CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-044

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals Products, Inc.

Approval Date: November 30, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-044

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-044

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-044

Aventis Pharmaceuticals Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Global Drug Regulatory Affairs
Global Therapeutic Area head
Route 202-206, P.O. Box 6800
Bridgewater, NJ 08807-0800

Dear Mr. Carrado:

Please refer to your supplemental new drug application dated May 31, 2001, received June 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

This supplemental application, submitted as a "Supplement – Changes Being Effected in 30 days" supplement, provides for the following change: an increase in the Lovenox Injection formulation batch size to [redacted] for Line –(Maisons-Alfort) used to [redacted] fill the syringe sizes of 0.6 mL (60 mg), 0.8 mL (80 mg), and 1.0 mL (100 mg) Lovenox Injection.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou

11/30/01 12:53:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-044

CHEMISTRY REVIEW

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-164
3. Name and Address of Applicant (City & State): Aventis Pharmaceuticals 10236 Marion Park Drive, P.O. Box 9627 Kansas City, MO 64134		4. AF Number:
		5.Supplement(s)
6. Name of Drug: Lovenox Injection	7. Nonproprietary Name: enoxaparin sodium injection	Numbers: SCS-044 Dates: 31-May-2001
8. Supplement provides for: the increase in the Lovenox Injection formulation batch size to for Line (Maisons-Alfort, France) used to fill the syringe sizes of 0.6 mL (60mg), 0.8 mL (80 mg) and 1.0 mL (100 mg) Lovenox Injection.		9. Amendments and Other (Reports, etc.) Dates: EER has DO and OC Recommendations of ACCEPTABLE, 29-NOV-2001. Microbiologist Review #1 dated, 16-NOV-2001.
10. Pharmacological Category: anti-thrombotic	11.How Dispensed: RX -XXX OTC	12. Related IND/NDA/DMF(s): SCS-026 Approved 14-Sep-99
13.Dosage Form: injection (subcutaneous)	14. Potency: 100 mg/mL	
15. Chemical Name and Structure: See USP Dictionary (2001)		16. Records and Reports:
		Current Yes X No
		Reviewed Yes X No
17. Comments: 1. Aventis notes: "There are no changes to components, composition or packaging for the drug product." 2. The fifth year Expected Introduction Concentration (EIC) is calculated to be at a level below 1 ppb for the EIC (Adequate). 3. The Microbiologist's review, by Dr. N. Sweeney, recommends for approval for microbiology issues concerning sterility issues. 4. Compliance: EES completed-"Acceptable". 5. The supplement is for a batch scale-up; no chemistry issues are pending and the supplement is acceptable from a chemistry viewpoint. cc: NDA 20-164 HFD-180/Div File HFD-181/CSO/KOliver		
18. Conclusions and Recommendations: Based on the submitted chemistry information, the microbiologist's review, and the FDA CDER EES report, this chemistry reviewer from a chemistry viewpoint recommends that the supplement should be approved. The CSO should prepare an approval letter for the Team Leaders signature.		
19.Reviewer		
Name: Joseph Sieczkowski, Ph.D.	Signature	Date Completed: November 29, 2001

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/s/

Joe Sieczkowski
11/29/01 02:13:56 PM
CHEMIST

Liang Zhou
11/29/01 02:29:11 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-044

MICROBIOLOGY REVIEW

REVIEW FOR HFD-180

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review #1 of NDA 20-164/SCS-044

November 16, 2001

A. 1. **APPLICATION NUMBER:** 20-164/SCS-044

APPLICANT: Aventis Pharmaceuticals
10236 Marion Park Drive
P.O. Box 9720
Kansas City, MO 64134-9720
Phone: 816-966-5100
FAX: 816-966-6794

2. **PRODUCT NAME:** Lovenox Injection

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Sterile enoxaparin sodium solution in 30, 40, 60, 80, and 100 mg concentrations in pre-filled syringes for subcutaneous injection.

4. **METHODS OF STERILIZATION:** ———————

5. **PHARMALOGICAL CATAGORY and/or PRINCIPLE INDICATION:** Low molecular weight heparin indicated for treatment of deep vein thrombosis or pulmonary embolism.

6. **DRUG PRIORITY CLASSIFICATION:** Standard

B. 1. **DATE OF INITIAL SUBMISSION:** 5/31/01

2. **DATE OF CONSULT:** 6/12/01

3. **ASSIGNED FOR REVIEW:** 6/15/01

4. **RELATED DOCUMENTS:** NDA 20-164 SCS-026

C. **REMARKS:** The CBE-30 supplement provides for an increase in batch size (from ——— to ———) for the 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/1.0 mL pre-filled syringe strengths of Lovenox. NDA 20-164/SCS-026, approved 9/14/99, provided for the ——— batch size for the 30 mg/0.3 mL and 40 mg/0.4 mL pre-filled syringe strengths of Lovenox.

D. CONCLUSIONS:

The submission is recommended for approval for microbiology issues concerning sterility assurance. Specific comments are provided in section "E. REVIEW NOTES".

Neal Sweeney, Ph.D.

cc: NDA 20-164/SCS-044
HFD-180/Division File
HFD-180/K. Oliver
HFD-180/J. Sieczkowski
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, November 16, 2001
R/D initialed by P. Cooney, November 16, 2001

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of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

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/s/

Neal Sweeney
11/28/01 04:13:17 PM
MICROBIOLOGIST

Peter Cooney
11/29/01 11:29:53 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-044

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-044

CBE-30 SUPPLEMENT

Aventis Pharmaceuticals
Attention: Dhiren N. Shah, Ph.D.
Director - CMC, US Drug Regulatory Affairs
10236 Marion Park Drive, P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Shah:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lovenox® (enoxaparin sodium) Injection

NDA Number: 20-164

Supplement Number: S-044

Date of Supplement: May 31, 2001

Date of Receipt: June 1, 2001

This supplemental application, submitted as a "Supplement - Changes Being Effected in 30 days" supplement, proposes the following change: increasing the batch size for the 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1.0 mL Lovenox® Injection pre-filled syringes from —— to

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 31, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 1, 2001.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, Rm. 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Karen Oliver
6/12/01 02:48:11 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

DO *(Division/Office)*: HFD-160
ATTENTION: Dr. Peter Cooney

FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) Phone # 827-7457

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT :	DATE OF DOCUMENT
June 12, 2001		NDA20-164/S-044	NDA Supplement-044 CBE	May 31, 2001

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lovenox (enoxaparin sodium) Injection	Standard		User fee Due Date: 6 mo: 12/01/01

NAME OF FIRM: Aventis Pharmaceuticals Products 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 DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

☐ DISSOLUTION
BIOAVAILABILITY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

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 ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: CBE Supp-044 provides for the following: a batch size increase for the 60 mg/0.6 mL, 80 mg/0.8mL and 100 mg/1.0 mL Lovenox Injection pre-filled syringes, from [redacted] to [redacted]). I am consulting the complete submission (5 volumes) Please review. Dr. Joseph Sieczkowski is the review chemist. Thanks, Karen Oliver, Project Manager

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Karen Oliver
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