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:

Proprietary:	Lovenox® Injection
Nonproprietary/USAN:	enoxaparin sodium injection
Code Name/#	RP54563
Chem.Type/Ther.Class:	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 [redacted] in the manufacture of enoxaparin sodium.
2. [redacted] bags prepared from [redacted] (sourced from [redacted] (sourced from [redacted] 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 [redacted] and [redacted]. [redacted] 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 [redacted] 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 Synopis 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 Sieczkowski May 24, 1999
Joseph Sieczkowski, Ph.D.
Review Chemist, HFD-180

Eric P. Duffy 6/8/99
Eric P.Duffy, Ph.D.
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.Sieczkowski
R/D Init: E.Duffy/
dob DRAFT 5/19/99/**F/T 5-21-99**/Word: n:\wordfiles\chem\S\10164023.1JS

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

CHEM. REVIEW #2	1. Organization: HFD-180	2. NDA number: 20-164
3. Name and Address of Applicant (City & State): Rhone-Poulenc Rorer P.O. Box 1200 500 Arcola Road Collegeville, PA 19426-0107		4. AF Number 5. Supplements:
		Numbers: SCM-023 AC Dates: 26 JAN 99 21 JUL 99
6. Name of Drug: Lovenox® Injection	7. Nonproprietary Name: enoxaparin sodium injection	
Supplement Provides For: See page 2.		9. Amendments and Other (Reports, etc.) Dates:
10. Pharmaceutical Category: anti-thrombotic	11. How Dispensed: RX _XX__ OTC___	12. Related IND NDA DMF(s): See page 2.
13. Dosage Form: Prefilled Syringe/Injection.	14. Potency: 30, 40, 60, 80, 100 mg/Syringe (100mg/1mL)	
15. Chemical Name and Structure: See Original NDA Chemistry Review #1.		16. Records and Reports: Current ____YES____NO Reviewed ___YES ___NO
17. Comments: 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		
Conclusions and Recommendations: 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. Reviewer:		
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 [redacted] in the manufacture of enoxaparin sodium.

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-023

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RHÔNE-POULENC

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

NDA NO 20164 REF. NO. 022
NDA SUPPL FOR SC 5
SCM 023
SSC 024
Admin Split per CBO

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

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

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Rhône-Poulenc Rorer Pharmaceuticals Inc.	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*)	PROPRIETARY NAME (*trade name*) IF ANY
enoxaparin sodium	Lovenox Injection

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
N/A	RP 54563

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Sterile Solution	30, 40, 60, 80, 100 mg	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE: For the treatment of deep vein thrombosis or pulmonary embolism.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☒ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Drug Substance: New Source of Starting Material (heparin sodium); increased batch size.

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 7

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ 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) ☐ Draft Labeling ☐ 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

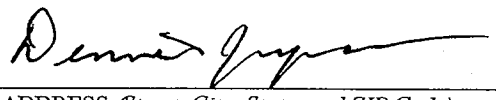
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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	DATE
	Dennis Jurgens, Associate Director Regulatory Affairs, CMC Conformance	January 26, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
500 Arcola Road, Collegeville, PA 19426-0107	(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 K. Oliver 02/09/99
Final: KO/02/09/99/c:\mydocuments\NDA20164-02-08-99-S-022-023-024ack-admsplit

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 [redacted] bags manufactured by [redacted] manufactured by [redacted] and [redacted] manufactured by

   b. Certificate of Analysis (COA) for [redacted]

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

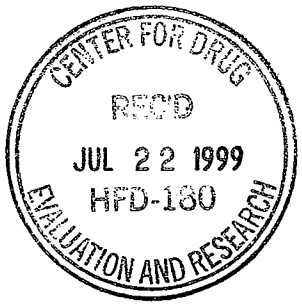
SCM-023
BCAC

RHÔNE-POULENC

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.

[ ]

With this letter, we are providing a complete response to all items listed in the letter. A bibliography of [redacted] 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,

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

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Rhône-Poulenc Rorer Pharmaceuticals Inc.	July 21, 1999
TELEPHONE NO. (*Include Area Code*)	**FACSIMILE (FAX) Number** (*Include Area Code*)
610-454-3364	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*)	PROPRIETARY NAME (*trade name*) IF ANY
enoxaparin sodium	Lovenox Injection
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	**CODE NAME** (*If any*)
N/A	RP 54563

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Sterile Solution	30, 40, 60, 80, 100 mg	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE: For the treatment of deep vein thrombosis or pulmonary embolism.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: Drug Substance Changes - Plant Expansion/Scale-up/New Equipment

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION IS
1	☒ PAPER ☐ PAPER AND ELECTRONIC ☐ 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) ☐ Draft Labeling ☐ 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

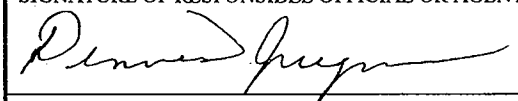
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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	DATE
	Dennis Jurgens, Associate Director Regulatory Affairs, CMC Conformance	July 21, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
500 Arcola Road, Collegeville, PA 19426-0107	(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
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Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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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:

We acknowledge receipt on July 22, 1999 of your July 21, 1999 resubmission to your supplemental new drug application for Lovenox® (enoxaparin sodium) Injection.

This resubmission contains additional Chemistry, Manufacturing and Controls (CMC) information on the drug substance stability storage bags in response to our June 11, 1999 action letter.

With this amendment, we have received a complete response to our June 11, 1999 action letter.

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

Sincerely,

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

cc:
Archival NDA 20-164/S-023
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/Reviewers and Team Leaders
HFD-180/M. Kidwell
DISTRICT OFFICE
Drafted by: mk 7/26/99
Initialed by: K. Oliver 7/27/99
final: M. Kidwell 7/27/99
filename: N20164S023701.ko
RESUBMISSION ACKNOWLEDGEMENT (AC)