coagulation parameters is not required (see PRECAUTIONS, Laboratory Tests).

b. In the "Adult Dosage" subsection:

(1) In the "*Hip or Knee Replacement Surgery*" sub-subsection:

The firm should be requested to change the sentence [redacted] to the wording in the September 8, 1997 approvable letter for S-016.

(2) A sub-subsection titled "*Treatment of Deep Vein Thrombosis and Pulmonary Embolism*" was added.

This information should be reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and DIVISION DIRECTOR, Dr. Lilia Talarico, and the information is UNACCEPTABLE. The firm should be requested to delete the sub-subsection and insert the following to read:

DRAFT LABELING

[redacted]

11. In the HOW SUPPLIED section, information about the 60, 80 and 100 mg graduated prefilled syringes was added to the "How Supplied" table.

a. Superscript 1 was added after the second column heading [redacted] and the following information was added as superscript 1 in the footnote section:

[redacted]

This information was reviewed by the REVIEW CHEMIST, Dr. Joseph Sieczkowski, and it is ACCEPTABLE.

b. In superscript 2 of the footnote section of the table, the word [redacted] added before the words [redacted] ., DRAFT LABELING

This information was reviewed by the REVIEW CHEMIST, Dr. Joseph Sieczkowski, and it is ACCEPTABLE.

c. In the body of the table, the graduated prefilled syringe strength DRAFT LABELING was added.

This information was reviewed by the REVIEW CHEMIST, Dr. Joseph Sieczkowski, and it is UNACCEPTABLE. The firm should be requested to delete the graduated prefilled syringe strength "80mg/0.6mL" and insert "80mg/0.8mL".

d. In the body of the table:

The firm should be requested to add the following title heading to the first column: "dosage unit".

12. After the HOW SUPPLIED section, the underlined information in the following sentence was changed

from: DRAFT LABELING

to: [redacted]

This information was reviewed by the REVIEW CHEMIST, Dr. Joseph Sieczkowski, and it is UNACCEPTABLE. In the sentence, the firm should be requested to delete the word [redacted] and insert the word [redacted] read:

DRAFT LABELING [redacted]

Immediate Container Labels and Cartons

Mock up copies of the labels for the 60, 80, and 100 mg immediate container labels, blister packets, and cartons were provided.

13. The firm should be requested to provide the following information:

    a. Indicate on unit package cartons where the lot number and the expiration date will be displayed.

    b. Indicate the following on the syringe label:

        (1) The orientation of the label information on the syringe barrel.

        (2) Where the expiration date will be displayed.

        (3) The graduation which will appear on the label (if any).

Conclusions

1. The firm should be requested to provide final printed labeling incorporating the changes identified in this review including: 1.(a.-i); 2.(1)-(4); 4.a.-b(1)-(2); 5.; 6.a.-b.(1)-(3); 7.a., c., d.(3), e. (1)-(2), f.; 8.a.-b.(1)-(3), c.(1)-(2), d.; 9.; 10.; 11.c.-d.; 12.; and 13.a.-b.(1)-(3).

2. The following should be reviewed by the biopharmaceutics reviewer: 3.

/S/ [redacted] 02/27/98
Karen Oliver
Regulatory Health Project Manager

EXCLUSIVITY SUMMARY for NDA # 20-164 SUPPL # S-015

Trade Name Lovenox Inj. **Generic Name** enoxaparin sodium
Applicant Name Rhone-Poulenc Rorer **HFD-** 180

Approval Date 12/31/98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES / / NO /X/

   b) Is it an effectiveness supplement?

   YES /X/ NO / /

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO / /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac
20-164/S-015 HFD-180

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-164 Lovenox (enoxaparin sodium) Injection

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /X / NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CPK 2091

Investigation #2, Study # 529

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 CPK 2091	YES /___/	NO / X /
Investigation #2 529	YES /___/	NO / X /
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA #_____ Study #_____
NDA #_____ Study #_____
NDA #_____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA #_____ Study #_____
NDA #_____ Study #_____
NDA #_____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # CPK 2091

Investigation #2, Study # 529

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/ [redacted] 12/10/98

Signature Date

Title: Project Manager

/S/ [redacted] 12-31-98

Signature of Division Director Date

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

RHÔNE-POULENC RORER

ORIGINAL

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107

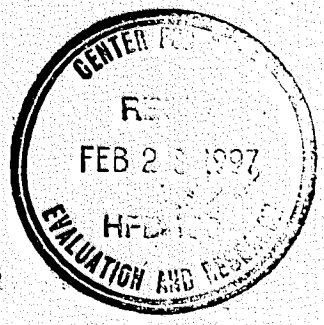
THOMAS E. DONNELLY, JR., Ph.D.
GROUP DIRECTOR
WORLDWIDE REGULATORY AFFAIRS

TEL: 610-454-3023
FAX: 610-454-5299
VM# 610-454-8666, BOX 3023

NDA NO. 20-164 SERIAL NO. 015

NDA SUPPLEMENT NO. SE1

February 28, 1997



Stephen B. Fredd, 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, Maryland 20857

NDA 20-164
Lovenox® (enoxaparin sodium)
Injection
SUPPLEMENTAL NEW DRUG APPLICATION
New Indication
New Syringes: Graduations, size and fill volumes
(60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1.0 mL)
Qualification of a New Manufacturing Line

Dear Dr. Fredd:

Reference is made to our approved NDA 20-164 for Lovenox (enoxaparin sodium) Injection, which is indicated for prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip or knee replacement surgery.

New Indication:
In accordance with 21 CFR 314.50 and 314.71 and with reference to approved NDA 20-164, Rhone-Poulenc Rorer is submitting a Supplemental New Drug Application for Lovenox (enoxaparin sodium) Injection which demonstrates the safety and efficacy of the product in the treatment of deep vein thrombosis and pulmonary embolism.

We initially indicated in a submission dated May 4, 1993 that we intended to further develop Lovenox Injection for this indication. You responded to this on June 30, 1993 which was followed by an RPR response on October 12, 1993. The efficacy parameters in study 529 of clinical monitoring, venograms and ventilation-perfusion lung scans were agreed to in a conversation held on November 22, 1993. On

3/14/97 /S/ [redacted]