

subjects similar to those reported here, while the values obtained by Dawes & Pepper (1979), using ¹²⁵I, were different (80 min). These differences may be due to differences in the behaviour of the isotopes themselves as demonstrated for other radiopharmaceuticals (Oberhausen *et al.* 1987), differences in injected doses, sample numbers, experimental duration or the curve-fitting methods used.

The radioactivity measurement also show that plasma kinetics (Psuja, 1988) and kinetics of elimination from organs and via the urine of heparin and Enoxaparin are quite similar. The half-lives determined by biological activity were shorter than those obtained from tracer studies for both heparin and enoxaparin. This discrepancy may have several explanations:

(i) *Labelled compounds instability.* This is unlikely, since the labelled and unlabelled products have the same biological activities, and the labelled compounds were shown to be stable *in vivo*, as indicated by the absence of free pertechnetate and by the presence of radioactivity and biological activity in the same elution peaks. The small differences which are observed remain compatible with the labelling of molecules showing an anti Xa activity.

(ii) *Non-comparable methods of measurements.* All the fragments of heparin and enoxaparin are labelled (Colas-Linhart *et al.* 1986), irrespective of their molecular weights, and can thus be monitored by following radioactivity. On the other hand, biological activity assays only detect the molecules which have an affinity for AT III.

(iii) *Release of an endogenous biologically active factor.* The amount of enoxaparin in whole plasma and fractionated plasma, calculated from anti Xa activity, is higher than the amount calculated from radioactivity measurements during the initial 3 h post injection.

Several authors (Marcum & Rosenberg, 1985; Dawes *et al.* 1986a, b; Uzan *et al.* 1987; Thomas, 1985) have suggested that an endogenous biologically active factor might be released in response to LMWH but such a factor cannot be detected by tracer measurements.

Like others (Briant *et al.* 1989; Matzch *et al.* 1987), we found that the biological half-lives were longer for enoxaparin than for heparin. Some hypothesis to explain this difference are given here:

(i) *Differences in the organ distribution of labelled heparin and enoxaparin.* The distribution of radioactivity in the heart and liver was the same for heparin and enoxaparin. The scintigraphic measurements give overall elimination rates which do not distinguish between the organ itself, blood within it or vessel endothelial tissue (which binds heparin) (Barzu *et al.* 1985; Van Rijn *et al.* 1987). There is also no correction for variations in tissue absorption within each organ. Nevertheless, the data clearly show that both heparin and enoxaparin are initially taken up by the liver and that their elimination from the liver is slower than from the blood. Both heparin and enoxaparin are eliminated via the urine at the same rate. The differences in their blood kinetics are therefore probably not due to differences in their heart or liver distribution or urinary elimination, and this hypothesis should be withdrawn.

(ii) *Differences in protein fixation.* The differences may be due to protein fixation. Enoxaparin could bind almost exclusively

to AT III (which induces a high biological activity) whereas heparin also binds to other proteins such as albumin. Thus addition of AT III to ACA 54 separated fractions of heparin-containing plasma induces high heparin biological activity. The results obtained with and without addition of AT III support this hypothesis (Table II).

(iii) *Metabolism of injected heparin and enoxaparin.* When using ³⁵S, desulphation can result in a loss of the ³⁵S label (Uzan *et al.* 1987) from heparin, such that the label no longer reflects the elimination of heparin. However, ^{99m}Tc probably remains bound to the circulating molecule even after they have lost their biological activity. Thus, heparin could be degraded into inactive metabolites which retain their radioactivity, whereas enoxaparin is eliminated in a biologically active form which is detectable by adding AT III.

(iv) *Low molecular weight heparin neutralization.* Some authors (Lane *et al.* 1985; Lijnen *et al.* 1983; O'Brien *et al.* 1985) suggested that low molecular weight heparin may be expected to be more resistant to neutralization by histidine-rich glycoprotein and PF4 than standard heparin.

CONCLUSION

Plasma and urinary radioactivity measurements show that standard heparin and enoxaparin have very similar biodistribution and urinary excretion kinetics, when they are injected intravenously into human subjects. The blood anti Xa activity 5 min after injection is higher in response to enoxaparin than after heparin injection, and is more persistent after enoxaparin. This suggests that phenomena other than distribution are involved. The two most likely explanations are differences in metabolism and/or the release of an endogenous factor.

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Oliver

FEB 26 1998



CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-164/SE1-015 and SE1-016
Enoxaparin sodium injection

SUBMISSION DATES:
February 28 and March 5, 1997 (SE1-015)
March 18 and May 16, 1997 (SE1-016)

BRAND NAME: LOVENOX®

SPONSOR: Rhone-Poulenc Rorer
Pharmaceuticals Inc., Collegeville, PA

REVIEWER: Arzu Selen, Ph.D.

TYPE OF SUBMISSION:

Supplemental New Drug Application
(Original NDA approved March 29, 1993)

Code: SE1

TITLE: Review Of Sponsor's Comments to the Questions Raised During Review of the Supplemental NDA Supporting 1-ml Prefilled Syringes Containing 60, 80, or 100 mg Enoxaparin Sodium (100 mg/ml)

SUMMARY:

Lovenox®, a low molecular weight heparin (LMWH), is currently marketed for prevention of deep vein thrombosis. It is administered by s.c. injection, 30 mg twice daily in patients undergoing hip or knee replacement surgery and 40 mg once daily in patients who are undergoing abdominal surgery and may be at risk for thromboembolic complications. If clinically warranted, Lovenox doses may continue for 7 days after the surgery. The Sponsor claims that administration of Lovenox up to 14 days has been well-tolerated in controlled clinical trials.

In these supplemental submissions, SE1-15 (nonpriority) and SE1-16 (priority), the objective of the Sponsor is to get approval for 1ml graduated prefilled syringes containing 60 mg/0.6 ml, 80 mg/0.8 ml or 100 mg/ml enoxaparin sodium. The proposed indications for these submissions are treatment of unstable angina and non-Q-wave infarction with concurrent administration of aspirin (1 mg/kg q12 h s.c.) and treatment of deep vein thrombosis and pulmonary embolism (1.5 mg/kg qd sc or 1 mg/kg q12h sc). These prefilled syringe dosage forms will be an addition to the currently marketed Lovenox products (30 mg/0.3 ml ampoules and 40 mg/0.4 ml prefilled syringes).

The reports (K9001006, RP54563Q-133, RP54563Q-260 and RP54563Q-261) supporting these Supplemental NDAs SE1-015 and 016 were reviewed by Dr. Lydia Kaus and reported in the Clinical Pharmacology and Biopharmaceutics Review dated July 14, 1997. The questions raised by Dr. Kaus were communicated to the Sponsor on July 24, 1997 and the Sponsor's response was received August 8, 1997 (Attachment 1). An assessment of Sponsor's response, comments that need to be communicated to the Sponsor and the recommendation for this supplemental NDA are in the following sections. The revised proposed package insert is in Attachment 2.

REVIEW OF SPONSOR'S RESPONSES:

In the July 24, 1997 letter to the Sponsor, in addition to the two questions which were related to two Studies (RP54563Q-133 and RP-54563Q-260), it was recommended that the Sponsor should consider a drug-drug interaction study of aspirin and enoxaparin in healthy elderly subjects and nonlinear mixed effect modeling of the enoxaparin data for better characterization of covariates influencing anti-Xa activity of enoxaparin.

A brief description of the questions from the FDA (in the sequence as in the original letter), the responses from the Sponsor and recommended follow-up action items are given below.

1. **Statistical reanalysis of data from Study RP54563Q-133 was requested with emphasis on determining gender and gender and product interaction effects. In the recommended statistical model, the following effects were identified for further testing: weight, sequence, gender, sequence and gender interaction, subject nested within sequence and gender interaction term, period, product, product and gender interaction, weight and product interaction, a term representing interactions of sequence, product, period and gender. It was also indicated that if the term representing interactions of sequence, product, period and gender was not significant at the $p < 0.1$ then the term could be removed from the model and the analysis would be repeated with the remaining effects. Further instructions were provided to explore the significance of the contribution of these effects.**

The Study RP54563Q-133 was conducted in 1995 in healthy male and female subjects (n=24). The objectives of this study were pharmacokinetic characterization of two formulations of enoxaparin sodium (100 mg/ml and 200 mg/ml) administered subcutaneously, once a day at 1.5 mg/kg dose for 5 days and to verify that the pharmacokinetic parameters after the 200 mg/ml formulation were similar to the parameters obtained after the 100 mg/ml formulation. The three treatments were Treatment A: daily s.c. 1.5 mg/kg dose of 100 mg/ml enoxaparin sodium, Treatment B: daily s.c. dose of 1.5 mg/kg dose of 100 mg/ml enoxaparin sodium injected concomitantly at two different sites at 0.75 mg/kg dose and Treatment C: daily s.c. 1.5 mg/kg dose of 200 mg/ml enoxaparin sodium. The pharmacokinetic parameters were derived from anti-Xa and anti-IIa activities, [REDACTED] and aPTT measurements obtained on Day 5 of the study. A description of the analytical and statistical methods and a summary of the results are provided in the Clinical Pharmacology and Biopharmaceutics Review (Dr. Kaus, July 14, 1997). Statistically significant gender effects ($p < 0.0001$) were noted on volume of distribution (apparent volume of distribution) and $t_{1/2}$ derived from anti-Xa activity. In anti-IIa derived parameters, a statistically significant ($p = 0.0324$) gender effect was noted in AUC(0-t). Statistically significant gender effects were noted in Heptest derived parameters but not in aPTT derived parameters. The 90% confidence intervals of anti-Xa activity derived A_{max} , AUC(0-24) and AUC(0- ∞), anti-IIa activity derived A_{max} , and AUC(0-8) and [REDACTED] derived parameters ($A(\Delta t_{max})$ and AUC(0-24)) were all within the 80% to 125% range. The 90% confidence intervals for the anti-IIa activity derived AUC(0-t) values were 107% to 126% for comparison of Treatment C with Treatment A

and comparison of Treatment C with Treatment B. Overall, the three treatments are similar.

The gender effects observed in this study (RP54563Q-133) led to the request for further reanalysis of data according to an FDA described model. The Sponsor was also requested to provide an ASCII file of the data as well as the SAS code used for reanalysis.

The Sponsor's response and statistical reanalysis results are included in Attachment 1. The results from the final model testing effects of weight, sequence, gender, gender and sequence interaction, subject within sequence, period, treatment, treatment and gender interaction, and weight and treatment interaction on log-transformed anti-Xa derived parameters are summarized in Table 1. Because some discrepancies were noted between the tabular summary provided by the Sponsor and the statistical analysis printouts, Table 1 is prepared by the reviewer, based on the Sponsor's reanalysis printouts (Attachment 1).

Table 1: A summary of statistical significance of the effects (as identified in the final model) on anti-Xa activity derived parameters (RP54563Q-133)

Source	DF	Log-transformed anti-Xa derived parameters			
		Amax	AUC(0-24)	AUC(0-36)	AUC(0-∞)
Weight	1	0.0002	0.0001	0.0001	0.0001
Sequence ⁺⁺	5	NS	NS	NS	NS
Gender	1	NS	0.0029	0.0027	0.0030
Gender*Sequence	5	0.0002	0.0001	0.0001	0.0001
Subject(sequence)	6	0.0004	0.0001	0.0001	0.0001
Period	2	NS	NS	NS	NS
Treatment	2	NS	NS	NS	NS
Treatment*Gender	2	NS	NS	NS	NS
Weight*Treatment	2	NS	NS	NS	NS

Note:

- Sequence⁺⁺ indicates that in determining sequence effect, Type III MS for Subject(sequence) was used as the error term.

In the reanalysis provided by the Sponsor it is apparent that while there is no gender and treatment interaction, there is significant gender effect in all anti-Xa AUC parameters. It appears that an incorrect error term was used for assessment of gender effect. The gender effect was further evaluated by the reviewer using Type III MS for Subject(sequence) as the error term, and it was found that it was no longer statistically significant. (Attachment 3). This observation, as well as other related comments are listed under the section of Questions/Comments to be communicated to the Sponsor.

2. In FDA's July 24 1997 letter, the Sponsor was requested to comment on the following:
 - a) the difference between the clearance values observed in the Study RP54563Q-260 and the earlier studies,
 - b) that the clearance in RP54563Q-133 is 70% higher than the values obtained in previous studies in healthy subjects,

c) the higher ratio of anti-Xa activity to anti-IIa activity (14 ± 3.1) in this study compared to that in the original submission.

The Sponsor has provided a joint response for the two items, a and b, and essentially agrees that the mean clearance values in this study, RP54563Q-260 are higher than those reported in the submission (RP54563Q-K91006, RP54563Q-K91107 and RP54563Q-133).

This Study RP54563Q-260 was conducted in patients over a period of one year, starting in August 1994 and completing in August 1995. The patients were admitted to the hospital with unstable angina or acute non-Q-wave myocardial infarction. The objectives of the study were to evaluate safety and efficacy of 5 weeks of enoxaparin therapy (60 mg/0.3 ml, s.c. once daily) in combination with aspirin (100 mg, po once daily) and also, to assess the pharmacokinetic profile on Day 4 of the study based on anti-Xa and anti-IIa activities and Heptest and aPTT measurements. The mean CL/F value derived from anti-Xa activity was 1.02 ± 0.33 l/h (17.0 ± 5.5 ml/min).

In the same submission (SE1-15 and SE1-16), as pointed out by Dr. Lydia Kaus, the mean CL/F values of the four treatments ranged from 0.64 l/h to 0.72 l/h (PK9001006) and from 0.59 l/h to 0.61 l/h in the male subjects and from 0.55 l/h to 0.60 h/l in female subjects (RP54563Q-133) and were significantly lower than the values observed in Study RP54563Q-260. The enoxaparin sodium doses were 1, 1.25, 1.5 and 2.0 mg/kg in Study PK9001006, 1.5 mg/kg in Study RP54563Q-133 and 60 mg daily in RP54563Q-260. This observation is consistent with the possible dose-dependency in anti-Xa derived CL/F values as observed during review of the Lovenox studies submitted for the Supplemental NDA 20-164/S-018.

The Sponsor agrees that the values were high and attributes it to the fact that the pharmacokinetic data were obtained only from 16 patients and that the variability in this study was higher compared to other studies. It is stated that the CV% for CL/F was 33% in RP54563Q-260 while it is mostly in the 15% to 20% range in the Phase I studies. Furthermore, the Sponsor indicates that for these reasons, they have relied more on data from Study RP54563Q-261 in which "peak" and trough samples were collected in over 350 patients at two doses (1.25 mg/kg and 1 mg/kg) after the third enoxaparin sodium dose. The Sponsor further discusses RP54663Q-261 and how the results from this study are consistent with that predicted from the pharmacokinetic modeling of data from Study RP 54563Q-K91006 (note: in both studies the enoxaparin sodium dose was at least 1 mg/kg). Finally, the Sponsor states that based on data from RP54563Q-261, any difference in pharmacokinetics of enoxaparin observed between healthy subjects and patients is significantly overestimated in RP54563Q-260.

The Sponsor's response that the difference in the CL/F values is due to higher variability in this study compared to others is considered unacceptable. This item is further discussed in the section for comments to be communicated to the Sponsor.

For item c of this question, the Sponsor indicates that the ratio of anti-Xa and anti-IIa activities reported in the original NDA 20-164 was 3.95 (and is 3.35 ± 0.89 in the package insert) based on intravenous administration of enoxaparin. The Sponsor continues to state that the ratio is higher after s.c. dosing than reported in the package insert and finally, states that the ratios reported in the current submission are comparable to those observed in the original submission.

The Sponsor essentially has not responded to item 2C. The Sponsor is stating that 14.0 in RP54563Q-260 (where individual values range from 6 to 15) is comparable to other reported values and to 3.95 as listed in the original NDA.

A follow up to this response is in the section for comments to be communicated to the Sponsor.

3. In the July 24 1997 letter, the Sponsor was asked to consider a drug-drug interaction study for enoxaparin and aspirin in healthy elderly subjects. The Sponsor has agreed to conduct the interaction study and also indicates that they are unclear of a biopharmaceutical mechanism that may lead to an enoxaparin and aspirin interaction.

Comments to this are also under the section for comments to be communicated to the Sponsor.

4. In the July 24, 1997 letter, the Sponsor was asked to consider a nonlinear mixed effects analysis of data obtained from anti-Xa activity from the enoxaparin studies. The Sponsor indicates that they are planning the analysis of the available "enoxaparin" data using the nonlinear mixed effects modeling and that the patient data from RP54563Q-261 would also be included in this analysis.

A follow-up question for this item is also listed under the section for comments to be communicated to the Sponsor.

Comments to be Communicated to the Sponsor:

1. The gender effect observed in anti-Xa derived parameters particularly gender and treatment interaction in RP54563Q-133 has been a concern as it was communicated to the Sponsor in the July 24, 1997 letter. Possible approaches to further explore gender effect in anti-Xa derived parameters were considered and it is unclear whether these approaches were communicated verbally to the Sponsor as the FDA Biopharmaceutics Reviewer who initiated the reanalysis of data from RP54563Q-133 is no longer with the FDA. A proposed reanalysis model was based on evaluation of the gender effect utilizing Type III MS from subject within sequence as the error term.

Following reanalysis of the submitted data, using Type III MS from subject within sequence as the error term, the gender effect was no longer statistically significant. In future analyses, please use Type III MS from subject within sequence as the error term for evaluating gender effect.

2. During review of the Summary Table provided in the August 7, 1997 response, several discrepancies between the information in the table and the printouts in the attachment were noted. The table is stated to reflect the p values from the final model, however, based on the entry for "weight" and "Subject(gender*sequence)" in the source column of the Summary Table, this statement is inaccurate. Furthermore, the sequence effect is represented inaccurately in the table (based on the SAS printouts provided by the Sponsor, the sequence effect is not significant for any one of the parameters that were tested).

3. Items 2a and 2b:

It is possible that the data from RP54563Q-260 is more variable compared to other studies, however, we do not believe that the differences observed in the mean CL/F values represent variability in the data or an overestimation of anti-Xa derived parameters. A review of enoxaparin sodium studies (100537, 100539, 100541, 100542, 105640, K9001006, and RP54563Q-133) has shown that the anti-Xa derived CL/F values may be lower after administration of high (1 mg/kg or higher) enoxaparin sodium doses than the CL/F values obtained after administration of low enoxaparin sodium doses (such as 60 mg in RP54563Q-260). This relationship suggesting dose-dependency in the anti-Xa derived CL/F values needs to be further investigated as requested in the response to the Supplemental NDA Submission (20-164/S-018).

Please provide data and an assessment of the correlation between anti-Xa activity and enoxaparin doses covering the studied dose range (40-mg to 2 mg/kg for an average body-weight of 70 kg).

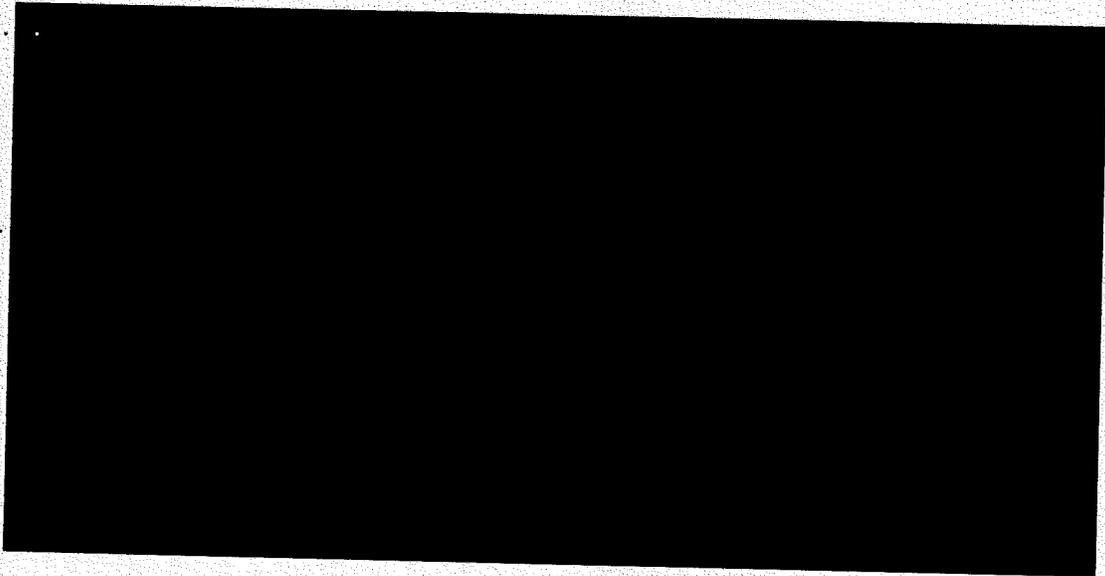
Please provide ASCII data files on a disk for anti-Xa activity vs time (and pharmacokinetic parameters if available) from all subjects in RP54563Q-260 and RP54563Q-261 with the patient/subject demographics in the same file.

4. Item 2c:

During review of Lovenox studies, submitted for s.c. dosing, it was noted that the ratio of anti-Xa activity to anti-IIa activity is consistently higher than that indicated in the current package insert (3.35 ± 0.89). In the September 8, 1997 letter to the Sponsor, the Sponsor was requested to revise the package insert to reflect the anti-Xa and anti-IIa ratio obtained after s.c. dosing. The anti-Xa to anti-IIa ratio as presented in the package insert should be clarified to indicate that it was obtained after iv dosing, and the anti-Xa to anti-IIa ratio obtained after s.c. dosing (median value across studies) should also be included in the package insert.

5.

6.



LABELING COMMENTS (CLINICAL PHARMACOLOGY SECTION)

The Sponsor has provided a revised labeling (February 10, 1998) to address comments made for the Supplement SE1-015 and the following items refer to the sections of this February 10, 1998 proposed revised package insert.

1. First paragraph, second sentence: please modify this sentence to indicate that the reported ratio is based on activity derived following iv dosing of enoxaparin sodium and also provide the anti-Xa to anti-IIa activity ratio (median value across studies) after the s.c. dosing as requested in the September 8, 1997 letter.
2. First paragraph, third sentence: please provide the data that supports this sentence.
3. Last sentence, first paragraph: Please provide a tabular summary of data (study number, design, enoxaparin sodium dose, dosing frequency, patient population, and aPTT results) that support this sentence. Please verify whether data from studies other than that indicated in the Footnote 9 were used to support this sentence as both reports K9001006 (taken to be the report listed as PK91006:RP54563) and PK 91007 are single dose studies.
4. Pharmacodynamics Section, first paragraph, fifth sentence: Please provide the reference and the information supporting this sentence related to clearance of enoxaparin including the enoxaparin sodium dose at which this estimate was obtained.
5. Pharmacodynamics Section, second paragraph, first sentence: Please provide the reference and the information supporting this sentence related to clearance and Cmax derived from anti-Xa activity after single and multiple doses in elderly subjects and in subjects with renal impairment.
6. Pharmacodynamics Section, second paragraph, third sentence: Please provide the data and the method used for calculation of the AUC values that are indicated to be 25% higher on Day 10 compared to Day 1.
7. Please provide the data that supports this paragraph related to decline of total radioactivity and anti-Factor Xa activity.

APPEARS THIS WAY ON ORIGINAL

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the information submitted for both Lovenox NDA 20-164 Supplements filed on February 28 and March 5, 1997 (SE1-015) and March 18 and May 16, 1997 (SE1-016) for additional strengths of prefilled syringe dosage forms of enoxaparin sodium. Based upon the review of the provided information and data, it is concluded that Supplements SE1-015 and SE1-016 are acceptable assuming that it is not critical from a safety and efficacy perspective to have Comment Nos. 1-6 (pages 5 and 6 of this review) addressed prior to the approval of Supplement SE1-015. However, it should be agreed by the Sponsor that they will address these comments within 30 days of receipt. Additionally, the Labeling Comments Nos. 1-7 (page 7 of this review) should be communicated to the Sponsor for resolution before the approval of Supplement SE1-015.

/s/

Arzu Selen, Ph.D.
Division of Pharmaceutical Evaluation II

/s/ [redacted]
RD initialed by [redacted] 2/25/98
John Hunt, B.Sc.
Deputy Director and Acting Team Leader

/s/ [redacted] 2/26/98
FT initialed by [redacted]
Mei-Ling Chen, Ph.D.
Director, DPEII

cc: NDA 20-164, HFD-180 (Markovic, Oliver), HFD-720(Chen),
HFD-870 (Chen, Hunt, Selen), HFD-850 (Lesko),
HFD-340 (Viswanathan), Central Document Room (Barbara Murphy)

APPEARS THIS WAY ON ORIGINAL

ATTACHMENT 1:

AUGUST 7, 1997 DATED RESPONSE FROM THE SPONSOR

**LOVENOX
SUPPLEMENTAL NDA 20-164/SE1-015 AND SE1-016**

RP RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

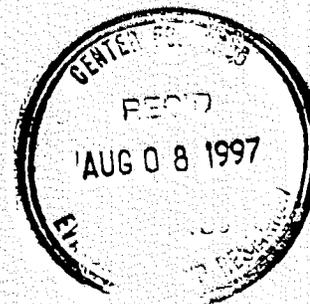
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August 7, 1997

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NDA 20-164/ S-016

**Lovenox® (enoxaparin sodium)
Injection**

RESPONSE TO FDA REQUEST

Dear Dr. Talarico:

Reference is made to supplement S-016 submitted March 18, 1997 for the use of Lovenox Injection in the treatment of unstable angina and non-Q-wave myocardial infarction, concurrently administered with aspirin. This submission also provided for qualification of new 1 mL graduated syringes filled with either 60, 80, or 100 mg of the previously approved 100mg/mL enoxaparin sodium formulation.

ISI 8-13-97