CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-004

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Approval Date: March 15, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-004

APPROVAL LETTER

NDA 20-164\S-004

MAR 15 1996

Rhone-Poulenc Rorer Pharmaceuticals
Attention: Thomas E. Donnelly, Jr., Ph.D.
P.O. Box 1200
500 Arcola Road
Collegeville, Pennsylvania 19426-0107

Dear Dr. Donnelly:

Please refer to your October 11, 1995 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection.

We also acknowledge receipt of your amendment dated January 2, 1996.

The supplemental application provides for the use of heparin sodium from ———— ———— in the manufacture of the drug substance, enoxaparin 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.

Sincerely yours,

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164
HFD-180
HFD-181/CSO/KOliver
HFD-180/SFredd
HFD-180/JSieczkowski 3-14-96
DISTRICT OFFICE
R/D init: JGibbs/3-6-96
dob DRAFT 3-6-96\F/T 3-13-96\WP: c:\wpfiles\chem\N\20164004.1JS

3/15/96

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-004

CHEMISTRY REVIEW

CHEMIST REVIEW: #1	1. Organization: HFD-180	2 NDA Number: 20-164 MAR 15 1996	
3. Name and Address of Applicant (City & State): Rhone-Poulenc Rorer Pharmaceuticals, Inc. 500 Arcola Road, P. O. Box 1200 Collegeville, PA 19426-0107		4. AF Number:	
		5. Supplement(s)	
		Number(s):	Dates(s):
6. Name of Drug: Lovenox Injection	7. Nonproprietary Name: enoxaparin sodium	SCM-004 BC	11 OCT 1995 01 JAN 1996
8. Supplement Provides for: the use of heparin sodium from ——— in the manufacture of the drug substance, enoxaparin sodium.		9. Amendments and Other (Reports, etc.) Dates: 1. Clinical Pharm. & Biopharm. Rev., JAN 31, 1996 by Lydia Kaus, Ph.D. 2. Statistical Review and Evaluation, Stability, MAR 1, 1995 by Ted Guo. 3. Annual Report Y-002, JUL 14, 1995.	
10. Pharmacological Category: antithrombotic	11. How Dispensed: RX XX OTC __	12. Related IND/NDA/DMF(s): Heparin Sodium: 1. DMF ——— 2. DMF ———	
13. Dosage Form: Injection (SVP)	14. Potency: 30 mg/0.3 mL		
15. Chemical Name and Structure: See the USP directory of USAN and International Drug Names 1996.		16. Records and Reports: Current _____ Yes _____ No Reviewed _____ Yes _____ 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: JGibbs/3-5-96
dob DRAFT 3-6-96\ **F/T 3-13-96**\Wp: c:\wpfiles\chem\S\20164004.1js

18. Conclusions and Recommendations: Based on the submitted information on the manufacture of heparin sodium and enoxaparin sodium, and the stability of enoxaparin sodium and enoxaparin sodium injection, the supplement is recommended for approval. RPR Pharmaceuticals should be notified of the approval by letter.

(See attached APPROVAL letter and the CSO should send the Biopharm Comments to the applicant for future submissions.)

19. Reviewer

Name:	Signature:	Date Completed:
Joseph Sieczkowski, Ph.D.	Joseph Sieczkowski 3-14-96	March 5, 1996

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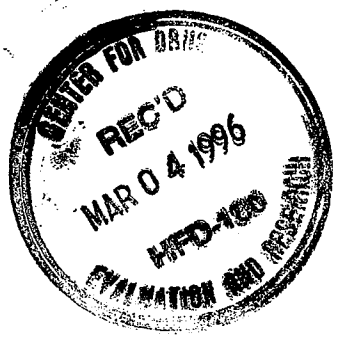
CHEMISTRY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-004

STATISTICAL REVIEW



STATISTICAL REVIEW AND EVALUATION
STABILITY

Date: MAR - 1 1996

NDA#:	20-164
Applicant:	Rhone-Poulenc Rorer Pharmaceuticals, Inc.
Name of Drug:	Lovenox (enoxaparin sodium)
Documents Reviewed:	Supplement to the original, volume 1 of 3, with applicant's letter of October 13, 1995
Statistical Reviewer:	Ted (Jiyang) Guo, DOBII/OEB, HFD-715
Chemist:	Joseph Sieczkowski, ODE III, HFD-180

3/1-/96

3/6/96

Table of Contents

1. Introduction

Heparin sodium is a starting material for synthesis of the drug substance, enoxaparin sodium that is used in the drug product, Lovenox. The sponsor submitted this supplemental NDA to justify the qualification of an alternative manufacturing site for heparin at ———————— ————————. The currently approved source for heparin is ————————

In this supplemental NDA, the sponsor compared the drug substance, enoxaparin sodium manufactured on the two sites. The goal was to show that the stability of ———— enoxaparin sodium and ———— enoxaparin sodium were similar based on a number of parameters.

The stability analysis on the anti-Xa activity of the drug product using the heparin sodium manufactured at ———————————— was provided for review. The analysis was based on three batches of enoxaparin sodium 30mg/0.3 ml pre-filled syringes manufactured at ———. The focus of this review was the stability of the anti-Xa activity of the drug product, Lovenox, as was requested in this consultation.

2. The Sponsor's Analysis

The testing batches of enoxaparin sodium were maintained at 25^{0}C during three years for batch CB05091 and six weeks for batches 5286 and 3008. The sponsor compared the anti-Xa activities among the batches CB05091, 5286 and 3008 and did not find any significant differences among these batches. Because batch CB05091 satisfied the specifications after three years of storage at 25^{0}C, the sponsor concluded that the shelf life was expected to be greater than two years. The sponsor also pointed out that this result was going to be updated when further data were available.

3. The Reviewer's Analysis

The stability was analyzed by the reviewer based on the data provided by the sponsor on a 3.5" diskette. The variable of interest was anti-Xa activity. The sponsor's specification limits of 2700-3300 IU/PFS were used in the analysis. To decide the expiry period, two-sided 90% confidence limits were used.

The batch poolability test showed that the linear regression lines for the batches had a common slope and separate intercepts (A-1). The estimated expiry period was 150 weeks, which was equivalent to 2 years and 11 months (A-2). Note that the sponsor proposed a —— expiry period.

4. Discussions and Conclusions

Based on the three-year data for batch CB05091 and the six-week data for batches 5286 and batch 3008, an expiry period of ——— was calculated. According to the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics regarding sampling-time considerations, "stability testing generally may be done at 3-month intervals during the first year, 6-month intervals during the second, and yearly thereafter." Observations up to six weeks only do not provide enough information about the degradation patterns for the batches 5286 and 3008. The comparisons among these batches may not be reliable. The sponsor argued that "the stability of ——— [manufacturing site in ———————] and ——— [manufacturing site in ———] Enoxaparin sodium batches are similar." This argument was based entirely on different sets of batches, i.e., 9103599, 9404601 and 9429101 at ——— vs. 9131600, 9405699, and 9435799 at ———. It might well occur that with more observations, the comparing batches (CB5091, 5386 and 3008) might show very different degradation patterns. Also, the differences in degradation pattern between the ———site and the ——————— site might appear to be significant. Therefore, more data are needed for batches 5286 and 3008 in order to support the proposed ——— expiry dating period.

Jiyang Guo

Ted (Jiyang) Guo
Mathematical Statistician

Karl K. Lin 2/29/96

Concur: Dr. Karl K. Lin

cc:
Archival NDA 20-164/S-004
HFD-180/Division file
HFD-180/SFredd
HFD-180/JSieczkowski
HFD-180/KOliver
HFD-715/Division file
HFD-715/SWilson
HFD-715/TGuo
HFD-701/CAnello

TG/Feb 12, 1996/Feb 28, 1996/c:\data\indas\n20164.wpd

Appendix

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STATISTICAL REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-004

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

JAN 31 1996

331

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-164 SCM/004 (BB)
Enoxaparin sodium Injection
Lovenox™ 30mg in 0.3mL WFI
Rhone-Poulenc Rorer
Philadelphia

Submission Dates: 10/11/95
11/27/95

Priority: 1P

Type of submission: Supplement - bioequivalence study for alternate manufacturing site.

Synopsis

The sponsors have submitted a bioequivalence study to obtain approval for an alternate site of heparin sodium manufacture. Heparin sodium is the starting material for the synthesis of the drug substance enoxaparin sodium. The proposed alternate site of manufacture for heparin sodium is ———. The current approved manufacturing site is ———

The original NDA 20-164 was reviewed in July 1992 by Dr. Hisham Abdallah. In this review it was decided (in consultation with HFD-180) that anti-Xa is the more relevant surrogate pharmacodynamic measurement, although its correlation with clinical endpoints is yet to be shown conclusively. Anti-IIa activity was considered a poor marker for bioavailability of LMWH due to the lower and more variable plasma drug levels observed compared to anti-Xa activity.

RECOMMENDATION:

Bioequivalence was shown between the ——— and ——— sites of manufacture of enoxaparin based on anti-Xa activity. This was shown by the two one-sided tests procedure that a 90% CI for the ratio of the mean response (both Amax and AUC) of the test to the reference was within the range of 80 to 125% using log transformed data. The same two sites were bioinequivalent based on anti-IIa activity (Amax was within the 90% CI range; however, AUC was outside the acceptable range).

Additional comments are provided (1 to 5) at the end of this review. Comments 1 to 3 should be sent to the sponsors.

1/29/96

Lydia C. Kaus, M.S., Ph.D.
Team Leader, DPE II

FT intialed by 1/29/96
Mei-Ling Chen, Ph.D.
Director, DPEII

cc:NDA 20-164, HFD-180, HFD-870(MChen et al), HFD-850 (Lesko, Chron, Drug, Reviewer), HFD-860(Malinowski), HFD-880(Fleischer), HFD-340(Viswanathan), HFD-205(FOI)

2/5/96

2/6/96

Title: A single-center, double-blind, randomized, three period crossover study to compare the bioavailability of three enoxaparin batches (40 mg s.c. dose) in 24 healthy male volunteers. **(Study PK 128)**

Clinical Investigator: Dr. ———, Dr. ———
Clinical Study Site: ———
Study dates: May 14 to June 18, 1992.

Objective: To compare the bioavailability of three enoxaparin batches obtained from three distinct unfractionated heparins: sites of manufacture= ———. To qualify ——— as an alternative manufacturing site to the approved ——— site of manufacture.

Assay dates: June 17 to July 31, 1992
Assay site: RPR, Antony Cedex, France.

Batches:
CB 05369 (——— UF-Heparin/Treatment A) - approved site = **Reference**
CB 05367 (——— UF-Heparin/Treatment B) - possible future site not the subject of this submission
CB 05368 ——— UF-Heparin/Treatment C) - alternate proposed site 40mg/0.4 mL = **Test**

Demographics:

	MEAN ± SD	RANGE
AGE (YEARS)	23 ± 2.7	20 - 33
WEIGHT (KG)	75 ± 6.1	66 - 87
HEIGHT (CM)	180.3 ± 5.4	171 - 189

METHODOLOGY:
Study design:

Double-blind, three period, crossover study. 24 healthy *male* subjects. Single injection of 40 mg sc randomized and crossed over to each treatment with a seven day wash-out between each single dose administration. Administration occurred at 8 am, after a 10 h overnight fast. Day 1 site of injection was in the right anterolateral part of the waist. Day 8 site of injection was the left anterolateral part of the waist and Day 15 site of injection was the right anterolateral part of the waist.

Blood sampling:

pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours post-dose. All samples were centrifuged at 1200g for 15 minutes at 4°C . Plasma samples were frozen at -80 °C until analysis.

Biological Measurements:

Anti-Xa and anti-IIa activities, Heptest[R], A.P.T.T. and P.T. were measured.

ANOVA and the two one-sided tests procedure was used in the statistical evaluation of bioequivalence. Data were analyzed by non-compartmental methods. The biological parameters for maximum activity level and area-under-the activity curve are Amax and AUC, respectively. This applies to both endwise and anti-IIa activity. In addition to AUC, A(Δt) max (Heptest clotting time prolongation) was used for Heptest.

Assay Methodology:

The amidolytic (chromogenic) assay methodology is the same as that used in the original NDA 20-164 report #105464. There is a full description of the assay in Dr. Hisham's July 1992 review. The assay at that time was found to be acceptable. The sponsors have provided assay validation information; however this has been taken from the same report (#105464). Therefore, please refer to this information described in the review dated July 1992.

RESULTS:

Arithmetic, geometric and harmonic means ±SD for Amax, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$:

Anti-Xa Activity:

	Arithmetic			Geometric			Harmonic
	Mean ± SD	**CV%**	**Range**	**Mean**	**Mean+ SD**	**Mean- SD**	**Mean**
Trt. A							
Amax IU/mL	0.615±0.118	19.2		0.605	0.725	0.505	0.596
$AUC_{0\text{-}24h}$ h.IU/mL	5.176±0.701	13.5		5.132	5.851	4.502	5.091
$AUC_{0\text{-}\infty}$ h.IU/mL	5.448±0.726	13.3		5.404	6.157	4.742	5.360
Trt. B							
Amax IU/mL	0.579±0.111	19.1		0.569	0.683	0.474	0.561
$AUC_{0\text{-}24h}$ h.IU/mL	4.704±0.638	13.6		4.662	5.349	4.063	4.619
$AUC_{0\text{-}\infty}$ h.IU/mL	4.952±0.667	13.5		4.908	5.632	4.277	4.863
Trt. C							
Amax IU/mL	0.575±0.091	15.8		0.568	0.665	0.484	0.561
$AUC_{0\text{-}24h}$ h.IU/mL	4.883±0.64	13.1		4.842	5.525	4.244	4.802
$AUC_{0\text{-}\infty}$ h.IU/mL	5.144±0.651	12.7		5.104	5.805	4.488	5.063

Anti-IIa Activity:

	Arithmetic			Geometric			Harmonic
	Mean ± SD	**CV %**	**Range**	**Mean**	**Mean+ SD**	**Mean-SD**	**Mean**
Trt. A							
Amax IU/mL	0.076±0.018	24.1		0.074	0.094	0.058	0.072
AUC_{0-24h} h.IU/mL	0.364±0.144	39.7		0.338	0.500	0.229	0.314
$AUC_{0-4.5h}$ h.IU/mL	0.222±0.072	32.5		0.211	0.293	0.153	0.201
Trt. B							
Amax IU/mL	0.077±0.020	25.4		0.075	0.097	0.058	0.073
AUC_{0-24h} h.IU/mL	0.379±0.180	47.5		0.341	0.553	0.210	0.302
$AUC_{0-4.5h}$ h.IU/mL	0.229±0.074	32.2		0.217	0.311	0.151	0.202
Trt. C							
Amax IU/mL	0.084±0.022	26.7		0.081	0.108	0.060	0.077
AUC_{0-24h} h.IU/mL	0.454±0.190	41.8		0.408	0.686	0.242	0.349
$AUC_{0-4.5h}$ h.IU/mL	0.253±0.089	35.1		0.235	0.361	0.153	0.211

APPEARS THIS WAY
ON ORIGINAL

HEPTEST Clotting time prolongation:

	Arithmetic			Geometric			Harmonic
	Mean ± SD	CV %	Range	Mean	Mean+ SD	Mean- SD	Mean
Trt. A							
A(Δt)max s	58.358±9.108	15.6		57.642	67.846	48.97	56.893
AUC $_{0\text{-}24h}$h*s	603.21±78.9080	13.1		598.356	681.192	525.594	593.578
AUC $_{0\text{-}\infty}$h*s	637.235±86.026	13.5		631.8	721.956	552.903	626.457
Trt. B							
A(Δt)max s	60.067±7.645	12.7		59.582	67.964	52.234	59.078
AUC $_{0\text{-}24h}$h*s	583.09±83.535	14.3		576.974	670.22	496.701	570.598
AUC $_{0\text{-}\infty}$ h*s	608.173±90.7	14.9		601.437	701.958	515.310	594.405
Trt. C							
A(Δt)max s	60.308±8.475	14.1		59.72	69.014	51.677	59.111
AUC $_{0\text{-}24h}$h*s	605.74±85.981	14.2		599.508	696.317	516.159	592.872
AUC $_{0\text{-}\infty}$h*s	638.71±94.391	14.8		631.637	737.557	540.929	624.18

GLM SAS Statistical results:

Anti-Xa activity:

The results of the GLM SAS procedure showed a significant ($p<0.001$) period and treatment effect in comparisons for AUC but not a significant sequence effect. The results for Amax showed a significant period but not treatment nor sequence effect.

Anti-IIa activity:

No significant treatment, period nor sequence effects were shown in any of the parameters tested.

Heptest™:

Significant period but neither sequence nor treatment effects were shown for the BE parameters tested.

Two one sided tests procedure results:

Anti-Xa activity:

Parameter	90% CI (Trt. A vs. Trt. C)*	Power of two one-sided tests
Amax IU/mL	87.0-99.9	>99.0
AUC_{0-24h} IU.h/mL	90.7-98.0	>99.0
$AUC_{0-\infty}$ IU.h/mL	90.7-98.1	>99.0

* Calculated by reviewer

Anti-Xa activity (log transformed):

Parameter	90% CI (Trt. A vs. Trt. C)*	Power of two one-sided tests
Amax IU/mL	88.0-100.2	>99.0
AUC_{0-24h} IU.h/mL	90.8-98.1	>99.0
$AUC_{0-\infty}$ IU.h/mL	90.9-98.2	>99.0

* Calculated by reviewer

Anti-IIa activity:

Parameter	90% CI (Trt. A vs. Trt. C)*	Power of two one-sided tests
Amax IU/mL	98.5-120.8	83.76
AUC_{0-t} IU.h/mL	103.5-146.4	32.78
$AUC_{0-4.5h}$ IU.h/mL	100.0-128.7	64.86

* Calculated by reviewer

Anti-IIa activity (log transformed):

Parameter	90% CI (Trt. A vs. Trt. C)*	Power of two one-sided tests
Amax IU/mL	97.0-121.6	>75
AUC_{0-t} IU.h/mL	97.4-149.0	>28.53
$AUC_{0-4.5h}$ IU.h/mL	95.4-129.8	>48.96

* Calculated by reviewer

Heptest™

Parameter	90% CI (Trt. A vs. Trt. C)*	Power of two one-sided tests
A(Δtmax) s	98.2-108.3	99.99
$AUC_{0\text{-}24h}$ h*s	95.7-105.1	99.99

* Calculated by reviewer

The sponsors in order to overcome the significant period effects shown in some of the results, decided to normalize the data to take into account different potencies of the batches used in terms of IU/mL. All batches used were within the specification range for manufacture. Normalizing the data in such a way is not acceptable. Therefore, the results from the normalized data are not reported here.

No significant effects were shown in the statistical model used in the BE study in the original NDA; the same designs in terms of washout period, single crossover etc. was used in this BE study.

Since there were no sequence effects, the significant period effects by themselves have not biased the statistical analyses.

Comments:
Comments 1 to 3 should be sent to the sponsors to keep in mind for future submissions.
1. The sponsors are requested not to use parameters normalized to a particular activity for bioequivalence testing eg. $AUC_{0\text{-}\infty}$ anti-Xa normalized to 4000IU. This is equivalent to normalizing to actual weight or active content of a batch of tablets used in a bioequivalence trial, which is not acceptable practice.

2. The sponsors in future submissions need to provide full and current assay validation information for assay runs on biological samples in each study. Providing assay validation information from the same assay methodology used in a previous submission is not acceptable.

3. The sponsors should provide the results from the two one-sided tests procedure for bioequivalence in terms of actual 90% confidence intervals for each parameter compared. Providing t-values and referring to those same values in response to a request for 90% confidence intervals is not a suitable way of presenting the information. Specifically these need to be given as :

90% CI: (E-t(0.95)*sk), (E+t(0.95)*sk) expressed as (L, U)

where E: ln(Test mean)- ln(Reference mean)
sk: standard error of estimate
L: lower value

U: upper value
90% CI: confidence interval
t(0.95):t-value for p=0.05, degrees of freedom from error term
Lower limit of CI = exp(L)
Upper limit of CI = exp(U)

The upper and lower limits are often expressed in terms of percentages. The acceptable 90% CI range is 80 to 125% for log transformed data.

4. The approved dosage regimen is 30 mg s.c. bid. The single dose used in this study was 40 mg; this dose is used in Europe and was also the dose used in the bioequivalence study #105640 in the original NDA. The 40 mg/0.4 mL formulation is compositionally proportional to the 30 mg/0.3 mL strength of enoxaparin sodium.

5. The statistical analysis of the bioequivalence study (#105640) in the original NDA for enoxaparin used non log transformed data and similarity of the formulations was based on anti-Xa activity since anti-IIa activity parameters were shown to be bioinequivalent.

APPENDIX

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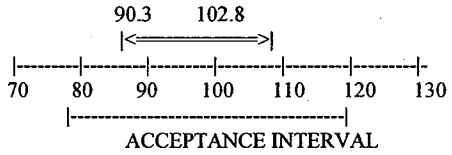
CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

. enoxaparin ln(Amax) Anti-Xa POWER ANALYSIS

ERROR MEAN SQUARE . . 1.787417E-02 POWER FOR .2 M(r)= 99.52715 %
REFERENCE MEAN . . . . .605 POWER FOR -.2 M(r)= 99.98671 %
TEST MEAN 568
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 11.69303 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 12 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 17.44431 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 90.31686 p< 80 % REF MEAN: <0.00012
UPPER CI (% OF REF MEAN): 102.8237 p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS CONCLUSION: PASS



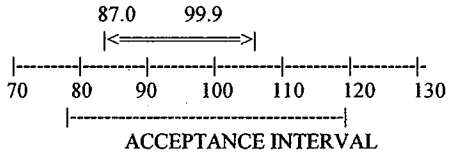
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 90.3% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 102.8% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -6.12% OF THE REFERENCE MEAN.

→ enoxaparin Amax for anti-Xa POWER ANALYSIS

ERROR MEAN SQUARE . . 6.68668E-03
REFERENCE MEAN . . . . .61475 POWER = 99.87938 %
TEST MEAN 57454
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 11.00237 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 9 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 18.89169 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 87.00739 p< 80 % REF MEAN: 0.00055
UPPER CI (% OF REF MEAN): 99.91088 p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS CONCLUSION: PASS



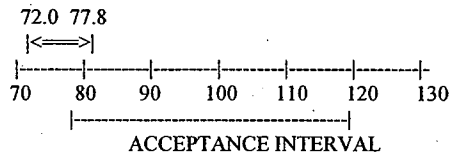
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 87.0% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 99.9% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -6.54% OF THE REFERENCE MEAN.

. enoxaparin ln(AUC0-24) Anti-Xa POWER ANALYSIS

ERROR MEAN SQUARE . . 6.33705E-03 POWER FOR .2 M(r)= > 99.9878 %
REFERENCE MEAN . . . . 5.132 POWER FOR -.2 M(r)= > 99.9878 %
TEST MEAN 4.842
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 6.806124 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 6 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 15.81724 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 71.99229 p< 80 % REF MEAN: 0.99712
UPPER CI (% OF REF MEAN): 77.772 p> 120 % REF MEAN: <0.00012
CONCLUSION: FAIL CONCLUSION: FAIL



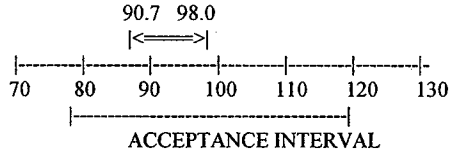
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO
OF THESE PARAMETER MEANS TO BE AS LOW AS 72.0% OF THE OBSERVED REFERENCE MEAN,
AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 77.8%
OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND
REFERENCE MEANS IS -5.65% OF THE REFERENCE MEAN.

. enoxaparin AUC0-24 Anti-Xa POWER ANALYSIS

ERROR MEAN SQUARE . . .1527045
REFERENCE MEAN . . . . 5.176 POWER = > 99.9878 %
TEST MEAN 4.883
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 6.244693 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 9 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 10.72249 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 90.67739 p< 80 % REF MEAN: <0.00012
UPPER CI (% OF REF MEAN): 98.00111 p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS CONCLUSION: PASS



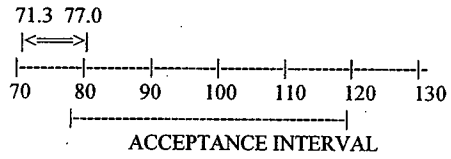
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO
OF THESE PARAMETER MEANS TO BE AS LOW AS 90.7% OF THE OBSERVED REFERENCE MEAN,
AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 98.0%
OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND
REFERENCE MEANS IS -5.66% OF THE REFERENCE MEAN.

. enoxaparin ln(AUC0-inf) Anti-Xa POWER ANALYSIS

ERROR MEAN SQUARE . . 6.37632E-03 POWER FOR .2 M(r)= > 99.9878 %
REFERENCE MEAN . . . . 5.404 POWER FOR -.2 M(r)= > 99.9878 %
TEST MEAN 5.104
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 6.827879 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 6 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 15.86986 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 71.26746 p< 80 % REF MEAN: 0.99861
UPPER CI (% OF REF MEAN): 77.00738 p> 120 % REF MEAN: <0.00012
CONCLUSION: FAIL CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 71.3% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 77.0% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -5.55% OF THE REFERENCE MEAN.

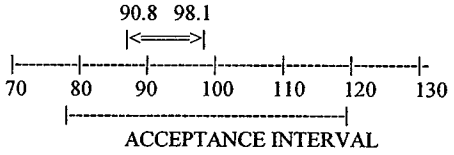
APPEARS THIS WAY
ON ORIGINAL

. enoxaparin AUC0-inf Anti-Xa POWER ANALYSIS

ERROR MEAN SQUARE . . .1694316
REFERENCE MEAN . . . . 5.448 POWER = > 99.9878 %
TEST MEAN 5.144
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 6.249419 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 9 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 10.7306 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 90.75534 p< 80 % REF MEAN: <0.00012
UPPER CI (% OF REF MEAN): 98.0846 p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 90.8% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 98.1% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -5.58% OF THE REFERENCE MEAN.

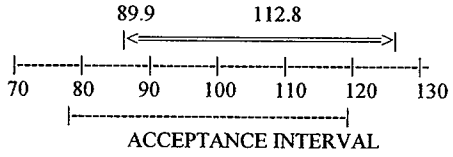
APPEARS THIS WAY
ON ORIGINAL

. enoxaparin ln(Amax) Anti-IIa POWER ANALYSIS

ERROR MEAN SQUARE . . 5.434218E-02 POWER FOR .2 M(r)= 75.43537 %
REFERENCE MEAN . . . . .074 POWER FOR -.2 M(r)= 89.99366 %
TEST MEAN 081
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 21.26622 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 27 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 19.87698 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 89.93636 p< 80 % REF MEAN: 0.00071
UPPER CI (% OF REF MEAN): 112.7573 p> 120 % REF MEAN: 0.00631
CONCLUSION: PASS CONCLUSION: PASS



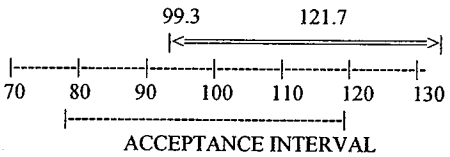
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 89.9% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 112.8% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +9.46% OF THE REFERENCE MEAN.

. enoxaparin Amax Anti-IIa POWER ANALYSIS

ERROR MEAN SQUARE . . 3.0884E-04
REFERENCE MEAN . . . . .076 POWER = 83.39483 %
TEST MEAN 084
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 19.12638 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 24 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 19.12638 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 99.31069 p< 80 % REF MEAN: <0.00012
UPPER CI (% OF REF MEAN): 121.7419 p> 120 % REF MEAN: 0.08214
CONCLUSION: FAIL CONCLUSION: FAIL



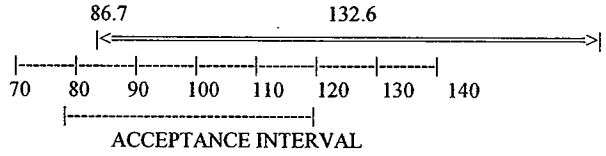
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 99.3% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 121.7% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +10.53% OF THE REFERENCE MEAN.

. enoxaparin ln(AUC0-t) Anti-IIa POWER ANALYSIS

ERROR MEAN SQUARE . . .1918216 POWER FOR .2 M(r)= 28.53946 %
REFERENCE MEAN . . . . .338 POWER FOR -.2 M(r)= 40.19497 %
TEST MEAN 408
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 43.65818 %
DEGREES OF FREEDOM . . 44 CALCULATED N OF 96 > PROGRAM LIMIT
NUMBER OF TREATMENTS . 3 DETECTABLE DIFFERENCE OF
DELTA . . . . . .2 77 SUBJECTS IS 22.02373 %

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 86.72469 p< 80 % REF MEAN: 0.01277
UPPER CI (% OF REF MEAN): 132.6351 p> 120 % REF MEAN: 0.19177
CONCLUSION: FAIL CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 86.7% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 132.6% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +20.71% OF THE REFERENCE MEAN.

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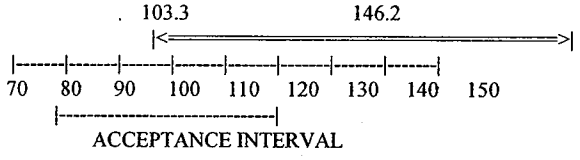
. enoxaparin AUC0-t Anti-IIa POWER ANALYSIS

ERROR MEAN SQUARE . . 2.593957E-02
REFERENCE MEAN . . . . .364 POWER = 32.80753 %
TEST MEAN 454
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 36.59818 %
DEGREES OF FREEDOM . . 44 CALCULATED N OF 81 > PROGRAM LIMIT
NUMBER OF TREATMENTS . 3 DETECTABLE DIFFERENCE OF
DELTA . . . . . .2 77 SUBJECTS IS 20.10867 %

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 103.2643 p< 80 % REF MEAN: 0.00055
UPPER CI (% OF REF MEAN): 146.1863 p> 120 % REF MEAN: 0.64186
CONCLUSION: FAIL CONCLUSION: FAIL



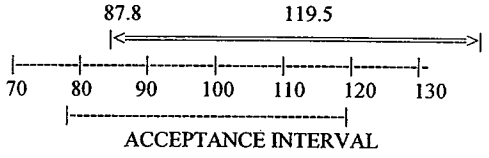
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 103.3% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 146.2% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +24.73% OF THE REFERENCE MEAN.

. enoxaparin ln(AUC0-4.5h) Anti-IIA POWER ANALYSIS

ERROR MEAN SQUARE . . .1008567 POWER FOR .2 M(r)= 48.95508 %
REFERENCE MEAN . . . . .211 POWER FOR -.2 M(r)= 66.1282 %
TEST MEAN 235
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 30.04143 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 51 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 19.47851 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 87.80637 p< 80 % REF MEAN: 0.00527
UPPER CI (% OF REF MEAN): 119.4869 p> 120 % REF MEAN: 0.04623
CONCLUSION: PASS CONCLUSION: PASS



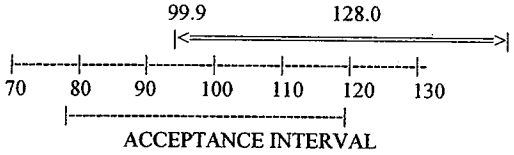
EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 87.8% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 119.5% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +11.37% OF THE REFERENCE MEAN.

. enoxaparin AUC0-4.5h Anti-IIa POWER ANALYSIS

ERROR MEAN SQUARE . . 4.11705E-03
REFERENCE MEAN . . . . .222 POWER = 64.77849 %
TEST MEAN 253
NUMBER OF SUBJECTS . . 24 DETECTABLE DIFFERENCE: 23.9067 %
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3 36 SUBJECTS NEEDED FOR A
DELTA . . . . . .2 19.36441 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL P VALUES OF TWO ONE-SIDED TEST

LOWER CI (% OF REF MEAN): 99.94517 p< 80 % REF MEAN: <0.00012
UPPER CI (% OF REF MEAN): 127.9827 p> 120 % REF MEAN: 0.23817
CONCLUSION: FAIL CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 99.9% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 128.0% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +13.96% OF THE REFERENCE MEAN.

. **enoxaparin Anti Xa lnAmax**

ERROR MEAN SQUARE . . 1.787417E-02
REFERENCE MEAN . . . . -.5028701
TEST MEAN . . . . . -.56618
NUMBER OF SUBJECTS . . 24
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= 99.52715 %
POWER FOR -.2 M(r)= 99.98671 %

DETECTABLE DIFFERENCE: 11.69303 %

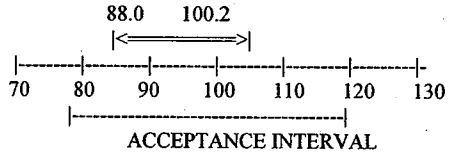
12 SUBJECTS NEEDED FOR A
17.44431 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 87.97162
UPPER CI (% OF REF MEAN): 100.1537
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 88.0% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 100.2% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +12.59% OF THE REFERENCE MEAN.

. enoxaparin Anti Xa Amax

ERROR MEAN SQUARE . . 6.68668E-03
REFERENCE MEAN 61475
TEST MEAN 57454
NUMBER OF SUBJECTS . . 24
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER = 99.87938 %

DETECTABLE DIFFERENCE: 11.00237 %

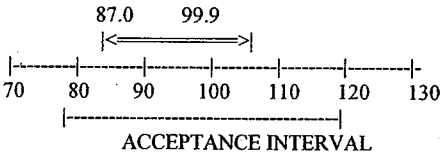
9 SUBJECTS NEEDED FOR A
18.89169 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 87.00739
UPPER CI (% OF REF MEAN): 99.91088
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: 0.00055
p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 87.0% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 99.9% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -6.54% OF THE REFERENCE MEAN.

. enoxaparin Anti Xa lnAUCinf

ERROR MEAN SQUARE .. 6.37632E-03
REFERENCE MEAN 1.6871
TEST MEAN 1.63001
NUMBER OF SUBJECTS .. 24
DEGREES OF FREEDOM .. 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= > 99.9878 %
POWER FOR -.2 M(r)= > 99.9878 %

DETECTABLE DIFFERENCE: 6.827879 %

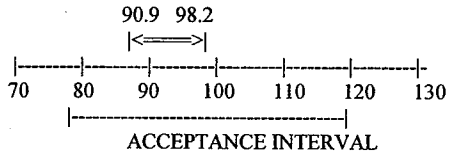
6 SUBJECTS NEEDED FOR A
15.86986 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 90.86269
UPPER CI (% OF REF MEAN): 98.18082
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 90.9% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 98.2% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -3.38% OF THE REFERENCE MEAN.

. enoxaparin anti Xa AUCinf

ERROR MEAN SQUARE .. .1694316
REFERENCE MEAN 5.4486
TEST MEAN 5.144
NUMBER OF SUBJECTS .. 24
DEGREES OF FREEDOM .. 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER = > 99.9878 %

DETECTABLE DIFFERENCE: 6.248729 %

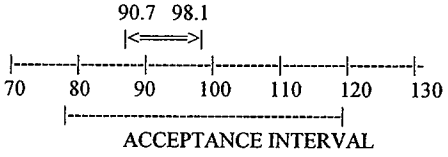
9 SUBJECTS NEEDED FOR A
10.72942 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 90.74534
UPPER CI (% OF REF MEAN): 98.07381
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 90.7% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 98.1% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -5.59% OF THE REFERENCE MEAN.

. enoxaparin Anti Xa lnAUC0-24h

ERROR MEAN SQUARE . . 6.33705E-03
REFERENCE MEAN 1.63555
TEST MEAN 1.57741
NUMBER OF SUBJECTS . . 24
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= > 99.9878 %
POWER FOR -.2 M(r)= > 99.9878 %

DETECTABLE DIFFERENCE: 6.806124 %

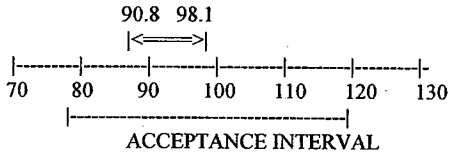
6 SUBJECTS NEEDED FOR A
15.81724 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 90.77817
UPPER CI (% OF REF MEAN): 98.06607
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 90.8% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 98.1% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -3.55% OF THE REFERENCE MEAN.

. enoxaparin anti Xa AUC0-24h

ERROR MEAN SQUARE . . .1527045
REFERENCE MEAN 5.1755
TEST MEAN 4.8827
NUMBER OF SUBJECTS . . 24
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER = > 99.9878 %

DETECTABLE DIFFERENCE: 6.245296 %

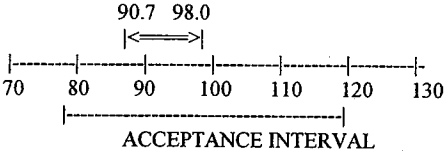
9 SUBJECTS NEEDED FOR A
10.72353 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 90.68036
UPPER CI (% OF REF MEAN): 98.00479
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: <0.00012
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 90.7% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 98.0% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -5.66% OF THE REFERENCE MEAN.

. enoxaparin Anti IIa lnAmax

ERROR MEAN SQUARE .. 5.434218E-02
REFERENCE MEAN .... -2.59963
TEST MEAN ..... -2.51748
NUMBER OF SUBJECTS .. 24
DEGREES OF FREEDOM .. 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= 75.43537 %
POWER FOR -.2 M(r)= 89.99366 %

DETECTABLE DIFFERENCE: 21.26622 %

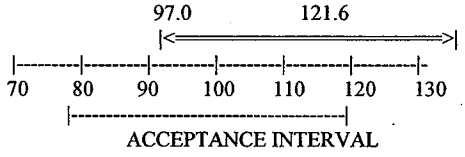
27 SUBJECTS NEEDED FOR A
19.87698 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 96.95555
UPPER CI (% OF REF MEAN): 121.5576
CONCLUSION: FAIL

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: 0.07304
CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 97.0% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 121.6% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -3.16% OF THE REFERENCE MEAN.

. enoxaparin Anti IIa Amax

ERROR MEAN SQUARE .. 3.0884E-04
REFERENCE MEAN .... .076375
TEST MEAN ..... .08375
NUMBER OF SUBJECTS .. 24
DEGREES OF FREEDOM .. 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER = 83.75735 %

DETECTABLE DIFFERENCE: 19.03247 %

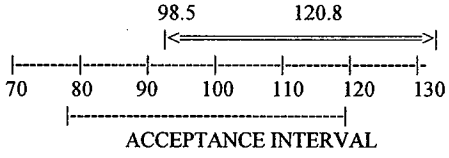
24 SUBJECTS NEEDED FOR A
19.03247 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 98.49574
UPPER CI (% OF REF MEAN): 120.8169
CONCLUSION: FAIL

P VALUES OF TWO ONE-SIDED TEST

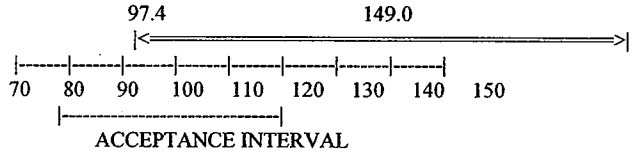
p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: 0.06358
CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 98.5% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 120.8% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +9.66% OF THE REFERENCE MEAN.

. enoxaparin AntiIIa lnAUC0-t

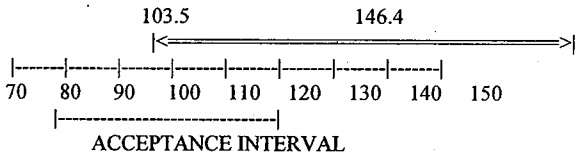
ERROR MEAN SQUARE . . .1918216	POWER ANALYSIS
REFERENCE MEAN . . . . -1.084	POWER FOR .2 M(r)= 28.53946 %
TEST MEAN . . . . . -.8975	POWER FOR -.2 M(r)= 40.19497 %
NUMBER OF SUBJECTS . . 24	DETECTABLE DIFFERENCE: 43.65818 %
DEGREES OF FREEDOM . . 44	CALCULATED N OF 96 > PROGRAM LIMIT
NUMBER OF TREATMENTS . 3	DETECTABLE DIFFERENCE OF
DELTA 2	77 SUBJECTS IS 22.02373 %
90% CONFIDENCE INTERVAL	P VALUES OF TWO ONE-SIDED TEST
LOWER CI (% OF REF MEAN): 97.44018	p< 80 % REF MEAN: 0.00148
UPPER CI (% OF REF MEAN): 149.0232	p> 120 % REF MEAN: 0.51048
CONCLUSION: FAIL	CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 97.4% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 149.0% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -17.20% OF THE REFERENCE MEAN.

. enoxaparin AntiIIa AUC0-t

ERROR MEAN SQUARE . . 2.593957E-02	
REFERENCE MEAN 36379	POWER = 32.77541 %
TEST MEAN 4545	
NUMBER OF SUBJECTS . . 24	DETECTABLE DIFFERENCE: 36.61931 %
DEGREES OF FREEDOM . . 44	CALCULATED N OF 81 > PROGRAM LIMIT
NUMBER OF TREATMENTS . 3	DETECTABLE DIFFERENCE OF
DELTA 2	77 SUBJECTS IS 20.12028 %
90% CONFIDENCE INTERVAL	P VALUES OF TWO ONE-SIDED TEST
LOWER CI (% OF REF MEAN): 103.4613	p< 80 % REF MEAN: 0.00053
UPPER CI (% OF REF MEAN): 146.4081	p> 120 % REF MEAN: 0.64663
CONCLUSION: FAIL	CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 103.5% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 146.4% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +24.93% OF THE REFERENCE MEAN.

. enoxaparin Anti Iia ln AUC0-4.5h

ERROR MEAN SQUARE . . .1008567
REFERENCE MEAN . . . . -1.55444
TEST MEAN . . . . . -1.44778
NUMBER OF SUBJECTS . . 24
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= 48.95508 %
POWER FOR -.2 M(r)= 66.1282 %

DETECTABLE DIFFERENCE: 30.04143 %

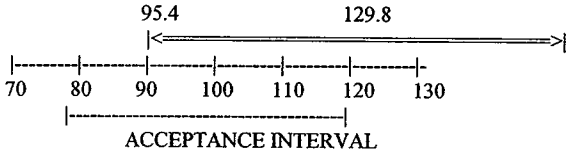
51 SUBJECTS NEEDED FOR A
19.47851 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 95.37286
UPPER CI (% OF REF MEAN): 129.7833
CONCLUSION: FAIL

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: 0.00044
p> 120 % REF MEAN: 0.20838
CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 95.4% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 129.8% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -6.86% OF THE REFERENCE MEAN.

. enoxaparin Anti IIa AUC0-4.5h

ERROR MEAN SQUARE . . 4.11705E-03
REFERENCE MEAN 22221
TEST MEAN 25331
NUMBER OF SUBJECTS . . 24
DEGREES OF FREEDOM . . 44
NUMBER OF TREATMENTS . 3
DELTA 2

POWER ANALYSIS

POWER = 64.8622 %

DETECTABLE DIFFERENCE: 23.8841 %

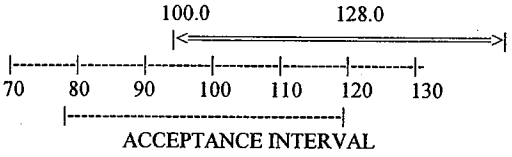
36 SUBJECTS NEEDED FOR A
19.34611 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 99.99022
UPPER CI (% OF REF MEAN): 128.0013
CONCLUSION: FAIL

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00012
p> 120 % REF MEAN: 0.23893
CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 100.0% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 128.0% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +14.00% OF THE REFERENCE MEAN.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RHÔNE-POULENC RORER

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

October 11, 1995

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, MD 20857

ORIGINAL

NDA NO. 20164 REF. NO. 004
NDA SUPPL FOR SCM

sNDA 20-164
Lovenox® (enoxaparin sodium)
Injection

GENERAL CORRESPONDENCE

Dear Dr. Fredd:

We are submitting a supplement under 21 CFR 314.70(b) to obtain the qualification of an alternate site of heparin sodium manufacture at ——— located in ——— ———. Heparin sodium is a starting material for the synthesis of the drug substance, enoxaparin sodium, used in the drug product, Lovenox. The currently approved source for heparin sodium is ———, located in ———. We have previously interacted with the Division concerning the content of this sNDA in a submission to the NDA on November 23, 1994, to which the agency replied on December 28, 1994.

This submission consists of 3 volumes, with volume 1 containing the appropriate Chemistry, Manufacturing and Controls information concerning the manufacture and stability of drug substance and drug product using heparin sodium prepared by ——— ——— Volumes 2 and 3 contain the supportive bioequivalence trial ——— 1686 entitled "A Single-Center, Double-Blind, Randomized, Three-Period Cross-Over Study to Compare the Bioavailability of Three Enoxaparin Batches (40 mg single doses s.c.) in Healthy Male Volunteers". The objective of this report is to compare the bioavailability of

10/18/95

three enoxaparin batches obtained from three distinct unfractionated heparins: ——— ———. The ——— material was part of the study but is not intended as an alternate supplier. If ——— is considered as an alternate supplier in the future, it will be the subject of a separate supplement.

Stability data on three industrial scale lots of enoxaparin sodium drug substance are included. The data consists of four years on one lot, one year on a second, and three months on the third. This data is consistent with our November 23, 1994, commitment. A stability commitment to continue to monitor the stability for 36 months is included.

Drug product stability data for three lots of Lovenox 30 mg pre-filled syringes, formulated with 100 mg/ml of ———sourced heparin sodium is included. SAS statistical analysis to support a 24 month shelf life is also included. The SAS datasets are provided on diskette in this submission. The data included is three years on one lot, three months on a second, and six weeks on the third. Except for the source of heparin sodium, these drug product lots were manufactured according to the same specifications as those currently approved for the Lovenox drug product, which has a shelf life of 24 months. A stability commitment to continue to monitor the stability for 36 months is included.

Please note that a copy of this entire sNDA has been submitted to Ms. Debra Pagano of the Philadelphia District Office.

If you have any questions, please feel free to call me at (610) 454-3023.

Sincerely yours,

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

TED/bnh
Attachment

32.1

NDA 20-164/S-004 OCT 19 1995

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

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-004

Therapeutic Classification: Standard

Date of Supplement: October 11, 1995

Date of Receipt: October 12, 1995

This supplement provides for an alternate site of heparin sodium manufacture at ———— located in ———————— .

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 December 11, 1995 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

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

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Karen Oliver
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-004
HFD-180/Div. Files
HFD-80
HFD-180/CSO/K.Oliver
drafted: KO/October 17, 1995 K. Oliver 10/17/95
Final: K/10/17/95/c:\wpwin\karenfil\nda\20164510.0ko

SUPPLEMENT ACKNOWLEDGEMENT

32.1

NDA 20-164/S-004

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

NOV -2 1995

Dear Dr. Donnelly:

Please refer to your pending 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 biopharmaceutic section of your submission, we request the following:

1. The summary section contains page 6-1-5 only. Please submit the complete summary.

2. Please provide the intra and inter- assay precision from the calibration and quality controls for anti-Xa and anti-IIa assays.

3. Please provide information on the linearity and minimal quantifiable activity for the anti-Xa and anti-IIa assays.

4. Please state whether the assays are the same methodology as used in the original NDA. Alternatively, if a different assay is being used, submit the details of the methodology.

5. We note that the t-values for the two one sided test were reported rather than the 90% CI as normally reported. Please define all the terms used in the summary table on the two one sided test such as Table 100, page 6-1-186.

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
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

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-004
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/J.Sieczkowski
HFD-180/L.Talarico
HFD-426/L.Kaus
DISTRICT OFFICE

drafted: KO/November 1, 1995 11/2/95
r/d Initials: S.Fredd 11/01/95
final: KO/11/01/95/c:\wpwin\karenfil\nda\20164511.0ko

INFORMATION REQUEST (IR)

331

NDA 20-164/S-004

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

Dear Dr. Donnelly:

Please refer to your pending October 11, 1995 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 amendment dated November 27, 1995.

We have completed our review of the biopharmaceutics section of your submissions and have the following recommendations and requests for future submissions:

1. Please do not use parameters normalized to a particular activity for bioequivalence testing eg. $AUC_{0-\infty}$ anti-Xa normalized to 4000 IU. This is equivalent to normalizing to actual weight or active content of a batch of tablets used in a bioequivalence trial, which is not acceptable practice.

2. Please provide full and current assay validation information for assay runs on biological samples in each study. Providing assay validation information from the same assay methodology used in a previous submission is not acceptable.

3. Please provide the results from the two one-sided tests procedure for bioequivalence in terms of actual 90% confidence intervals for each parameter compared. Providing t-values and referring to those same values in response to a request for 90% confidence intervals is not a suitable way of presenting the information.

Specifically, these need to be given as:

90% CI: (E-t(0.95)*sk), (E+t(0.95)*sk) expressed as (L, U)

where E: ln(Test mean)-ln(Reference mean)
sk: standard error of estimate
L: lower value
U: upper value
90% CI: confidence interval
t(0.95): t-value for p=0.05, degrees of freedom from error term
Lower limit of CI=exp(L)
Upper limit of CI=exp(U)

The upper and lower limits are often expressed in terms of percentages. The acceptable 90% CI range is 80 to 125% for log transformed data.

If you have any questions, please contact:

Karen Oliver
Consumer Safety Officer
Telephone Number: (301) 443-0487

Sincerely yours,

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-004
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/J.Sieczkowski
HFD-870/L.Kaus

drafted: KO/February 21, 1996
r/d Initials:S.Fredd 02/26/96 K.Oliver 02/26/96
final:KO/02/26/96/c:\wpwin\karenfil\nda\20164602.0ko

INFORMATION REQUEST (IR) SF 2/26/96