Draft

OCT - 9 1997

NDA 20-164/S-015

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

Dear Dr. Donnelly:

Please refer to your pending February 28, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

To complete our review of the biostatisical section of your submission, we request the following information for Studies 2091 and 529:

1. Provide a separate summary table for each of the studies and include the following information in hard copy and on SAS data sets (extension: .sd2):

   a. Study #,
   b. Center,
   c. Patient #,
   d. What drug after randomization: Enoxaparin/Heparin,
   e. Pre-heparinization prior to randomization: yes/no. If yes, duration of heparin prior to randomization,
   f. Outcome of efficacy at the end of study drug duration period, i.e., VTE occurrence,
   g. Outcome of efficacy at 1 month after randomization, i.e., VTE occurrence,
   h. Outcome of efficacy at 3 months after randomization, i.e., VTE occurrence,
   i. Time to first VTE occurrence,
   j. Outcomes of safety,
   k. Age,
   l. Weight,
   m. Total daily dose.

2. Define the following patient populations: A. Enoxaparin heparinized patients; B. Enoxaparin non-heparinized patients; and C. Heparin patients. For these three defined patient populations, provide the clinical equivalence analyses (95%

and 90% Confidence Intervals) for the following comparisons at end of the study drug duration time, at 1 month, and 3 month endpoints after randomization:

A versus B,
A versus C,
B versus C, and
(A + B) versus C.

3. Provide a safety summary table of elderly patients (age 65 years and older) who received a daily Lovenox dose of 150 mg or greater.

4. Provide SAS data sets (extension .sd2) for all randomized patients involved in the above analyses for questions 1., 2., and 3. above.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

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

Sincerely yours,

/S/ [redacted] 10-7-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Oliver

NDA 20-164/S-015

JUN 14 1997

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

Dear Dr. Donnelly:

Please refer to your pending February 28, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

To complete our review of the biostatistical section of your submission, we request the following information for Study 2091 and Study 529:

1. Both trials are active (Lovenox + Warfarin) vs active control (Heparin + Warfarin). To support the validity of a clinical equivalence trial, assess the ability of the study to have detected a difference between treatments, as required under 21 CFR 314.126(b)(2)(iv), and submit the supportive documentation.

2. The clinical delta is 3% in Study 2091 and 10% in Study 529. Please explain the rationale for these two different deltas. Identify at what time point in the trial development that the two deltas were selected, e.g., the protocol stage. Provide justification for the relatively high delta of 10% for Study 529 given the low recurrence rate for this trial.

3. In the first treatment period, patients were treated only with the study medications enoxaparin and heparin for the first 5 to 14 days (see patient consent form). Please provide the following regarding the first treatment period:

   a. A comparison of the treatment groups for the primary endpoint, including both the all-treated and evaluable patient analyses.

   b. Frequency tables, by treatment group, listing the number of days the patients were treated with the study medications.

4. Please specify the patient population targeted in the proposed new indication and provide background summaries of patient characteristics supporting that specified patient population.

5. Please provide details about randomization including:

   a. The type of randomization, central or by center. Any methods that would be considered "special" to this randomization process.

   b. The stratification, the blocking factors, and the selection and allocation of random assignments to the different strata. A copy of the pre-study randomization chart with the seed numbers used in the generation of random numbers.

   c. The process specific to the assignment of patients to the outpatient and in-patient treatment groups. Identify all inclusion/exclusion criteria associated with the process.

   d. The location of the randomization codes and who had access to the codes.

   e. Any changes to the randomization procedure throughout the course of the studies.

   f. Any additional, relevant information which may be helpful to the reviewer in assessing the randomization process.

6. For Study 529, please provide point estimates and 90 and 95 percent confidence intervals for the primary endpoint data by country and by center for both of the ITT and evaluable patient data sets. If the small centers are to be pooled to one center, provide details of the pooling process. Please provide the test for consistency of results across country/centers.

7. For Study 2091, please provide point estimates and 90 and 95 percent confidence intervals for the primary endpoint data by center for both of the ITT and evaluable patient data sets. If the data from the small centers are pooled to one center, provide details of the pooling process. Please provide the test for consistency of results across centers.

8. Please provide all patient data in the requested analyses (in SAS 6.11 format with .sd2 extension), including SAS codes for these analyses. These data sets should include codes for country, center, treatment group, and an identifier for ITT or evaluable.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

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

Sincerely yours,

/S/ [redacted] 8-14-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-164/S-015
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/N.Markovic
HFD-870/M.Huque
HFD-870/Wen-Jen Chen
HFD-820/ONDC Division Director (only for CMC related issues)

APPEARS THIS WAY ON ORIGINAL

Drafted by: KO/August 11, 1997
Initialed by: N.Markovic 08/11/97
Initialed by: L.Talarico 08/13/97
final: KO/08/14/97/c:\wpwin\karenfil\nda\20164708.lko /S/ [redacted] 08/14/97

INFORMATION REQUEST (IR)

APPEARS THIS WAY ON ORIGINAL

NDA 20-164/S-015
NDA 20-164/S-016

" " 2 4 1997

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

Dear Dr. Donnelly:

Please refer to your pending February 28 (S-015) and March 18, 1997 (S-016) supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We also refer to your biopharmaceutics amendments dated March 5 (S-015) and May 16, 1997 (S-015 and S-016).

We have completed our review of the biopharmaceutics sections of your submissions and have the following requests:

1. Please submit the statistical analysis on the data, the SAS code, and the ASCII data sets in Study RP 54563Q-133 using the following gender analysis model:

   - Y= Weight sequence gender sequence*gender subject (sequence*gender) period product product*gender weight*product sequence*product*period*gender

   - Using the model, if the interaction term "*sequence*product*period*gender*" is not significant at the $p < 0.1$ level, this term could be dropped from the model and the data re-analyzed. If no terms show significance at the 0.05 level, then the analysis could be repeated dropping the weight term. It is noted that to some extent, weight is taken into account through the weight based dosing. The model further explores gender effects in terms of the gender*product interaction.

2. Please comment on the following:

   a. The difference in mean clearance of anti-Xa activity in the population studied under Protocol Report RP 54563Q-260 as compared to earlier studies. Consider consistency in units when comparing mean clearance across studies, i.e whether clearance is based on "IU anti-Xa" or "mg"

of enoxaparin. Avoid comparison of ranges since these are dependent on the number of subjects used in the analyses.

b. The present study suggests that clearance is 70% higher than shown previously in healthy subjects.

c. The higher ratio of anti-Factor Xa to anti-Factor IIa activity (14±3.1) shown in these studies than in the original submission.

In addition, we have the following recommendations:

3. Consider conducting a drug-interaction study in healthy elderly subjects with two treatment arms: enoxaparin and enoxaparin with aspirin.

4. Consider conducting a non-linear mixed effect modeling of the data in the healthy elderly subject study and other studies where sampling for determination of anti-Xa activity etc. has occurred. Properly conducted, non-linear mixed effect modeling studies could identify enoxaparin effects on different populations and the influence of cofactors such as age and co-administered drugs.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental applications.

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

Sincerely yours,

/S/ [redacted] 7-24-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Oliver

NDA 20-164/S-015

MAR - 1997

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
500 Arcola Avenue
P.O. Box 5096
Collegeville, PA 19426-0107

Dear Dr. Donnelly:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Lovenox (enoxaparin sodium) Injection

NDA Number: NDA 20-164

Supplement Number: S-015

Therapeutic Classification: Standard

Date of Supplement: February 28, 1997

Date of Receipt: February 28, 1997

This supplement provides for: a new indication, "the treatment of deep vein thrombosis and pulmonary embolism"; (2) three new packages in 1cc pre-filled syringes (60mg/0.6mL, 80mg/0.8mL, and 100mg/1.0mL); (3) two new dosing regimens (1.5mg/kg qd sc or 1.0mg/kg q12h sc); and (4) the qualification of a new manufacturing line.

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 April 29, 1997 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) 443-0487.

Sincerely yours,

APPEARS THIS WAY ON ORIGINAL

Karen Oliver
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-015
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/L.Talarico
HFD-180/N.Markovic
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
DISTRICT OFFICE

Drafted by: KO/March 6, 1997 /S/ [redacted] 03/06/97
Final: KO/03/06/97/c:\wpwin\karenfil\nda\20164703.1ko

SUPPLEMENT ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20164	**Trade Name:**	LOVENOX (ENOXAPARIN SODIUM)
Supplement Number:	15	**Generic Name:**	ENOXAPARIN SODIUM
Supplement Type:	SE1	**Dosage Form:**	INJ
Regulatory Action:	AP	**Proposed Indication:**	The inpatient treatment of acute deep vein thrombosis with and without pulmonary embolism, when administered in conjunction with warfarin sodium The outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, KAREN OLIVER

/S/ [redacted]
Signature

Project Manager

12/31/98
Date

/S/ [redacted]

12-31-98

[redacted] APPEARS THIS WAY ON ORIGINAL

NDA 20-164/S-015

APR 25 1997

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
500 Arcola Avenue
P.O. Box 5096
Collegeville, PA 19426-0107

Dear Dr. Donnelly:

Please refer to your pending February 28, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection.

We also refer to your amendments dated February 28 and March 5, 14, and 26, 1997.

To complete our review of the biopharmaceutics and biostatistics sections of your submission, we request the following:

Biopharmaceutics

1. The site of manufacture for the formulations used in the clinical and pharmacokinetic studies, specifically batches CB 4337, CB 06071, and CB 06053.

2. The SAS code and ASCII data set with individual Amax and AUC data on anti-Xa and anti-IIa activities and [redacted] assays for Study K91006.

3. Any information on the pharmacokinetic/pharmacodynamic behavior of enoxaparin with concomitant administration of aspirin or warfarin.

4. Any pharmacokinetic/pharmacodynamic information on enoxaparin sodium given as 1.0 mg/Kg every 12 hours SC on a multiple dose basis.

5. Any gender analysis of the pharmacokinetic/pharmacodynamic data.

Biostatistics

6. Separate efficacy data on diskettes for Studies #CPK-2091 and #529. Include primary and secondary endpoints and the demographic and baseline information for each patient. Provide the data sets on SAS data 6.10 files (extension.sd2).

7. A description of variable names used in the SAS data sets submitted on the data diskettes for each of the studies.

8. The SAS programs, on diskettes, used to perform the efficacy analyses (presented in the submitted documents) for the two pivotal studies.

9. The file ENOX_DVT.DOC in the WordPerfect 6.1 version.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

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

Sincerely yours,

APPEARS THIS WAY ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-015
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/N.Markovic
HFD-870/L.Kaus
HFD-720/W.J.Chen
HFD-720/M.Huque
HFD-820/ONDC Division Director (only for CMC related issues)

APPEARS THIS WAY ON ORIGINAL