

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-023

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Approval Date: November 8, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-023

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-023

APPROVAL LETTER

NDA 20-164/S-023

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

Dear Mr. Jurgens:

Please refer to your supplemental new drug application dated January 26, 1999, received January 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submission dated July 21, 1999. Your submission of July 21, 1999 constituted a complete response to our June 11, 1999 action letter.

This supplemental new drug application provides for: (1) the extension of the Villeneuve-La-Garenne Plant, Villeneuve-Garenne, France, and the addition of new equipment to the plant extension for the production scale-up, by _____ in the manufacture of exoxaparin sodium; and (2) _____ bags prepared from _____ (sourced from _____) (sourced from _____) for drug substance commercial packaging and stability studies.

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, contact Karen Oliver, Project Manager, at (301) 827-7310.

Sincerely,

Liang Zhou, Ph.D.
Acting 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

cc:

Archival NDA 20-164/S-023

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Zhou

HFD-180/J.Sieczkowski

HFD-095/DDMS-IMT

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: KO/November 8, 1999

final: KO/11/08/99/c:\data\mydocuments\NDA20164-S-023-11-08-99-AP.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-023

CHEMISTRY REVIEWS

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

NDA 20-164 SUPPLEMENT: SCM-023 CHEM REVIEW: #1 REVIEW DATE: 5/19/99

SUBMISSION TYPE

DATES	DOCUMENT	CDER	
ORIGINAL	26 JAN 99	27 JAN 1999	
AMENDMENT			JUN - 8 1999

SUPPLEMENT PROVIDES FOR: See attached (page 2).

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

DRUG PRODUCT NAME:

<u>Proprietary:</u>	Lovenox® Injection
<u>Nonproprietary/USAN:</u>	enoxaparin sodium injection
<u>Code Name/#</u>	RP54563
<u>Chem.Type/Ther.Class:</u>	low molecular weight heparin

PHARMACOLOGICAL CATEGORY: anti-thrombotic

INDICATION: For the treatment of deep vein thrombosis or pulmonary embolism.

DOSAGE FORM: Sterile Solution/small volume Parenteral.

STRENGTH: 30, 40, 60, 80, 100 mg/syringe (100mg/1mL).

ROUTE OF ADMINISTRATION: Subcutaneous injection

HOW DISPENSED: XX Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See original NDA Chemistry Review #1.

**APPEARS THIS WAY
ON ORIGINAL**

SUPPLEMENT PROVIDES FOR:

1. The extension of the Villeneuve-La-Garenne Plant, Villeneuve-La Garenne, France, and the addition of new equipment to the plant extension for the production scale up, by _____ in the manufacture of enoxaparin sodium.
2. _____ bags prepared from _____ (sourced from _____) (sourced from _____) for drug substance commercial packaging and stability studies.

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
			Adequate	Chem. Rv. #4 Aug 14, 1996	--
			Adequate	Chem. Rv. #2 Jan 14, 1993	--
			Adequate	Chem. Rv. #2 Dec 22, 1994	--

RELATED DOCUMENTS (if applicable): NDA 20-164/SCS-022 & SCS-024.

CONSULTS: None


REMARKS/COMMENTS:

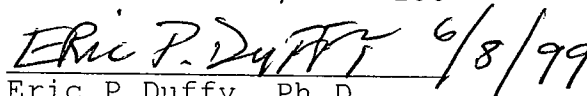
1. The approved suppliers of heparin sodium are _____ and _____ is being added as an additional heparin sodium supplier and they will only use animals native to the United States and inspected by USDA (FAX received 11 May 1999).
2. The bulk drug substance _____ storage bag has been changed.
3. Request for categorical Exclusion under 21 CFR 25.31(b) is Adequate.
4. Below is the index of information provided in volumes 2, 3, 4, 5, 6, & 7.
 - Vol. 2
 - 4.3.2.1. Master batch record translation template for stability batch records. (pages 2-2 to 174).
 - 4.3.2.2 Provides translations for handwritten comments onto batch record 4261. (pages 2-175 to 220).
 - 4.3.2.3 Batch Record for Stability Lot 4261 (pages 2-221 to 423; FRENCH)
Partial Batch Record for Stability Lot 4264

- Partial Batch Record for Stability Lot 4264
(pages 2-424 to 425, FRENCH).
- Vol. 3. Batch Record for Stability Lot 4262
(pages 3-1 to 228; FRENCH)
Batch Record for Stability Lot 4264
(pages 3-229 to 440; FRENCH)
- Vol. 4. Translation Template for Bioequivalence Study Batch
Records Lots 4116 and 4141
(pages 4-1 to 97)
Batch Record for Bioequivalence Study Lot 4116
(pages 4-98 to 268; FRENCH)
- Vol. 5. Batch Record for Bioequivalence Study Lot 4141
(pages 5-1 to 236; FRENCH)
4.4 Environmental Assessment
(pages 5-237 to 238; Categorical exclusion under 21
CFR 25.31(b).
- Vol. 6. 6.1 Human Pharmacokinetics and Bioavailability
Section
(Vol. 6, pages 6-1 to 280; Study Synopsis pages 6-9
to 12).
- Vol. 7. 6.1 Continued
(Vol. 7, pages 7-1 to 261)
Certificates of Analysis for enoxaparin sodium from
_____ heparin sodium: Lot numbers 97 087 99,
97 085 99, and 97 065 98.
(Vol. 7 pages 7-262 to 265)

CONCLUSIONS & RECOMMENDATIONS:

The supplement is deficient and a not approvable letter should be sent to Rhone Poulenc Rorer with respect to the supplement's deficiencies. (See Deficiencies at the end of the review.)


Joseph Sięczkowski, Ph.D. May 24, 1999
Review Chemist, HFD-180


Eric P. Duffy, Ph.D. 6/8/99
Chemistry Team Leader, HFD-180

NDA 20-164/S-023

HFD-180/Div File/NDA 20-164

HFD-180/DivDir/L.Talarico

HFD-181/CSO/K.Oliver

HFD-180/E.Duffy

HFD-180/J.Sięczkowski

R/D Init: E.Duffy/

dob DRAFT 5/19/99/F/T 5-21-99/Word: n:\wordfiles\chem\S\10164023.1JS

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

CHEM. REVIEW #2		1. <u>Organization:</u> HFD-180	2. <u>NDA number:</u> 20-164	
3. <u>Name and Address of Applicant (City & State):</u> Rhone-Poulenc Rorer P.O. Box 1200 500 Arcola Road Collegetown, PA 19426-0107			4. <u>AF Number</u>	
			5. <u>Supplements:</u>	
			<u>Numbers</u>	<u>Dates:</u>
6. <u>Name of Drug:</u> Lovenox® Injection		7. <u>Nonproprietary Name:</u> enoxaparin sodium injection	SCM-023 AC	26 JAN 99 21 JUL 99
8. <u>Supplement Provides For:</u> See page 2.			9. <u>Amendments and Other (Reports, etc.) Dates:</u>	
10. <u>Pharmaceutical Category:</u> anti-thrombotic		11. <u>How Dispensed:</u> RX <u>XX</u> OTC <u> </u>	12. <u>Related IND NDA DMF(s):</u> See page 2.	
13. <u>Dosage Form:</u> Prefilled Syringe/Injection.		14. <u>Potency:</u> 30, 40, 60, 80, 100 mg/Syringe (100mg/1mL)		
15. <u>Chemical Name and Structure:</u> See Original NDA Chemistry Review #1.			16. <u>Records and Reports:</u> Current <u> </u> YES <u> </u> NO Reviewed <u> </u> YES <u> </u> NO	
17. <u>Comments:</u> See Review Notes: CC: NDA 20-164/S-023 HFD-180/Div.File/NDA 20-164 HFD-180/CSO/K.Oliver HFD-180/L.Talarico HFD-180/J.Sieczkowski R/D Init:L.Zhou dob DRAFT 11-4-99/F/T 11-7-99/Word: c:\wordfiles\chem\S\20164023.2JS				
18. <u>Conclusions and Recommendations:</u> Based on the submitted information in response to the Agency's NOT APPROVABLE letter of June 11, 1999, this supplemental application should be approved. The CSO should prepare an APPROVAL letter for signature by the Chemistry Team Leader.				
19. <u>Reviewer:</u>				
Name: Joseph Sieczkowski, Ph.D.		Signature:	Date Completed: October 28, 1999	

8. Supplement provides for:

1. The extension of the Villeneuve-La-Garenne Plant, Villeneuve-Garenne, France, and the addition of new equipment to the plant extension for the production scale up, by a _____ in the manufacture of enoxaparin sodium.

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information from

CHEMISTRY REVIEW #2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-023

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

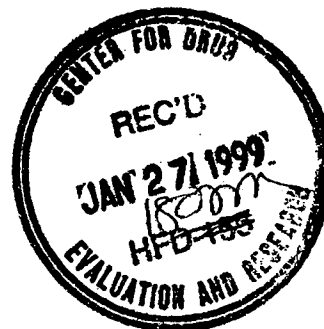
Rhône-Poulenc Rorer

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

January 26, 1999

Federal Express # 5023300866

Lilia Talarico, M.D., Director
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-164
RP 54563

Lovenox® (enoxaparin sodium) Injection
SUPPLEMENTAL NEW DRUG APPLICATION
DRUG SUBSTANCE CHANGES:
New Source of Heparin sodium (SPL)
Increase Batch Size

NDA NO. 20164 REF. NO. 022
NDA SUPPL FOR SCS

SEM 023
SSC 024
Admin split per 180

Dear Dr. Talarico:

Reference is made to NDA 20-164, approved March 29, 1993. The purpose of this supplemental NDA is to qualify for the drug substance :

1. an alternative supplier for the starting material heparin sodium, USP
2. an expansion of the approved manufacturing facility at Villeneuve-La-Garenne Plant (project name, _____) which is associated with the increased batch size
3. a new regulatory method for residual solvents and clarity testing
4. an increase in the production scale by _____

Heparin sodium, is the starting material used to manufacture enoxaparin sodium drug substance, which is the active ingredient in Lovenox®. The currently approved suppliers for heparin sodium, USP are _____ located in _____ and _____ located in _____. The manufacturing process for heparin sodium, USP at _____ is described in their DMF, number _____. An authorization letter for access to this DMF on behalf of Rhône-Poulenc Rorer was provided in the original NDA 20-164, volume 2.2 page 170. The manufacturing process for heparin sodium, USP at _____ is described in their DMF, number _____. An authorization letter for access to this DMF on behalf of Rhône-Poulenc Rorer was provided in supplement S-004 to the original NDA 20-164, volume 1 page 3-2-2.

ORIGINAL



In order to meet the increased demands for Lovenox® drug product, additional supplies of heparin sodium are required. This supplement provides for an additional supplier for the starting material heparin sodium, USP:

[]

The manufacturing process for heparin sodium, USP at _____ is described in their Type II DMF, number _____. An authorization letter for access to this DMF on behalf of Rhône-Poulenc Rorer is included in this submission.

The currently approved site of manufacture for enoxaparin sodium drug substance and the site of the facility extension is:

Rhône-Poulenc Rorer
Villeneuve-La-Garenne Plant
35, Avenue Jean Jaures
92390 Villeneuve-La-Garenne
France

There are no changes to the method of synthesis, or the specifications and analytical methods for the drug substance, enoxaparin sodium. The current release specifications and analytical methods for enoxaparin sodium are identical to those described in supplement S-011, approved on February 24, 1998. A new regulatory method for the determination of residual solvents _____ in enoxaparin sodium has been introduced. This method using _____ techniques, along with the associated validation report is included in this submission. An alternate method for the determination of the clarity of a solution of enoxaparin sodium has been introduced. This method using a _____ method, along with the associated validation report is also included in this submission.

The extension to the approved facility will have a capacity approximately _____ what is currently approved, however, the increased capacity is only related to the

[]

The project to scale up the process is referred to as _____. The qualification of an additional source of heparin sodium, USP, has been performed using this scaled up process.

A comparison of the data obtained from 3 batches of _____ sourced heparin to three batches of heparin from currently approved suppliers demonstrates the _____ heparin source and the process scale up produce enoxaparin sodium which is comparable to that obtained from approved heparin sources and the current production process. Additionally, a bioequivalence study has been performed demonstrating that the new source of heparin sodium _____ is bioequivalent to the currently approved sources of heparin sodium. The bioequivalence report is included with this submission.



We are providing the pertinent documentation to support a new source of supply for heparin sodium, which is the starting material for the enoxaparin sodium drug substance, and an increase in the batch size for the drug substance in accordance with 21 CFR 314.70(b) (1).

This submission contains an application form FDA 356h, both an archival copy and review copy. This submission contains a User Fee Form. This certifies that a field copy of this submission has been provided to the Philadelphia, PA District Office, the home office of the NDA holder, Rhône-Poulenc Rorer Pharmaceuticals Inc.

If you have any questions concerning this submission please contact the undersigned or Connie Gombatz, (Manager, CMC) at (610)454-5430.

Sincerely,

Dennis Jurgens
Associate Director, CMC Conformance
Regulatory Affairs

Phone: (610) 454-3364
FAX: (610) 454-2949

Field Copy:

Debra L. Pagano
Philadelphia District Pre-Approval Manager
U.S. Food and Drug Administration
Room 900, U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106-2973

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT Rhône-Poulenc Rorer Pharmaceuticals Inc.		DATE OF SUBMISSION January 26, 1999	
TELEPHONE NO. (Include Area Code) 610-454-3364		FACSIMILE (FAX) Number (Include Area Code) 610-454-2949	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Rhône-Poulenc Rorer Pharmaceuticals Inc. 500 Arcola Road P.O. Box 1200 Collegeville, PA 19426-0107		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-164			
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) enoxaparin sodium		PROPRIETARY NAME (trade name) IF ANY Lovenox Injection	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N/A		CODE NAME (If any) RP 54563	
DOSAGE FORM: Sterile Solution	STRENGTHS: 30, 40, 60, 80, 100 mg	ROUTE OF ADMINISTRATION: subcutaneous injection	
(PROPOSED) INDICATION(S) FOR USE: For the treatment of deep vein thrombosis or pulmonary embolism.			

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507			
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Holder of Approved Application			
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input checked="" type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER			
REASON FOR SUBMISSION Drug Substance: New Source of Starting Material (heparin sodium); increased batch size.			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED 7	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Rhone-Poulenc Rorer - Villeneuve-La-Garenne Plant 35, Avenue Jean Jaures 92390 Villeneuve-La-Garenne, France CFN# 9610113

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-164,
DMF — — — — — DMF — — — — — DMF — — — — —

This application contains the following items (Check all that apply)

	1. Index
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION


I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact law.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Dennis Jurgens, Associate Director Regulatory Affairs, CMC Conformance	DATE January 26, 1999
---	---	--------------------------

ADDRESS (Street, City, State, and ZIP Code) 500 Arcola Road, Collegeville, PA 19426-0107	Telephone Number (610) 454-3364
---	------------------------------------

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

NDA 20-164/S-022, 023, & 024

FEB - 9 1999

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

Dear Mr. Jurgens:

We acknowledge receipt of your supplemental application. After preliminary review of the submission, the Agency administratively separated the submission into three supplemental applications as follows:

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

NDA Number: NDA 20-164

Supplement Numbers: S-022, 023, & 024

Therapeutic Classification: Standard

Date of Supplements: January 26, 1999

Date of Receipts: January 27, 1999

These supplements propose the following changes: (S-022) _____
_____ as an alternate supplier of the porcine
sourced intermediate, heparin sodium; (S-023) the expansion of the Velleneuve-La-
Garenne Plant, Villeneuve-La-Garenne, France, and the addition of new equipment to the
plant expansion for the production scale-up, by _____ in
the manufacture of enoxaparin sodium; and (S-024) alternate methods for the enoxaparin
sodium specifications "Residual solvents: _____ and
"Aqueous solution: - clarity".

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 March 28, 1999 in accordance with 21 CFR 314.101(a).

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

Food and Drug Administration
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

If you have any questions, please contact me at (301) 827-7310.

Sincerely yours,

Karen Oliver, RN, MSN
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-022, 023, 024

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/E.Duffy

HFD-180/J.Sieczkowski

r/d init: J.Sieczkowski 02/08/99

r/d Init: E.Duffy 02/08/99

DISTRICT OFFICE

Drafted by: KO/February 8, 1999

Final: KO/02/09/99/c:\mydocuments\NDA20164-02-08-99-S-022-023-024ack-admsplit

K. Oliver 02/09/99

SUPPLEMENT ACKNOWLEDGEMENT (AC)

NDA 20-164/S-023

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

Dear Mr. Jurgens:

Please refer to your supplemental new drug application dated January 26, 1999, received January 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

This supplement proposes the following change: the expansion of the Velleneuve-La-Garenne Plant, Villeneuve-La-Garenne, France, and the addition of new equipment to the plant expansion for the production scale-up, by _____ in the manufacture of enoxaparin sodium.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

For the Drug Substance and Stability Storage Bags:

1. Provide safety information for the use of the following packaging components to assure the safety of enoxaparin sodium which is being used in a parenteral formulation:
 - a. _____
 - b. []
 - c. Any other agents present in or on the finished _____ bags before their use for _____

2. Where Drug Master Files (DMFs) are available, provide DMF letters of authorization for the following:
 - a. []
 - b. []
 - c. []

3. Where DMFs are not available, provide the following:
- a. General manufacturing information regarding the production of _____
_____ bags manufactured by _____
manufactured by _____ and _____ manufactured by _____
 - b. Certificate of Analysis (COA) for _____

4. Provide a letter of commitment by _____ to notify you (RPR) of any changes, chemical and/or physical, to the bulk drug substance _____ bags.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Eric P. Duffy, 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

cc:

Archival NDA 20-164/S-023
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/June 8, 1999
Initialed by: E.Duffy 06/10/99
final: 06/11/99/c:\mydocuments\NDA20164-S-023-06-08-99-NA

NOT APPROVABLE (NA)



ORIGINAL

SOM-023
BCAC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

July 21, 1999

Lilia Talarico, M.D., Director
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**NDA 20-164/S-023
RP 54563**

Lovenox® (enoxaparin sodium) Injection

**AMENDMENT
SUPPLEMENTAL NEW DRUG APPLICATION
DRUG SUBSTANCE CHANGES:
Plant Expansion/Scale-up/New Equipment**

Dear Dr. Talarico:

Reference is made to supplement S-023 to NDA 20-164, submitted January 26, 1999. Reference is also made to the not approvable letter dated June 11, 1999 which requested additional information on the drug substance stability storage bags.



Dr. Lilia Talarico
NDA 20-164/S-023
July 21, 1999
Page 2 of 2



With this letter, we are providing a complete response to all items listed in the letter. A bibliography of safety information is also provided (Appendix 14). If you have any questions concerning this submission please contact the undersigned or Connie Gombatz, (Manager, CMC) at (610)454-5430.

Sincerely,

A handwritten signature in cursive script, appearing to read "Dennis Jurgens".

Dennis Jurgens
Associate Director, CMC Conformance
Regulatory Affairs
Rhône-Poulenc Rorer Pharmaceuticals Inc.
Phone: (610) 454-3364
FAX: (610) 454-2949

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT Rhône-Poulenc Rorer Pharmaceuticals Inc.		DATE OF SUBMISSION July 21, 1999	
TELEPHONE NO. (Include Area Code) 610-454-3364		FACSIMILE (FAX) Number (Include Area Code) 610-454-2949	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Rhône-Poulenc Rorer Pharmaceuticals Inc. 500 Arcola Road P.O. Box 1200 Collegeville, PA 19426-0107		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 20-164			
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) enoxaparin sodium		PROPRIETARY NAME (trade name) IF ANY Lovenox Injection	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) N/A		CODE NAME (if any) RP 54563	
DOSAGE FORM: Sterile Solution	STRENGTHS: 30, 40, 60, 80, 100 mg	ROUTE OF ADMINISTRATION: subcutaneous injection	
(PROPOSED) INDICATION(S) FOR USE: For the treatment of deep vein thrombosis or pulmonary embolism.			

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507			
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Holder of Approved Application			
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER			
REASON FOR SUBMISSION: Drug Substance Changes - Plant Expansion/Scale-up/New Equipment			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED 1	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Rhône-Poulenc Rorer PHARMASPECIALITES 180, rue Jean Jaures 94700 Maisons-Alfort, France - CFN# FCFR218
Site Contact: Mr. Michel Nouyrigat, Director, Quality Phone: 331-4518-8311 FAX: 331-4353-2663
Rhône-Poulenc Rorer, Villeneuve-la-Garenne Plant, 35, Avenue Jean Jaures, 92390 Villeneuve-Garenne, France - CFN# 9610113

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

	1. Index
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
X	17. Field copy certification (21 CFR 314.5 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

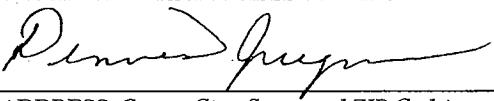
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact law.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Dennis Jurgens, Associate Director Regulatory Affairs, CMC Conformance	DATE July 21, 1999
	ADDRESS (Street, City, State, and ZIP Code) 500 Arcola Road, Collegeville, PA 19426-0107	Telephone Number (610) 454-3364

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Washington, DC 20201

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