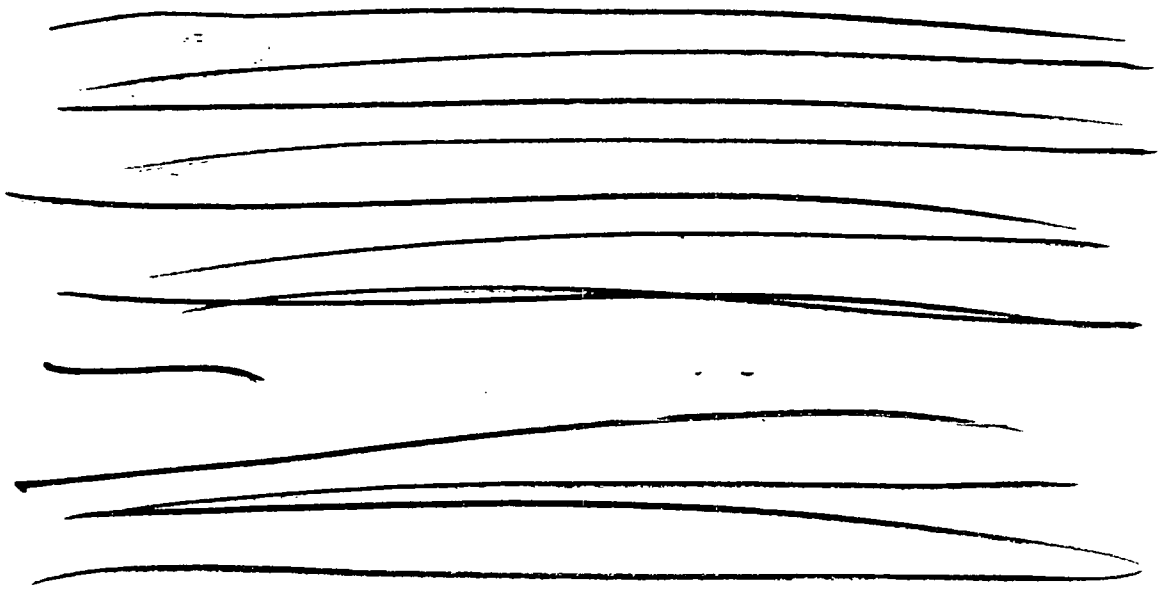


Safety:

The safety database for tinzaparin from the controlled clinical studies submitted for the proposed indications indicates that the most frequently encountered problems with the drug relate to its therapeutic action. It is an anticoagulant and bleeding events (particularly injection site bleeding) are among the most commonly encountered adverse events. These events do not typically lead to discontinuation of tinzaparin treatment.

The sponsor reports an overall incidence of bleeding events in completed clinical studies of tinzaparin in the NDA (involving 3681 patients treated with the drug) at 10.3%. Major hemorrhage rates appear comparable to warfarin (2.1%). Key safety concerns for tinzaparin appear similar to those associated with heparin and other low molecular weight heparins. These include bleeding events (especially major hemorrhage, surgical wound hematoma, spinal/epidural hematoma, and injection site hematoma), other injection site findings (mainly pain, inflammation), thrombocytopenia, and anaphylactic reaction. Incidence of thrombocytopenia was about 1% in all clinical studies (platelet count $<50x10^9$/L, 0.13%).

The tinzaparin completed studies database includes 20% patients ≥75 yrs, about 45% males, about 3% non-White patients. Duration of exposure of patients in the treatment of DVT studies ranged up to 17 days and in the preventions of DVT studies up to 54 days. In long-term studies of tinzaparin for other indications (308 patients) dosing has extended up to 4 months. Individual doses of tinzaparin have ranged from 50 to 300 anti-factor Xa IU/kg weight adjusted doses and from 2500 to 12,250 IU/day fixed dose.

Tinzaparin has been marketed for as long as nine years in some European and other countries. The sponsor estimates that at least 2.8 million patients have received tinzaparin between 2/91 and 12/98.

Conclusions and Recommendations:

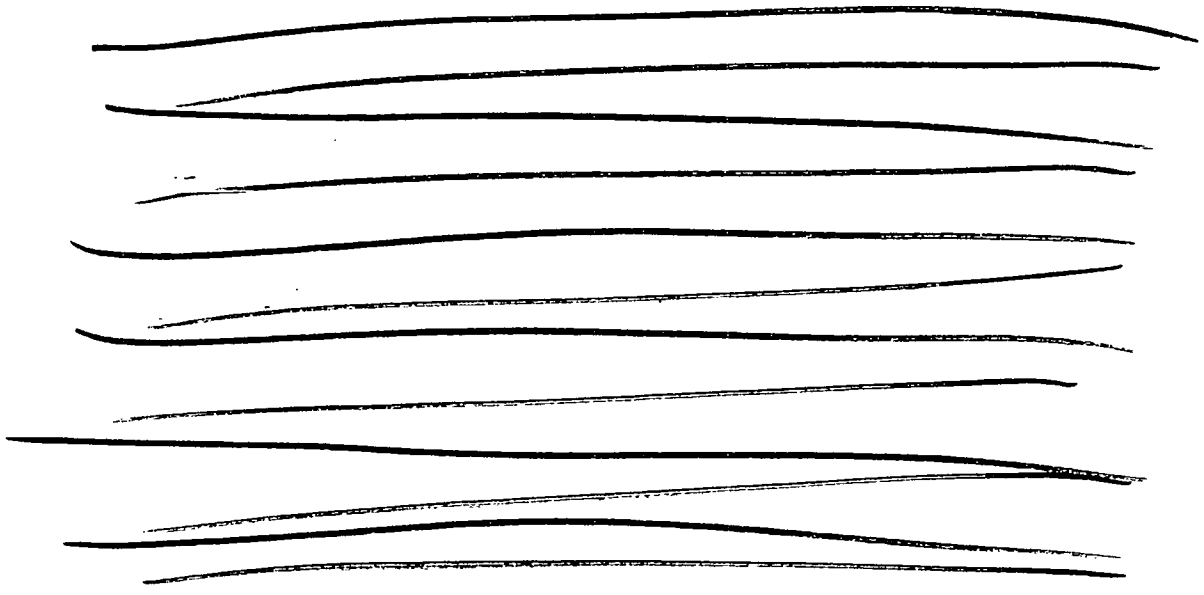
Treatment of acute deep vein thrombosis (DVT) with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium:

The sponsor has submitted two studies which contribute meaningful efficacy information for use of tinzaparin in inpatient treatment of DVT when administered in conjunction with warfarin sodium. In Study DMP 702-900 both treatments (heparin and tinzaparin) showed event rates supportive of effectiveness, with tinzaparin tending to perform better than heparin dosed in accordance with labeled recommendation. Study DMP 702-904, a study in patients with symptomatic PE about 79% of whom also had objectively demonstrated DVT on study entry, provides some evidence of clinical effectiveness of the treatment regimens used in the study by virtue of the very low event rates observed in the study-- event rates considerably lower than reported in the literature for suboptimally treated patients.

This application does not provide adequate support for use of tinzaparin in treatment of PE. The single PE trial, Study DMP 702-904, failed to show any meaningful suggestion of a benefit in the primary and secondary efficacy analyses. The study was likely not large enough to meet its prespecified objectives. Also the study population appears to represent a selected, possibly less severely ill, subpopulation of PE patients.

I recommend that this application be approvable for inpatient treatment of DVT when administered in conjunction with warfarin sodium. The treatment regimen should be: tinzaparin sodium 175 anti-factor XA IU/kg subcutaneously once daily for at least 6 days and until the patient is adequately anticoagulated with warfarin. For approval the sponsor should address CMC deficiencies and revise labeling appropriately.

I recommend that at this time tinzaparin is not approvable for treatment of PE. The sponsor should conduct additional efficacy studies for this specific indication.



/S/
Kathy M. Robie-Suh, M.D., Ph.D. 4/12/00

cc:
NDA 20-484
HFD-180/Division File
HFD-180/LTalarico 4-13-00
HFD-180/SAurecchia
HFD-180/RHe
HFD-180/KOliver
HFD-180/MFan
HFD-180/TPemutt
HFD-180/KRobie-Suh
HFD-180/JChoudary
HFD-870/SAl-Fayoumi

Concur with above comment and recommendation

/S/
4-13-00

DMP 702-900 (CAN/LOG/002/TRE)
SUMMARY TABLE

FEBRUARY 15, 1999

TABLE 6.6.1

LISTING OF DEATHS
SAFETY POPULATION

Treatment Group#	Patient ID	Age (yrs)	Sex	Day of Death@	End of Initial Therapy Day@	Adjudicated Cause of Death	Comments From End of Study Form
TNZ	A013	64	Female	58	5	Metastatic Carcinoma (Insidious)	
	A015	80	Female	17	5	Metastatic Carcinoma (Abrupt)	
	A020	66	Male	32	5	Metastatic Carcinoma (Insidious)	
	B013	48	Female	12	4	Metastatic Carcinoma (Abrupt)	
	L012	60	Female	41	5	Metastatic Carcinoma (Insidious)	
	L029	77	Male	77	5	Metastatic Carcinoma (Insidious)	
	S011	85	Female	6	5	Sudden Death Poss Due to Pulmonary Embolism	NO AUTOPSY DONE
	T039	52	Male	31	5	Metastatic Carcinoma (Insidious)	
	Z034	84	Male	57	5	Pulmonary Tuberculosis(Insidious)	
	Z037	48	Male	2	1	Amyotrophic Lat Sclerosis (Insidious)	
HEP	BU31	51	Female	13	1	Metastatic Carcinoma (Abrupt)	
	C018	69	Male	84	7	Metastatic Carcinoma (Insidious)	
	C041	76	Male	12	5	Metastatic Carcinoma (Abrupt)	
	C049	55	Female	84	6	Metastatic Carcinoma (Abrupt)	
	C051	63	Male	1	1	Pulmonary Embolism (Abrupt)	
	D017	67	Male	8	6	Sudden Death Poss Due to Pulmonary Embolism	
	E021	56	Male	56	6	Metastatic Carcinoma (Abrupt)	NO AUTOPSY PERFORMED ON THIS PATIENT. FAMILY PHYSICIAN DR GRYMALOWSKI SUSPECTS PULMONARY EMBOLISM DUE TO THE SUDDENESS OF PATIENT DETERIORATION.
	H030	76	Male	38	6	Pneumonia (Insidious)	
	L007	78	Female	51	1	Pulmonary Embolism (Abrupt)	
	S022	41	Male	38	9	Metastatic Carcinoma (Abrupt)	
	S037	52	Male	75	7	Metastatic Carcinoma (Abrupt)	NO AUTOPSY-PATIENT POSSIBLY HAD P.E.

TNZ = Subcutaneous LMW heparin (Tinzaparin) 175 FXa IU/kg body weight once every 24 hours; HEP = Continuous intravenous unfractionated heparin.
@ Days from initialization of study drug.
Note: Patients Z004 and Z036 also had major bleeding at the time of death.
Note: This table lists patients who died within 90 days of treatment initialization. Patient D021 (Tinzaparin) died of ovarian cancer on day 93 of treatment.

DMP 702-900 (CAN/LOG/002/TRE)
SUMMARY TABLE

FEBRUARY 15, 1999

TABLE 6.6.1 (CONT'D)

LISTING OF DEATHS
SAFETY POPULATION

Treatment Group#	Patient ID	Age (yrs)	Sex	Day of Death@	End of Initial Therapy Day@	Adjudicated Cause of Death	Comments From End of Study Form
HEP	S040	83	Female	71	5	Metastatic Carcinoma (Insidious)	
	V017	65	Male	29	5	Metastatic Carcinoma (Insidious)	
	W026	66	Female	41	6	Pneumonia (Insidious)	PATIENT WAS RECOVERING FROM DVT AND HAD A NL IPG. WAS TX WI TH STANDARD SQ HEPARIN BECAUSE SHE WAS UNABLE TO ABSORB COUMADIN.
	✓Z004	64	Male	10	5	Metastatic Carcinoma (Abrupt)	
	Z021	81	Female	16	5	Metastatic Carcinoma (Abrupt)	12/20/89 IPG POSITIVE LEFT LUNG NEGATIVE RIGHT LUNG. 12/21/89 VENOGRAM-EXTENSIVE DT. LT LEG.SCAN INDETERMINATE 12/27/89 & 12/29/89 IPG POSITIVE BILAT. DIFFICULTY DOING BOTH TESTS.1/03/90 BY VENOGRAM PROXIMAL DVT
	✓Z036	75	Male	5	5	Pulmonary Embolism (Abrupt)	
	Z052	82	Male	87	4	Metastatic Carcinoma (Insidious)	
	Z063	63	Female	61	5	Metastatic Carcinoma (Insidious)	
	Z102	81	Male	13	4	Cardiomyopathy (Abrupt)	
	Z107	64	Female	85	4	Metastatic Carcinoma (Insidious)	

TNZ = Subcutaneous LMW heparin (Tinzaparin) 175 FXa IU/kg body weight once every 24 hours; HEP = Continuous intravenous unfractionated heparin.
@ Days from initialization of study drug.
Note: Patients Z004 and Z036 also had major bleeding at the time of death.
Note: This table lists patients who died within 90 days of treatment initialization. Patient D021 (Tinzaparin) died of ovarian cancer on day 93 of treatment.

Other

MEMORANDUM OF TELECON 4

DATE: April 10, 2000
TIME: 10:00 am-11:00 am

APPLICATION NUMBER: NDA 20-484 innohep® (tinzaparin sodium injection)

BETWEEN:

Name: Kristian Johansen, Director, Biological Development, Leo Pharmaceutical Products

[redacted]

Damaris DeGraft-Johnson, Sr. Director, Regulatory Affairs, DuPont Pharmaceuticals Inc.

Jim Gaskill, Associate Director, Regulatory Affairs, DuPont Pharmaceuticals Inc.

Nirdosh Jagota, Associate Director, Regulatory Affairs, DuPont Pharmaceuticals Inc.

Jeri May, Manager, Quality Assurance, DuPont Pharmaceuticals Inc.

Karen Veronich, Director, Quality Assurance, DuPont Phamaceuticals Inc.

Phone: 302-892-7308

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Liang Zhou, Ph.D., Chemistry Team Leader
Ali Al-Hakim, Ph.D., Chemistry Reviewer
Karen Oliver, RN, MSN, Regulatory Health Project Manager

SUBJECT: Chemistry, Manufacturing and Controls (CMC) and DMF issues identified in February 28 and February 24, 2000 Agency letters, respectively.

BACKGROUND:

On June 30, 1999, DuPont Pharmaceuticals Inc. submitted NDA 20-484 [innohep® (tinzaparin sodium injection)] for the following proposed two indications: (1) the treatment of acute deep vein thrombosis (DVT) with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium, and [redacted]

On February 24, 2000, the Agency issued DMF deficiency letters to DMF [redacted] and DMF [redacted]. On February 28, 2000, the Agency issued a Chemistry, Manufacturing and Controls Discipline Review letter. On April 3, 2000, the sponsor submitted a brief outline of the information they intended to submit in response to the Agency letters, and requested a teleconference to discuss their proposed responses.

Telephone Conversation:

The Division stated that the preliminary information outlined in the April 3, 2000 submission appears to be adequate. The submission of the complete response, including appropriate supportive data, will be reviewed by the Agency for adequacy and completeness.

The sponsor stated that the full response would be submitted in May, 2000.

The call was concluded.

Minutes Preparer:

/S/ 04/14/00
Karen Oliver, RN, MSN
Regulatory Health Project Manager

Chair Concurrence:

/S/ 4/14/00
Liang Zhou, Ph.D.
Chemistry Team Leader

cc: Original NDA 20-484
HFD-180/Div. File
HFD-180/K.Oliver
HFD-180/L.Zhou
HFD-180/A.Al-Hakim
R/D init: A.Al-Hakim 04/14/00
R/D init: L.Zhou 04/14/00
draft: KO/April 14, 1999
final: [redacted]

TELECON

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 17, 1999

FROM: Timothy W. Robison, Ph.D.
Pharmacologist, HFD-180

SUBJECT: Specific Activities (anti-Xa IU/mg) of Tinzaparin batches used in GLP Toxicology Studies - Needed Information.

TO: NDA 20,484

The specific activities (anti-Xa IU/mg) of tinzaparin batches used in the GLP Toxicology studies listed below are needed for completion of the Pharmacology Review. The draft labeling refers to human doses in terms of anti-Xa IU/mg. The nomenclature of units used is also needed. Drug Batch F84001 is believed to be [redacted]

TOXICOLOGY:	Study number	Drug Batch
ACUTE TOXICITY IN MICE AND RATS.	0786 884 0686 784 0586 4584 0486 3184	F85010 F84001 F85010 F84001 F85010 F84001 F85010 F84001
RATS		
CHRONIC TOXICITY		
1-Year subcutaneous study followed by a 6-week reversibility period.	89/NLP031/0142	100487 110487 120487
DOGS		
CHRONIC TOXICITY		
1-Year subcutaneous study.	88/NLP026/0843	170487 808330 180487 190487
REPRODUCTIVE TOXICOLOGY		
Rats		
Segment I subcutaneous fertility and reproductive performance study.	88/NLP027/458	100487 110487 120487
Segment II subcutaneous teratology study.	88/NLP025/100	100486 120487
Rabbits		
Segment II subcutaneous teratology study.	88/NLP063/360	100487 110487 120487
Segment II subcutaneous teratology study.	88/NLP083/178	830030 830031 830032
Rats		
Segment III subcutaneous perinatal and postnatal development study.	88/NLP030/245	100487 110487 120487
GENOTOXICITY		
Bacterial reverse mutation assay with strains TA1535, TA1537, TA100, and TA98 (Ames Test).	85/NLP006/462	F85010
Bacterial reverse mutation assay with strains WP2 and WP2 uvrA.	88/NLP081/0649	F547
Mouse micronucleus test.	85/NLP007/726	F85010
Human lymphocyte chromosomal aberration assay.	87/NLP032/734	
Chinese hamster ovary forward mutation assay (CHO/HGPRT).	87/NLP033/768	190487
SPECIAL TOXICITY STUDIES		
Active anaphylaxis in guinea pigs.	92/NLP060/0344	F682X
Passive cutaneous anaphylaxis assay in guinea pigs.	88/NLP061/0401	F682X
Passive hemagglutination assay in rabbits.	88/NLP062/0403	F682X
Local irritation in rabbits after intramuscular injection.	3785	

Therefore, the sponsor should be asked to provide specific activities (anti-Xa IU/mg) of tinzaparin batches used in the listed GLP Toxicology studies as the draft labeling refers to human doses in terms of anti-Xa IU/mg. The nomenclature of units used should also be provided.

/S/

Timothy W. Robison, Ph.D.

11-17-99
Date

cc:
NDA 20,484
HFD-180
HFD-181/CSO, Ms. Oliver
HFD-180/Dr. Choudary
HFD-180/Dr. Robison

/S/ 11/18/99

R/D Init.: J. Choudary 11/15/99

TWR/hw/11/16/99

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 4, 1999

FROM: Timothy W. Robison, Ph.D.
Pharmacologist, HFD-180

SUBJECT: NDA 20,484 Segment II Intravenous Teratology Study in Rabbits, LSR Report No. 92/NLP140/0183; Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 89/NLP083/178; and Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 88/NLP063/360 - Needed Information.

TO: NDA 20,484

For the three Segment II teratology studies in rabbits, listed below, examination of fetuses for visceral anomalies, malformations, and variations appear to be missing. For each study at necropsy, the neck and thoracic and abdominal cavities of all fetuses from each litter were dissected and the contents examined; however, these examinations appeared to be at the gross level. Each study did include skeletal examinations of fetuses and visceral examinations of fetal heads only. All three studies state that "torsos and remaining intact fetuses were fixed in industrial methylated spirit." There is no mention of further processing of torsos/intact fetuses. Examination of fetal internal organs generally done by using Wilson's free-hand serial sectioning technique appears to be lacking from each study. Results of complete visceral examinations of fetuses are required for comprehensive reviews of these studies.

1. Segment II Intravenous Teratology Study in Rabbits, LSR Report No. 92/NLP140/0183 (Volumes 26 and 27 of 218 or Item 5 Volumes 17 and 18)

2. Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 89/NLP083/178
(Volume 27 of 218 or Item 5 Volume18)

3. Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 88/NLP063/360
(Volume 27 of 218 or Item 5 Volume18)

Therefore, the sponsor should be asked to provide results of complete visceral examination of fetuses, preferably using Wilson's free-hand serial sectioning technique, in all three studies. At a minimum, the sponsor should provide complete visceral examination of fetuses, preferably using Wilson's free-hand serial sectioning technique, for the Segment II Subcutaneous Teratology Study in Rabbits (LSR Report No. 89/NLP083/178).

/S/
Timothy W. Robison, Ph.D.

11-4-99
Date

cc:
NDA 20,484
HFD-180
HFD-181/CSO, Ms. Oliver
HFD-180/Dr. Choudary
HFD-180/Dr. Robison

/S/ 11/4/99

R/D Init.: J. Choudary 11/4/99

TWR/hw/11/4/99

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 29, 1999

FROM: Timothy W. Robison, Ph.D.
Pharmacologist, HFD-180

SUBJECT: NDA 20,484 Segment II Intravenous Teratology Study in Rabbits, LSR Report No. 92/NLP140/0183; Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 89/NLP083/178; and Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 88/NLP063/360 - Needed Information.

TO: NDA 20,484

For the three Segment II teratology studies in rabbits, listed below, examination of fetuses for visceral anomalies, malformations, and variations appear to be missing. Each study included external examinations of fetuses, skeletal examinations of fetuses, and examinations of fetal heads only. All three studies state that "torsos and remaining intact fetuses were fixed in industrial methylated spirit." There is no mention of further processing of torsos/intact fetuses or complete visceral examination of fetuses. Results of complete-visceral examinations of fetuses are required for complete reviews of these studies.

1. Segment II Intravenous Teratology Study in Rabbits, LSR Report No. 92/NLP140/0183 (Volumes 26 and 27 of 218 or Item 5 Volumes 17 and 18).

2. Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 89/NLP083/178 (Volume 27 of 218 or Item 5 Volume18).

3. Segment II Subcutaneous Teratology Study in Rabbits, LSR Report No. 88/NLP063/360 (Volume 27 of 218 or Item 5 Volume18).

Therefore, the sponsor should be asked to provide results of complete visceral examination of fetuses in all three studies. At a minimum, the sponsor should provide complete visceral examination of fetuses for the Segment II Subcutaneous Teratology Study in Rabbits (LSR Report No. 89/NLP083/178).

/S/
Timothy W. Robison, Ph.D.

10-29-99
Date

R/D Init.: J. Choudary 10/28/99

TWR/hw/10/29/99

/S/ 10/29/99

CC:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Robison

OTW

MEMORANDUM OF MEETING MINUTES

APR 16 1999

Meeting Date: March 8, 1999
Time: 1:00pm-3:00pm
Location: Parklawn Building, The Potomac Conference Room

Application: [redacted]/innohep (tinzaparin sodium) Injection

Type of Meeting: Pre-NDA Meeting

Meeting Chair: Lilia Talarico, M.D.

Meeting Recorder: Karen Oliver, RN, MSN

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Lilia Talarico, M.D., Division Director
Ann Farrell, M.D., Medical Reviewer
Kathy Robie-Suh, M.D., Medical Reviewer
Eric Duffy, Ph.D., Chemistry Team Leader
Ali Al-Hakim, Ph.D., Chemistry Reviewer
Jasti Choudary, B.V.Sc., Ph.D., Pharmacology Team Leader
Karen Oliver, Regulatory Health Project Manager

Division of Biometrics, HFD-715

Milton Fan, Ph.D., Biometrics Reviewer

External Constituent Attendees and titles:

DuPont Pharmaceuticals Company

Mary A. Buesing, M.D., Director, Regulatory Affairs
Thomas E. Donnelly, Ph.D., Executive Director, Regulatory Affairs
James W. Hainer, M.D., M.P.H., Medical Director, Cardiology
T.A. (Augie) Hua, Ph.D., Senior Director, Biometrics
Michelle R. Modesto, MBA, Project Manager
Alison J. Pilgrim, BM, B.Ch., D.Phil., Vice President, Clinical Development

Leo Pharmaceutical Products

Claus Bay, M.S., Head of Statistics
Merete Jarlbaeck, D.D.S., Group Manager, Regulatory Affairs
Anders Ljungqvist, M.S., Vice President, Regulatory Affairs and QA/QC
Per Sprogel, M.D., Group Manager, Medical Department

Consultant

Lloyd Fisher, Ph.D., University of Washington

Background:

Tinzaparin/innohep injection is a low molecular weight heparin, currently marketed in Europe and Canada. The Division and the sponsors of the drug have met on three occasions to discuss clinical, statistical, and CMC issues related to innohep (see meeting minutes from the June 17, 1992, December 12, 1997, and March 3, 1998 meetings).

In a December 18, 1998 submission by Leo Pharmaceuticals Products LTS. A/S to [redacted] transfer of sponsorship of [redacted] was acknowledged. Further, [redacted], as their authorized representative and DuPont Pharmaceuticals as having the US marketing rights for the proposed NDA. In a December 11, 1998 submission by DuPont Pharmaceuticals Company to [redacted], DuPont stated that they would be the sponsor of the pending NDA for [redacted] Injection.

On December 11, 1998, DuPont Pharmaceuticals Company submitted a background package requesting two meetings, a face-to-face meeting to re-discuss pre-NDA clinical and statistical issues, and a teleconference to discuss pre-NDA electronic submission and formatting questions. As a result of discussion with the Division at the December 1997 meeting, DuPont revised the target indications to include: (1) the treatment of acute deep vein thrombosis (DVT) with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium, and [redacted]

In a January 14, 1999 teleconference, pre-NDA electronic submission and formatting issues were discussed (see Memorandum of Telecon dated January 14, 1999).

The March 8, 1999 meeting was scheduled to discuss clinical and statistical issues.

Meeting Objectives:

1. To discuss clinical and statistical issues previously discussed with the Division on December 12, 1997 and June 17, 1992 (see Memorandum of Meeting dated March 3, 1998, and June 17, 1992).

2. To discuss new clinical and statistical issues r/t a pending submission, an NDA for Logiparin Injection.

Discussion Points (bullet format): See Attached Overheads

In response to the sponsor's specific questions in their December 11, 1998 background package, the following agreements were reached after discussion. The format provides the sponsor's questions (1-10), followed by the Agency's response in bolded lettering.

Issues previously discussed with the division

1. Does the Division feel the evidence presented is sufficient to warrant a labeling claim of superiority for tinzaparin over unfractionated heparin in the treatment of DVT?

   - The evidence presented in the single pivotal Study DMP 702-900 (CAN/LOG/002/TRE) does not demonstrate robust, convincing data to support the claim of tinzaparin superiority. A second study replicating the results of Study DMP 702-900 would be needed to support the proposed indication.

   - For Study DMP 702-900, additional information should be provided for the assessment of "all-cause mortality" as listed in Table 2.1, page 94, of the background package.

   - A single study to support approval of an indication must meet the criteria guidance for a single study as described in *Guidance for Industry, Providing Effectiveness for Human Drugs and Biological Products* (May 1998). Such a study is expected to be a large, multi-center, adequate and well-controlled study with strong and robust superiority results across centers. The general expectation is that a p-value $\leq .001$ is needed to provide sufficient and adequate support for the claimed indication. Superiority study design is required for single study consideration.

   - At the moment, there is no Agency guidance for a single study submission for non-inferiority or clinical equivalence claims. The .001 p-value requirement is for a superiority claim. It could be argued, however, that a clinical equivalence claim based on a 100 (1-.001)% or 99.9% 2-sided CI with a narrow margin (delta) might also provide convincing evidence in support of such a claim. Generally, the Agency's

expectation is that 2 adequate and well controlled studies will be provided in support of a non-inferiority or clinical equivalence claim.

- The proposed wording of the indication, "the treatment of DVT with or without PE", would be acceptable if supported by the clinical trial data.

- Heparin would be an acceptable comparator for this indication.

- Based on the information submitted in the background package, the trials conducted to support the treatment of DVT and PE indication appear to demonstrate superiority over "putative" placebo and, therefore, could be considered supportive of the proposed indication, based upon equivalency to heparin. However, review of the data would be needed.

2. Does the Division agree that this study is relevant and supportive of the proposed indication for treatment of DVT?

   - The French study [Study DMP 702-904 (IN 9502 FR)] provides supportive data for

3. [redacted]

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Additional NDA topics for discussion:

10. For each of the points described in Section 4, does the Division concur with the proposed approach?

    - The content and format of the NDA, refer to *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications* (July 1988).

    - Serious adverse events should include the following: anaphylaxis, thrombocytopenia, and bleeding. Further, on treatment SAE's should be extended to 72 hours post-dosing.

AGENCY ADDENDUM:

Pre-Clinical Data

- Provide information requested in the Agency's meeting minutes dated June 17, 1992.

- Identify each pre-clinical study in terms of whether the study was submitted to [redacted] If the study was submitted to the IND, submission date(s) of all information related to each study.

- In an introductory statement for each pre-clinical study provide the following: (1) doses of [redacted] used in the study in terms of "mg/Kg" and "anti-Xa Units"; (2) the batch number(s) and the anti-Xa equivalence for each batch(es); and (3) the drug formulation(s).

- Provide adequate information on any new pre-clinical studies.

Biopharmaceutics Data

- Provide information requested in the Agency's meeting minutes dated June 17, 1992 and March 3, 1998.

- Identify each biopharmeutic study in terms of whether the study was submitted to [redacted] If the study was submitted the IND, specify the submission date(s) of all information related to each study.

- Provide adequate information on all new studies (BE and population PK).

- Provide a biopharmaceutic data table that lists each biopharmaceutic study, the date(s) the study was conducted, study title, study size, and volume and page number(s) cross-referencing the study data in the NDA submission.

Overall Submission Reminders

- Provide manufacturing sites, site specific address, function, and CFNs.

- Provide a statement in the cover letter that the sites are ready for inspection.

- The User Fee check must have cleared prior to the submission of the application.

- Provide a pediatric statement describing the studies completed and planned [reference FDAMA, Section 111 and Pediatric Final Rule (Published December 2, 1998, 63 FR 66632)].

- Provide color mock-ups of cartons and immediate container labels.

- List foreign countries where the drug is approved, specify indication, and provide English translations of the labeling from the major EU countries.

- Provide financial certification/disclosure requirements.
- The name "innohep" will be consulted to the Nomenclature Committee upon submission of the application.
- If possible, provide line listings in SAS transport format filing (uncompressed), compatible with JMP.
- If possible, provide the appropriate statistical information on SAS files (version 6.12) with analysis programs.
- Duplicate volumes (i.e., medical and statistical technical volumes) should be exact duplicated including electronic files.
- If possible, provide electronic hypertext linking from the overall table of contents to the study reports.

Minutes Preparer: /S/ 04/15/95
Karen Oliver, RN, MSN

Chair Concurrence: /S/ 4-15-95
Lilia Talarico, M.D.

Attachments/Handouts: Overheads

cc: Original
HFD-/Div. Files
HFD-/Meeting Minutes files
HFD-/K. Oliver
HFD-/reviewers & attendees
Drafted by: K.Oliver 02/24/99
Initialed by: L.Talarico 04/12/99
final: KO/04/15/99/

MEETING MINUTES

MEMORANDUM OF TELECON

DATE: January 14, 1999
TIME: 11am-12nn

APPLICATION NUMBER: ——————— ' innohep (tinzaparin sodium) Injection

BETWEEN:

Name: Mary A. Buesing, M.D., Director, Regulatory Affairs
Thomas E. Donnelly, Ph.D., Executive Director, Regulatory Affairs
Christine L. Frangakis, Document Management Specialist
James L. Gaskill, Regulatory Affairs, Manager
Ann M. Grumet, Senior Director, Regulatory Operations
James W. Hainer, M.D., Ph.D., Medical Director, Cardiology
Tsushung A. Hua, Ph.D., Senior Director, Biometrics
Rosemarie Peters, Supervisor, Submissions
Susan E. Wilson, Medical Writer
Phone: 302-992-4006
Representing: DuPont Pharmaceuticals Company

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Lilia Talarico, M.D., Division Director
Jasti Choudary, B.V.Sc., Ph.D.
Karen Oliver, RN, MSN, Regulatory Health Project Manager

Division of Biometrics, HFD-715

A.J. Sankoh, Ph.D., Team Leader, Biostatistics

Division of Clinical Pharmacology and Biopharmaceutics, HFD-870

David Lee, Ph.D., Team Leader, Biopharmaceutics

SUBJECT: Electronic Submission and Formatting

BACKGROUND:

Tinzaparin/innohep injection is a low molecular weight heparin, currently marketed in Europe and Canada. The Division and the sponsors of the drug have met on three occasions to discuss clinical, statistical, and CMC issues related to innohep (see meeting minutes for the June 17, 1992, December 12, 1997, and March 3, 1998 meetings).

As a result of discussion with the Division at the December 1997 meeting, DuPont has revised the target indications to include: (1) the treatment of acute deep vein thrombosis (DVT) with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium and

On December 11, 1998, DuPont Merck Pharmaceuticals Company submitted a background package requesting two meetings, a face-to-face meeting to re-discuss pre-NDA clinical and statistical issues, and a teleconference to discuss pre-NDA electronic submission and formatting questions.

In response to the sponsor's questions regarding electronic submission and formatting issues, the following discussion ensued. The format provides the sponsor's questions, followed by the Agency's recommendations and the sponsor's response to the recommendations in bolded lettering.

Telephone Conversation:

1. To avoid extensive renumbering and repagination, we propose that Section 10, Statistics, be an exact duplicate of Section 8, Clinical Data. The page numbers and section numbers will be identical. The only difference will be the color of the binder covers indicating the intended reviewer. Does the Division concur with this approach?

   Division's Recommendations:

   The two sections can be exact duplicates of each other. However, page numbers are identifiers, and, therefore, each page in the submission should have a unique pagination number, i.e., no two pages in the submission should have the same pagination number. In the page numbering sequence, include the volume number (if possible), the section number, and the page number.

   Sponsor's Response:

   Due to resource constraints, paginating the submission in this manner may not be possible. The page numbers will be sequentially numbered in each volume, that is, each volume will start with page 1. The Division's recommendations will be discussed with upper management and the sponsor will notify the Division, in writing, of the pagination formatting of the submission.

2. We proposed to add all elements of Section 6, Human PK and Bioavailability, to the beginning of Section 8.2, Clinical Pharmacology (please refer to the NDA Table of Contents in Appendix 8, Section 12). An exact duplicate with identical page numbers and section numbers of Section 8.2 will be used for Section 6. The only difference will be the color of the binder covers indicating the intended reviewer. Does the Division concur with this approach?

   Division's Recommendations:

   See "Division's Recommendations to questions #1.

   Sponsor's Response:

   See "Sponsor's Response" to question #1.

3. Does the Biopharm reviewer want all clinical study reports from Section 8 or only those referenced in Section 8.2?

   Division Recommendations:

   Provide the following information in the biopharmaceutics section of the submission:

   - **Study summary of safety and efficacy of clinical studies.**
   - **Strongly recommend that the biopharmaceutics section be submitted in electronic format (Microsoft Word 97 SR-1, Microsoft Office 97) as well as paper copy. The electronic format should include all tables, profiles, etc.**
   - **Submit biopharmaceutics statistical analysis on SAS diskette(s) with data sets and programs (specify the format of the program). NO transport files, but compressed files (with adequate directions on how to decompress the files) are acceptable.**

   Sponsor Response:

   - **Clarified that both compressed files and/or data set (not compressed) files are acceptable to the Division.**
   - **Will provide biopharmaceutics data as SAS 6.12 data sets and the corresponding SAS programs.**

4. We proposed to not include any CRTs and CRFs as appendices to the clinical study reports, but to include them in items 11 and 12, respectively. Does the Division concur?

Division's Comments/Recommendations:

The proposal is acceptable with the following provisions:

- **The CRTs and CRFs must be specifically and appropriately cross-referenced in the clinical studies (volume, section, page number).**

- **Provide a comprehensive "All Clinical Studies" table which includes the specific location in the NDA of the following items for each of the clinical studies: the study report, the study summary, the original study protocol, all protocol amendments, final protocol (if available) and CRTs and CRFs.**

Sponsor's Response:

- **Only limited cross-referencing from the CRTs and CRFs to the study data will be provided due to the labor intensity of the request.**

- **Will consider providing a comprehensive "All Clinical Studies" table after the labor intensity of the task is evaluated.**

5. For Section 11, Case Report Form Tabulations (CRTs), we propose to provide the tabulations only electronically. These tabulations will adhere to the requirements for domain profiles provided as SAS transport files, Version 5, as stated in the (April 1998) Draft Guidance, "Providing Regulatory Submissions in Electronic Format – NDAs." The SAS programs will be provided for all safety and efficacy analyses along with SAS Proc Contents for variable and file definitions. Does the Division concur with this approach?

Division's Recommendations:

- **Submit CRTs in paper copy as well as electronic copy.**

- **Provide clinical (safety and efficacy) data as SAS data sets, in floppy diskettes or CD rom. Please do NOT transmit clinical and biopharmaceutics SAS data sets as SAS transport. Provide the SAS programs used to run the efficacy and safety analysis.**

- **Compressed SAS data sets are acceptable if adequate directions to decompress them are provided.**

Sponsor's Response:

- **The CRFs are only available in paper format and will NOT be submitted in electronic format.**

- **The sponsor agreed not to submit SAS transport data sets for clinical and biopharmaceutics data.**

- **Section 11 will contain CRTs and CRFs for the pivotal studies only.**

6. We propose that all study reports will follow the reference documents at the end of each NDA item, rather than after the individual summaries within the subsections (see NDA Table of Contents, Appendix 7). Does the Division concur with this approach?

Division's Recommendations:

- **Specify, in the index, what is included in the "reference documents" section.**

- **Provide the specific study summary before each of the studies.**

- **For the individual study summaries, provide the specific cross-reference to the study data.**

Sponsor's Response:

- **Agreed to provide a study synopsis before each study.**

- **Specific cross-referencing from the individual study summaries to the study data will be considered, but will probably not be initiated due to the labor intensity of the request.**

7. We propose to number the pages with the NDA Item number and Page number on each page. The volume number will appear on the binder cover and in each volume's Table of Contents. Does the Division concur with this approach?

Division's Recommendations:

See "Division's Recommendations", question #1.

Sponsor's Response:

See "Sponsor's Response" to question #1.

8. We propose to cross reference from summary documents to the first page of the appropriate study reports. The Annotate Labeling will be cross-referenced to individual pages. Does the Division concur with this approach?

Division's Recommendations:

- **A summary report should precede each of the study reports.**
- **The annotated labeling must provide specific references to the study data supporting the labeling.**
- **Each study should be identified in the index with a unique subsection number.**

Sponsor's Response:

- **Agreed to provide a synopsis of the study before each study report.**
- **Agreed to reference annotated labeling to specific data rather than summary reports.**
- **Agreed to reference each clinical study in the index with a unique subsection number.**

9. In addition to the paper copies, we can provide the Division with electronic copies (in PDF format) of the summary documents and the pivotal clinical study reports' text. Does the Division desire to have electronic copies of these documents? (Note: CRFs will only be provided in paper.)

Division's Recommendations:

- **Electronic copies of the summary documents and the pivotal clinical study report text in Word; PDF format is acceptable.**
- **Submit CRFs in both electronic and paper format.**

Sponsor's Response:

- **The CRFs are only available in paper format and will NOT be submitted in electronic format.**

- **The electronic documents will be submitted in PFD format. The hyperlinks will be specific to each electronic document, and will not cross-reference other documents submitted electronically.**

- **If needed, the sponsor agreed to provide instructions to the reviewers on how to negotiate through the electronic submission.**

- **Electronic book marks are available within the submission.**

10. We plan to provide the draft labeling in MS word. Is this acceptable to the Division?

Division's Response:

Provide both the annotated and the unannotated versions of the package insert labeling in Microsoft Word 97 SR-1.

Sponsor' Response:

Agreed to request.

11. In lieu of photographs of some macroscopic and microscopic findings (a local irritation study in rabbits) and autoradiographs from a pharmacokinetics study in rats, we will include color, and black and white copies produced on a Canon 950 color copier in the NDA. Sample copies are provided in Appendix 10. Does the Division concur that this approach is adequate?

Division's Response:

The approach appears to be adequate.

Sponsor's Response:

None.

12. For the five pivotal studies (DMP 702-900, -904, [redacted] plus the large general surgery study (DMP 702-933), we will provide CRTs by patient domain (e.g. hematology demography, etc.). The statistical reviewer will be provided with a format library for each

trial and for each file within a trial the variable names and labels will be provided from SAS 'PROC CONTENTS'. The SAS programs for the primary and secondary efficacy and primary safety analyses will be provided. In addition, we will provide the WHO AE and the medication dictionaries. Is this acceptable to the Division?

Division's Response:

- **In the case that this submission is put on the network, the Division requests floppy diskettes or CD rom for the clinical, statistical, and biopharmaceutics data sets. For the clinical and biopharmaceutics data sets, please do NOT transmit as SAS transport data sets.**

Sponsor's Response:

- **The sponsor agreed not to submit SAS transport data sets for clinical and biopharmaceutics data.**

Prior to completing the teleconference, the project manager requested that the sponsor provide the following information:

- Questions for clinical/statistical meeting on diskette (Word 97).
- A letter of transfer acceptance from —(information provided by — via facsimile was incomplete).

The sponsor agreed to provide the requested information.

The call was concluded.

Minutes Preparer: /S/ 11/25/99

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Chair Concurrence: /S/ 1-25-99

Lilia Talarico, M.D.
Division Director

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 3, 1998
Time: 1pm-3pm
Location: Parklawn Building, Conference Room "L"

Application: [redacted]

Type of Meeting: CMC Pre-NDA Meeting

Meeting Chair: Eric Duffy, Ph.D; Chemistry Team Leader

Meeting Recorder: Karen Oliver, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Eric Duffy, Ph.D., Chemistry Team Leader
Ali Al-Hakim, Ph. D., Review Chemist
Arthur Shaw, Ph.D., Review Chemist
Karen Oliver, MSN, Regulatory Health Project Manager

Division of Clinical Pharmacology and Biopharmaceutics Evaluation II

John Hunt, B.Sc., Acting Team Leader, Clinical Pharmacology and Biopharmaceutics
Arzu Selen, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

External Constituent Attendees and titles:

The DuPont Merck Pharmaceutical Company

David Koruhauser, Clinical Pharmacology
Karen Veronich, Ph.D., Director, Quality, Contract Operation
James Gaskill, R.Ph., Regulatory Affairs Manager
Edward C. Bradley, M.D., Executive V.P., Clinical Development
Mark Taisy, Regulatory Affairs
Gene Kotz, R.Ph., Senior Director, Corp. Business Development
James W. Hainer, M.D., M.P.H., Medical Director, Cardiology Clinical Research
Clem Wachinski, Exec. Dir., Corp Business Development
Jeri L. May, MS, QA Manager
Philippa Lammey, Project Management

Michelle R. Modesto, Sr. Project Coordinator, Project Management
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Christopher C. Kowtna, Dir., Regulatory Support, Marketed Products
Pasquale J. Perfetto, Jr., Quality Engineer

[redacted]

Leo Pharmaceuticals

Anders Ljungqvist, M.Sc.Pharm., Director, QC and Pharm Development
Ivan Moller, Pharmaceutical Development
Merete Jarlkaek, D.D.S., Group Manager/Regulatory Affairs
Morten Benthin, Pharmaceutical Development
Kristian B. Johansen, Ph.D., Director, Biological Development
Karin Bredal Jensen, M.Sc.Pharm., QA Manager
Birgit Poulsen, Director, Regulatory Affairs

Background:

The sponsor requested a Pre-NDA meeting to discuss the strategic approach and content of the chemistry, manufacturing and controls (CMC) information for tinzaparin sodium that will be provided in the NDA currently planned for submission in third quarter 1998. The trade names for the two products containing tinzaparin sodium are Innohep® (Leo Pharmaceutical Products) and [redacted].

Meeting Objective:

To come to an agreement on the proposed content and format of the CMC information, with specific attention to the transfer of manufacturing from [redacted]

Discussion Points (bullet format): See Attached Overheads

1. The firm briefly over viewed the tinzaparin formulations (drug substance, drug product, and pharmacokinetic/pharmacodynamic data) and the collaborative development history of the finished drug products Innohep® [redacted] produced by [redacted] respectively.

2. The firm reviewed the comparability of the drug substance , drug product, and biopharmaceutics of the [redacted] products.

3. The firm identified the starting material for the drug product as "Heparin Sodium" of porcine origin.

4. The firm briefly described the role of heparinase, as a catalyst that is removed from the drug substance in the early phase of the synthesis.

5. The firm described the proposed stability protocol for the intended-for-market configuration.

6. The firm reviewed the following proposals: (1) to submit an exclusion for the environmental assessment; (2) the structure and content of the type II DMFs for the active substance and drug product; and (3) the structure and content of the CMC section.

7. The firm's questions in their February 12, 1998 background package were discussed.

Decisions (agreements) reached:

1. Regarding the drug substances (produced with different volumes of ethanol) produced by [redacted]

   - Molecular weight distribution and Xa/IIa ratio are essential parameters in establishing equivalence.

   - Additional supportive parameters: (1) proof and comparison of chemical structure and NMR; (2) compare/contrast process differences and discuss the significance, or lack thereof, of the differences;
   (3) compare/contrast adsorption differences and discuss the significance, or lack thereof, of the differences; (4) provide the animal source of the heparin for the drug substances, source specifications, certificate of analysis (porcine/bovine), and animal country of origin.

2. Regarding the enzyme Heparinase:

   - Provide detailed information regarding the enzyme activity and the process adjustments used to control the endpoint.

   - Compare/contrast the actual specific enzyme activity used by [redacted]

- Provide the information regarding the enzyme manufacturing, preparation, and specifications in a DMF.

3. Regarding the starting material:

   - Provide the analytical data and the certificate of analysis for the starting material (sodium heparin)

   - Based on the information that is available, provide a scientific discussion comparing and contrasting the differences in the starting materials for the clinical trials.

   - Provide the information for the starting material, Heparin, in a DMF. Include appropriate validated standards (European Pharmacopeia and/or USP).

   - Discuss the hydrogen peroxide treatment of [redacted] Include, in the discussion, the effect on molecular weight distribution and its removal at the end of the process.

   - Provide validation for sterilization process.

   - Provide all re-processing procedures.

   - Provide all in-process controls including de-polymerization in-process controls.

   - Provide an explanation for the absence of the following: (1) in-process controls for the removal of heparinase, and (2) protein content validation.

   - For the specifications of tinzaprin sodium, provide: (1) an explanation for the bacterial endotoxin units; (2) a tighter specification assay (currently listed as 70.0-120.0 IU/mg; (3) batch results and specifications; (4) justification for the listed specifications.

4. Regarding the drug product:

   - Provide preservative effectiveness study results. Provide documentation for the minimum level of preservative effectiveness.

- Provide justification for the sodium bisulfate in the drug product including information on the loss of sodium bisulfate during the shelf-life of product.

- For the finished product specifications, provide: (1) an anti-IIa assay or justification for why not; (2) the regulatory release specifications for the finished product; (3) a definition, explanation and discussion of the colored impurity, what controls are set for color control, and the correlation of color change and loss of sulfate; (4) explain the effect, if any, of highly colored material *in vivo*; (5) assay values for color and activity in clinical trials.

5. Regarding biopharmaceutics- PK/PD Studies:

- The firm agreed to provide the manufacturing information for the [redacted] batches used in clinical studies will be linked effectively with the anti-Xa and anti-IIa activity obtained in the clinical studies. That is, information in a table such as Table 2.6 on page 28 of the pre-NDA Meeting Document (Overview of Tinzaparin sodium manufactured by [redacted] and in figures such as Figures 1 and 2 on pages 39 and 40 of the pre-NDA Meeting Document (PK/PD Comparison between the major clinical studies and the pharmacokinetic studies) will be revised and adequately labeled to link the manufacturing information with the anti-Xa and anti-IIa activity obtained in all of these studies.

- The firm agreed to provide all of the supportive information for these studies such as sample handling, analytical methods, assay validations and data analysis methods in the NDA submission.

- The firm agreed to provide the sample sizes of the mean values such as the anti-Xa and anti-IIa activities of the 3-5 h postdose samples (presented in Tables 2 and 3 on pages 42 and 43 of the pre-NDA Meeting Document). In addition, the firm agreed to provide all of the anti-Xa and anti-IIa activity data collected in these studies (with their collection times with respect to time of dosing).

- The firm agreed to assess and provide for each study in the submission the following: the extent of variability, in addition to the mean of pharmacokinetic parameters/data; the standard deviation or the correlation coefficient of the mean as well as the range of individual values; and the sample size presented in the tables.

- The firm agreed to provide the data from the [redacted] Study (TI 93AB FR) in the population pharmacokinetic analysis. Although, on page 69 of the pre-NDA Meeting Document, it is indicated that data from 3 [redacted] studies (F/LOG/002/PGE, USA/LOG/004/POR and CAN/LOG/002/TRE) will be used for the population pharmacokinetic analysis, it was agreed at the meeting that the data from the [redacted] Study (TI 93AB FR) will also be included in this analysis. The firm agreed to determine the population pharmacokinetic parameters and whether these parameters are influenced by covariates such as patient gender, body-weight, height, age, and race.

- Since individual data and the extent of variability in parameters were not provided in the pre-NDA Meeting Document, an assessment of linearity of tinzaparin pharmacokinetics or its accumulation characteristics has not been possible and will be made when all of the data are submitted.

6. Regarding Type I and Type II DMFs: (1) do not submit Type I DMFs; (2) recommend that Type II DMFs not be submitted, but rather the information be submitted directly to the NDA; (3) file a Type 5 DMF for the sterile process facility. The sterility information should also be submitted to the NDA.

7. Regarding stability:

   - Provide 6 months accelerated and room temperature data on 3 batches of each of the 2 strengths in the 2 mL vial on SAS data diskettes.

   - The proposed antioxidant, preservative and particulate stability studies appear adequate.

8. Regarding the environmental assessment: provide the calculation supporting the requested exclusion.

9. Regarding the container/closure system:

   - Information on all components can be provided in a DMF.

- If not the holder of the DMF, provide a LOA from the DMF holder. Include the specific page and date of information pertinent to the NDA review.

Minutes Preparer: /S/ 04/22/98

Chair Concurrence: /S/ 4/23/98

Attachments/Handouts: Overheads

cc: Original [redacted]
HFD-/Div. Files
HFD-/Meeting Minutes files
HFD-/K.Oliver
HFD-/reviewers & attendees

Drafted by: KO/April 17, 1998
Initialed by: A.Al-Hakim 04/20/98
Initialed by: E.Duffy 04/21/98
Initialed by: A.Selen 04/22/98
final: [redacted] ko

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 12, 1997
Time: 1pm-3pm
Location: Conference Room C, Parklawn Building

Application: [redacted], innohep, [redacted] (tinzaparin sodium) Injection

Type of Meeting: Pre-NDA Meeting

Meeting Chair: Lilia Talarico, M.D., Division Director

Meeting Recorder: Karen Oliver, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

L. Talarico, M.D., Division Director, HFD-180
K. Sizer, M.D., Medical Officer, HFD-180
N. Markovic, M.D., Ph.D, Medical Officer, HFD-180
E. Duffy, Ph.D., Chemistry Team Leader, HFD-180
K. Oliver, MSN, Regulatory Health Project Manager, HFD-180
A. J. Sankoh, Ph.D., Biometrics Acting Team Leader, HFD-720
F. Harrison, Ph.D., Biometrics Reviewer, HFD-720

External Constituent Attendees and titles:

Leo Pharmaceutical Products

P. Sprogel, M. D., Group Manager, Medical Department
A. Coley, Director, Regulatory Affairs (Leo Canada)
M. Jarlbaek, D.D.S., Group Manager, Regulatory Affairs
K. B. Johansen, Ph.D., Director, Biological Development
K. B. Jensen, QA Manager
B. Poulsen, Director, Regulatory Affairs

DuPont Merck Pharmaceuticals Company

C. Wachinski, VP Marketing
J. May, QA Manager
E. Bradley, M.D., VP Clinical Operations
C. Powtna, Regulatory Support
M. J. Taisey, Senior Director, Regulatory Affairs
P. Pinto, Associate Director, Regulatory Affairs
W. D. Michaelis, M.D, Executive Medical Director, Clinical R&D
R. N. Daly, Ph.D., Associate Medical Director, Clinical R&D

G. S. Kotz, Senior Director, Corporate Business Development
G. E. Raskob, M.Sc., Consultant to DuPont Merck
[redacted]

Background:

On September 30, 1997, [redacted] requested a pre-NDA meeting with the Agency to discuss clinical issues related to innohep® (tinzaparin sodium) with an expected filing date of the third quarter, 1998. The indications being proposed for innohep are: (1) the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); [redacted]

Meeting Objectives:

To obtain Agency feedback regarding:

1. The format of the submission.
2. The adequacy of the trials for the proposed indications.
3. Customary medical practice issues.
4. The approach to the submission of the NDA.

Discussion Points:

1. The firm presented background information of the business relationship of [redacted] and DuPont Merck Pharmaceutical Company and each company's responsibility in the chemical, pre-clinical, clinical development; the European marketing of innohep (see attached overheads 1-10); and the comparison of the formulation used in clinical trials with the formulation intended for marketing (see overheads 36-37).

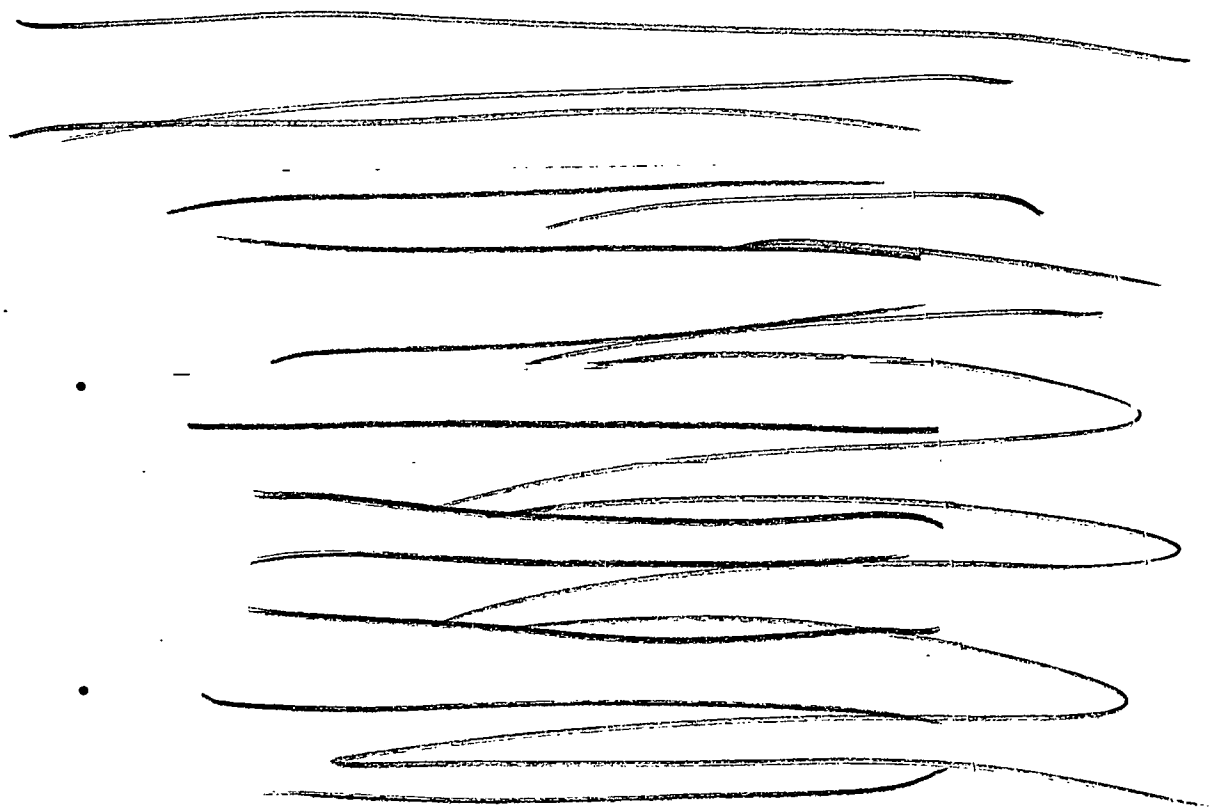
2. The firm presented information on the completed pivotal studies to support the proposed indications for innohep (see overhead 11-14).

   a. In support of the indication for treatment of DVT and PE, the firm conducted Study CAN/LOG/002/TRE, a controlled US-Canadian trial for treatment of DVT and Study IN 9502 FR for the treatment of PE. The studies compared innohep vs heparin.

      - The firm presented a summary of the pivotal studies supporting the indication (see overheads 15-19).

      - In response to Dr. Talarico's question regarding the high mortality rate in the treatment DVT study (10% in heparin arm and 5% in the innohep arm), the firm stated the patient population "broad spectrum", high risk, with multiple associated co-morbidities.

      - In response to Dr. Talarico's question regarding inclusion and exclusion criteria, the firm stated that patients who received thrombolytic treatment for PE were excluded from the study population.



1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[redacted]

Decisions reached:

1. At the Division's request the firm agreed to provide additional chemistry, manufacturing and controls (CMC) information at the CMC pre-NDA meeting (requested October 7, 1997 by [redacted] scheduled for January 22, 1998. The Division requested that the following specific issues related to the drug product manufactured by [redacted] and the drug product manufactured by [redacted] be addressed at this CMC meeting:

   - comparability
   - bioequivalence
   - anti-Xa/IIa ratio
   - molecular distribution
   - drug substance processing
   - drug product manufacturing processes
   - benzyl alcohol content.

2. Regarding the pivotal trials, the Division had the following recommendations and suggestions:

   a. Regarding the treatment of PE study:

      - the patient population for the treatment of PE with innohep is limited by the exclusion criteria, namely it includes only patients not requiring thrombolytic therapy or vena cava interruption;

      - the efficacy results are similar to heparin which is the conventional treatment for PE.

   b. Regarding the treatment of DVT study:

      - the efficacy and safety results appear to indicate superiority of innohep to heparin;

- the wording for the proposed indication would be similar to heparin, i.e., "treatment of DVT, and its extension".

b. Regarding the prophylaxis of DVT following orthopedic surgery:

- Coumadin is not an approved regimen for the prophylaxis of DVT following orthopedic surgery, and therefore, the validity of Coumadin as a comparator in the study must be established based on Coumadin as "standard of practice";

- a safety analysis comparing the 75 unit dose vs the 50 units dose should be provided;

- the wording for the proposed indication would be "prophylaxis of DVT, which may lead to PE, in patients undergoing hip or knee replacement surgery".

c. Regarding the prophylaxis of DVT following general surgery:

- the FDA draft document regarding single study trials would be used to evaluate the support of a single study for a new indication;

- "splitting" the analysis of the 3-arm trial did not constitute two trials;

- a post hoc co-variant risk assessment of the patient population may be helpful to establish the efficacy and safety response in high risk vs low risk surgical patients using the criteria established by the American College of Surgeons;

- the wording for the proposed indication would be "prophylaxis of DVT, which may lead to PE, in patients undergoing abdominal surgery who are at risk for thromboembolic complications" (the specific risk to be determined by data analysis).

d. Regarding the use in spinal cord injury:

- as per regulation, study data from 2 adequate and well-controlled trial were necessary to support the proposed indication;

- consider conducting a second study expanding the patient population to non-hemorrhagic strokes and other high risk patients.

3. It was also recommended that criteria for the two specific dosing regimens be established by analyzing the study population in terms of body weight, safety data, and surgical procedure.

4. Regarding electronic submissions:

   a. CRFs and CRT's should be submitted in electronic format.

   b. The firm and the Division may negotiate the submission of other documents in electronic submission, including study reports, but hard copies must also be submitted.

   c. The following disciplines request electronic data in addition to hard copy of the data: biostatistics and biopharmaceutics. In addition, unannotated labeling should be provided electronically.

   d. Other Agency suggestions/recommendations to be included with the application:

      - statement verifying that the specific manufacturing facilities are ready for inspection;
      - statement verifying that the User Fees have been paid;
      - comprehensive, user friendly index;
      - submission of English translations of the foreign labeling;
      - listing of the foreign countries where the drug is approved;
      - an environmental assessment or a waiver with appropriate documentation.

   e. The Agency confirmed that documentation supporting all of the proposed indication could be submitted simultaneously for review, or alternatively, the application could be submitted with data supporting a single proposed indication, followed by supplemental applications for additional indications after approval after the initial indication.

f. The information presented appears adequate for an NDA submission, but the adequacy of the proposed pivotal studies to support the proposed indications cannot be determined until the scientific data is submitted and analyzed.

g. The adequacy of the information to support a flexible dosing regimens for orthopedic and abdominal surgery cannot be determined until the scientific data is submitted and analyzed.

h. The information presented does not appear to support the proposed spinal cord injury indication.

Minutes Preparer: /S/ 01/22/98

Chair Concurrence: /S/ 1-22-98

Attachments/Handouts: Overheads

cc: Original [redacted]
HFD-/Div. Files
HFD-/Meeting Minutes files
HFD-/K.Oliver
HFD-/reviewers & attendees

Drafted by: KO/January 6, 1998
Initialed by: L.Talarico 01/22/98

[redacted]

MEETING MINUTES

CLINER

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: NDA 20-484 AUG 17 1999

Name of Drug: innohep® (tinzaparin sodium) Injection

Sponsor: DuPont Merck Pharmaceuticals Company

Material Reviewed

Submission Date: June 30, 1999

Receipt Date: June 30, 1999

Filing Date: August 29, 1999

User-fee Goal Date(s): April 30, 2000 (10 month)
June 30, 2000 (12 month)

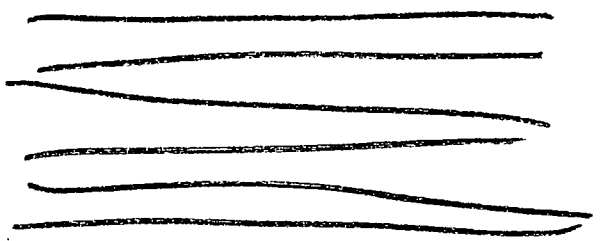
Proposed Indication: (1) Treatment of acute deep vein thrombosis (DVT), with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium; [redacted]

Other Background Information:

Innohep is a low molecular weight heparin, currently marketed in Europe and Canada. The Division and the sponsors of the drug have met on five occasions to discuss the clinical, statistical, CMC, electronic submission, and formatting issues related to the drug (see Memoranda of Meeting Minutes dated March 8, 1999, March 3, 1998, December 12, 1997, and June 17, 1992, and Memorandum of Telecon dated January 14, 1999.

Review

PART I: OVERALL FORMATTING[a]

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	Y		Volume 1.1
2. Form FDA 356h (original signature)	Y		Volume 1.1
a. Reference to DMF(s) & Other Applications	Y		
3. Patent information & certification		N	States that information is not applicable. There is not patent available for low molecular weight heparins.
4. Debarment certification	Y		Volume 1.1, Item 16
5. Financial disclosure	Y		Volume 1.1, Item 19
6. Comprehensive Index	Y		218 Volumes are sequentially numbered 1.1-1.218. Single, overall, comprehensive index for the submission located in volume 1.1 only, and all technical review copies included a copy of volume 1.1. An Item specific Table of Contents (TOC) is located in the front of each volume for each specific Item Number; and a volume specific TOC in the front of each volume, located behind the overall Item TOC.

7. Pagination	Y		Each Item number has continuous pagination 1-... for each volume. Subsequent volumes, with the same item number, starts numbering with page 1. Pagination is located in the bottom right corner, identified as Item--, Volume --, Page - The Volume number in this pagination system refers to the volume within the item number, not the overall submission volume number. Some individual study reports within an item have pagination specific to that report starting with page 1.
8. Summary Volume	Y		Volume 1.1
9. Review Volumes	Y		Volumes 1.2-1.218
10. Labeling (PI, container, & carton labels)	Y		Volume 1.1
a. unannotated PI	Y		Volume 1.1, Item 2, Volume No. 1, Pages 7-25
b. annotated PI	Y		Volume 1.1, Item 3, Volume No. 1, Pages 43-63.
c. immediate container	Y		Volume 1.1, Item 2, Volume 1, pages 1, 4
d. carton	Y		Volume 1.1, Item 2, Volume 1, pages 2, 3, 5, and 6
e. foreign labeling (English translation)	Y		Volume 1.59, Item 8/10, Volume No. 2, pages 161-441.
11. Foreign Marketing History	Y		Volume 1.1, Item 3, Volume No. 1, Page 68

12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	Y		Item 11, Case Report Tabulations, only provided electronically
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	Y		Volumes 1.160-1.218, Item 12, only provided as paper copies.

Y = Yes (Present), N = No (Absent)

PART II: SUMMARY[b]

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	Y		Volume 1.1, Item 3, Volume No. 1, pages 65-67
2. Summary of Each Technical Section	Y		
a. Chemistry, Manufacturing, & Controls (CMC)	Y		CMC: Volumes 1.1-1.6, Item 4; EA Volume 1.6, Item 4, Volume No. 5, pages 1-3 [Note: (1) requested claim for categorical exclusion from EA requirements; and (2) the Methods Validation (MV) has dual pagination in the lower bottom right hand side of the page-the upper set of pagination maintains the pagination from the original documents, and the lower set of pagination is the overall MV pagination of the submission.]
b. Nonclinical Pharmacology/Toxicology	Y		Volumes 1.10-1.31, Item 5
c. Human Pharmacokinetic & Bioavailability	Y		Volumes 1.32-1.54, Item 6
d. Microbiology	Y		Volume 1.57, Item 7. Item 7, Microbiology, is an exact copy of Item 4, Section 3, CMC, with unique Item 7 pagination.

e. Clinical Data & Results of Statistical Analysis	Y		Volumes 1.58-1.156, Item 8/10. Item 8 Clinical and Item 10 Statistical are identical including page numbers and section numbers; each page number is uniquely characterized by: Item 8/10, volume number, and page number.
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	Y		Volume 1.70, Item 8/10, Volume No. 13, pages 178-189
4. Summary of Safety	Y		Volume 1.63-1.69, Item 8/10, Volume No. 6 through 12. [Note: Safety Update will be provided in paper format 120 days after the application is filed].
5. Summary of Efficacy	Y		Volume 1.61 and 1.62, Item 8/10, Volume No. 4 and 5.

Y = Yes (Present), N = No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	Y		Volume 1.58; Item 8/10, Volume No. 1, pages 1-213.
2. Controlled Clinical Studies	Y		Item 8 Clinical and Item 10 Statistical are identical, including page numbers and section numbers; each page number is uniquely characterized by the following: Item 8/10, volume number --, and page --
a. Table of all studies	Y		Volume 1.58, Item 8/10, Volume No. 1, pages 215-241

b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	Y		Volume 1.58, Item 8/10, Volume No. 1, pages 242-282
c. Optional overall summary & evaluation of data from controlled clinical studies		N	
3. Integrated Summary of Efficacy (ISE)	Y		Volume 1.61: Item 8/10, Volume No. 4, pages 1-175
4. Integrated Summary of Safety (ISS)	Y		Volume 1.63: Item 8/10, Volume 6., starting on page 1
5. Drug Abuse & Overdosage Information	Y		Volume 1.70: Item 8/10, Volume No. 13, page 177 states: "See Section 15 of Item 8/10.5 Integrated Summary of Safety of this NDA".
6. Integrated Summary of Benefits & Risks of the Drug	Y		Volume 1.70: Item 8/10, Volume No.13, page 178.
7. Gender/Race/Age Safety & Efficacy Analysis Studies	Y		Volume 1.58, Item 8/10, Volume No. 1, page 365-369

Y = Yes (Present). N = No (Absent)

PART IV: MISCELLANEOUS

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	Y		Volume 1.58, Item 8/10, Volume No. 1, page 366. [Note: No studies conducted in pediatric patients, however, a pediatric pharmacokintetic study is planned.]
2. Diskettes	Y		
a. Proposed unannotated labeling in MS WORD 8.0		N	Diskette with proposed unannotated and/or annotated labeling could not be located.
b. Stability data in SAS data set format	Y		CDROM contains datasets in SAS version 6.12
c. Efficacy data in SAS data set format	Y		CDROM contains datasets in SAS transport 5.0 format for pivotal studies.
d. Biopharmacological information & study summaries in MS WORD 8.0	Y		CDROM contains datasests in SAS version 6.12 for 2 bioequivalence studies. SAS programs also included.
e. Animal tumorigenicity study data SAS data set format		N	Unable to locate. Not applicable to this application.
3. User-fee payment receipt	Y		User Fee paid and the sponsor not in arrears for any payments.

Y = Yes (Present). N = No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments:

Filing meeting scheduled for August 16, 1999 at 3:30pm in the 13B-45 Conference Room.

Conclusions

1. The application should be filed as agreed upon in an August 16, 1999 filing meeting with Drs. Florence Houn (Office Director, ODE III), Victor Raczkowski (Deputy Director, ODE III), Kathy Robie-Suh (Hematology Team Leader), Ann Farrell (Medical Reviewer), Ruyi He (Medical Reviewer), Eric Duffy (Chemistry Team Leader), Ali Al-Hakim (Chemistry Reviewer), Jasti Choudary (Pharmacology Team Leader), David Lee (Biopharmaceutics Team Leader), K. Malek (DSI), and Karen Oliver (Project Manager).

2. During the August 16, 1999 filing meeting, the team agreed to the following:

   a. The need for DSI inspections. The project manager will draft a memo requesting that specific sites (as determined by the clinical reviewers) be inspected (2 sites for each indication), and send it to K. Malek by August 20, 1999.

   b. The need for established internal goal dates as follows: primary reviews completed by February 1, 2000; secondary reviews completed by March 7, 2000; to the Office for review of the package and signature of the action letter by April 1, 2000.

   c. The need for a "Labeling" section in each of the technical reviews. The project manager will be responsible for incorporating the labeling recommendations within the technical reviews into the sponsor's proposed labeling. The revised proposed labeling will then be the labeling document that is reviewed by the review team at the third team meeting.

   d. The need for team meetings as follows: the first meeting to be scheduled mid-Oct to mid-Nov to discuss the progress of the reviews; the second meeting to be scheduled the first week of January to discuss the progress of the reviews; and the third meeting to be scheduled mid-March to discuss labeling issues. The project manager will be responsible for scheduling the team meetings at the designated time intervals.

/S/ 9/17/99

Karen Oliver
Regulatory Health Project Manager

cc:

Original NDA 20-484
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/A.Farrell
HFD-180/R.He
HFD-180/J.Choudary
HFD-180/E.Duffy
HFD-180/A.Al-Hakim
HFD-870/D.Lee
HFD-103/F.Houn
HFD-103/V.Raczkowski
HFD-344/K.Malek
draft: KO/August 12, 1999
R/D init: K.Robie-Suh 08/17/99

Concur.
8/17/99

ADMINISTRATIVE REVIEW