CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-022

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.

Approval Date: July 21, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-022

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter	
Labeling	
Labeling Review	
Medical Review	
Chemistry Review	X
Pharmacology / Toxicology Review	
Statistical Review	
Microbiology Review	
Clinical Pharmacology / Biopharmaceutics Review	X
Administrative and Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-022

APPROVAL LETTER

NDA 20-164/S-022

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 May 21, 1999.

This supplemental new drug application provides for [redacted], as an alternate supplier of the porcine sourced intermediate, heparin sodium.

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, 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-022
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-870/D.Lee
HFD-870/s.Al-Fayoumi
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/July 2, 1999
final: KO/07/02/99/c:\mydocuments\NDA20164-S-022-07-02-99-AP

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-022

CHEMISTRY REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 20-164 SUPPLEMENT:SCS-022 CHEM REVIEW:#1 REVIEW DATE: 6/23/99

SUBMISSION:

	DATES	
TYPE	DOCUMENT	CDER
ORIGINAL	26 JAN 1999	27 JAN 1999
AMENDMENT	21 MAY 1999	24 MAY 1999

SUPPLEMENT PROVIDES FOR:

---

as an alternate supplier of porcine sourced heparin sodium which is an intermediate in the manufacture of enoxaparin sodium.

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/#:	RP 54563
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, 100mg /syringe (100 mg/mL)
ROUTE OF ADMINISTRATION:	subcutaneous injection

HOW DISPENSED: XX Rx ___OTC

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

SUPPORTING DOCUMENTS:

DMF Number	Item Referenced	Holder	Status	Review Date	Letter Date
			Adequate	Chem.Rv.#4 14 AUG 1996	---
			Adequate	Chem.Rv. #2 14 JAN 1993	---
			Adequate	Chem.Rv. #2 22 DEC 1994	---

RELATED DOCUMENTS (if applicable):
1. NDA 20-164/SCM-023 and SCS-024.
2. Correspondence dated April 19, 1999.
3. FAX dated 11 May 1999. (Included in the 21 May 1999 Amendment.)

CONSULTS:
Biopharmaceutics Consult (Vols. 6 & 7); Clinical Pharmacology and Biopharmaceutics Review.
Review Date: May 27, 1999. Final Date: July 2, 1999

Conclusion:
The supplemental application to NDA 20-164 was submitted on Jan. 26, 1999 in support of proposed changes in the source of heparin used to prepare enoxaparin. The submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable. Enoxaparin manufactured from heparin of ——— is bioequivalent to enoxaparin manufactured from heparin of ——— origin.

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). (See attachment.)
2. The bulk drug substance ——— storage bag has been changed. (SCM-023)
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
(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 [redacted] heparin sodium: Lot numbers 97 087 99,97 085 99,and 97 065 98.
Vol. 7, pages 7-262 to 265).

CONCLUSIONS & RECOMMENDATIONS:
The submitted information appears satisfactory to support the use of [redacted] as a supplier of heparin sodium (intermediate) to Rhone-Poulenc Rorer Pharmaceuticals (Villenveuve-La-Garenne, FRANCE) for the manufacture of enoxaparin sodium. It is recommended that an approval letter for this supplement be sent to Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA.

Joseph Sieczkowski, Ph.D.
Review Chemist, HFD-180

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-164
HFD-180/L.Talarico
HFD-180/NDA 20-164/S-022
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-181/CSO/K.Oliver
R/D Init by: E.Duffy
dob DRAFT 6/28/99/F/T 7-9-99/WORD: N:\wordfiles\chem\S\20164022.1JS

Redacted 19 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-022

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

Clinical Pharmacology and Biopharmaceutics Review

IND: 20-164/S-022 **Submission Date**: 1/26/1999

Trade Name: LOVENOX® Injection **Stamp Date**: 1/27/1999 JUL - 2 1999

Active Ingredient: Enoxaparin Sodium **Review Date**: 5/27/1999

Sponsor: Rhône-Poulenec Rorer Pharmaceuticals Inc. **Draft Date**: 6/30/1999

Reviewer: Suliman I. Al-Fayoumi, Ph.D. **Final Review Date**: 7/2/1999

Type of Submission: Supplemental New Drug Application for Bioequivalence Study

Synopsis

Lovenox® (Enoxaparin sodium) injection is a low molecular weight heparin currently approved for prevention of deep vein thrombosis (DVT). It is administered as subcutaneous (sc) injection, 30 mg B.I.D. in patients undergoing hip or knee surgery and 40 mg Q.D. in patients undergoing abdominal surgery and may be at risk of thromboembolic complications.

The currently marketed formulation of enoxaparin is prepared using heparin from ———. In this supplemental NDA, the Firm aims at assessing the bioequivalence of enoxaparin prepared from heparin of ——— administered as a single s.c. 40 mg dose, in comparison with enoxaparin prepared from heparin of ——— origin (pre-filled syringes).

The current application includes a study report entitled,
"A Phase 1, Randomized, 2-Period Cross-Over Study to Assess the Bioequivalence of Enoxaparin (RP54563) Prepared from Unfractionated Heparin from Two Different Sources ——— after Single 40 mg S.C. Dose (Pre-filled Syringes, 40 mg in 0.4 ml) In Healthy Male Volunteers" (DMPK/FR/2192).

Study Results

Study Design

Open, randomized, single-center, two-period crossover study

Subjects	12 subjects.
Key Inclusion Criteria	Healthy males, 18-35 yrs of age Within 10% of ideal body weight range No evidence of active disease, primarily a bleeding disorder and/or bleeding risk
Key Exclusion Criteria	Evidence of haemolytic anaemia, bone marrow insufficiency, respiratory, cardiovascular or renal insufficiency, CNS disease, G6PDH deficiency History of allergy or hypersensitivity to any medication, mainly to heparin compounds Evidence of history of diseases associated with a bleeding disorder or bleeding risk Any medication that could induce or inhibit hepatic microsomal enzymes within three months of the start of the study.

Reference Product	Pre-filled enoxaparin (from [redacted]) syringes 40 mg in 0.4 ml, administered subcutaneously as a single 40 mg dose
Test Product	Pre-filled enoxaparin (from [redacted]) syringes 40 mg in 0.4 ml, administered subcutaneously as a single 40 mg dose
Washout	At least 14 days
Sampling Times	Serum samples collected at the following time points (for both treatments): **Pre-dose** (within 20 min of drug administration) **Post-dose**: at 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16 and 24 hrs
Safety	Subjects monitored for adverse events. One subject had a mild adverse event (postural hypotension), which was considered unlikely to be related to the treatment by the investigator

Analytical Assay

Four pharmacodynamic markers were used to determine the activity of enoxaparin in biological samples for the assessment of enoxaparin pharmacokinetics: anti-Xa and anti-IIa activities (using amidolytic methods) and APTT and Heptest clotting time. The anti-Xa and anti-IIa assays demonstrated acceptable precision and accuracy throughout the study.

Anti-Xa Assay

The amidolytic methods are based on an enzymatic reaction in which the target enzyme interacts with a specific substrate. This substrate is an oligopeptide which contains a specific site for binding to a given enzyme, with an attached chromophore end group: paranitroaniline. The binding of the substrate with the target enzyme (factor Xa or factor IIa) releases the chromophore group, which can be quantified spectrophotometrically at 405 nm.
The anti-Xa standard calibration range was validated from 0.0 to 0.4 IU anti-Xa/ml with a minimum limit of quantification (LOQ) at 0.025 IU anti-Xa/ml. The accuracy of the anti-Xa assay was between –10% and 6% (expressed as % relative error) and the precision was between 0% and 8% (expressed as %CV).

Anti-IIa Assay

The Anti-IIa assay was validated between 0.0 and 0.3 IU Anti-IIa/ml with a minimum LOQ at 0.025 Anti-IIa/ml. The accuracy of the Anti-IIa assay was between –10% and 6% (expressed as % relative error) and the precision was between 1% and 10% (expressed as %CV).

Pharmacokinetics

The following pharmacokinetic parameters were determined according to standardized methods using WinNonLin® software: Areas under the curve; $AUC_{0\rightarrow last}$ and $AUC_{0\rightarrow\infty}$, the maximum plasma activity (A_{max}) and time of its appearance (t_{max}), the mean residence time (MRT), the distribution volume (Vz F), total body clearance (CL/F) and the apparent half-life of elimination ($t_{1/2\lambda z}$) (see attachments).

Relevant PK equations

$MRT = AUMC / AUC_{0\rightarrow\infty}$

$CL/F = Dose / AUC_{0\rightarrow\infty}$

$Vz/F = CL/F \times ke$ or $Vz/F = Dose \times ke / AUC_{0\rightarrow\infty}$

$t_{1/2\lambda z} = 0.693 / ke$

Results

1. Anti-Xa Activity

Table 1. Mean (± S.D.) pharmacokinetic parameters of the anti-Xa activity (n = 12)

Treatment	A_{max}	$AUC_{0\rightarrow last}$	$AUC_{0\rightarrow\infty}$	MRT	CL/F	Vz/F	$t_{1/2\lambda}$
[redacted]	0.50 (0.06)	4.36 (0.56)	4.62 (0.64)	8.05 (1.32)	0.90 (0.11)	5.97 (1.13)	4.70 (1.04)
[redacted]	0.48 (0.06)	4.28 (0.60)	4.55 (0.69)	8.14 (1.04)	0.90 (0.10)	6.25 (0.89)	4.87 (0.74)

Table 2. Schuirmann confidence intervals for anti-Xa activity PK parameters

Parameter	Treatment Comparison	Estimate %	Confidence Interval
Log A_{max}	[redacted]	103	(99-108)
Log $AUC_{0\rightarrow last}$		102	(98-106)
Log $AUC_{0\rightarrow\infty}$		102	(97-106)

Upon applying the Schiurmann two one-sided tests, the two treatments were shown to be bioequivalent in terms of maximum plasma anti-Xa activity and area under the curves at $\alpha = 0.1$, the 90% confidence intervals being included in the 80-125% bioequivalence interval.
According to the *Proc Mixed* performed on log transformed pharmacokinetic parameters t_{max}, $AUC_{0\rightarrow last}$ and $AUC_{0\rightarrow\infty}$, there is no statistically significant "treatment", "period" or "sequence" effects on t_{max}, $AUC_{0\rightarrow last}$ or $AUC_{0\rightarrow\infty}$ (see attachment).

2. Heptest Clotting Time Prolongation

Table3. Mean (± S.D.) pharmacokinetic parameters of the Heptest clotting time prolongations (s) (n = 12)

Treatment	A_{max}	$AUC_{0\rightarrow last}$	$AUC_{0\rightarrow\infty}$	MRT	$t_{1/2\lambda}$
[redacted]	102 (9)	1063 (74)	1146 (91)	9.5 (1.2)	5.9 (0.8)
[redacted]	104 (7)	1071 (95)	1156 (116)	9.5 (1.2)	5.9 (0.9)

Table 4. Schuirmann confidence intervals for Heptest clotting time prolongation bioavailability parameters

Parameter	Treatment Comparison	Estimate %	Confidence Interval
Log $A_{(\Delta)max}$	[redacted]	98	(95-102)
Log $AUC_{0\rightarrow last}$		99	(96-103)
Log $AUC_{0\rightarrow\infty}$		99	(96-103)

Bioequivalence was shown between the two enoxaparins ([redacted]) on A_{max}, $AUC_{0\rightarrow last}$ and $AUC_{0\rightarrow\infty}$ parameters. There was no statistically significant difference between the two treatments for t_{max} (see attachment).

3. The applicant submitted mean pharmacokinetic parameters for anti-IIa activity and APTT clotting time prolongations. However, bioequivalence calculations were not performed for these two markers. No explanation was provided by the applicant as to why those calculations were not performed.

Discussion

In previous Lovenox® submissions to the Agency, bioequivalence determination for enoxaparin formulations has been primarily based on anti-Xa activity. However, even though bioequivalence based on anti-Xa activity was considered sufficient, it was indicated that it would be desirable to demonstrate bioequivalence based on both anti-Xa and anti-IIa activities.

It is currently not clear to this reviewer why the applicant did not perform bioequivalence calculations for anti-IIa activity and APTT clotting time prolongations. Enoxaparin anti-IIa activity and APTT clotting time prolongation data showed high variability. For anti-IIa activity, plasma levels were at the limit of quantification. For APTT clotting time prolongations, AUC value was not calculated.

It might be that the high variability in the data did not allow for the determination of all the pharmacokinetic parameters for anti-IIa activity and APTT clotting time prolongations, hence bioequivalence based on those two markers was not assessed. Based on the available pharmacokinetic parameters, this reviewer calculated bioequivalence for anti-IIa activity and APTT clotting time prolongations (Tables 6 and 8), and the two enoxaparin formulations demonstrate bioequivalence according to those two markers.

Table 5. Mean (± S.D.) pharmacokinetic parameters of the anti-IIa activity (n = 12)

Treatment	A_{max}	$AUC_{0\rightarrow t}$
[redacted]	0.07 (0.01)	0.34 (0.13)
	0.06 (0.01)	0.29 (0.11)

Table 6. Schuirmann confidence intervals for anti-IIa bioavailability parameters

Parameter	Treatment Comparison	Estimate %	Confidence Interval
Log A_{max}	[redacted]	95	(94-95)
Log $AUC_{0\rightarrow last}$		87	(82-91)

Table 7. Mean (± S.D.) pharmacokinetic parameters of the APTT clotting time prolongations (n = 12)

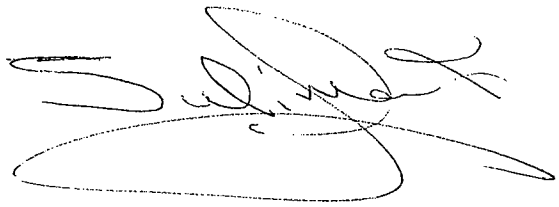
Treatment	Baseline	A_{max}	$A(\Delta t)_{max}$
[redacted]	33.7 (5.3)	44.5 (7.7)	10.8 (2.8)
	34.0 (5.0)	43.9 (7.4)	9.9 (2.6)

Table 8. Schuirmann confidence intervals for APTT clotting time prolongation bioavailability parameters

Parameter	Treatment Comparison	Estimate %	Confidence Interval
Log $A_{(\Delta)max}$	[redacted]	104	(103-105)

Recommendations

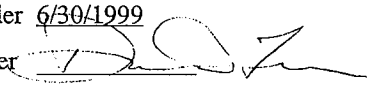
The supplemental application to NDA 20-164 was submitted on Jan 26, 1999 in support of proposed changes in the source of heparin used to prepare enoxaparin. The submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable. Enoxaparin manufactured from heparin of [redacted] is bioequivalent to enoxaparin manufactured from heparin of [redacted] origin.



7/2/99

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by David Lee, Ph.D., Team leader 6/30/1999

FT initialed by David Lee, Ph.D., Team leader 

7/2/99

cc: HFD-180: NDA 20,164 (1x); DIV FILE (1x); KOLIVER (1x); DLEE (1x); HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

Table 17 : Anti-Xa activity-Individual pharmacokinetic parameters - enoxaparin 40 mg s.c.

Subject	*Tmax (h)*	*Amax (IUaXa/ml)*	*AUClast (h.IUaXa/ml)*	*AUC (h.IUaXa/ml)*	*MRT (h)*	*Cl/F (l/h)*	*Vz/F (l)*	*t1/2λz (h)*
1								
2								
3								
4								
5								
6								
7								
9								
10								
11								
12								
13								
Mean	-	0.48	4.28	4.55	8.14	0.90	6.25	4.87
SD	-	0.06	0.60	0.69	1.04	0.10	0.89	0.74
CV%	-	13	14	15	13	12	14	15
n	12	12	12	12	12	12	12	12
median	3.00	0.48	4.08	4.34	8.13	0.93	6.48	4.91
min								
max								

Table 18 : Anti-Xa activity-Individual pharmacokinetic parameters - enoxaparin 40 mg s.c.

Subject	*Tmax (h)*	*Amax (IUaXa/ml)*	*AUClast (h.IUaXa/ml)*	*AUC (h.IUaXa/ml)*	*MRT (h)*	*Cl/F (l/h)*	*Vz/F (l)*	*t1/2λz (h)*
1								
2								
3								
4								
5								
6								
7								
9								
10								
11								
12								
13								
Mean	-	0.50	4.36	4.62	8.05	0.90	5.97	4.70
SD	-	0.06	0.56	0.64	1.32	0.11	1.13	1.04
CV%	-	11	13	14	16	12	19	22
n	12	12	12	12	12	12	12	12
median	3.00	0.49	4.28	4.54	7.91	0.90	6.17	4.90
min								
max								

Table 19: Anti-IIa activity-Individual pharmacokinetic parameters - enoxaparin 40 mg s.c.

Subject	*Amax (IUaIIa/ml)*	*Tmax (h)*	*AUClast (h.IUaIIa/ml)*
1			
2			
3			
4			
5			
6			
7			
9			
10			
11			
12			
13			
mean	0.06	-	0.29
SD	0.01	-	0.11
CV%	17	-	39
n	12	12	12
median	0.06	3.25	0.25
min	[		]
max			

Table 20 : Anti-IIa activity-Individual pharmacokinetic parameters - enoxaparin 40 mg s.c.

Subject	*Amax (IUaIIa/ml)*	*Tmax (h)*	*AUClast (h.IUaIIa/ml)*
1			
2			
3			
4			
5			
6			
7			
9			
10			
11			
12			
13			
mean	0.07	-	0.34
SD	0.01	-	0.13
CV%	13	-	37
n	12	12	12
median	0.07	3.50	0.31
min	[		]
max			

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-022

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

RE: NDA 20-164
RP 54563

NDA NO. 20164 REF. NO. 020
NDA SUPPL FOR SC5
SCM 023
SSC 024
Admin Splitper 180

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

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)