CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-287/S-015

Name: Fragmin (Dalteparin Sodium) Injection

Sponsor: Pharmacia & Upjohn Company

Approval Date: August 5, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-015

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Chemistry Reviews	X
Bioequivalence Reviews	
Statistical Review(s)	
Microbiology Review(s)	X
Administrative Documents	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-015

APPROVAL LETTER

NDA 20-287/S-015

Pharmacia & Upjohn Company
Attention: Ms. Leslie A. Franks
7000 Portage Road
Kalamazoo MI 49001-0199

Dear Ms. Franks:

Please refer to your supplemental new drug application dated February 5, 1999, received February 8, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection).

This supplemental new drug application provides for: an alternate supplier, [redacted], of pre-washed (endotoxin removal) 20 mm stoppers ([redacted]) for the 9.5 mL multi-dose vial, 10,000 IU/mL.

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.

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

Sincerely,

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-287/S-015
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.duffy
HFD-180/A.Al-Hakim
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/August 4, 1999
final: KO/08/04/99/c:\mydocuments\data\NDA20287-S-015-08-04-99-AP.doc

APPROVAL (AP)

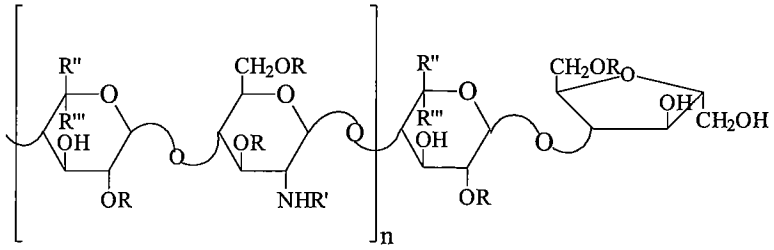
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-015

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-287/S-015	
3. Name and Address of Applicant (City & State): Pharmacia & Upjohn 7000 Portage Road, Kalamazoo, MI 49001-0199		4. AF Number:	
		5. Supplement(s)	
6. Name of Drug: Fragmin®	7. Nonproprietary Name: Deltaparin Sodium injection	Numbers	Dates
		SCP/015	02/05/1999
8. Supplement Provides for: Alternate use of pre-washed stoppers for the 10ml multi-dose vial. Currently the stoppers are washed and sterilized by Pharmacia & Upjohn. The alternate site is the manufacturer of the stoppers (————).		9. Amendments & Other (Reports, etc.) Dates:	
10. Pharmacological Category: Anticoagulant	11.How Dispensed: RX X OTC __	12. Related DMF(s): —	
13.Dosage Form: Solution for Injection	14. Potency: 2500 IU, 5000 IU		
15. Chemical Name and Structure: Sulfated polysaccharide chains at the non-reducing end and 6-O-sulfo-2,5-anhydro-Dmannitol at reducing end.		16. Records and Reports:	



R= H or SO_3Na
R'= $COCH_3$ or SO_3Na
R"= H R"= COONa
OR
R"= COONa R'"= H
n= 3,20

Current Yes X No __	
Reviewed Yes X No __	

17. Comments: The CMC information provided in this supplement is satisfactory. The microbiology reviewer (D.Hussong) recommended approval of this supplement. See review dated 08/03/1999.
CC: NDA 20-287/S-015
HFD-180/Div File/NDA 20-287
HFD-181/CSO/K. Oliver
HFD-180/L.Talarico
HFD-180/A.Al-Hakim
R/D init:E.Duffy/
AA/ **F/T** /WORD: N:\Wordfiles\chem\S\20287015.1AA

18. Conclusions and Recommendations: Recommend An "Approval" letter be issued by the regulatory Health Project Manager.

19.Reviewer

Name: Ali Al-Hakim, Ph.D.	Signature	Date Completed: 07/23/1999

REVIEW NOTES

The firm has submitted this supplemental application (Special Supplement; changes being effected) and requested approval of an alternative site alternate use of pre-washed stoppers for the 10ml multi-dose vial.

Currently the stoppers are washed and sterilized by Pharmacia & Upjohn in facility in Stockholm, Sweden. The alternate site will be the actual manufacturer of the stoppers (————————). Description of the alternative site and the corresponding washing process is provided in DMF # ——. Letter of authorization to this DMF (dated 04/30/1998) was provided in the supplement. DMF —— was reviewed in conjunction with this supplement. The DMF was found acceptable to support the use of the alternative site for pre-washed stoppers. See DMF review dated 7/23/1999.

The supplement contains the following supporting documents:

- Attachment 1 described the difference between the current and the new procedure. The new procedure consists of the following steps:

1. Washing

- Attachment 2

This attachment contains the results of the endotoxin test. Data indicated that all stoppers tested were within the proposed specifications.

- Attachment 3

This attachment contains description of the equipment (and the location) which come into contact with the product.

- Attachment 4

This document contains the description of the flow of the components and product from

formulation to finished dosage form (overall manufacturing operation). This includes —— stoppers, ————————, caps, vials, drug substance, inactive ingredients, bulk solution vessels and filling process.

- Attachment 5

This attachment contains the authorization letter to Drug Master File # ——.

Conclusion:
The supplement contains satisfactory information regarding CMC section of the new alternative washing process at ————————.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-015

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-180
MICROBIOLOGIST'S REVIEW #1 OF SUPPLEMENT
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY REVIEW STAFF

August 3, 1999

NDA/Supplement Number: 20-287/SCP-015

Document Date: February 05, 1999

Date Assigned for Review: March 01, 1999

Amendments and Others: none

Name and Address of Applicant: Pharmacia and Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

Name of Drug: Fragmin® (dalteparin sodium injection)

Supplement Provides For: Alternate use of pre-washed stoppers (———————) for the 10 mL multiple dose vial filled (9.5 mL) in the approved production facility in Stockholm, Sweden. The same stopper is currently used but is washed at Pharmacia and Upjohn.

Pharmacological Category: Anti-coagulant

Dosage Form: The product is a sterile solution in pre-filled syringes (0.2 mL in a 0.5 cc HYPAK) and as 9.5 mL in a 10 cc multiple dose vial preserved with benzyl benzyl alcohol. The current supplement applies to the multiple dose vial dosage form only.

Related Documents: DMFs ——————— , May 30, 1997, pages 1-6), ——
———————————————————
and ——————— Also, IND ———————

Comments: The DMF for the stopper manufacturer was briefly examined, but there is no formal review of the May 30, 1997 DMF submission.

Conclusions and Recommendations: The supplement is recommended for approval.

David Hussong, Ph.D.

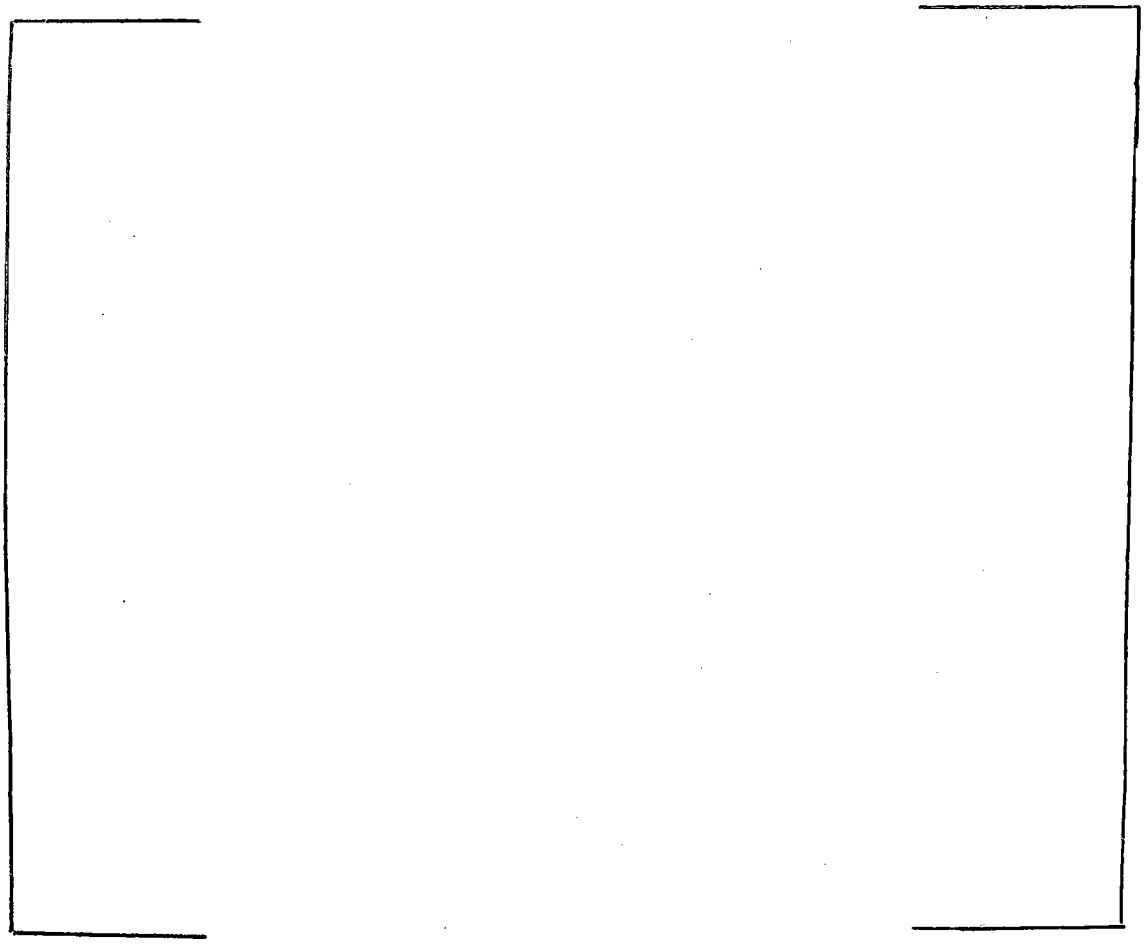
cc:

Original NDA 20-287/SCP-015
HFD 180/Division Files
HFD 160/Consult File
HFD 180/CSO/K. Oliver
HFD 180/Chemist/Al-Hakim
HFD 805/D. Hussong

Drafted by: D. Hussong, 08/03/99
R/D initialed by: P. Cooney

Filename, d:\nda\s\20-287r1.s15.doc

Review Notes: The approved NDA describes the method for preparing stoppers as the standard



SATISFACTORY

Comments. The endotoxins removal appears to be satisfactory based on the data provided. No discussion of particulate removal was provided, but that is not a microbiology issue. In addition, no discussion was provided concerning ——— related to the ———, although this might be better assessed by product-specific stability studies. These are largely academic concerns noted only for completeness.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-015

CORRESPONDENCE

NDA 20-287/S-015

Pharmacia & Upjohn
Attention: Ms. Leslie A. Franks
7000 Portage Road
Unit 0635-298-110
Kalamazoo, Michigan 49001

Dear Ms. Franks:

We acknowledge receipt of your labeling supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fragmin® (dalteparin sodium injection)

NDA Number: 20-287

Supplement Number: S-015

Date of Supplement: February 5, 1999

Date of Receipt: February 8, 1999

This supplement proposes the following change: an alternate supplier, ———————— , of pre-washed (endotoxin removal) 20 mm stoppers (————————) for the 9.5 mL multi-dose vial, 10,000 IU/mL.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 9, 1999 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7310.

Sincerely,

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

cc:
Archival NDA 20-287/S-015
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
DISTRICT OFFICE

Drafted by: KO/February 23, 1999
final: KO/02/23/99
filename: c:\mydocuments\NDA20287-S-015-02-23-99-ack

SUPPLEMENT ACKNOWLEDGEMENT (AC)