

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-011

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.

Approval Date: February 24, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-011

APPROVAL LETTER



NDA 20-164/S-011

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

FEB 24 1998

Dear Dr. Donnelly:

Please refer to your supplemental new drug application dated April 15, 1996, received April 16, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submissions dated October 11, 1996, and March 5 and 21, July 29, and September 9, 1997. The User Fee goal date for this application is March 10, 1998.

This supplemental application provides for the following specification changes and stability protocol changes:

1. The addition of a _____ specification (NMT _____%) and method to the Heparin Sodium (enoxaparin sodium starting material) Specification.
2. For the enoxaparin sodium specification:
 - a. To add to the specification the following:
 - i. _____ test (proof of structure only).
 - ii. UV Spectrum/Specific absorbance test.
 - iii. _____ Ratio test.
 - iv. Anti-IIa and Anti-Xa to Anti-IIa activity ratio tests.
 - v. Bacterial Endotoxins test.
 - b. To modify the specification for the following:
 - i. Molecular Mass (MM) Distribution test (for new MM Distribution Method).
 - ii. Color test.
 - iii. pH test.
 - iv. Sodium test (for a new Sodium Assay).
 - v. Benzethonium Chloride test.

- c. To delete from the specification the following:
 - i. Special Optical Rotation test.
 - ii. Proteins test.
 - iii. Residue on Ignition test.
 - iv. Sulfur test.
 - v. Anticoagulant activity and Anti-Xa to anticoagulant activity ratio.
 - vi. Biological Safety tests.
3. Enoxaparin Sodium Stability Protocol changes, to accommodate enoxaparin sodium specification changes, for pre-approval batches and post-approval batches.
4. For the enoxaparin sodium injection specification:
 - a. To add to the specification the following:
 - i. Anti-IIa activity.
 - ii. Bacterial Endotoxins.
 - b. To modify the specification for Free Sulfates (for a new Free Sulfate Method).
 - c. To delete from the specification the following:
 - i. Anticoagulant activity.
 - ii. Pyrogens (Rabbit Test).
5. Enoxaparin Sodium Injection Stability Protocol changes, for pre-approval and post-approval batches, to reflect enoxaparin sodium injection specification changes and to reflect a change to the molecular mass distribution specification and method.

We have completed the review of this supplemental application and it is approved.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely yours,

Eric P. Duffy 2/24/98

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

cc:

Original NDA 20-164/S-011
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-160/P.Cooney
HFD-160/B.Uratani
HFD-720/A.J.Sankoh
HFD-720/M.Rashid

62-23-98

HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

Drafted by: KO/February 20, 1998
final: KO/02/20/98/c:\wpfiles\karenfil\nda\20164802.1ko
dob F/T 2-20-98

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-011

APPROVABLE LETTER

72.1

NDA 20-164/S-011

AUG 14 1997

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

Dear Dr. Donnelly:

Please refer to your supplemental new drug application dated April 15, 1996, received April 16, 1996, 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 March 5, 1997 in response to our October 15, 1996 not approvable letter. We also acknowledge receipt of your submissions dated March 21 and July 29, 1997. The User Fee goal date for this application is September 6, 1997.

The supplemental application provides for updated specifications, methods and stability protocols for the drug substance and drug product as outlined on page two of your cover letter. In the course of our review, we found that you intend to add, modify or delete specifications as outlined in our October 15, 1996 letter.

We have completed the review of this supplemental application and it is approvable. Before this supplement may be approved, however, it will be necessary for you to provide an adequate Methods Validation (MV) package for the added and modified drug substance and drug product specifications and test methods.

Please be advised that, within the MV package, cross references to the U.S. Pharmacopeia (USP) are acceptable if no method modifications are proposed. However, cross references to the European Pharmacopeia (EP) within the MV package are not acceptable, but the EP method may be included if no method modifications are proposed.

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 314.110. In the absence of such action FDA may take action to withdraw the application.

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

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

Sincerely yours,

ERIC P. DUFFY 8/14/97

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

cc:

Original NDA 20-164/S-011
HFD-180/Div. Files
HFD-92/DDM-DIAB
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-870/M.Huque
HFD-180/M.Rashid
DISTRICT OFFICE

Drafted by: KO/August 11, 1997

Initialed by: J.Sieczkowski 08/12/97 *J.S.* 08/14/97

Initialed by: E.Duffy 08/14/97

Final: KO/08/14/97/c:\wpwin\karenfil\nda\20164708.0ko *K.Oliver* 08/14/97

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-011

CHEMISTRY REVIEWS

CHEMIST REVIEW: #1		1. Organization: HFD-180		2. NDA Number: 20-164	
3. Name and Address of Applicant (City & State): Rhone-Poulenc Rorer 500 Arcola Road, P.O. Box 1200 Collegetown, PA 19426-0107				4. AF Number: OCT 15 1996	
				5. Supplement(s)	
				Number(s):	Dates(s):
6. Name of Drug: Lovenox® Injection		7. Nonproprietary Name: enoxaparin sodium		SCS-011	15 APR 1996
8. Supplement Provides for: See page 2.				9. Amendments and Other (Reports, etc.) Dates: Microbiologist's Review #1 dated Sept. 16, 1996 by Brenda Uratani, Ph.D., HFD-805. Production Site is withdrawn; General Correspondence dated October 11, 1996. <i>10/15/96</i>	
10. Pharmacological Category: anti-coagulant		11. How Dispensed: RX <u>XX</u> OTC <u> </u>		12. Related IND/NDA/DMF(s): SE1-008 SE1-010 SCM-012	
13. Dosage Form: Injection (SVP)		14. Potency: 30 mg.			
15. Chemical Name and Structure: See The Merck Index, Twelfth Edition.				16. Records and Reports:	
				Current <input type="checkbox"/> Yes <input type="checkbox"/> No	
				Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No	
17. Comments: See Review Notes cc: NDA 20-164 HFD-180/Div/File HFD-181/CSO/KOliver HFD-180/SFredd HFD-180/JSieczkowski R/D init by: EDuffy <i>EDUFFY 10/15/96</i> dob DRAFT 9-26-96/F/T 10-11-96\ WP: c:\wpfiles\chem\SI\20164011.1JS					
18. Conclusions and Recommendations: The changes proposed for the starting material (heparin sodium) specification, enoxaparin sodium specification, the enoxaparin sodium injection specification, and the enoxaparin sodium and enoxaparin sodium injection stability protocols were not adequately supported by the supplemental information submitted and therefore, the supplement should not be approved. The supplement deficiencies should be conveyed to Phone-Poulenc Rorer via letter. (See attached NOT APPROVABLE letter.)					

Signature:		Date Completed:
<i>Joseph Siefke</i> Oct. 15, 1996		September 25, 1996
ski, Ph.D.		

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confidential commercial

information from

CHEMISTRY REVIEW #1

62.1

CHEMIST REVIEW #2		1. Organization: HFD-180		2 NDA Number: 20-164	
3. Name and Address of Applicant (City & State): Phone-Poulenc Rorer 10 Arcola Road, P.O. Box 1200 Collegetown, PA 19426-0107				4. AF Number: AUG 14 1997	
				5. Supplement(s)	
				Number:	Dates:
6. Name of Drug: Lovenox® Injection		7. Nonproprietary Name: enoxaparin sodium		SCS-011 AC BS	15 APR 1996 05 MAR 1997 21 MAR 1997
8. Supplement Provides for: See page 2 and 3.				9. Amendments and Other (Reports, etc.) Dates: Microbiologist's Review #1 dated Sept. 16, 1996 by Brenda Uratani, Ph.D., HFD-805 _____ Production Site is withdrawn; General Correspondence dated 11, 1996.	
10. Pharmacological Category: anti-coagulant		11. How Dispensed: RX <u>XXX</u> OTC <u> </u>		12. Related IND/NDA/DMF(s): SE1-008 SE1-010 SCM-012	
13. Dosage Form: Injection (SVP)		14. Potency: 30 mg and 40 mg			
15. Chemical Name and Structure: See the Merck Index, Twelfth Edition.				16. Records and Reports:	
				Current _____ Yes _____ No	
				Reviewed _____ Yes _____ No	

Comments:
See Review Notes

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

Drafted by: J Sieczkowski/8-7-97/WP: c:\wpfiles\chem\S\20164011.2JS
Initaled by: EDuffy
DRAFT dob 8-7-97
final: dob F/T 8-12-97

EDUFFY 8/14/97

18. Conclusions and Recommendations: The supplement is approvable upon the submission of an adequate Methods Validation (MV) package for the added and modified drug substance and drug product specifications and test methods (see MV comment at the end of the review.) The R. H. Project should prepare an Approvable letter (H16) for the Team Leaders signature.

19. Reviewer		
Name:	Signature:	Date Completed:
Joseph Sieczkowski, Ph.D.	<i>Joseph Sieczkowski Aug 13, 1997</i>	August 7, 1997

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confidential commercial

information from

CHEMISTRY REVIEW#2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-004

STATISTICAL REVIEW

STATISTICAL REVIEW AND EVALUATION

AUG - 6 1997

NDA#: 20-164/S-011

Applicant: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Name of drug: Lovenox Injection (enoxaparin sodium 30 mg)

Documents reviewed: Submission dated March 21, 1997.



I. Introduction: In this NDA submission Rhone-Poulenc Rorer Pharmaceuticals Inc. has requested for an expiration dating period of 36 months for Lovenox injection (both anti-Xa activity and anti-coagulant activity). Dr. J. Sieczkowski, the reviewing chemist, HFD-180 has requested the Division of Biometrics III to perform a statistical review and evaluation of the sponsor's stability data analyses.

II. Design

Number of package types: Hypack SCF syringes consisting of a 0.5 ml Type 1, USP glass syringe fitted with a ½ inch 26 gauge needle and a _____ black stopper.

Package configuration: 30 mg/0.3ml syringes(one-type)

Number of batches: 3; CB05596, CB05596, and CB05598.

Tested Parameters: Anti-Xa activity results and anti-coagulant activity results of Enoxaparin 30 mg syringes.

Temperature: 30° C.

Specification limits of Enoxaparin 30 mg syringes: _____% (_____potency) for anti-Xa activity; _____ (potency) for anti-coagulant activity.

458-12-97

Sampling times: For temperature 30° C all batches were sampled at 0, .5, 1, 1.5, 2, 3, 6, 9, 12, 18, 24, and 36 months.

III. Sponsor's analysis

The sponsor analyzed the assay (potency) data using the linear regression model. From the statistical analysis, the sponsor declared that the batches, CB05596, CB05597 and CB05597 supported expiration period of 36 months for anti-Xa and anti-coagulant activities of Lovenox injection at 30° C.

IV. Reviewer's analysis

The reviewer analyzed the stability data (both anti-Xa and anti-coagulant activities) using the SAS program developed by the Division of Biometrics, FDA. The procedures consist of the following two steps.

Step 1: Model selection (Test for pooling of stability batch data).

An assessment is made as to whether or not the degradation curves, considering all individual batches separately, are similar. If the degradation curves are similar, it is desirable to pool the data in order to obtain more precise estimates of expiration dating periods. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data, and applying statistical tests for equality of slopes and/or zero-time intercepts to these models. The following two conditions must be satisfied to allow such pooling of the data.

a) The test of hypothesis that a model with separate intercepts and separate slopes (H_1) fits the data better than a model with separate intercepts and common slope (H_0) should have a p-value of 0.25 or greater, (equality of slopes) and,

b) The test of hypothesis that a model with separate intercepts and the estimated common slope (H_1) fits the data better than a model with common intercept and common slope (H_0) should have a p-value of 0.25 or greater (equality of intercepts given parallel lines).

The rationale for using p-value of 0.25 for tests of this nature is presented in the paper of Bancroft "Analysis and inference for incompletely specified models involving the use of preliminary test of significance", Biometrics, pp. 427-442 (1964).

At the end of step 1, one of the following models is selected for the degradation curves,

- a) separate intercepts and separate slopes,
- b) separate intercepts and common slope,

c) common intercept and common slope.

Step 2: Construction of 95% lower and 95% upper confidence intervals for the mean degradation curve.

A 95% lower, and/or a 95% upper confidence intervals are constructed for the mean degradation curve based on model selected at step 1.

Acceptance criteria

In order to have an acceptable potency level of the assay under test, the 95% lower confidence bound should be above the lower specification limit and the 95% upper confidence bound should be below the upper specification limit when both upper and lower specification limits are required. However, if only one specification limit is needed, then either the 95% lower confidence bound should be above the lower specification limit or the 95% upper confidence bound should be below the upper specification limit.

Data analysis and results

There were two types of assays included in this study. The analysis of variance and the p-values of the two different types of assays (anti-xa activity and anti-coagulant activity) with room temperature 30° C for the selections of degradation models are presented in Table 1 through table 2, respectively. Based on the p-values models with common intercept and common slope for anti-Xa activity, the expiration date is selected. Based on the p-values models with separate intercepts and common slope for anti-coagulant activity, the expiration date is selected.

Assay	Selected Model	Expiration Date
Anti-Xa Activity(pooled)	Common Slope and Common intercept	36 months
Anti-Coagulant Activity(each batch)	Common slope and Separate Intercept	- months

The 95% upper and 95% lower confidence bounds were calculated. The estimated degradation lines along with their 95% upper and 95% lower confidence bounds for the room temperatures 30° C are presented in figure 1a (anti-Xa activity) and figures 1b through 1d(anti-coagulant activity) respectively.

V. Summary

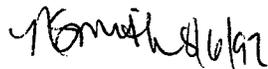
The sponsor submitted the data of both anti-Xa activity and anti-coagulant activity at 30° C in a diskette. The results of reviewer's analyses on both activities (anti-Xa and anti-coagulant activities) showed that the data support the request for an expiration date of 36 months for both assays at 30° C.



Mushfiqur Rashid, Ph.D.
Mathematical Statistician

8/5/97

Concur: Dr. N. Smith


8/6/97

Dr. M. F. Huque


8/5/97

cc: Original NDA 20-164/SCS - 011

HFD-180/Dr. Talarico

HFD-180/Dr. Sieczkowski

HFD-180/ Karen Oliver

HFD-720/Dr. Smith

HFD-720/Dr. Huque

HFD-720/ Chron Copy

Rashid/x73121/MMR/8-5-97

Table 1 (Reviewer) Anti-Xa Activity for Lovenox Injection
 Room Temperature 30° c

P-Values for Model Testing

Model	P-value
Separate intercepts and separate slope common intercept and common slope	.80853
separate intercept and common slope common intercept and common slope	.74817
separate intercepts and separate slopes separate intercept and common slope	.60981

Expiration Dating Periods

Batch Number	Estimated Expiration Date
CB05596	36 months
CB05597	36 months
CB05598	36 months

Table 2 (Reviewer) Anti-Coagulant Activity for Lovenox Injection
 Room Temperature 30° c

P-Values for Model Testing

Model	P-value
Separate intercepts and separate slope common intercept and common slope	.03641
separate intercept and common slope common intercept and common slope	.01357
separate intercepts and separate slopes separate intercept and common slope	.41383

Expiration Dating Periods

Batch Number	Estimated Expiration Date
CB05596	months
CB05597	months
CB05598	months

Figure 1a (Reviewer)
Expiration Date for Lovenox Injection (anti-Xa activity)
Room Temperature 30° C

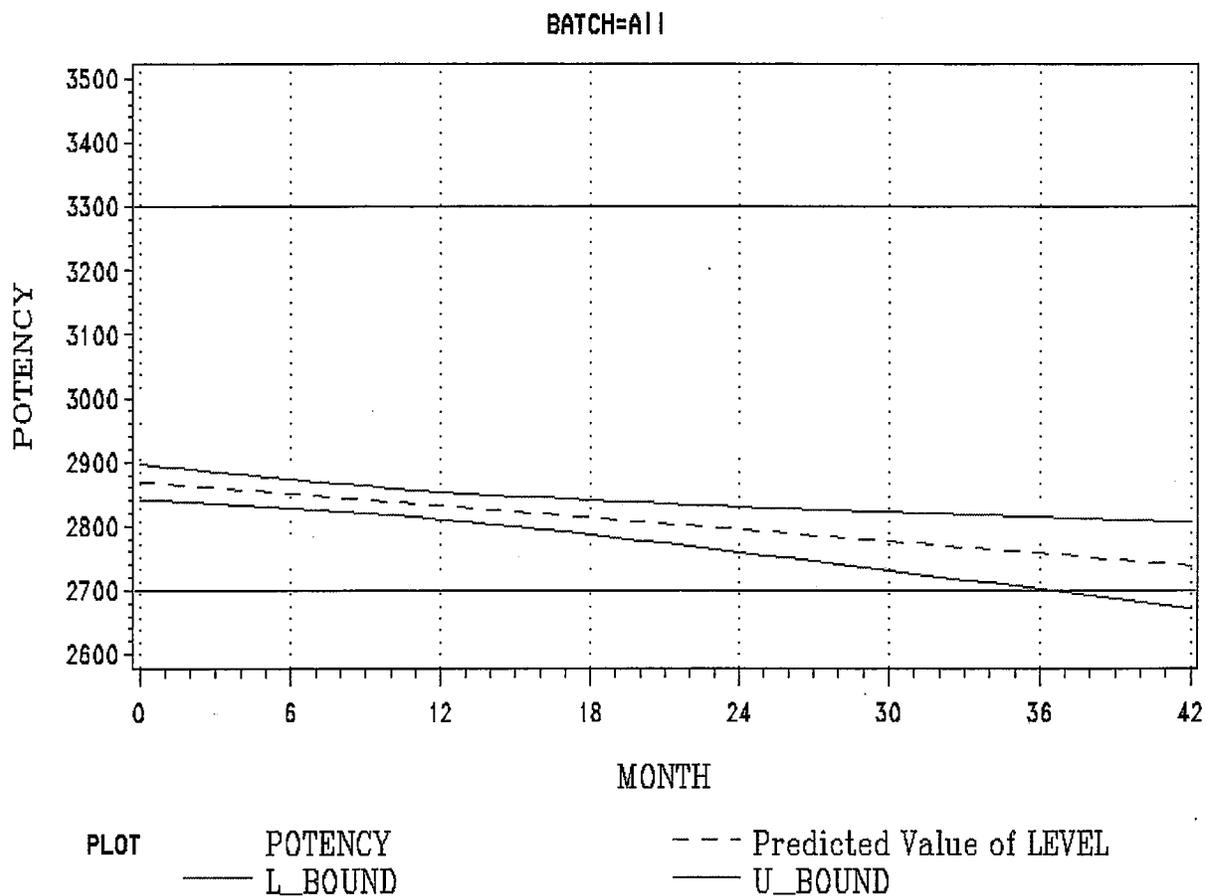


Figure 1b(Reviewer)
Expiration Date for Lovenox Injection (anti-Xa activity)
Room Temperature 30° C

BATCH=CB05596

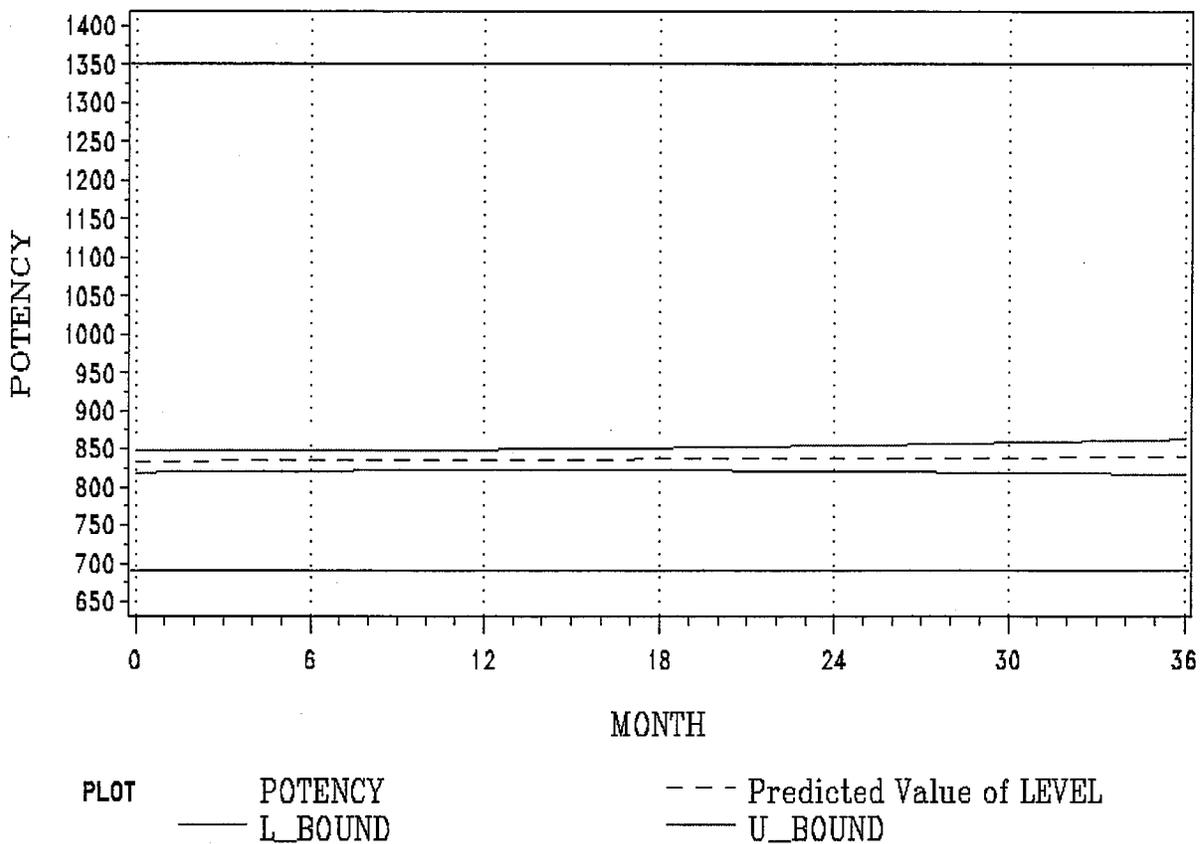
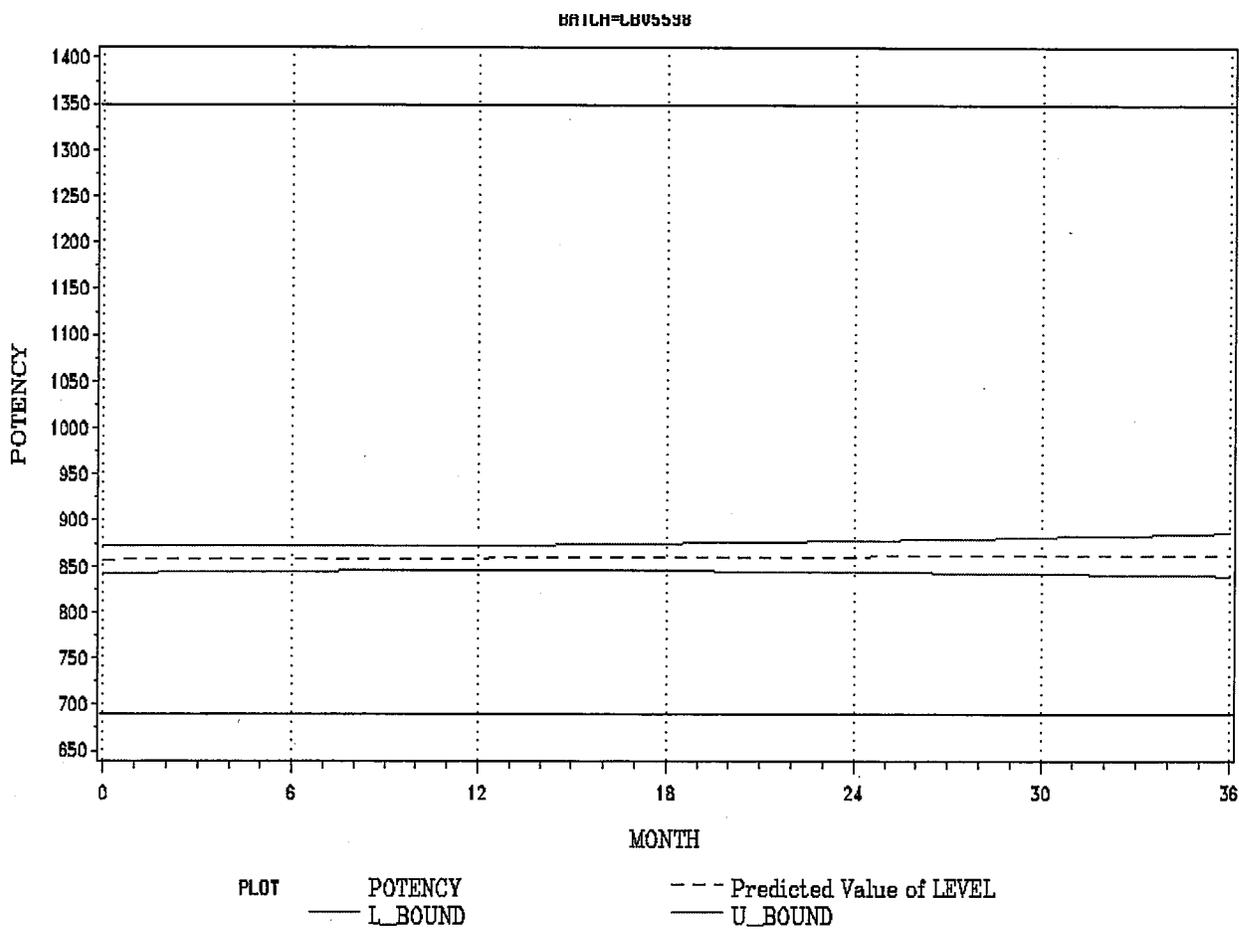


Figure 1d (Reviewer)
Expiration Date for Lovenox Injection (anti-coagulant) activity)

Room Temperature 30° C



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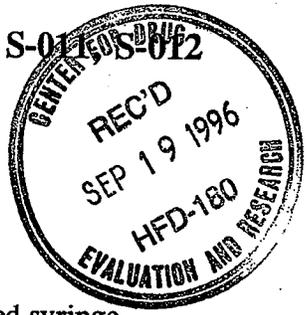
APPLICATION NUMBER:
NDA 20-164/S-011

MICROBIOLOGY REVIEW

48.1 SEP 16 1996

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

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



A. 1. APPLICATION NUMBER:

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

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

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

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

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

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

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

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

4. METHOD(S) OF STERILIZATION: ———

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

B. 1. DATE OF INITIAL SUBMISSION:

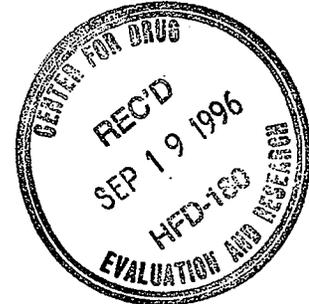
NDA 20-164/S-008: December 27, 1996
NDA 20-164/S-010: March 29, 1996
NDA 20-164/S-011: April 15, 1996
NDA 20-164/S-012: May 24, 1996

9/24/96
JH

NDA 20-164/S-008, S-010, S-011, S-012

Microbiologist's Review # 1

2. **AMENDMENT:** None
3. **RELATED DOCUMENTS:** NDA 20-164
4. **ASSIGNED FOR REVIEW:** July 15, 1996
5. **DATE OF CONSULT REQUEST:**
 NDA 20-164/S-008, S-010, S-011: July 10, 1996
 NDA 20-164/S-012: July 5, 1996



C. **REMARKS:**

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

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

D. **CONCLUSIONS:**

The submissions are recommended for approval for issues concerning microbiology.

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

Ptc 9/16/96

cc:

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

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MICROBIOLOGY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-011

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
PO BOX 5096
COLLEGEVILLE, PA 19426-0800

THOMAS E. DONNELLY, JR., Ph.D.
GROUP DIRECTOR
WORLDWIDE REGULATORY AFFAIRS
TEL 610-454-3023
FAX 610-454-5299
VM 610-454-8666, BOX 3023

July 29, 1997

Lilia Talarico, M.D., Acting 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

SCS/BS
011



NDA 20-164/S-011
Lovenox® (enoxaparin sodium)
Injection

**RESPONSE TO REQUEST FOR
INFORMATION -STATISTICAL
ANALYSIS OF DRUG PRODUCT
STABILITY DATA**

Dear Dr. Talarico:

Please refer to the March 5, 1997 response by RPR to the FDA questions for S-011, dated October 15, 1996. Attachment 20 of the March 5 response provides stability data obtained on 3 batches of 30 mg/0.3ml enoxaparin sodium prefilled syringes stored at 30° C. Reference is also made to the submission of March 21, 1997 which provided the stability data from these 3 lots on diskette.

Reference is also made to the conversation with Ms. Karen Oliver on July 28, 1997 in which she requested that we provide the full statistical analysis of this stability data in conformance with the FDA and ICH Stability requirements. Attachment 1 provides the analysis of the Anti-Xa activity results for Enoxaparin 30 mg syringes (batches CB 05596,

LT 8-4-97

Dr. Lilia Talarico
Page 2 of 2
July 29, 1997
NDA 20-164/S-011



CB 05597 and CB 05598) stored at 30° C. Attachment 2 provides the analysis of the anti-coagulant activity results for Enoxaparin 30 mg syringes stored at 30° C. Attachment 3 provides the full stability report of the same 3 batches after 36 months of storage at 4° C, 25° C, 30° C and 37° C.

Please call me at (610) 454-3023 if we may provide any additional information.

Sincerely yours,

Thomas E. Donnelly, Jr., Ph.D.
Group Director
World Wide Regulatory Affairs

TED/bnh
Attachment



RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
PO BOX 5096
COLLEGEVILLE, PA 19426-0800

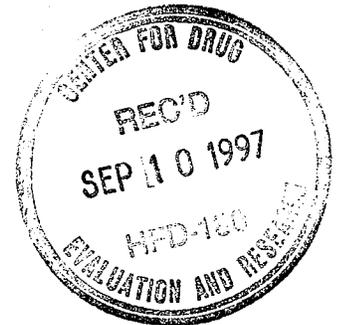
THOMAS E. DONNELLY, JR., Ph.D.
GROUP DIRECTOR
WORLDWIDE REGULATORY AFFAIRS
TEL 610-454-3023
FAX 610-454-5299
VM 610-454-8666, BOX 3023

SCS 1^{AC}
611

ORIGINAL

September 9, 1997

Lilia Talarico, M.D., Acting 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-011

Lovenox® (enoxaparin sodium) Injection

**SUPPLEMENTAL NEW DRUG
APPLICATION**

CHEMISTRY

Dear Dr. Talarico:

Reference is made to our approved NDA 20-164 for Lovenox® (enoxaparin sodium) Injection, supplemental application, sNDA-011, dated April 15, 1996, and the FDA letter dated October 15, 1996. This was followed by our submissions of March 5, March 21, and July 29, 1997.

In response to your August 14, 1997, approvable letter, this submission provides the Methods Validation package for the added and modified drug substance and drug product specifications and test methods as requested.

Dr. Lilia Talarico
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September 9, 1997
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Please do not hesitate to contact me at (610) 454-3023 if you have any questions regarding this submission.

Sincerely yours,

Thomas E. Donnelly, Jr., Ph.D.
Group Director
World Wide Regulatory Affairs

TED/bnh
Attachment

cc: Ms. Debra Pagano