CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-013

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Approval Date: May 16, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-013

APPROVAL LETTER

53.1

NDA 20-164/S-013

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
P.O. Box 5096
500 Arcola Road
Collegeville, Pennsylvania 19426-0107

MAY 16 1997

Dear Dr. Donnelly:

Please refer to your supplemental new drug application dated September 19, 1996, received September 20, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt, on May 13, 1997, of your May 12, 1997 amendment to your supplemental application in response to our March 13, 1997 approvable letter. We consider this a major amendment under 21 CFR 314.60 of the regulations and its constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is November 13, 1997.

The supplemental application provides for the addition of a new filling line ——— for Lovenox® (enoxaparin sodium) 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, please contact Karen Oliver, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

Eric P. Duffy 5/15/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Original NDA 20-164/S-013
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/J.Sieczkowski 05/15/97
HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

Drafted by: KO/May 15, 1997 K. Oliver 05/15/97
Final: KO/05/15/97/c:\wpwin\karenfil\nda\20164507.0ko

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-013

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

53 n 1

NDA 20-164/S-013

Rhone-Poulenc Rorer Pharmaceuticals, Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
P.O. Box 5096
500 Arcola Road
Collegeville, Pennsylvania 19426-0107

MAR 13 1997

Dear Dr. Donnelly :

Please refer to your supplemental new drug application dated September 19, 1996, received September 20, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

The User Fee goal date for this application is March 20, 1997.

The supplemental application provides for the addition of a new filling line ——— for Lovenox® (enoxaparin sodium) Injection (40 mg/0.4 mL prefilled syringes) in the manufacturing facility at Rhone-Poulenc Rorer, PROPHARMASPECIALITIES, 180, rue Jean Jaures, 94700 Maisons-Alfort, France.

We have completed the review of this supplemental application and it is approvable pending approval of your supplemental new drug application (S-008), submitted December 27, 1995.

Within 10 days after the date of this letter, your required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In absence of such action, FDA may take action to withdraw this supplemental application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Karen Oliver, Project Manager, at (301) 443-0487.

Sincerely yours,

Eric P. Duffy 3/13/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-013
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/J. Sieczkowski 3-12-97
HFD-180/E. Duffy
HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

Drafted by: J.Sieczkowski/February 26, 1997/WP: c:\wpfiles\chem\S\20164013.bjs
Initialed by: E.Duffy/3-10-97
K.Oliver/3-11-97
dob DRAFT 2-26-97
final: dob **F/T 3-11-97**

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-013

CHEMISTRY REVIEW

CHEMIST REVIEW #1	1. Organization: HFD-180	2 NDA Number: 20-164	
3. Name and Address of Applicant (City & State): Rhone-Poulenc Rorer Pharmaceuticals, Inc. 500 Arcola Road, P.O. Box 1200 Collegeville, PA 19426-0107		4. AF Number: MAR 13 1997	
		5. Supplement(s)	
		Number:	Dates:
6. Name of Drug: Lovenox® Injection	7. Nonproprietary Name: enoxaparin sodium	SCM-013	19 SEP 1996
8. Supplement Provides for: the addition of a new filling line ——— for Lovenox® (enoxaparin sodium) Injection (40 mg/0.4 mL prefilled syringes) in the manufacturing facility at Rhone-Poulenc Rorer, Propharma Specialities, 1800, rue Jean Jaures, 94700 Maisons-Alfort, FRANCE.		9. Amendments and Other (Reports, etc.) Dates: Microbiologist's Review #1 dated October 28, 1996 by Brenda Uratani, Ph.D., HFD-805.	
10. Pharmacological Category: Anticoagulant	11. How Dispensed: RX XX OTC ___	12. Related IND/NDA/DMF(s): SE1-008 SE1-010 SCM-011 SCM-012	
13. Dosage Form: SVS (Parenteral)	14. Potency: 100 mg/mL		
15. Chemical Name and Structure: See The Merck Index, Twelfth Edition.		16. Records and Reports: Current _____ Yes _____ No Reviewed _____ Yes _____ No	

17. Comments:
See Review Notes

cc:
Original NDA 20-164
HFD-180/Div/File
HFD-180/CSO/KOliver
HFD-180/SFredd
HFD-180/JSieczkowski

Drafted by: J. Sieczkowski, Feb. 24, 1997/WP: c:\wpfiles\chem\S\20164013.1js
Initaled by: E. Duffy
dob DRAFT 2-24-97
final:dob **F/T 2/26/97**

EDuffy 3/13/97

18. Conclusions and Recommendations: Based on the submitted CMC information, Microbiologist's Review #1 and the acceptance by Compliance (HFD-324) of RPR's manufacturing facility at Maison-Alfort, FRANCE, it is recommended from a chemistry viewpoint that this supplement should be approved. This supplement should not be approved prior to Supplement SE1-008 which is the efficacy supplement supporting the use of the 40 mg/0.4 mL prefilled syringe. (See attached APPROVAL letter.)

19. Reviewer

	Signature:	Date Completed:
Joseph Sieczkowski, Ph.D.	Joseph Sieczkowski 2-27-97	February 25, 1997

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-013

MICROBIOLOGY REVIEW

OCT 29 1996

REVIEW FOR HFD-180
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 1 of NDA 20-164/ S-013
October 28, 1996

A. 1. **APPLICATION NUMBER:** 20-164/S-013

APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

2. **PRODUCT NAMES:** Lovenox (enoxaparin) injection pre-filled syringe

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:**

Lovenox is available in prefilled syringes (10 mg enoxaparin sodium per 0.1 ml WFI, anti-Factor Xa activity is 1000 IU per every 10 mg of drug). The solution is preservative free and intended for use only as a single-dose injection.

Lovenox Injection is administered by subcutaneous injection. It must not be administered by intramuscular injection.

4. **METHOD(S) OF STERILIZATION:** _____

5. **PHARMACOLOGICAL CATEGORY:** Lovenox is indicated for prevention of deep vein thrombosis following hip replacement surgery.

B. 1. **DATE OF INITIAL SUBMISSION:** September 19, 1996

2. **AMENDMENT:** None

3. **RELATED DOCUMENTS:** NDA 20-164/S-012

4. **ASSIGNED FOR REVIEW:** July 15, 1996

5. **DATE OF CONSULT REQUEST:** October 4, 1996

C. REMARKS:

Supplements S-012 and S-013 provide for an additional filling line ——— for use in the manufacture of the approved Lovenox 30 mg/0.3 ml and 40 mg/0.4 ml, respectively. Supplement S-012 was recommended for approval with respect to microbiology in September 1996. The same validation data were submitted for both supplements and they are adequate to support the sterility assurance for the 40 mg/0.4 ml dosage.

Please refer to the microbiology review of NDA 20-164/S-012 for details.

D. CONCLUSIONS:

The submissions are recommended for approval for issues concerning microbiology.

Brenda Uratani 10/28/96

Brenda Uratani, Ph.D.

10/29/96

cc:

NDA 20-164/S-013
HFD-180/ Div. File
HFD-805 /Uratani
HFD-180/CSO/ K. Oliver
drafted by: Brenda Uratani, 10/28/96
R/D initialed by P.Cooney, 10/28/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

53.1

NDA 20-164/S-013

SEP 27 1996

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
P.O. Box 5096
500 Arcola Road
Collegeville, PA 19426-0800

Dear Dr. Donnelly:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Lovenox (enoxaparin sodium) Injection

NDA Number: NDA 20-164

Supplement Number: S-013

Therapeutic Classification: Standard

Date of Supplement: September 19, 1996

Date of Receipt: September 20, 1996

This supplement provides for an additional filling line ——— at the Maisons-Alfort, France, site to manufacture Lovenox Injection supplied as a 40 mg/0.4 mL pre-filled syringe containing a 100 mg/mL solution of enoxaparin sodium in Water for Injection.

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 November 19, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

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

cc:
Original NDA 20-164/S-013
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/J.Sieczkowski
HFD-180/L.Talarico
DISTRICT OFFICE

drafted: KO/September 26, 1996 KOliver 09/26/96
Final: KO/09/26/96/c:\wpwin\karenfil\20164609.1ko

SUPPLEMENT ACKNOWLEDGEMENT

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

REQUEST FOR CONSULTATION

645

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

FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products)

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
October 4, 1996		20-164	SCM-013	September 19, 1996

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lovenox (enoxaparin sodium) Injection	S		User Fee Due Date: March 20, 1997 Target Date: February 1, 1997

NAME OF FIRM: Rhone-Poulenc Rorer Pharmaceuticals 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)*: Supplement

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:

P. B. Arabani 10/16/96

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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 RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Supplement provides for an additional filling line at the Maison-Alfort, France, site to manufacture Lovenox Injection supplied as a 40mg/0.4 mL pre-filled syringe containing a 100 mg/mL solution of enoxaparin sodium in Water for Injection. Cover letter to supplement and information regarding the sterilization process included. Please review. Thanks, Karen Oliver

cc: Original NDA 20-164/S-013
HFD-180/Div. Files
HFD-180/J.Sieczkowski
HFD-180/E.Duffy

SJS 10-4-96

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one):
Karen Oliver CSO 10/04/96 HFD-180	☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER: Marian Jenkins	SIGNATURE OF DELIVERER: 10/8/96