CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-012

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Approval Date: October 23, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-012

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APPLICATION NUMBER:

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APPROVAL LETTER

48.1

NDA 20-164/S-012

OCT 23 1996

Rhone-Poulenc Rorer
Attention: Thomas E. Donnelly, Jr., Ph.D.
P.O. Box 1200
500 Arcola Road,
Collegeville, Pennsylvania 19426-0107

Dear Dr. Donnelly:

Please refer to your May 24, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We also acknowledge receipt of your amendments dated June 20, and August 7, 1996.

The supplemental application provides for the addition of a new filling line ——— for Lovenox® (enoxaparin sodium) Injection (30 mg/0.3 mL prefilled syringes) in the manufacturing facility at Rhone-Poulenc Rorer, Propharmaspecialities, Maisons-Alfort, 180, rue Jean Jaures, 94700 Maisons-Alfort, France.

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, (301) 443-0487.

Sincerely yours,

Eric P. Duffy 10/23/96

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

cc:
Original NDA 20-164/S-012
HFD-180/Division Files
DISTRICT OFFICE
HFD-180/CSO/KOliver
HFD-232
HFD-820/ONDC/Div Dir
HFD-180/JSieczkowski 10-23-96
R/D init: EDuffy/10-22-96
dob DRAFT 10-7-96/**F/T 10-22-96**/WP: c:\wpfiles\chem\S\20164012.AJS

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-012

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 Arcola Road, P. O. Box 1200 Collegeville, PA 19426-0107		4. AF Number: OCT 23 1996	
		5. Supplement(s)	
		Number(s):	Dates(s):
6. Name of Drug: Lovenox® Injection	7. Nonproprietary Name: enoxaparin sodium	SCM-012 BC BC	24 MAY 1996 20 JUN 1996 7 AUG 1996
8. Supplement Provides for: the addition of a new filling line for Lovenox® (enoxaparin sodium) Injection (30 mg/0.3 mL prefilled syringes) in the manufacturing facility at Rhone-Poulenc Rorer, Propharmaspecialities, Maisons-Alfort, 180 rue Jean Jaures, 94700 Maisons-Alfort, France.		9. Amendments and Other (Reports, etc.) Dates: Microbiologist's Review #1 dated 16 SEP 1996 by Brenda Uratani, Ph.D.	
10. Pharmacological Category: Anticoagulant	11. How Dispensed: RX XX OTC ___	12. Related IND/NDA/DMF(s): SE 1-008 SE 1 -010 SCM -011	
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: NDA 20-164
HFD-180/Div/File
HFD-181/CSO/KOliver
HFD-180/SFredd
HFD-180/JSieczkowski
R/D init : EDuffy
dob DRAFT 10-7-96/ **F/T 10-22-96**\WP: c:\wpfiles\chem\S\20164012.1JS

EDuffy 10/23/96

18. Conclusions and Recommendations: Based on the submitted CMC information, the Microbiologist's Review #1 and the acceptance by compliance (HFD-324) of the manufacturing facility at Maisons-Alfort, it is recommended that this supplement be approved. Rhone-Poulenc Rorer should be notified of the supplement approval via letter.

(See attached APPROVAL letter.)

19. Reviewer

Name:	Signature:	Date Completed:
Joseph Sieczkowski, Ph.D.	Joseph Sieczkowski 10-23-96	October 3, 1996

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CHEMISTRY REVIEW #1

A. Microbiologist's Review #1 recommends approval of the supplement for issues concerning microbiology.

B. EER for NDA 20-164/S-007 for both the Rhone-Poulenc Rorer Limited, Dagenham Essex, England and the Rhone-Poulenc Rorer Propharmaspecialites, Maisons-Alfort, France sites were noted by Compliance HFD-324 as "Acceptable" dated 10-1-96.

COMMENT:
Based on the information submitted in the Original Supplement and the Amendments, the information submitted for the CMC of Lovenox® Injection, the Microbiologist's Review #1, and the response by Compliance to the evaluation of the manufacturing facility as acceptable, it is recommended that the supplement be approved.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

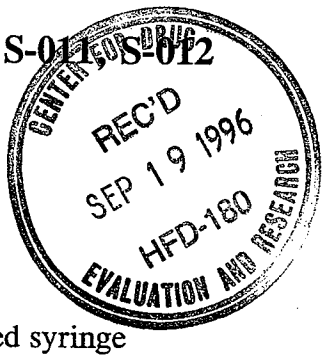
NDA 20-164/S-012

MICROBIOLOGY REVIEW

48.1 SEP 16 1996

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

Microbiologist's Review # 1 of NDA 20-164: S-008, S-010, S-011, S-012
September 16, 1996



A. 1. **APPLICATION NUMBER:**

20-164/S-008 and 20-164/S-010: Qualification of a 40 mg pre-filled syringe (Lovenox), the recommended dosage for the new indication of the prevention of deep vein thrombosis after hip replacement surgery.

20-164/S-011: Update specifications and analytical methods for Lovenox to harmonize methods worldwide.

20-164/S-012: Qualification for an additional filling line —— in the manufacture of the approved 30 mg/0.3 ml Lovenox.

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:**

NDA 20-164/S-008:	December 27, 1996
NDA 20-164/S-010:	March 29, 1996
NDA 20-164/S-011:	April 15, 1996
NDA 20-164/S-012:	May 24, 1996

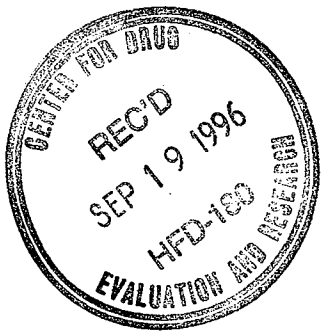
9/24/96

2. **AMENDMENT:** None

3. **RELATED DOCUMENTS:** NDA 20-164

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

5. **DATE OF CONSULT REQUEST:**
   NDA 20-164/S-008, S-010, S-011: July 10, 1996
   NDA 20-164/S-012: July 5, 1996



C. REMARKS:

Supplement S-008, S-010 and S-011 were submitted in response to the FDA Chemist's request for additional information. With regard to microbiology issues, these supplements provide the alternate methods used in endotoxin determinations. The same validation data was provided for all three supplements, and they are the subject of this review.

Supplement S-012 provides for an additional filling line ——— for use in the manufacture of the approved 30 mg/0.3 ml Lovenox.

D. CONCLUSIONS:

The submissions are recommended for approval for issues concerning microbiology.

Brenda Uratani 9/16/96
Brenda Uratani, Ph.D.
Pltc 9/16/96

cc:

NDA 20-164/S-008, S-010, S-011, S-012
HFD-180/ Div. File
HFD-805 /Uratani
HFD-180/CSO/ K. Oliver
drafted by: Brenda Uratani, 9/16/96
R/D initialed by P.Cooney, 9/16/96

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MICROBIOLOGY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

48.1

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)*: ginal ☐ Follow-Up ☐ FUR	DATE: **May 30, 1996**	PHONE NO.: (301) 443-0487	EER ID #
CHEMIST NAME: Joseph Sieczkowski, Ph.D.	DIVISION: Gastrointestinal and Coagulation Drug Products		MAIL CODE: **HFD-180**
APPLICATION AND SUPPLEMENT NUMBER: NDA NDA 20-164/S-012			
BRAND NAME: Lovenox Injection	ESTABLISHED NAME: Enoxaparin Sodium Injection		
DOSAGE STRENGTH: 30 mg/0.3mL and 40 mg/0.4mL			STERILE: ☒ Yes ☐ No
PROFILE CLASS: SVS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3): Standard		
APPLICANT'S NAME: Rhone-Poulenc Rorer Pharmaceuticals Inc.			
ADDRESS: 500 Arcola Road Collegeville, PA 19426-0107			

COMMENTS :Supplement provides for an additonal filling line ——— at the Maison-Alfort, France, site to manufacture Lovenox supplied as a 30 mg/0.3mL and a 40 mg/0.4mL pre-filled syringe containing a 100 mg/mL solution of enoxaparin sodium in Water for Injection. **USER FEE DUE DATE**: November 28, 1996. **NOTE**: Firm states filling line ___ was inspected when filling line ___ was inspected (4/25 to 5/3/96) due to ——————————— by Dr. David Pulham of the Phoenix branch, FDA on behalf of the international inspections branch.

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY/ CIRTIS ID	HFD-324 USE ONLY
1. Rhone-Poulenc Rorer Propharm Maisons-Alfort 180, rue Jean Jaures 94700 Maisons-Alfort France	Line _ will manufacture Lovenox as a 30mg/0.3mL and 40mg/0.4mL pre-filled syringe containing 100mg/mL suolutio of enoxaprin sodium in Water for Inj.	N/A IP		
2				
3.				
4.				

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.

cc: al NDA NDA 20-164/S-012 HFD-180/Div. File, HFD-180/CSO/K.Oliver, HFD-180/Joseph Sieczkowski, Ph.D. HFD-180/Kati Johnson

48.1

NDA 20-164/S-012

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

MAY 31 1996

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-012

Therapeutic Classification: Standard

Date of Supplement: May 24, 1996

Date of Receipt: May 28, 1996

This supplement provides for an additional filling line ——— at the Maisons-Alfort, France, site to manufacture Lovenox Injection supplied as a 30 mg/0.3 mL and 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 July 27, 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-012
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/J.Sieczkowski
HFD-180/L.Talarico
DISTRICT OFFICE

drafted: KO/May 30, 1996 K Oliver 05/30/96
Final: KO/05/30/96/c:\wpwin\karenfil\nda\20164605.1ko

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

48.1

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)*: ☐ Original XX Follow-Up ☐ FUR	DATE: **September 13, 1996**	PHONE NO.: (301) 443-0487	EER ID #
CHEMIST NAME: Joseph Sieczkowski, Ph.D.	DIVISION: Gastrointestinal and Coagulation Drug Products		MAIL CODE: **HFD-180**
APPLICATION AND SUPPLEMENT NUMBER: NDA NDA 20-164/S-012			
BRAND NAME: Lovenox Injection	ESTABLISHED NAME: Enoxaparin Sodium Injection		
DOSAGE STRENGTH: 30 mg/0.3mL and 40 mg/0.4mL			STERILE: ☒ Yes ☐ No
PROFILE CLASS: SVS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3): Standard		
APPLICANT'S NAME: Rhone-Poulenc Rorer Pharmaceuticals Inc.			
ADDRESS: 500 Arcola Road Collegeville, PA 19426-0107			
COMMENTS :Supplement provides for an additonal filling line ——— at the Maison-Alfort, France, site to manufacture Lovenox supplied as a 30 mg/0.3mL and a 40 mg/0.4mL pre-filled syringe containing a 100 mg/mL solution of enoxaparin sodium in Water for Injection. **USER FEE DUE DATE**: November 28, 1996. **NOTE**: Original EER #10373. Maison-Alfort UN, now reportedly corrected deficiencies. Please check with Rick Friedman, as he said re-inspection not necessary.			

FACILITIES TO BE EVALUATED

(Name and Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY/ CIRTIS ID	HFD-324 USE ONLY	
1. Rhone-Poulenc Rorer Propharm Maisons-Alfort 180, rue Jean Jaures 94700 Maisons-Alfort France	Line – will manufacture Lovenox as a 30mg/0.3mL and 40mg/0.4mL pre-filled syringe containing 100mg/mL suolutio of enoxaprin sodium in Water for Inj.	N/A IP			
2					
3.					
4.					

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FO[illegible]DA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: Original NDA NDA 20-164/S-012 HFD-180/Div. File, HFD-180/CSO/K.Oliver, HFD-180/Joseph Sieczkowski, Ph.D. HFD-180/Kati Johnson