringe – Y.YmL." Herein, the "Y.Y" denotes the syringe amount for each respective syringe size (i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL).

   The information was added to the bottom of the first column. The deletions are acceptable.

7. The sponsor revised the second paragraph in the second column that reads "**FOR SUBCUTANEOUS INJECTION**" to read as follows:

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

   The revisions are acceptable.

8. In the third column following the storage conditions, the sponsor added the following warning phrase:

   "**WARNING:** Keep out of reach of children."

   The addition is acceptable.

9. The sponsor moved the phrase "Made in France" from the top of the third column (following the NDC number) to the bottom of the third column following the sponsor information.

   The revision is editorial and acceptable.

10. The sponsor revised the manufacturer information that reads "**Aventis Pharmaceuticals Products Inc.** Bridgewater, NJ 08807 USA" to read "Mfd for: Aventis Pharmaceuticals Inc. Bridewater, NJ 08807 ©2002."

    The revisions are editorial and acceptable.

11. The identification number was revised. (See above chart entitled "BLISTER LABELING CHART" for specific identification numbers for each strength).

    The revision is editorial and acceptable.

12. The lot numbers were added on the left end of the blister backing labeling. (See above chart entitled "BLISTER LABELING CHART" for specific identification numbers for each strength).

    The additions are acceptable.

B. 30mg/0.3 mL Prefilled Syringe Blisterfoil Labeling

The following revision was made to the 30mg/0.3 mL Pre-filled Syringe blisterfoil labeling:

In the first column, third line, the sponsor added the phrase "[100mg/mL]" to the phrase that reads "30 mg/0.3 mL" so that the phrase reads "30mg/0.3mL [100mg/mL]."

The addition clarifies the dosage strength. The revision is acceptable.

C. 40mg/0.4 mL Prefilled Syringe Blister Backing

The following revisions were made to the 40mg/0.4 mL Pre-filled Syringe blisterfoil labeling:

1. In the first column, third line, the sponsor added the phrase "[100mg/mL]" to the phrase that reads "40 mg/0.4 mL" so that the phrase reads "40mg/04mL [100mg/mL]."

   The addition clarifies the dosage strength. The revision is acceptable.

2. The sponsor revised the color from black numbers inside a yellow rectangular box to ——— letters in a yellow rectangular box.

   This is not acceptable. The letters are difficult to distinguish.
   On April 18, 2003, the sponsor submitted a general correspondence to Supplement 051 agreeing to revise the color of the letters "40 mg/0.4 mL" and "60 mg/0.6 mL" in the syringe label and foil backing to reflex blue at the next printing.

   On May 9, 2003, the sponsor submitted revised labeling for the 40 mg/0.4 mL syringe foil backing. The 40 mg/0.4 mL prefilled syringe foil backing submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the syringe foil backing submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067138). The sponsor revised the color from the——— letters in a yellow rectangular box to reflex blue letters in a yellow rectangular box. The reflex blue color gives an acceptable contrast for the 40 mg/0.4 mL prefilled syringe foil backing. This proposed revision is acceptable. Because the labeling was a mock-up representation, the lot number was not included. This is acceptable. However, the sponsor added ———————— on the first line of the foil backing. This is inconsistent with labeling for the other Lovenox strengths and is not recommended by the Division of Medication Errors and Technical Support (DMETS) (see consult to NDA 20-164/S-043 for review of the proprietary name ———— requested May 1, 2002 and completed July 29, 2002). The