CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-484

ADMINISTRATIVE DOCUMENTS

ITEM 13: PATENT AND EXCLUSIVITY INFORMATION

INNOHEP® NDA
(tinzaparin sodium injection)

NEW DRUG APPLICATION
DuPont Pharmaceuticals Company
Wilmington, DE 19805

EXCLUSIVITY INFORMATION

1) The applicant, DuPont Pharmaceuticals Company, believes that after approval of the New Drug Application, INNOHEP® (tinzaparin sodium injection) will be entitled to a five year period of marketing exclusivity under the provision of 21 CFR 314.108, and is therefore claiming exclusivity.

2) Reference is made to 21 CFR 314.108 (b)(2) to support the applicant's claim to exclusivity for INNOHEP® injection.

3) The applicant claims exclusivity under 21 CFR 314.108 (b)(2), and accordingly must submit information to show that to the best of the applicant's knowledge or belief, a drug has not previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act containing any active moiety in the drug for which the applicant is seeking approval. This information is as follows:

   The sole active moiety in the drug for which the applicant is seeking approval, INNOHEP® injection, is tinzaparin sodium. To the best of the applicant's knowledge and belief, no drug containing tinzaparin as an active moiety has previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act.

   The manufacturing process, structure and properties, including molecular weight distribution and *in vitro* potency, of tinzaparin differ from other low molecular weight heparins. Tinzaparin sodium is the sodium salt of a low molecular weight heparin that is obtained by controlled enzymatic depolymerization of heparin from porcine intestinal mucosa using heparinase from *Flavobacterium heparinum*. The majority of the components have a 2-O-sulpho-4-enepyranosuronic acid structure at the non-reducing end and a 2-N,6-O-disulpho-D-glucosamine structure at the reducing end of their chain. The mass-average molecular mass ranges between 5,500 and 7,500 daltons. The mass percentage of chains lower than 2,000 is not more than 10 per cent. The mass percentage of chains between 2,000 and 8,000 ranges between 60 and 72 per cent. The mass percentage of chains above 8,000 ranges between 22 and 36 percent. The *in vitro* anti-factor Xa activity of tinzaparin is not less than 70 IU and not more than 120 IU of anti-factor Xa activity per milligram.

By: _____ Date: April 7 ,1999

Blair Q. Ferguson, Ph.D., J.D.
Associate General Counsel
DuPont Pharmaceuticals Company

ITEM 13: PATENT AND EXCLUSIVITY INFORMATION

INNOHEP® NDA
(tinzaparin sodium injection)

NEW DRUG APPLICATION
DuPont Pharmaceuticals Company
Wilmington, DE 19805

PATENT INFORMATION

1)	Trade Name of Drug Product	INNOHEP®
2)	Active Ingredient(s)	tinzaparin sodium
3)	Strengths(s)	10,000 IU/mL and 20,000 IU/mL
4)	Dosage Form	multiple dose vial
	Route of Administration	subcutaneous injection
5)	Name of Applicant	DuPont Pharmaceuticals Company
6)	NDA Number	20-484
7)	Applicable Patent Numbers and Expiration Date of Each	None

By: _____ Date: April 7 ,1999

Blair Q. Ferguson, Ph.D., J.D.
Associate General Counsel
DuPont Pharmaceuticals Company

Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 20-484 **SUPPL #**_____

Trade Name: Innohep **Generic Name:** tinzaparin Sodium injection

Applicant Name: DuPont Pharmaceuticals Inc. **HFD #** 180

Approval Date If Known:_____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES/ X **/ NO /** ___ **/**

b) Is it an effectiveness supplement?

YES / ___ **/ NO /** X **/**

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

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

YES / X **/ NO /** ___ **/**

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

_____

_____

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

_____

_____

Form OGD-011347 Revised 8/27/97
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES / X **/ NO /** ___ **/**

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ **/ NO /** X **/**

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? **(Rx to OTC switches should be answered NO - please indicate as such)**

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

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

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

YES /___/ NO /_X_/

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /_X_/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /_X_/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

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

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

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

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new

clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

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

Investigation #2

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

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Signature: *Date:* 07/03/00

Title: /S/ , Project Manager

Signature of Office/Division Director

Signature: /S/ *Date:* 7-5-00

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Previous Page

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20484	**Trade Name:**	INNOHEP(TINZAPARIN SODIUM)INJ 10,000IU/M
Supplement Number:		**Generic Name:**	TINZAPARIN SODIUM
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AP	**Proposed Indication:**	INNOHEP is indicated for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin therapy. The safety and effectiveness of INNOHEP were established in hospitalized patients.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

In the action letter, the sponsor is requested to either submit a waiver of the pediatric study requirement or submit a pediatric drug development plan within 120 days from the date of the action letter.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, KAREN OLIVER

/S/

Signature

7-17-00

Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20484	**Trade Name:**	INNOHEP(TINZAPARIN SODIUM)INJ 10,000IU/M
Supplement Number:	-	**Generic Name:**	TINZAPARIN SODIUM
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AE	**Proposed Indication:**	Treatment of acute symptomatic deep vein thrombosis (DVT) when administered in conjunction with warfarin therapy.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, KAREN OLIVER

Signature /S/ _____ April 4, 2000 Date

NDA ASSIGNMENT AND REVIEW TRANSMITTAL

1. NDA NO.	2. DATE RECEIVED	3. NAME OF APPLICANT
20-484	30 Jun 99	DuPont Pharmaceuticals Company

4. NAME OF DRUG

Innohep(tinzaparin sodium) inj. 10,000 IU/ml/20,000 IU/ml

5. INDICATION

Treatment of Deep Vein Thrombosis [illegible] and Acute Pulmonary Embolism

6. RELATED IND(s)

Deliver to the last addressee indicated below; cross through your name before forwarding to the next addressee:

HFD-	
180	Document Room

GROUP CONSUMER SAFETY OFFICER

REVIEWERS OF RELATED IND(s)

GROUP LEADER / SUPERVISOR: Duffy

1. Enter the name of the Reviewer and assignment date in next block.
2. GROUP LEADER ONLY: Enter classification of application here.
3. Separate 1st and 2nd copies.
   Leave 2nd copy attached to Jacket for delivery to the Reviewer.
4. Check 1st copy for delivery to Document Control Room.

CLASSIFICATION

REVIEWER: Al-Hakim

DATE ASSIGNED: 7/6/99

Deliver to Document Control Room when this box is checked.	Post and Destroy

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 0 1 1999
HFD-180

FDA 2817 (2/92)

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

DO *(Division/Office)*: Microbiology, HFD-160 ATTENTION: Dr. Peter Cooney, Team Leader			FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) Phone # 827-7310	
DATE: 07/08/99	IND NO.:	NDA NO.: 20-484	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT 06/30/99
NAME OF DRUG: innohep (tinzaparin sodium injection)	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: User fee Due Date: 10 mo: April 30, 2000

NAME OF FIRM: Rhone-Poulenc Rorer Pharmaceuticals Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW 'D OF PHASE II MEETING :ROLLED STUDIES .OTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: New drug application for a LMWH. Provides for (2) indications: (1): treatment of DVT with and without PE when administered in conjunction with warfarin sodium; and (2) prevention of DVT, which may lead to PE, in patients undergoing knee or hip replacement surgery. I am consulting the "micro" section of the submission, a total of 2 volumes. The volume numbers are: 1.1 and 1.57. Please review. I will be scheduling a filing meeting...stay tuned. Thanks. Karen Oliver, Project Manager

cc: Orig NDA 20-484
180/Div. Files; HFD-180/K.Oliver; A.Al-Hakim

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
DuPont Pharmaceuticals Company	July 12, 2000
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(302) 892-7308	(302) 992-3011
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):	**AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE**
Chestnut Run Plaza, MR 2146 974 Centre Road Wilmington, DE 19805	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-484

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
tinzaparin sodium injection	Innohep®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)
Low Molecular Weight Heparin	CAS # 9041-08-1

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
injection	20,000 Iu/mL	Subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Deep Vein Thrombosis

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Response to Proposed Draft Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

SEE ATTACHED

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.5 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. OTHER (Specify) Response to Proposed Draft Labeling

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
James L. Gaskill	James L. Gaskill, R.Ph., Associate Director, Regulatory Affairs	July 12, 2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Chestnut Run Plaza, MR 2146, 974 Centre Road, Wilmington, DE 19805	(302) 892-7308

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
DuPont Pharmaceuticals Company	July 6, 2000
TELEPHONE NO. (Include Area Code) (302) 892-7308	FACSIMILE (FAX) Number *(Include Area Code)* (302) 992-3011
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Chestnut Run Plaza, MR 2146, 974 Centre Road, Wilmington, DE 19805	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-484

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
tinzaparin sodium injection	Innohep®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*): Low Molecular Weight Heparin

CODE NAME (*If any*): CAS # 9041-08-1

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
injection	20,000 Iu/mL	Subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE: Treatment of Deep Vein Thrombosis

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: Draft Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

SEE ATTACHED

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☒	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.5 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	James L. Gaskill, R.Ph., Associate Director, Regulatory Affairs	July 6, 2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Chestnut Run Plaza, MR 2146, 974 Centre Road, Wilmington, DE 19805	(302) 892-7308

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

29

TO *(Division/Office)*:
ciate Director, Medication Error Prevention
e of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM:: GI and Coagulation Drug Products, HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 13, 2000		NDA 20-484		April 10, 2000

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Innohep (tinzaparin sodium injection)			May 30, 2000

NAME OF FIRM: DuPont Pharmaceuticals Company

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIFIC INSTRUCTIONS:

The sponsor's initial request for the tradename "innohep" was consulted to OPDRA and found to be unacceptable. Sponsor notified by letter. The April 10, 2000 submission is in response to the Agency's letter. The status of the application is still pending. An approvable action is anticipated by April 28, 2000 (the 10 month due date). **Due to time constraints, the tradename review will NOT be included in this review cycle.** Thanks, Karen Oliver 7-7457

PDUFA DATE: 10 month due date: April 28, 2000; 12 month due date June 28, 2000.
ATTACHMENTS: (1) volume
CC:
Archival NDA 20-484; HFD-180Division File; HFD-180/K.Oliver; HFD-180/L.Zhou; HFD-180/A.Al-Hakim
180/L.Talarico; HFD-180/R. He, HFD-180/K.Robie-Suh, HFD-870/S.Al-Fayoumi

TYPE OF REQUESTER	METHOD OF DELIVERY (Check one)
/S/ HFD-180 Proj Manager 04/17/00	MAIL ☐ HAND ☒
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
/S/ Safety Evaluator 4/13/00	

OLDER

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: December 14, 1999	DUE DATE: December 28, 1999	OPDRA CONSULT #: 99-077

TO (Division): Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
(HFD-180)

PRODUCT NAMES: innohep® (tinzaparin sodium injection) NDA#: 20-484	MANUFACTURER: DuPont Pharma

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to an October 27, 1999 request by the Division of Gastro-Intestinal and Coagulation Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary name, innohep, with other approved proprietary/generic names. *According to the Division, this proposed proprietary name is specifically spelled with a small case "i".* This review includes a study conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of the proposed proprietary name.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name, innohep. See review.

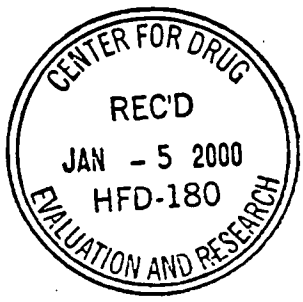
/S/ 1/3/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/4/00

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research



Proprietary Name Review

DATE OF REVIEW: **December 14, 1999**

NDA#: **20-484**

NAME OF DRUG: **innohep (tinzaparin sodium injection)**
20,000 anti-Xa IU per 2 ml (10,000 anti-Xa IU per ml)
40,000 anti-Xa IU per 2 ml (20,000 anti-Xa IU per ml)

NDA HOLDER: **DuPont Pharma**

I. INTRODUCTION

This consult is in response to a request sent on October 27, 1999, from the Division of Gastro-Intestinal and Coagulation Drug Products, to review a proposed proprietary drug name, innohep, regarding potential name confusion with other proprietary/generic drug names. In addition, container label, carton labeling, and package insert were reviewed for possible interventions in minimizing medication errors.

According to the Division, this proposed proprietary name is specifically spelled with a small case "i".

The proposed proprietary name, innohep, was previously reviewed by the Labeling and Nomenclature Committee (LNC) on October 27, 1999 and was found to be unacceptable, with the following comments:

"There are 3 approved products with significant look-alike/ sound-alike conflicts with INNOHEP. These are INNOVAR, INOCOR and INNOGEL. INNOGEL has only a low significance, but INNOVAR and INOCOR have more confusion potential since they are all parenteral products that may be stored in the same areas. Additionally, there are 2 pending products, INNOFEM (HFD-510) and INOMAX (HFD-110) that are possible conflicts, but I don't know where those applications are in their approval process (they may be withdrawn). Our overall opinion is that the name INNOHEP is unacceptable."

PRODUCT INFORMATION

Innohep (tinzaparin sodium injection) is a low molecular weight heparin solution for subcutaneous (SC) injection. Tinzaparin sodium is the sodium salt of a low molecular weight heparin that is obtained by controlled enzymatic depolymerization of heparin from porcine intestinal mucosa using heparinase from *Flavobacterium heparinum*. Potency is determined by means of a biological assay and interpreted by the first

International Low Molecular Weight Heparin Standard as units of anti-factor Xa (anti-Xa) activity per milligram. The mean tinzaparin anti-factor Xa activity is approximately 100 IU per milligram. Tinzaparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. It acts as a potent co-inhibitor of several activated coagulation factors, especially factor Xa and IIa (thrombin). Tinzaparin induces release of tissue factor pathway inhibitor, which may contribute to the antithrombotic effect. Bleeding time is usually unaffected by tinzaparin and neither aPTT nor PT can be used for therapeutic monitoring of tinzaparin.

Plasma levels of anti-Xa activity increase in the first 2 to 3 hours following SC injection of tinzaparin and reaches a maximum within 4 to 5 hours. The elimination half-life following SC administration of 4,500 IU tinzaparin is approximately 3.4 hours based on anti-Xa activity. The primary route of elimination is renal. Innohep is indicated for the initial treatment of acute symptomatic deep vein thrombosis with and without pulmonary embolism when administered in conjunction with warfarin sodium. Weight-based innohep doses are available in tables 8 & 9 of the package insert. Innohep is available in the following strengths:

20,000 anti-Xa IU per 2 ml (10,000 anti-Xa IU per ml) – 1 x 2 ml vial
20,000 anti-Xa IU per 2 ml (10,000 anti-Xa IU per ml) – 10 x 2 ml vial
40,000 anti-Xa IU per 2 ml (20,000 anti-Xa IU per ml) – 1 x 2 ml vial
40,000 anti-Xa IU per 2 ml (20,000 anti-Xa IU per ml) – 10 x 2 ml vial

II. RISK ASSESSMENT

In order to predict the potential medication errors and to determine the degree of confusion of the proposed proprietary name, innohep, with other drug names, the medication error staff of OPDRA searched the MICROMEDEX Healthcare Intranet Series (1999), which includes the following: DrugDex, Poisindex, Martindale, Emergindex, Reprodisk, and Index Nominum. Other references include American Drug Index (43rd Edition), Drug Facts and Comparisons (Monthly Updates), PDR (53rd Edition, 1999), Electronic Orange Book, US Patent and Trademark Office online database, Drug Product Reference File (DPRF), Decision Support System (DSS), EES (Established Evaluation System), and the LNC database for possible sound-alike or look-alike names to approved and unapproved drug products. A focus group discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted a study of written and verbal analyses of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. Study conducted within FDA

1) Methodology

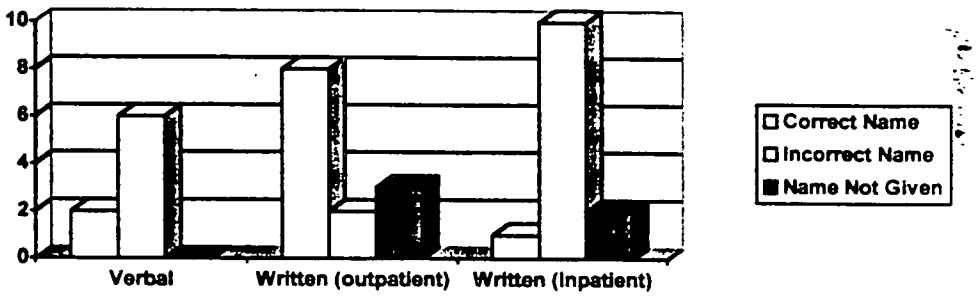
This study involved forty-seven health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of innohep with other drug names due to the similarity in handwriting and verbal

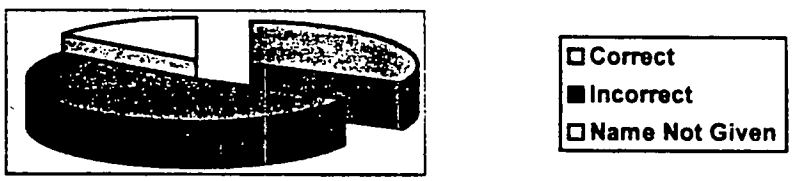
pronunciation of the name. Random samples of either inpatient or outpatient written orders were delivered to the participating health professionals via e-mail. In addition, verbal orders via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions via e-mail to the medication error staff. After receiving the interpretations, the correct spelling of the proposed proprietary name was sent to the health professionals.

2) Results

Inpatient written orders were sent to fifteen participants. Outpatient written orders and verbal orders were each sent to sixteen participants. We received responses from thirty-four participants. Thirteen interpretations of outpatient written orders, eight interpretations of verbal orders, and thirteen interpretations of inpatient written orders were received. Eleven (out of thirty-four) participants interpreted innohep correctly. The results are as follows:

innohep





Incorrect names: Immohep (3), Imohep (6), Imuohep, Indohep, Inohep (3), Innohop, Enohep, Ismohep, & Imnohep

B. Focus Group Findings

1) The proposed proprietary name, innohep, is similar to Innovar, Inocor, and Innogel and may cause name confusion. Proprietary names with similar beginning syllables are often confused for one another when combined with indistinct physician handwriting of terminal syllables, leading to medication errors. Furthermore, Innovar and Inocor are injectable prescription drugs and

may be stored in close proximity to innohep, making it possible for dispensing errors to occur. Moreover, the usual doses for these drugs are patient dependent (i.e. weight-based). In addition, medication errors involving these three drugs can be serious because of their indications for use. Inocor is an inotropic agent for congestive heart failure, innohep is an anticoagulant for treatment of acute deep vein thrombosis, and Innovar is an anesthetic for induction and maintenance of anesthesia. Misadventures or substitution of any of these drugs for one another can have significant outcomes, including pulmonary embolism, respiratory depression, bleeding, arrhythmia, and worsening of heart failure. Innogel is an over-the-counter (OTC) drug kit and poses less risk of name confusion.

2) There are two other names similar to innohep. Innofem, a tablet formulation of estradiol, was recently approved in November 1999, and Inomax, nitric oxide, is a pending application. Since Innofem is a tablet formulation and Inomax is yet to be approved, the concern of medication errors is less compared to the above mentioned drugs.

C. Discussion

The results of the written and verbal analyses demonstrate that only eleven (out of thirty-four) participants interpreted innohep correctly. Moreover, all of the participants who gave an interpretation of the name (twenty-nine out of thirty-four) capitalized the first letter of innohep. We recognize that the inaccurate interpretations of the proposed proprietary name did not overlap with any existing approved drug products. However, once this application is approved and health professionals are more familiar with the drug, the possibility of name confusion with other similar drug names and the associated risks of medication errors are significant to render the proprietary name, innohep, objectionable. In addition, searches in available texts, databases, and the handwriting samples did not produce any significant new information.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the packaging and the labeling of innohep, OPDRA has attempted to focus on safety issues relating to possible medication errors. The item discussed in this consult involves an issue normally reviewed by the chemist and the medical officer.

OPDRA has reviewed the current labeling and has identified an area of possible improvement, which might minimize potential user error.

CARTON LABELING

1) For item 2 Volume 1 Pages 2 & 5, the proprietary name, the established name, and the strength are labeled vertically on one of the panels, making this information hard to read when stored upright. We recommend changes that will make this information easily readable.

2) The strength for this product, "40,000 anti-Xa IU per 2 ml (20,000 anti-Xa IU per ml)" is not consistent with the current labeling of low molecular weight heparin strength, which is in mg per ml, and is too complicated. Furthermore, "IU" can be misconstrued as "IV" and cause medication errors. If possible, we recommend that the strength be labeled in mg/ ml. If this change is not possible, we recommend that the strength of this product be labeled as 20,000 **units**/ ml since most health practitioners would prescribe this drug in units.

IV. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name, innohep.

B. The firm should be requested to submit a new name for review and evaluation.

C. OPDRA recommends the above labeling revision which might lead to safer use of the product. We would be willing to revisit this issue if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301) 827-3243.

/S/ 1/3/2000

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 1/3/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC: NDA 20-484
HFD-180; DivFiles; Karen Oliver, Project Manager, DGCDP
HFD-180; Lilia Talarico, Division Director
Office Files
HFD-400; Lauren Lee, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-2 ; Mac Lumpkin, Acting Director, OPDRA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
20-484

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
DuPont Pharmaceuticals Company	December 17, 1999
TELEPHONE NO. *(Include Area Code)* (302) 892-7308	FACSIMILE (FAX) Number *(Include Area Code)* (302) 992-3011
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Chestnut Run Plaza, MR 2146 974 Centre Road Wilmington, DE 19805	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-484

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
tinzaparin sodium injection	innohep®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: Low Molecular Weight Heparin (LMWH)
CODE NAME *(If any)*: CAS # 9041-08-1

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
injection	10,000 Iu/ml and 20,000 Iu/ml	Subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Deep Vein Thrombosis; Prevention of Deep Vein Thrombosis in Hip and Knee Replacement Surgery

APPLICATION INFORMATION

APPLICATION TYPE (check one) ■ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ■ OTHER

REASON FOR SUBMISSION: Response to FDA request for information

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ■ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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SEE ATTACHED

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FDA&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to FDA request for information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	James L. Gaskill, R.Ph. Associate Director, Regulatory Affairs	Dec. 17, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Chestnut Run Plaza, MR2146, 974 Centre Road, Wilmington, DE 19805	(302) 892-7308

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please **DO NOT RETURN** this form to this address.

Oliver

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Karen Oliver, Project Manager /S/ 07/08/99	**Phone:** 827-7310
Date: July 8, 1999	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: innohep®	**NDA/ANDA#** NDA 20-484
Established name, including dosage form: tinzaparin sodium injection	
Other trademarks by the same firm for companion products: unknown	
Indications for Use (may be a summary if proposed statement is lengthy): (1) treatment of acute DVT with and without PE when administered in conjunction with warfarin sodium; and [redacted]	
Initial Comments from the submitter (concerns, observations, etc.): The proposed trade name "innohep" is specifically spelled with a small case "i". This is rather unusual.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-484; HFD-180/division file; HFD-180/K.Oliver; HFD-180/A.Ali-Hakim

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

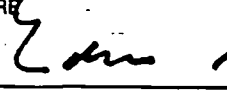
Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Edward C. Bradley, M.D.	Executive Vice President, Medical Science & Development
FIRM/ORGANIZATION	
DuPont Pharmaceuticals Company	
SIGNATURE	**DATE**
	June 17, 1999

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Delivered

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: April 13, 2000	DUE DATE: May 28, 2000	OPDRA CONSULT #: 00-0121 (follow-up)

TO: Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
(HFD-180)

THROUGH: Karen Oliver
Project Manager
(HFD-180)

PRODUCT NAMES: Innohep® (tinzaparin sodium injection) NDA#: 20-484	MANUFACTURER: DuPont Pharma

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

In regard to the consult request to evaluate the research report conducted by [redacted] we have consulted with an epidemiologist in our office to review the submitted data for Innohep. According to our epidemiologist, the report submitted by Brand Institute shows that Innohep sounds-alike Inocor and Innovar. In conclusion, we do not recommend the use of the proprietary name, Innohep. See review.

/S/ 5/8/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

MEMORANDUM

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

DATE: July 17, 2000

FROM: Alice Kacuba, Regulatory Health Project Manager
HFD-180, Division of Gastrointestinal and Coagulation Drug Products

SUBJECT: Memo to file

TO: NDA 20-484 file

Please archive the following documents into the file of NDA 20-484, Innohep (tinzaparin sodium injection):

1. Fax received from DuPont Pharmaceutical Company, dated July 14, 2000 at 2:07pm. This fax was their first counter proposal for the indication.

2. Fax received from DuPont Pharmaceutical Company, dated July 14, 2000 at 3:22pm. This fax was their second counter proposal for the indication.

Drafted: A.Kacuba/July 17, 2000
Final: AK/July 17, 2000
Filename: [redacted]

Telefax

2nd proposal to inactivate

The DuPont Pharmaceutical Company
MR-2416, Centre Road, Wilmington DE 19805
Phone (302) 892-7308 FAX (302) 992-3011

Date: July 14, 2000

To: Alice Kacuba (HFD-180) (301) 443-9285

From: James L. Gaskill, Associate Director, Regulatory Affairs

Total Pages: 1 (Please contact us if you have not received all pages)

Re: INNOHEP (tinzaparin sodium injection) NDA 20-484

Attached is DuPont's proposed Indication:

INNOHEP is indicated for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium.

The safety and effectiveness of INNOHEP have ~~only~~ been established in hospitalized patients.

OK c Victor, Lilia, Kathi But must be 1 para graph First agree

7.14.00 5pm Victor called + said "have been" doesn't read right. It was agreed to change it to ~~to~~ "were".

MEMORANDUM OF TELECON

DATE: July 14, 2000

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

BETWEEN:

Name: Mr. James Gaskill; Associate Director, Regulatory Affairs
Dr. Max Talbott; V.P., Regulatory Affairs
Dr. Tom Donnelly; Executive Director, Regulatory Affairs
Phone: (302) 892-7308
Representing: DuPont Pharmaceutical Company

AND

Name: Dr. Victor Raczkowski, Deputy Director
Office of Drug Evaluation III, HFD-103
Dr. Lilia Talarico, Division Director
Ms. Alice Kacuba; Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

BACKGROUND: On May 15, 2000, the firm submitted a complete response to the April 28, 2000 AE letter. On June 30, 2000, the firm was faxed a version of the "FDA revised labeling". The firm responded with a counter proposal on July 6, 2000. On July 10, 2000, the firm was faxed an updated "Divisional FDA Revised labeling". After review by Dr. Victor Raczkowski, at the office level, one point remained unresolved; the wording of the INDICATION section, specifically, whether to include the word "inpatient" in the indication. The purpose of today's teleconference was to resolve this issue and communicate the action on the application.

TODAY'S PHONE CALL: A call was placed. Dr. Raczkowski summarized the situation; the Agency was ready to take an action on the application. If the firm would agree to keep the word "inpatient" in the indication ("INNOHEP is indicated for the inpatient treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium."), we were ready to take an Approval action now, if not, we would take an Approvable action.

During the teleconference, the firm faxed in a counter proposal (see attached) with the indication reading:

"INNOHEP is indicated for the treatment of acute symptomatic deep vein thrombosis when administered in conjunction with warfarin sodium, and

INNOHEP is indicated for the inpatient treatment of acute symptomatic deep vein thrombosis with pulmonary embolism when administered in conjunction with warfarin sodium."

The Agency found this unacceptable and proposed:

"INNOHEP is indicated for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium. The safety and effectiveness of ONNOHEP have only been established in hospitalized patients."

The firm said they would have to talk with their marketing team and call the Agency back.

The call was concluded.

SECOND PHONE CALL:
BETWEEN:

Name: Mr. James Gaskill; Associate Director, Regulatory Affairs
Dr. Max Talbott; V.P., Regulatory Affairs
Dr. Tom Donnelly; Executive Director, Regulatory Affairs
Phone: (302) 892-7308
Representing: DuPont Pharmaceutical Company

AND

Name: Ms. Bronwyn Collier, Associate Director for Regulatory Affairs
Office of Drug Evaluation III, HFD-103
Ms. Alice Kacuba; Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

A call was placed. The firm has faxed a counter proposal, to which the Agency agreed to. The INDICATION section will read:

"INNOHEP is indicated for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium. The safety and effectiveness of INNOHEP were established in hospitalized patients."

At this time, we also reviewed some other editorial revisions. Agreement on the labeling was reached. The agreed upon labeling is attached to the AP letter.

/S/ 7-17-00

Alice Kacuba
Regulatory Health Project Manager

cc: Original NDA 20-484
HFD-180/Div. File
HFD-180/A.Kacuba
Drafted by: A.Kacuba/July 14, 2000
Final: AK/July 17, 2000
Filename: [redacted]

TELECON

MEMORANDUM **OFFICE OF POST-MARKETING DRUG RISK ASSESSMENT**
CENTER FOR DRUG EVALUATION AND RESEARCH
HFD-400; Rm 15B-03

CONSULT#s : 99-077/ 00-0121 JUN 27 2000

DATE: June 23, 2000

FROM: Lauren Lee, Pharm.D., Safety Evaluator
Medication Error Prevention, HFD-400

THROUGH: Jerry Phillips, R.Ph., Associate Director
Medication Errors Prevention, HFD-400 /S/ 6/27/2000

TO: Lilia Talarico, M.D., Director
Division of Gastro-Intestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA No. 20-484; Innohep (tinzaparin sodium injection)

I. INTRODUCTION:

This memorandum is in response to the letter dated June 13, 2000, in which Dupont Pharmaceuticals Company presented new information regarding the recent withdrawal of ——— from the market as of March 15, 2000 and therefore, the acceptability of the proposed proprietary name, Innohep. The firm also noted that the NDC for Innovar is no longer in use since 1995.

II. BACKROUND:

1. The proposed proprietary name, Innohep, was reviewed by the Labeling and Nomenclature Committee (LNC) on October 27, 1999 and was found to be unacceptable, with the following comments:

   "There are 3 approved products with significant look-alike/ sound-alike conflicts with INNOHEP. These are INNOVAR, INOCOR and INNOGEL. INNOGEL has only a low significance, but INNOVAR and INOCOR have more confusion potential since they are all parenteral products that may be stored in the same areas. Additionally, there are 2 pending products, INNOFEM (HFD-510) and INOMAX (HFD-110) that are possible conflicts, but I don't know where those applications are in their approval process (they may be withdrawn). Our overall opinion is that the name INNOHEP is unacceptable."

2. The proposed proprietary name, Innohep, was subsequently reviewed by the Office of Post-Marketing and Drug Risk Assessment (OPDRA) on December 14, 1999, and was found to be objectionable due to the sound-alike/ look-alike similarity to Inocor, Innovar, Innogel, Innofem, and Inomax. However, we noted less concern of medication errors

with Innogel, Innofem, and Inomax due the differences in dosage forms and the pending application of Inomax. *(Inomax has been approved since the review.)*

3. On April 10, 2000, Dupont Pharmaceuticals Company submitted a research report conducted by Brand Institute Inc. (March 13, 2000), regarding the analysis of the potential sound-alike/look-alike name confusion between Innohep and other drug products. According to an OPDRA epidemiologist, the report submitted by Brand Institute shows that Innohep sounds-alike Inocor and Innovar.

III. DISCUSSION:

Since OPDRA's review of the proposed name, Innohep, Inocor (amrinone lactate) was withdrawn from the market as of March 15, 2000. We also recognize that Innovar (fentanyl citrate/droperidol) was withdrawn in October 2, 1996. However, the generic formulation of these two drugs, amrinone lactate and fentanyl citrate/droperidol, are still available on the market per Abbott Laboratories and AstraZeneca. Moreover, both, Inocor and Innovar are still found in drug references such as Facts and Comparisons and American Drug Index.

When evaluating the safety of names, it is important to consider the possibility that pharmacists could substitute the generic drugs for the brand names that are listed in drug references, especially if the pharmacists are not aware that these brand drugs have been discontinued. Therefore, in the event of name confusion where a new drug name (e.g. Innohep) is mistaken for other brand names (e.g. Inocor, Innovar), the generic formulations (e.g. amrinone lactate and fentanyl citrate/droperidol) of these drugs could be utilized.

However, according to AstraZeneca, the 2 mL ampules of fentanyl citrate/droperidol, that are currently on the market, will expire in 5/2001, and due to a merger decision, the company has discontinued the manufacturing of this drug. Although amrinone lactate is still on the market, given the absence of the combined safety risk of Innocor and the expected expiration of its generic formulation, there is insufficient evidence at this time to render the proposed proprietary name, Innohep, objectionable.

IV. CONCLUSION

In light of the recent withdrawal of Inocor, OPDRA has no objections to the use of the proprietary name, Innohep.

/S/

Lauren Lee, Pharm.D.

Concur:

/S/ 6/27/2000

Jerry Phillips, RPh

CC: NDA 20-484
Office Files
HFD-180; DivFiles; Karen Oliver, Project Manager
HFD-180; Lilia Talarico, Division Director
HFD-400; Sammie Beam, Project Manager, Medication Errors, OPDRA (Electronic Only)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Mac Lumpkin, Deputy Center Director for Review Management (Electronic Only)

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

PID# : 99-077

DATE: May 8, 2000

FROM: Parivash Nourjah, Ph.D. Epidemiologist
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director /S/ 5-8-00
Division of Drug Risk Evaluation I, HFD-430
Office of Postmarketing Drug Risk Assessment, HFD-400

TO: Jerry Phillips, R.Ph., Director
Medication Errors Prevention, HFD-400
Office of Postmarketing Drug Risk Assessment, HFD-400

SUBJECT: Consult/Innohep name confusion study

EXECUTIVE SUMMARY:

This report is in response to a consult request from Lauren Lee, Pharm.D., HFD-400, to review the methodology and the results of the study conducted by Brand Institute on Innohep, proposed proprietary name, with potential for confusion with other approved proprietary/generic names. The results indicated that Innohep has sound alike confusion with Inocor and Innovar.

INTRODUCTION:

The proposed propriety name, Innohep, was not recommended by both OPDRA and the Labeling and Nomenclature Committee (LNC) for a new product manufactured by DuPont Pharma. The reason for not recommending Innohep was the potential for confusion with Innovar, Inocor, Innogel, Innofem and Inomax. The DuPont Pharma, through Brand Institute, conducted a study to review the potential for brand and generic product name confusion with Innohep in the US market. Below, we comment on their methodology and their findings regarding Innohep.

METHODOLOGY:

Brand Institute conducted a survey by randomly recruiting pharmacists and physicians across the selected geographic areas. The survey was a self-administered questionnaire via the Internet. The Brand institute provided only a limited description of their survey methodology. The following issues were not clearly addressed in their document:

1. What was the reference population? For example, was it all pharmacists (retail, hospital, and internet pharmacist) or only limited to one of these types of pharmacists?
2. What was the sampling frame? For example, were physicians selected from the list of the American Medical Association? If so, were both members and non-members included in the list?
3. What was the response rate?
4. What was the method of recruiting the physicians and pharmacists? For example, if the internet was used to recruit the participants; was an ad placed in a specific internet site or was electronic mail sent to pharmacists and physicians? If electronic mail was used, how was the mailing list obtained?
5. What were the selected geographic areas?

The Brand Institute included general practitioner/family physicians (GP/FPs), orthopedic surgeons, internists, and rheumatologists. These are the groups most likely to prescribe Innohep. It was not clear if the sample included physicians who prescribe comparison drugs.

The Brand Institute presented a table (target audience by specialty) which indicated there were 40 GP/FPs, 20 orthopedic surgeons, 20 internists, 20 rheumatologists, and 100 pharmacists. Since less than 100 individuals are included in each component of this study, it is not clear how the sponsor allocated the types of participants into different components of this study. It is important to explain the allocation method in order to assess the validity of the study.

Result and Methodology:

Phase I. Physician simulated "real world prescribing."

Were these physicians asked to write or pronounce the drug names under similar conditions in which they would normally prescribe the medication, for example, how slowly and clearly they spoke on the voice mail?

Phase II (pharmacist, panel A): In this phase, the sponsor tested for the ability to spell the name correctly and not necessarily for confusion/association with other brand/generic drugs. The pharmacists listened to the verbal prescription or viewed the handwritten prescription, and then interpreted the names.

On the verbal prescription, there were only 2% of respondents who spelled Innohep correctly. However, 58% of the respondents typed it as Inohep.

On the scripted prescription RX filling interpretation, 84% of respondent interpreted Innohep correctly.

Phase III. (Physicians and pharmacists):
Sound alike potential: In this phase, without prior knowledge of the drug information, respondents were asked to view the test drug names and then list the existing brand/generic drug names that sound like the test drug names and could be potentially confusing:

The respondents anticipated confusion of Innohep with the following drugs: Heparin (5%), Athrohist (1%), Imovax (1%), Innovar (1%), and Inocor (1%).

Look alike potential: Without prior knowledge of the drug information, respondents were asked to view the test drug names and then list the existing brand/generic drug names that look like the test drug names and could be potentially confusing:

The respondents anticipated confusion of Innohep with the following drugs: Heparin (3%), Imovax (1%), Indocin(1%), INH (1%), Ionamin (1%).

Hyperbole/name claim registration Issues, fit to concept, memorability, personal preferences:

These issues are irrelevant to the name confusion test. These procedures evaluate the drug names for over-claim or "hyperbole" issues (*hyperbole/name claim registration*), how well they fit to the concept statement (*fit to concept*), how fast the names can be recalled (*memorability*), and *personal preference*.

Product profile potential confusion: The test drug name profile was shown to respondents. They were asked to select from the following choices that could potentially result in patient safety issues due to confusion with the comparison brand/generic drug names. The choices were: potential patient harm, identical formulation, identical dosage, identical frequency, identical distribution, and not applicable.

In regard to Innohep, the measurement of product profile potential confusion was performed against heparin, not against other drugs names of interest identified in phase 3 studies and by the reviewing division (that means, Innovar, Inocor, Innogel, Inomax, and Innofem.)

Phase IV (pharmacists- Panel B): *Sound alike accuracy evaluation with positive & and negative controls - Aided):* The pharmacists listened to names pronounced by physicians in Phase I and then clicked a button to proceed to the next page of the survey. The pharmacists were instructed to select the test drug name that they heard a physician verbally prescribe in the sound file.

Options for selection were Inocor, Heparin, Insulin, Athrohist, and Isometheptene.

98% of pharmacists responded Innohep (correctly) and 2% Inocor. Note that, no comparison was made with Innovar, Innogel, Inomax, and Innofem suggested by the division. –

Phase IV (pharmacists - Panel B): *look alike accuracy evaluation with positive and negative controls-Aided).* Panel B pharmacists also performed the following exercise while taking the online survey. The pharmacists viewed the script created in phase I and then clicked a button to proceed to the next page of the survey. The pharmacists were instructed to select the previously viewed, hand-scripted test drug name.

Innohep was compared with Heparin, INH, Ionamin, Imovax, Indocin. All 50 respondents answered Innohep. Note that Innohep was not compared with the Innovar, Inocor, Innogel, Inomax, and Innofem.

Orthographic String Similarity Testing: This method measures the potential for confusion between the test drug names and the existing brand/generic drug names by using two statistical correlation tests (bigram and trigram) and the edit string distance test.

In regard to Innohep, the sponsor presented the result of comparison with Heparin. The sponsor did not present or did not perform the analysis of Orthographic String Similarity Test between Innohep with any other drugs of interest identified by their survey or the FDA division with potential for confusion with Innohep.

CONCLUSION:

The panel of physicians and pharmacists selected in this study were practitioners not expert in detecting medication errors. Thus, when asked about sound alike or look-alike confusion, they might not select all the drugs' names which could be potentially confused with Innohep. In spite of this problem, in a response to an unaided question, 2 out of 80 respondents responded that Innohep has a sound alike confusion with Inocor (1 out 80) and Innovar (1 out of 80). In a response to an aided question, 2% of respondents marked Inocor (1 out of 50 respondents, pharmacists) from a list of drug names as a sound alike confusion name with Innohep. However, on the list provided to the participants, the names of other test drugs of interest were not included. The list has Inocor, Heparin, Insulin, Atrohist, Isometheptene. The list did not have Innovar, Innogel, Inomax, and Innofem.

Although the study is limited in the number of potential confusing drug names it examined, it shows that Innohep has sound alike confusion with Inocor and Innovar at a minimum.

cc:
HFD-180:NDA 20-484,Talarico
HFD-400: Honig/Phillips
HFD-430: Beitz/Trontell/Guinn

CC: NDA 20-484
Office Files
HFD-180; DivFiles; Karen Oliver, Project Manager
HFD-180; Lilia Talarico, Division Director
HFD-430; Patrick Guinn, Project Manager, DDRE I, OPDRA
HFD-430; Ann Trontell, Deputy Director, DDRE I, OPDRA
HFD-430; Julie Beitz, Division Director, DDRE I, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Mac Lumpkin, Deputy Center Director for Review Management (Electronic Only)

Memorandum

Date: 21 April 2000

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Lillia Talarico, M.D., Dir., DGCDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGCDP (HFD-180)
Tim Robison, Ph.D., Pharm./Tox., DGCDP (HFD-180)

Subject: NDA 20-484
"Tradename"® unspecified (tinzaparin sodium) Injection
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Reviews of NDA 20-484, dated 22 Feb. 2000, written by Timothy W. Robison, Ph.D.
2. NDA 20-484 Action Package, with Draft Product Labeling (dated 4 June 1999).

II. Comments and Conclusions

1. A review of the action package for NDA 20-484, tinzaparin sodium injection, suggests that the product has been adequately evaluated in multiple non-clinical repeat-dose safety studies up to 12 months duration for approval of the requested indication (short-term subcutaneous administration in the initial treatment of symptomatic deep vein thrombosis in conjunction with warfarin sodium).

2. The non-clinical reproductive toxicology data do not suggest of a risk of congenital malformations or other alterations to fetal growth or viability, except as associated with abnormal hemostasis, for patients administered tinzaparin sodium injection during or immediately preceding pregnancy. However, because animal data are not always predictive of the human response, some residual level of risk can not be excluded based on the available animal data.

3. Specific comments related to the product label follow:

- No reference to the brand name (once selected) for tinzaparin sodium injection should be included in the discussion of any non-clinical safety studies in the product label, unless those studies were specifically conducted with the clinical drug formulation to be marketed. All discussions of non-clinical studies conducted with other than the clinical drug formulation

should make reference to the generic compound name of 'tinzaparin sodium.'

- The non-clinical ADME/Pharmacokinetic data for tinzaparin sodium suggest that the product is extensively sequestered within the extracorporeal volume of the blood following administration to rats and dogs. A similar pattern of sequestration within the extracorporeal blood space is apparent in the clinical pharmacokinetic data. Blood volume is generally considered to represent a relatively fixed fraction of the total body weight of mammalian species (although the plasma fraction varies slightly between species, it varies little within species except under extreme circumstances of abnormal hydration and/or hypovolemia). Therefore, it is recommended that all interspecies dose comparisons included in the product label be based on the administered tinzaparin sodium dose (in IU/kg or mg/kg) unless there is clear scientific justification for the use of another scaling method (i.e., allometric scaling).
- Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:
  - reference to the "AMES" assay be reworded as an "in vitro bacterial cell mutation assay (AMES test)", and
  - the text "(CHO/HGPRT)" be deleted.
- Under the heading of "Pregnancy Category" it is recommended that:
  - "Non-teratogenic Effects" be re-labeled as "Prior Human Experience" or "Limited Human Experience with Heparin Use during Pregnancy."

4. Consideration should be given to the inclusion of information on breast milk drug concentration and neo-natal drug exposure in rodents administered tinzaparin sodium during lactation.

Summary

A review of the action package for NDA 20-484, tinzaparin sodium injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication (short-term subcutaneous administration in the initial treatment of symptomatic deep vein thrombosis in conjunction with warfarin sodium). The proposed product label, with possible revision as suggested in the preceding section, adequately reflects the safety data for this product.

Memorandum

Date: 21 April 2000 /S/

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Lillia Talarico, M.D., Dir., DGCDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGCDP (HFD-180)
Tim Robison, Ph.D., Pharm./Tox., DGCDP (HFD-180)

Subject: NDA 20-484
"INNOHEP"® (tinzaparin sodium) Injection
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Reviews of NDA 20-484, dated 22 Feb. 2000, written by Timothy W. Robison, Ph.D.
2. NDA 20-484 Action Package, with Draft Product Labeling (dated 4 June 1999).
3. HEPARIN Sodium Vials® Injection (Lilly)
4. TUBEX®, Heparin Sodium Injection (Wyeth-Ayerst)

II. Comments and Conclusions

1. A review of the action package for NDA 20-484, tinzaparin sodium injection, suggests that the product has been adequately evaluated in multiple non-clinical repeat-dose safety studies up to 12 months duration for approval of the requested indication (short-term subcutaneous administration in the initial treatment of symptomatic deep vein thrombosis in conjunction with warfarin sodium).

2. The non-clinical reproductive toxicology data do not suggest of a risk of congenital malformations or other alterations to fetal growth or viability, except as associated with abnormal hemostasis, for patients administered tinzaparin sodium injection during or immediately preceding pregnancy. However, because animal data are not always predictive of the human response, some residual level of risk can not be excluded based on the available animal data.

3. Specific comments related to the product label follow:
   - No reference to the brand name (once selected) for tinzaparin sodium injection should be included in the discussion of any non-clinical safety studies in the product label, unless those studies were specifically conducted with the clinical drug formulation to be marketed. All discussions of non-clinical studies conducted with other than the clinical drug formulation should make reference to the generic compound name of 'tinzaparin sodium.'
   - The non-clinical ADME/Pharmacokinetic data for tinzaparin sodium suggest that the product is extensively sequestered within the extracorporeal volume of the blood following administration to rats and dogs. A similar pattern of sequestration within

the extracorporeal blood space is apparent in the clinical pharmacokinetic data. Blood volume is generally considered to represent a relatively fixed fraction of the total body weight of mammalian species (although the plasma fraction varies slightly between species, it varies little within species except under extreme circumstances of abnormal hydration and/or hypovolemia). Therefore, it is recommended that all interspecies dose comparisons included in the product label be based on the administered tinzaparin sodium dose (in IU/kg or mg/kg) unless there is clear scientific justification for the use of another scaling method (i.e., allometric scaling).

- Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:
  - reference to the "AMES" assay be reworded as an "in vitro bacterial cell mutation assay (AMES test)", and
  - the text "(CHO/HGPRT)" be deleted.
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  - "Non-teratogenic Effects" be re-labeled as "Prior Human Experience" or "Limited Human Experience with Heparin Use during Pregnancy."

4. Consideration should be given to the inclusion of information on breast milk drug concentration and neo-natal drug exposure in rodents administered tinzaparin sodium during lactation.

Summary

A review of the action package for NDA 20-484, tinzaparin sodium injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication (short-term subcutaneous administration in the initial treatment of symptomatic deep vein thrombosis in conjunction with warfarin sodium). The proposed product label, with possible revision as suggested in the preceding section, adequately reflects the safety data for this product.

MEMORANDUM

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

Date: April 12, 2000

From: Kathy M. Robie-Suh, M.D., Ph.D. KRS APR 12 2000
Medical Team Leader, HFD-180

Subject: NDA 20-484
innohep (tinzaparin sodium) Injection

To: Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

On June 30, 1999 the sponsor submitted an application seeking approval of tinzaparin sodium for use in:

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

and

[redacted]

Proposed dose for treatment of DVT is 175 anti-factor XA IU/kg subcutaneously once daily for at least 6 days and until the patient is adequately anticoagulated with warfarin

[redacted]

Tinzaparin sodium [referred to as tinzaparin in this review] (MW about 6500 daltons) is the sodium salt of a low molecular weight heparin (LMWH) derived from heparin from porcine intestinal mucosa by controlled enzymatic depolymerization. Like other LMWHs it differs from unfractionated heparin in that it has a higher ratio of anti-factor Xa activity to anti-factor IIa activity. At therapeutic doses tinzaparin has minimal effect on the bleeding time and prothrombin time (PT); it prolongs the activated partial thromboplastin time (aPTT). Tinzaparin effect on aPTT can be neutralized by protamine zinc. Advantages of tinzaparin over unfractionated heparin include once daily subcutaneous (s.c.) administration and no need for therapeutic monitoring of anticoagulant activity.

Tinzaparin is approved for use as an anticoagulant in a number of countries in Europe (earliest 1991), in Canada (1995) and some other countries. Indications include treatment of deep vein thrombosis (DVT), treatment of pulmonary embolism (PE), prevention of

DVT following hip or knee replacement surgery or general surgery, and anticoagulation of extracorporeal circuits during hemodialysis.

In animal models tinzaparin has been shown to inhibit thrombus formation. In rats tinzaparin showed dose-dependent inhibition of thrombus formation with complete inhibition observed at 5 mg/kg. Tinzaparin has been shown to be as effective as unfractionated heparin for inhibition of tissue thromboplastin-induced thrombus formation and had anti-factor Xa activities comparable to that of unfractionated heparin.

In preclinical studies most adverse effects of tinzaparin were bleeding events related to the pharmacologic action of the drug. From an acute study in mice the minimum lethal dose of tinzaparin sodium given intravenously or subcutaneously was about $20x10^3$ anti-Factor Xa IU/kg. In rats the subcutaneous minimum lethal dose was $7.3x10^3$ anti-Factor Xa IU/kg ($38x10^3$ anti-Factor Xa IU/m^2) which was about 42 (6) times the maximum recommended human therapeutic dose.

Long-term treatment (52 weeks) of rats resulted in development of radial cataracts and decreased bone density in some animals at high doses of the drug. Effects of tinzaparin on bone density appeared to be less than observed with unfractionated heparin. The drug did not appear to be mutagenic or genotoxic and did not have non-bleeding-related adverse effects on pregnancy or fertility and did not cause congenital malformations.

Tinzaparin is well-absorbed from subcutaneous injection sites reaching a maximum plasma concentration in 4-5 hrs. Following a single subcutaneous injection of tinzaparin ratio of plasma levels of anti Xa over time (AUC) to anti-IIa activity over time (AUC) is about 2.8 and is higher than that of unfractionated heparin (about 1.2). Tinzaparin is cleared primarily via the renal route with a plasma half-life of anti-factor Xa activity of about 1.6 hours in normal subjects versus 5.2 hours in hemodialysis patients (tinzaparin dose of 75IU/kg intravenously).

Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolus (PE):
Two pivotal studies are submitted in support of the treatment of DVT and PE indication. These are presented and discussed briefly below.

Study DMP 702-900: This was a multicenter (17 sites in the U.S. and Canada), randomized (1:1), double-blind (double dummy), active control, parallel groups investigation of tinzaparin versus continuous intravenous unfractionated heparin (UFH) for the initial treatment of proximal-vein thrombosis. Study subjects were patients presenting with acute DVT documented by venography (or if venography was not possible, abnormal impedence plethysmography that could not be otherwise accounted for or positive B-mode ultrasound. Where venography was not possible at presentation, non-invasive test had to be confirmed later by venography. Unilateral venograms were considered adequate if positive and inadequate if negative. Treatments were:

- an initial bolus followed by a continuous intravenous (IV) infusion placebo matching UFH plus a single, daily s.c. injection of 175 anti-Xa IU/kg tinzaparin sodium for 6 days, provided the INR (PT) was in the target range; or

- an initial bolus of 5,000 units of UFH followed by a continuous, IV infusion at a rate of 30,000-40,000 units per 24 hrs, plus a single, daily s.c. injection of placebo matching tinzaparin for 6 days, provided the INR (PT) was in target range; infusion rate was adjusted to maintain aPTT ratio at 1.5-2.5 times control value.

Beginning on day 2 of dosing all patients received oral anticoagulation with warfarin for about 90 days (dose adjusted to INR 2.0-3.0).

Venograms were performed at study entry and when signs or symptoms of a recurrent DVT or PE occurred. A perfusion lung scan (ventilation perfusion lung scan when possible) was performed in all patients within 48 hours of entry to serve as a baseline evaluation. If signs and symptoms of a PE occurred, a second ventilation perfusion lung scan was performed and/or pulmonary angiography was performed.

The primary efficacy measure was symptomatic recurrent thromboembolic events (DVT and/or PE) occurring during initial treatment (day 0-5) or during long-term warfarin therapy (up to 3 months). Secondary measures of efficacy included all cause death, composite of all deaths and thromboembolic events (DVTs and PEs), and composite of abrupt deaths and thromboembolic events.

A total of 438 patients were randomized (216 tinzaparin, 219 heparin; 435 dosed). Some of the baseline characteristics of these patients are summarized in the following table:

Study DMP 702-900: Baseline Characteristics of Study Population

	Number (%)	
	Tinzaparin (N=216)	Heparin (N=219)
Age (yrs)		
mean	62.6	59.2
median	66	63
Sex		
male	131 (61%)	110 (50%)
female	85 (39%)	109 (50%)
Body mass index (kg/m^2), mean	26.37	27.82
Smoking:		
non-smoker	98 (45%)	96 (44%)
smoker	46 (21%)	45 (21%)
ex-smoker	71 (33%)	74 (34%)
History of DVT	34 (16%)	35 (16%)
History of PE	9 (4%)	16 (7%)
History of surgery or trauma ≤6 months	109 (50%)	111 (51%)
History of coronary heart disease	43 (20%)	31 (14%)
History of chronic obstructive pulmonary disease	29 (13%)	34 (16%)
History of cancer	57 (26%)	55 (25%)
Diabetes	34 (16%)	23 (11%)
Baseline evidence of cancer or malignancy	47 (22%)	50 (23%)
Proximal DVT on entry	193 (89%)	201 (92%)
Symptomatic PE on entry	28 (13%)	37 (17%)

Mean age was higher in the tinzaparin patients and there were more males in the tinzaparin group as compared to the heparin group (62.6 yrs vs. 59.2 yrs and 61% vs.

50%, respectively). Otherwise, treatment groups were reasonably well-balanced with regard to demographics and risk factors.

Results of the sponsor's primary and secondary efficacy analyses are summarized in the following table:

Study DMP 702-900: Summary of Sponsor's Efficacy Analyses (Adjudicated Assessments at 90 Days)

	Number of patients (%)		p-value (Fisher's)	p-value (chi square)	Difference in proportions (95% CI)
	tinzaparin (N=216)	heparin (N=219)			
Recurrent thromboembolic events	6 (2.8%)	15 (6.8%)	0.071	0.048	4.1 (0.072, 8.071)
Recurrent DVT	3 (1.4%)	9 (4.1%)	0.141	0.083	2.7 (-0.337, 5.778)
Documented by:					
Venogram	1	3			
IPG	2	7			
PE	3 (1.4%)	6 (2.7%)	0.503	0.322	1.4 (-1.316, 4.017)
Documented by:					
V/Q lung scan	3	4			
Pulmonary angiogram	0	1			
Autopsy	0	2			
Deaths	10 (4.6%)	21 (9.6%)	0.061	0.044	5.0 (0.157, 9.761)
Abrupt	3 (1.4%)	13 (5.9%)	0.019	0.012	4.5 (1.050, 8.044)
Insidious	7	8			
Death, PE or recurrent DVT	15 (6.9%)	30 (13.7%)	0.027	0.021	6.8 (1.077, 12.431)
Abrupt death, PE recurrent DVT	8 (3.7%)	23 (10.5%)	0.008	0.006	6.8 (2.020, 11.577)

based on sponsor's tables, DMP-702-900 Study Report

There was a trend toward fewer patients with recurrent thromboembolic events in the tinzaparin group (2.8%) as compared to the heparin group (6.8%); however, this difference did not reach statistical significance by Fisher's Exact Test (p=0.071). There were significantly fewer abrupt deaths in the tinzaparin group as compared to the heparin group (p=0.019). The result for total death was marginal (p=0.061). Six of the deaths in the tinzaparin group and 14 of the deaths in the heparin group were attributed to metastatic carcinoma. Patients with cancer constituted 26% of the tinzaparin population and 25% of the heparin population. The sponsor's table of all deaths is attached to this review as Appendix A.

In the tinzaparin group of 19 suspected recurrent DVT events and 18 suspected PEs adjudicated by the monitoring committee 3 (16%) DVT and 3 (17%) PE events were confirmed as events. In the heparin group of 25 suspected recurrent DVT events and 16 ssuspected PEs adjudicated by the monitoring committee 9 (36%) DVT and 6 (38%) PE events were confirmed as events.

Mean duration of study drug infusion was 6.0 days in the tinzaparin group with mean daily dose ranging from 176.8 to 180.1 IU/kg over the 6 day treatment. Maximum daily doses ranged from 440-520.5 IU/kg. During the initial treatment period (0-7 days) there tended to be fewer patients with overt bleeding in the tinzaparin group as compared to the heparin group (p=0.098); there were significantly fewer patients with major bleeds in the tinzaparin group (1) as compared to the heparin group (9)(p=0.020). During the long-term warfarin treatment period there were no significant differences between groups in adverse events or bleeding. Three tinzaparin patients and 1 heparin patient had

thrombocytopenia (one tinzaparin patient with counts decreased to 14,000 and one heparin patient with counts decreased to 16,000). Eighteen tinzaparin patients and 28 heparin patients withdrew from study drug prematurely due to an adverse event. Six of the tinzaparin withdrawals and 9 of the heparin withdrawals were prior to day 8.

Reviewer's comments: Study 900 provides some support for effectiveness of tinzaparin in treating DVT in terms of a trend toward fewer thromboembolic events in the tinzaparin group as compared to the heparin group and an observed significantly lower rate of abrupt death in the tinzaparin patients. The heparin regimen used in this study was well-within the labeled dosing recommendations for heparin and monitoring of aPTT during the study indicated pharmacologic effect. The statistical result for the between treatment comparison in this study is not strong. However, the power of the study to demonstrate a difference between treatments may have been compromized somewhat by the anticoagulant effect of warfarin which was started in all patients on day two of study treatment.

This study has some limitations with regard to usefulness as a single study supporting efficacy of tinzaparin for the indication. Deficiencies of the study in this regard include:

1. some lack of consistency across centers - The greatest treatment effect occurred in the largest center with a TE rate of 0/40 (0%) in the tinzaparin group and 5/38 (13.2%) in the heparin group (p=0.024 in that center). In one center there was a numerical trend in favor of heparin with 2/27 (7.4%) TE event rate in the tinzaparin group and 0/29 (0%) in the heparin group (p=0.228). FDA Statistical Review found a significant treatment-by-center interaction and when the overall p-value for the primary outcome was adjusted for center the treatments were not statistically significantly different (p=0.122).

2. consistency across subsets of patients not clearly established - Tinzaparin appeared to perform better than heparin in whites and in patients with no history of cancer. (See FDA Statistical Review).

3. some inconsistency of results across endpoints – By the adjudicated analyses, the primary efficacy endpoint (recurrent TE) was not statistically significant (p=0.071) and secondary efficacy endpoints (not protocol specified) composite "death, DVT or PE" and "abrupt death, DVT, or PE" and "abrupt death" were statistically significant (p=0.027, p=0.008, and p=0.019). However, for the non-adjudicated analyses (i.e., investigator read) tinzaparin was superior only for abrupt death (p=0.019). There was no statistically significant difference between groups in all cause death (p=0.061)(adjudicated or investigator read).

4. efficacy result was not statistically persuasive.

In spite of these difficulties generally it appears that in this study tinzaparin could have been not more than 5% to 6% (absolute amount) worse than heparin with regard to proportion of patients having recurrent thromboembolic events. Studies in the literature suggest a recurrent thromboembolic event rate of about 15% to 20% with oral

anticoagulation in the absence of adequate initial heparin dosing. (Brandjes, PM et al NEJM 327:1485 (1992); Hull, RD et al. NEJM 315:1109 (1986)). Considering the information available it is reasonable to conclude that in this trial both the heparin and tinzaparin regimens were effective. However, superiority of tinzaparin over heparin cannot reasonably be concluded from this study.

Study DMP 702-904: This was an open-label, multicenter, randomized parallel groups European (France) study comparing tinzaparin versus heparin in patients with clinically suspected PE. All patients were to have either lung scan or pulmonary angiography. Patients with low probability lung scans could still be enrolled in the study if they had proximal or distal DVT confirmed by venography or compression ultrasonography. [About 82% of tinzaparin patients and 83% of heparin patients entering the study had lung scans interpreted as high probability of PE. About half of patients had proximal deep vein thrombosis diagnosed and 20% of tinzaparin and 16% of heparin patients had distal DVT].

Eligible patients were randomized to either single daily subcutaneous injection of tinzaparin (175 anti-Xa IU/kg) or an aPTT-adjusted continuous infusion regimen of unfractionated heparin. All patients received oral anticoagulation (warfarin or acenocoumarol) starting on day 1 to 3 of dosing. Tinzaparin or heparin was continued until patients had reached target INR (2.0 to 3.0) with not less than 5 days of overlap of oral and parenteral anticoagulation. Oral anticoagulation was continued to Day 90. Primary efficacy evaluation was the occurrence of a combined endpoint ("critical events") consisting of the following efficacy and safety parameters: symptomatic objectively documented new or recurrent PE and/or DVT, major bleeding events, and death assessed at Day 8. Secondary efficacy parameters included incidence of the individual components of the primary endpoint at Day 8 during the followup period (Day 9-90) and over the entire study period. The study was sized assuming a 15% failure ("critical event") rate with heparin and the intent of the study was to demonstrate superiority of tinzaparin over heparin.

A total of 1482 patients screened were confirmed as having PE (total patients screened is not given). Of these 870 patients were not randomized. The major reason for non-inclusion in the study was listed as "other treatment(s)" (676 patients, 78% of not randomized). A total of 612 patients were randomized (304 tinzaparin, 308 heparin). Of these 3 tinzaparin patients and 1 heparin patient never received study treatment. The ITT population consisted of 301 tinzaparin patients and 307 heparin patients. Some baseline characteristics of the study population are summarized in the following table.

Study DMP 702-904: Baseline Characteristics of Study Population

	Number (%)[@]	
	Tinzaparin (N=301)	Heparin (N=307)
Age (yrs)		
mean	66.4	66.1
median	70.0	70.0
Sex		
male	132 (44%)	139 (45%)
female	169 (56%)	168 (55%)
Obesity	101 (34%)	81 (26%)
Varicosity	87 (29%)	95 (31%)
Thromboembolic history	76 (25%)	79 (26%)
Tobacco >20 packs/yr	62 (21%)	42 (14%)[a]
Cardiopathy	55 (18%)	58 (19%)
Prolonged immobilization (>72 hrs)	53 (18%)	47 (15%)
Surgery within last 90 days	43 (14%)	52 (17%)
Malignancy	23 (8%)	29 (9%)
Perfusion lung scan, probability of PE::		
high	245/299 (82%)	251/307 (83%)
intermediate	46/299 (15%)	39/307 (13%)
Any DVT	216/301 (72%)	206/303 (68%)
proximal	156/301 (52%)	156/303 (51%)
distal	59/301 (20%)	50/303 (16%)

[a] significantly different between groups, p=0.024

table based on tables in sponsor's study report

Generally, treatment groups were well-balanced with regard to important baseline characteristics. There was significantly more tobacco use in the tinzaparin group (p=0.024) and there was a trend toward a higher proportion of obese patients in the tinzaparin group (p=0.063). About 45% of patients were males; mean age was 66 years. Almost all patients had a lung scan showing high or intermediate probability of PE (investigator read) and about 72% of tinzaparin patients and 67% of heparin patients had a venogram showing DVT on study entry.

A total of 238 (79%) tinzaparin patients and 234 (76%) heparin patients received heparin at a curative level prior to study participation; in most of these patients (93% of tinzaparin, 97% of heparin) this treatment lasted <24 hours. Sixteen tinzaparin patients and seven heparin patients received heparin at a curative dose level for more than 24 hours (but less than 36 hours) before enrollment in the study. About 3% of tinzaparin patients and 5% of heparin patients had received preventative doses of heparin pre-study. About 48% of patients had reached target INR by Day 5 of study treatment and 75% had reached the target by Day 8. Mean duration of treatment was 7.3 days (median, 7.0) for both tinzaparin and heparin groups.

Results of the sponsor's efficacy analysis are shown in the following table:

Study DMP-904: Summary of Sponsor's Efficacy Analyses

	Number of Patients (%)								
	Initial Phase			Followup Period			Entire Study Period		
	Tinzaparin (N=301)	Heparin (N=307)	p-value*	Tinzaparin (N=297)	Heparin (N=304)	p-value*	Tinzaparin (N=301)	Heparin (N=307)	p-value*
Any critical event:	9/301 (2.99%)	9/307 (2.93%)	1.00	12 (4.04%)	16 (5.26%)	0.563	18 (5.98%)	22 (7.17%)	0.625
DVT or PE	3 (1.0%)	2 (0.65%)	0.683	2 (0.67%)	4 (1.32%)	0.686	5 (1.66%)	6 (1.95%)	1.000
DVT	0	0	--	2 (0.67%)	4 (1.32%)	0.686	2 (0.66%)	4 (1.30%)	0.686
PE	3 (1.0%)	2 (0.65%)	0.683	1 (0.34%)	2 (0.66%)	1.000	4 (1.33%)	4 (1.30%)	1.000
Death	4 (1.33%)	3 (0.98%)	0.723	8 (2.69%)	11 (3.62%)	0.643	12 (3.99%)	14 (4.56%)	0.842
Major Bleed	3 (1.00%)	5 (1.63%)	0.725	4 (1.35%)	6 (1.97%)	0.752	6 (1.99%)	8 (2.61%)	0.788

*Fisher's Exact Test

table based on sponsor's tables, DMP-904 Study Report

No significant differences between treatment groups were seen in any of the efficacy parameters. Rates of DVT and/or PE were very low in both treatment groups throughout the study.

Treatment groups were similar with regard to number of deaths, study withdrawals due to adverse events, and major bleeding events. About half of patients in each treatment group had some adverse event while on study. One tinzaparin patient and 2 heparin patients had thrombocytopenia. Relatively more tinzaparin patients than heparin patients had adverse events that were considered possibly or probably related to study medication (20% vs. 13%, p=0.023). These included more cases of epistaxis, PE (not adjudicated), hematuria, and melena in tinzaparin patients. Overall, 8 of 71 suspected PEs were adjudicated as a definite or probable PE.

Reviewer's comments: This study failed to demonstrate superiority of tinzaparin over heparin for any efficacy endpoint. The event rate in the heparin group was considerably lower than was expected, so the sample size probably was inadequate to detect a difference. Also, any between treatment differences in this study may have been obscured by the oral anticoagulation overlapping the parenteral tinzaparin and heparin treatment. This would have made it more difficult to demonstrate a difference between the two treatments.

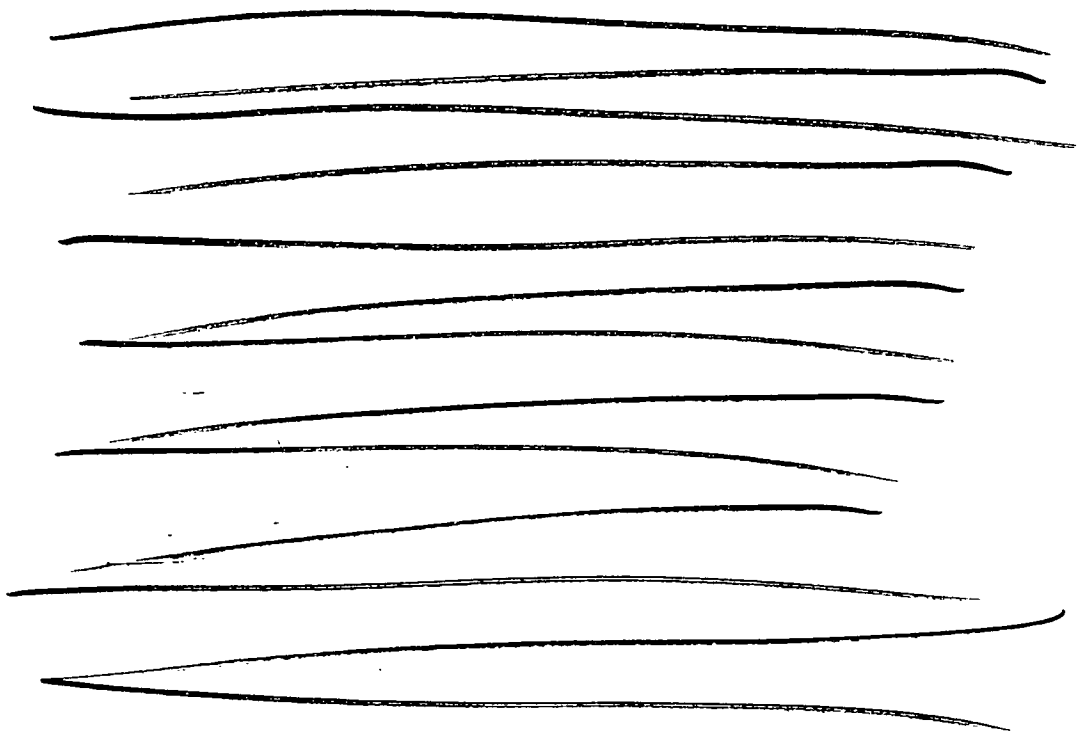
The PE population in this study did not include all PE patients. About 41% of eligible patients did not enter the study and the majority of these were not included because of unspecified other treatments. Possibly the study population represented a lower risk PE population than the general PE population. For example, the proportion of cancer

patients in this study was fairly low (about 9%). This may have contributed to the overall low thromboembolic event rate observed in the study

Nevertheless, the low thromboembolic event rates in both treatment groups suggest some effectiveness of both tinzaparin and heparin for preventing thromboembolic events in this study. A high proportion of patients enrolled in this study had DVT diagnosed by venogram at study entry (about 69% of patients). This study may be considered somewhat reassuring regarding tinzaparin as used in this study in treating DVT. FDA Statistical Review estimated that the confidence interval for the composite endpoint ("critical events") allowed up to 6% (adjudicated assessments) or 7% (investigator suspected) difference between treatments.

Tinzaparin did not appear to have a more favorable safety profile than heparin. The two treatment groups showed similar frequency and types of adverse events and withdrawals due to adverse events. More of adverse events in the tinzaparin groups were felt to be treatment related. Death rates were similar in the two treatment groups.

Additional treatment of DVT information: A small dose-finding pharmacokinetic /pharmacodynamic study (Study DMP 702-928) of tinzaparin 75 anti-Xa IU/kg BID and 150 anti-Xa IU/kg daily for 5 days in 20 patients with DVT showed some quantiatitve improvement in DVT from baseline with both treatments using the Marder score assessment at day 7. However, there was no difference between the two tinzaparin dose groups. All patients also received warfarin starting on day 1.



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