

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

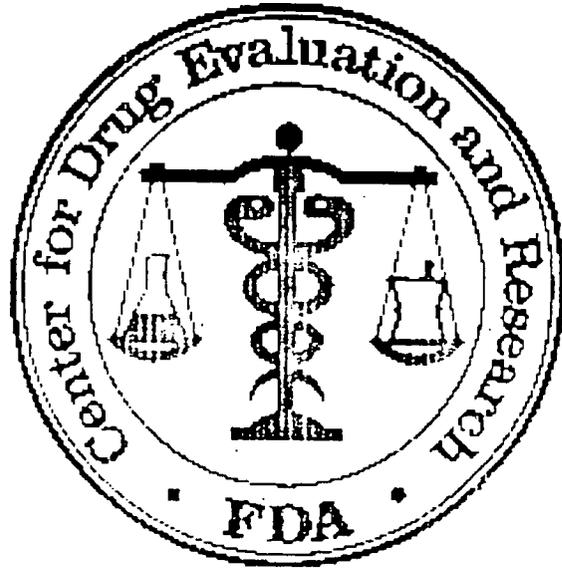
*APPLICATION NUMBER:*

**20-484**

**CORRESPONDENCE**

FOOD AND DRUG ADMINISTRATION  
DIVISION OF GICDP  
DOCUMENT CONTROL ROOM 6B-24  
5600 FISHERS LANE  
ROCKVILLE, MARYLAND 20857

DATE: July 14, 2000



**TO:**

**Name: James Gaskill**

**Fax No: 302-992-3011**

**Phone No: 302-892-7308**

**Location: DuPont**

**FROM:**

**Name: Alice Kacuba**

**Fax No: 301-443-9285**

**Phone No: 301-827-7450**

**Location: FDA/PKLN 6B-45/HFD-180**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

This fax is 24 pages long, which includes a 1 page cover sheet, a 3 page Approval letter for NDA 20-484, and 20 pages of agreed upon labeling for NDA 20-484. Please call 301-827-7450 to confirm receipt of the fax. Thank you.

3/



Before the application for the indication of "the initial inpatient treatment of acute symptomatic deep vein thrombosis when administered in conjunction with warfarin sodium" may be approved it will be necessary for you to:

1. Provide molecular weight distribution profiles of various tinzaparin sodium batches (peak pattern) which correspond to various polysaccharide chains. This information can be used for characterization of tinzaparin sodium and for monitoring batch to batch consistency.
  2. Demonstrate the equivalence of the drug substance manufactured at Leo and \_\_\_\_\_ by performing a head-to-head comparison on these two materials using the same analytical tools (testing methods).
  3. Provide the components/composition of the \_\_\_\_\_ used in the manufacturing process of \_\_\_\_\_.
  4. Provide the manufacturing details of the Tinzaparin Reference Standards (T51 and S43).
  5. Provide details of any testing performed on the powder of the drug substance before its formulation.
  6. Provide details of the UV method, including data. These details should demonstrate the specificity of this method for tinzaparin sodium.
  7. Include the free sulfate test in the specification section and provide details of the sampling plan used in the regulatory analytical methods of the drug substance, tinzaparin sodium.
  8. Provide tabulated formats of all the tinzaparin sodium batches used in pre-clinical, clinical, and stability studies.
- \_\_\_\_\_
- \_\_\_\_\_
10. Specify the time interval for each manufacturing step used in manufacturing the drug product.
  11. Provide the details of the sampling plan used in the regulatory specification and methods for the drug product.

Based on the submitted primary stability data, your proposed 24-month expiration dating for the drug product is not acceptable. The data support an 18-month expiration.

Further, Drug Master Files (DMFs) \_\_\_\_\_ referenced as supportive documentation for this application, are deficient. The DMF holders were notified of their deficiencies in letters issued on February 24, 2000. Approval of the NDA is contingent upon an adequate response to those letters.

In addition, it will be necessary for you to submit revised draft labeling for the drug, incorporating the requested revisions as identified in the enclosed labeling as well as the following revisions to the immediate container and carton labels:

### Immediate Container

#### 10,000 IU per mL

1. Delete the phrase "20,000 anti-Xa IU per 2 mL". This information, positioned above the phrase "10,000 anti-Xa IU per mL", makes the label cluttered, confusing, and difficult to read. Since both vials contain a net quantity of 2 mL, the drugs should be clearly identified as the IUs per mL, rather than the total mLs per vial.
2. Remove the parentheses around the phrase "10,000 anti-Xa IU per mL" and enlarge the type face, if possible.
3. Enlarge the name of the drug, if possible, to increase its prominence.

#### 20,000 IU per mL

4. Delete the phrase "40,000 anti-Xa IU per 2 mL". This information, positioned above the phrase "20,000 anti-Xa IU per mL", makes the label cluttered, confusing, and difficult to read. Since both vials contain a net quantity of 2 mL, the drugs should be clearly identified as the IUs per mL, rather than the total mLs per vial.
5. Remove the parentheses around the phrase "20,000 anti-Xa IU per mL" and enlarge the type face, if possible.
6. Enlarge the name of the drug, if possible, to increase its prominence.

**Cartons (1 multi-dose vial)****10,000 IU per mL**

7. Revise the storage statement to be consistent with that in the package insert and submitted data.
8. Delete the phrase 20,000 anti-Xa IU per 2 mL on all carton panels.
9. Remove the parentheses around the phrase "10,000 anti-Xa IU per mL" and enlarge the type face, if possible.
10. Revise the quantity statement to read: "2 mL multi-dose vial".
11. Enlarge the name of the drug, if possible, to increase its prominence.

**20,000 IU per mL**

12. Revise the storage statement to be consistent with that in the package insert and submitted data.
13. Delete the phrase 40,000 anti-Xa IU per 2 mL on all carton panels.
14. Remove the parentheses around the phrase "20,000 anti-Xa IU per mL" and enlarge the type face, if possible.
15. Revise the quantity statement to read: "2 mL multi-dose vial".
16. Enlarge the name of the drug, if possible, to increase its prominence.

**Cartons 10,000 and 20,000 IU per mL (10 multi-dose vials)**

17. Modify, as stated above for the 10,000 and 20,000 IU per mL cartons.
18. Provide the route of administration in prominent lettering on the front panel as follows: "FOR SUBCUTANEOUS USE ONLY".
19. Revise the quantity statement on the front panel to read: "10 x 2 mL multi-dose vials".
20. Add the "Rx only" phrase to the front panel.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage form, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirement of 21 CFR 314.55. Your pediatric drug development plan or request for a waiver with supporting information and documents will need to be submitted within 120 days of approval of this application.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,  
and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Karen Oliver, Project Manager, at (301) 827-7457.

Sincerely,

*151* *4/28/00*  
Victor F. C. Raczowski, M.D., M.S.  
Deputy Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

# Telefax

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

Date: July 12, 2000

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

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

Total Pages: 9 (Please contact us if you have not received all pages)

---

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

Alice,

Attached is our response to the Division's proposed insert. Please share this with Drs. Talarico and Raczkowski. If they would like to discuss the labeling language, please have them contact Dr. Max Talbott at 301-992-4827.

We intend to provide you with the revised adverse event Table 6 on Thursday. I'll contact you tomorrow to update you on the status of that table. Please call me if you have any other questions or requests.

Jim



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THIS DOCUMENT IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED, AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the intended recipient, any disclosure, copying or use of this telefax is strictly prohibited and you should immediately notify the sender to arrange for return of the documents.



FEDERAL EXPRESS

DuPont Pharmaceuticals Company

Desk copy: Alice Kacuba, HFD-180  
(by facsimile 301-443-9285)

July 12, 2000

Lilia Talarico, M.D.  
Director, Division of Gastrointestinal and  
Coagulation Drug Products (HFD-180)  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5600 Fishers Lane  
Rockville, Maryland 20857

**RE: NDA No. 20-484; Innohep® (tinzaparin sodium injection)  
RESPONSE TO PROPOSED DRAFT LABELING**

Dear Dr. Talarico:

Reference is made to our New Drug Application #20-484 for Innohep® (tinzaparin sodium) submitted June 30, 1999. Reference is also made to Divisions' proposed package insert for Innohep provided by Alice Kacuba on July 10, 2000.

At this time we are submitting our comments on the Division's proposal. We intend to submit the revised Adverse Event Table 6 (as requested on page 14 of the July 10, 2000 proposed insert) in a separate submission.

*- According to James Gaskill, due in 40 US via fax 7-13-00 apt 1102*

Should you have any question on this matter, please contact Jim Gaskill at (302) 892-7308.

*to discuss labeling indication*

Sincerely,  
*James L. Gaskill*  
James L. Gaskill, R.Ph.  
Associate Director, Regulatory Affairs

Attachments  
Submitted in duplicate



DuPont Pharmaceuticals Company

HAND DELIVERED

Desk copy: Karen Oliver, HFD-180  
(by facsimile 301-443-9285)

July 6, 2000

*Received  
July 6, 2000*

Lilia Talarico, M.D.  
Director, Division of Gastrointestinal and  
Coagulation Drug Products (HFD-180)  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5600 Fishers Lane  
Rockville, Maryland 20857

RE: NDA No. 20-484; Innohep® (tinzaparin sodium injection)  
DRAFT LABELING

Dear Dr. Talarico:

Reference is made to our New Drug Application #20-484 for Innohep® (tinzaparin sodium injection) submitted June 30, 1999. Reference is also made to the draft package insert provided by the Division on June 30, 2000.

At this time we are submitting DuPont Pharmaceuticals' proposed changes to the Division's draft package insert. Attached is a side-by-side comparison of the Division's proposal (left-hand column) with DuPont's proposal (right-hand column). Deletions to the Division's proposed language are indicated with "strike-through" and additions are in bold-italics. This side-by-side comparison is being provided in hard copy as well as MSWord file on disk. Please note that we have made our best attempt at meeting the Division's requests regarding adverse event tables. We ask that you consider combining Adverse Event Tables 7 and 8 from the DuPont proposal during your review.

We look forward to discussing this proposal with you. Should you have any questions on this matter, please contact Jim Gaskill at (302) 892-7308.

Sincerely,

James L. Gaskill, R.Ph.  
Associate Director, Regulatory Affairs

Attachments  
Submitted in duplicate

# Electronic Mail Message

**Date:** 4/17/00 7:47:29 AM  
**From:** Sammie Beam ( BEAMS )  
**To:** Karen Oliver ( OLIVERK )  
**Subject:** Proprietary name consult#00-0121 (5/30/00)

Hello,

Thank you for the proprietary name consult for NDA #20-484. The OPDRA consult number and desired date of completion is in the subject field above. I understand this is a re-review of the name and will give it to the original reviewer to evaluate research.

Thanks,  
Sammie Beam  
Project Manager  
Med Errors/OPDRA  
827-3161  
Fax 301 480-8173



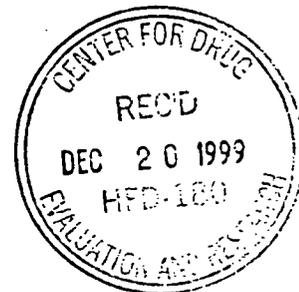
VIA FEDERAL EXPRESS

**Life Sciences Enterprise**  
DuPont Pharmaceuticals Company

December 17, 1999

Desk Copy: K. Oliver (HFD-180)  
by Facsimile (301-443-9285)

Lilia Talarico M.D.  
Division of Gastrointestinal and Coagulation  
Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Document Control Room 6B-24  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-484; innohep® (tinzaparin sodium injection)  
Response to FDA Request for Information

Dear Dr. Talarico:

Reference is made to our NDA #20-484 for innohep® (tinzaparin sodium injection) submitted June 30, 1999. Reference is also made to the telephone request from Karen Oliver on December 15, 1999 for information concerning the trademark status of innohep® in the United States, and specifically, whether the lower-case i was part of that trademark.

“ innohep® [generic name] ” is a registered trademark of \_\_\_\_\_ Ltd. in the United States. DuPont Pharmaceuticals has licensed the use of this trademark in the United States from \_\_\_\_\_, and our agreement with \_\_\_\_\_ Products requires us to sell tinzaparin sodium injection under the innohep® trademark in the US.

Hopefully this adequately answers any questions regarding the trademark. In the event any additional information is needed, please contact Jim Gaskill at (302) 892-7308.

Sincerely,

James L. Gaskill, R.Ph.  
Associate Director, Regulatory Affairs

ELECTRONIC MAIL MESSAGE

Sensitivity: COMPANY CONFIDENTIAL

Date: 27-Oct-1999 03:03pm EDT  
From: Dan Boring  
BORINGD  
Dept: HFD-530 CRP2 S447  
Tel No: 301-827-2396 FAX 301-827-2510

TO: Karen Oliver ( OLIVERK )  
CC: Jerry Phillips ( PHILLIPSJ )  
CC: Lilia Talarico ( TALARICO )  
CC: Karen Oliver ( OLIVERK )

Subject: Re: Trademark Review

Karen,

I didn't find the consult request, but our evaluation is as follows.

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 are 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) there 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.

thanx,  
dan

>Dan,  
>  
>On July 8, 1999, I submitted a consult to you, as then chair of the  
>Trademark Review committee, for NDA 20-484-innophep (tinzaparin sodium  
>injection).  
>  
>Has this name been reviewed by the committee? Do I need to send  
>another consult for this same application to Jerry Phillips?  
>  
>The sponsor is questioning if the name is "acceptable", so I am  
>following up on their request.  
>  
>Karen Oliver

E L E C T R O N I C M A I L M E S S A G E

Date: 27-Oct-1999 01:59pm EDT  
From: Karen Oliver  
OLIVERK  
Dept: HFD-180 PKLN 6B45  
Tel No: 301-827-7310 FAX 301-443-9285

TO: Dan Boring ( BORINGD )  
CC: Jerry Phillips ( PHILLIPSJ )  
CC: Lilia Talarico ( TALARICO )  
CC: Karen Oliver ( OLIVERK )

Subject: Trademark Review

Dan,

On July 8, 1999, I submitted a consult to you, as then chair of the Trademark Review committee, for NDA 20-484-innophep (tinzaparin sodium injection).

Has this name been reviewed by the committee? Do I need to send another consult for this same application to Jerry Phillips?

The sponsor is questioning if the name is "acceptable", so I am following up on their request.

Karen Oliver

# Electronic Mail Message

**Date:** 07/13/2000 4:37:13 PM  
**From:** David Morse (CDER/DAVDP) ( MORSED )  
**To:** See Below  
**Subject:** Comments re: Innohep

All

Just a few minor items -- otherwise the label looks good.

1) Were Seg 3 studies performed with Tinzaparin sodium, and if yes what were the results? This info should be included in the Impairment of Fertility section of the label

2) Under Teratogenic Effects: The label states that "no evidence of impaired fertility" was observed. ?? Since fertility is NOT an endpoint assessed in Seg 2 reproduction studies (organogenesis studies) I am unsure of the source and appropriateness of this statement, and therefore suggest it be removed or rewritten to more fully identify the endpoint measured.

3) I would suggest that a new heading of 'Limited Clinical Experience with In Utero Exposure to INNOHEP' be included in the label, following the section on PREGNANCY. I would further suggest that the header for 'Non-Teratogenic Effects' be removed, as the data which follows this heading is all based on clinical experience with INNOHEP.

4) Under the current heading of Non-Teratogenic effects: The second sentence of the paragraph makes reference to six percent of cases (?) - which doesn't appear to follow from the preceding sentence which makes reference to only 4 reported cases.

I hope this helps.

Dave Morse

**To:** Victor Raczkowski ( RACZKOWSKI V )  
**To:** Florence Houn ( HOUN F )  
**To:** Lilia Talarico ( TALARICO )  
**To:** Jasti Choudary ( CHOUDARY )  
**To:** Alice Kacuba ( KACUBAA )  
**To:** Bronwyn Collier ( COLLIER B )  
**Cc:** David Morse (CDER/DAVDP) ( MORSED )

# Electronic Mail Message

Date: 07/14/2000 8:28:57 AM  
From: Victor Raczkowski  
Subject: Re: innohep labeling

( RACZKOWSKIV )

What is the answer to number 1? Were seg 3 studies performed?

V.

....

- \* Hi,
- \* I have spoken with Jasti. He said to ignore Comment 1 & 2 from David Morse's email. He feels that it is not appropriate here. The language used in the Teratogenic Effects subsection, is the language from the CFR.
- \* Jasti does want a revision to the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection (This is page 10, second paragraph of the subsection). I will bring his comments up to you hardcopy so that you can see his revision.
- \* Alice

*They were performed, but the test was not intended to assess fertility & Reprod. performance of animals receiving the drug (male & female) directly. That information of seg. 3 studies is not meant for the part of labeling.*

# Electronic Mail Message

Date: 07/14/2000 8:32:16 AM  
From: Victor Raczkowski ( RACZKOWSKIV )  
To: Alice Kacuba ( KACUBAA )  
To: Bronwyn Collier ( COLLIERB )  
Cc: Victor Raczkowski ( RACZKOWSKIV )  
Subject: Clarification: Re: innohep labeling

Actually, my question had to do with #2. Was fertility assessed in some studies?

~~For~~ For this portion of labeling fertility denotes successful outcome of pregnancy when the drug is given to the pregnant females during organogenesis, i.e. apart from the effect on fetuses. In this case there was no adverse effect on the outcome of pregnancy. The treated dams carried the pregnancy successfully till the time of autopsy.

Printed by John Gibbs  
**Electronic Mail Message**

**Date:** 13-Jul-2000 08:47am  
**From:** John Gibbs  
GIBBS  
**Dept:** HFD-820 PKLN 14B31  
**Tel No:** 301-827-6420 FAX 301-827-0878

**TO:** Bronwyn Collier (COLLIERB)  
**TO:** Karen Oliver (OLIVERK)  
**CC:** Liang Zhou (ZHOUL)  
**CC:** Ali Al-Hakim (ALHAKIMA)  
**Subject:** NDA #20-484 Tert. Chemistry Review

NDA #20-484

**Drug:** Innohep (tinzaparin sodium) Injection

Chemistry Tertiary Review #2

**F:** Claim for Categorical Exclusion accepted in Chem. Rev. #1 dated 22 Feb 2000.

**EER:** Overall recommendation: Acceptable on 27 Jan 2000 per FDA CDER EES Detail Report on 12 July 2000.

**Microbiology:** Recommended for Approval in Microbiology Review #1 dated 2 Feb 2000.

**Tradename:** Per OPDRA Consult #99-077/00-0121 dated 23 June 2000 because of the recent withdrawal of Inocor from the market and the recent discontinuation of marketing of Innovar, OPDRA has no objections to the use of the proprietary name, Innohep.

**Labeling:** Adequate per Chemistry Review #2 dated 3 July 2000.

**CMC:** Based on Chemistry Review #2 dated 3 July 2000 this new drug application may be approved from the aspect of CMC with a tentative expiration period of 30 months for the drug product when stored at 25 degrees C and

John J. Gibbs

Printed by John Gibbs  
**Electronic Mail Message**

**Date:** 20-Apr-2000 11:06am  
**From:** John Gibbs  
GIBBS  
**Dept:** HFD-820 PKLN 14B31  
**Tel No:** 301-827-6420 FAX 301-827-0878

**TO:** Bronwyn Collier (COLLIERB)  
**TO:** Karen Oliver (OLIVERK)

**CC:** Liang Zhou (ZHOUL)  
**CC:** Ali Al-Hakim (ALHAKIMA)

**Subject:** Tertiary Chemistry Review of NDA 20-484

*[Handwritten initials]*

*NDA 20-484*

NDA #20-484  
Drug: Innohep (tinzaparin sodium) Injection

Chemistry Tertiary Review:

EA: Claim for Categorical Exclusion accepted in Chemistry Review #1  
Dated 22 Feb 2000.

EER: Acceptable per EES Summary Report dated 2 Feb 2000.

Microbiology: Recommended for Approval per Microbiology Review #1  
dated 1 Sept 1999.

Tradename: Not Acceptable per OPDRA Consult #99-077 dated 3 Jan 2000.

Labeling: Not Acceptable in the CMC area. See Chemistry Review #1  
dated 22 Feb 2000.

CMC: This NDA is APPROVABLE pending satisfactory resolution of  
issues raised in Chemistry Review #1 dated 22 Feb 2000.

*[Handwritten signature]*  
John J. Gibbs



**Life Sciences Enterprise**  
**DuPont Pharmaceuticals Company**

May 17, 1999

To whom it may concern,

The DuPont Pharmaceuticals Company hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the U. S. Federal Food Drug and Cosmetic Act in connection with the innohep® (tinzaparin sodium injection) NDA.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard S. Levy".

Richard S. Levy, M.D.  
Vice President  
Worldwide Regulatory Affairs & Pharmacovigilance

JLG/jc

*Oliver*

NDA 20-484

JUN 30 2000

DuPont Pharmaceuticals Company  
Attention: Max W. Talbot, Ph.D.  
Chestnut Run Plaza, MR 2146  
974 Centre Road  
Wilmington, DE 19805

Dear Dr. Talbot:

We acknowledge receipt on June 22, 2000 of your June 13, 2000 correspondence requesting a meeting to discuss issues regarding the proposed tradename "Innohep®". We have concluded that the meeting is unnecessary as the Agency finds the name "Innohep®" acceptable.

If you disagree that a meeting is not necessary at this time, we encourage you to discuss the matter with Karen Oliver, RN, MSN, Regulatory Health Project Manager, of this division. If the issue can not be resolved at the division level, you may formally request reconsideration of the matter at the office level after providing the division an opportunity to review any materials you intend to rely on in an appeal to Florence Houn, M.D., M.P.H., Director, Office of Drug Evaluation III. A copy of any appeal should be sent to this division.

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7457.

Sincerely,

*/s/* 6-30-00  
Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-484

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Talarico

HFD-180/J.Choudary

HFD-180/L.Zhou

HFD-180/A.Al-Hakim

HFD-103/F.Houn

HFD-103/V.Raczkowski

HFD-180/B.Collier

Drafted by: KO/June 30, 2000

151

2/30/00

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GENERAL CORRESPONDENCE

NDA 20-484

JUN 30 2000

DuPont Pharmaceuticals Company  
Attention: Max W. Talbot, Ph.D.  
Chestnut Run Plaza, MR 2146  
974 Centre Road  
Wilmington, DE 19805

Dear Dr. Talbot:

We acknowledge receipt on June 22, 2000 of your June 13, 2000 correspondence requesting a meeting to discuss issues regarding the proposed tradename "Innohep®". We have concluded that the meeting is unnecessary as the Agency finds the name "Innohep®" acceptable.

If you disagree that a meeting is not necessary at this time, we encourage you to discuss the matter with Karen Oliver, RN, MSN, Regulatory Health Project Manager, of this division. If the issue can not be resolved at the division level, you may formally request reconsideration of the matter at the office level after providing the division an opportunity to review any materials you intend to rely on in an appeal to Florence Houn, M.D., M.P.H., Director, Office of Drug Evaluation III. A copy of any appeal should be sent to this division.

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7457.

Sincerely,

*/s/ 6-30-00*

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-484

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Talarico

HFD-180/J.Choudary

HFD-180/L.Zhou

HFD-180/A.Al-Hakim

HFD-103/F.Houn

HFD-103/V.Raczkowski

HFD-180/B.Collier

Drafted by: KO/June 30, 2000

~~File # NDA 20-484-1001~~

*181* *06/30/00*

---

GENERAL CORRESPONDENCE

Oliver

NDA 20-484

MAY 22 2000

DuPont Pharmaceuticals Company  
Attention: Max Talbot, Ph.D.  
Chestnut Run Plaza, MR 2146  
974 Centre Road  
Wilmington, DE 19805

Dear Dr. Talbot:

We acknowledge receipt on May 15, 2000 of your May 16, 2000 resubmission to your new drug application (NDA) for Tinzaparin Sodium Injection.

This resubmission contains additional Chemistry, Manufacturing and Controls and Labeling information and a Safety Update submitted in response to our April 28, 2000 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is July 16, 2000 and the secondary user fee goal date is September 16, 2000.

If you have any questions, call me at (301) 827-7457.

Sincerely,

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

cc:  
Archival NDA 20-484  
HFD-180/Div. Files  
HFD-180/K.Oliver  
HFD-180/Reviewers and Team Leaders

DISTRICT OFFICE

Drafted by: KO/May 22, 2000

*/s/*

*05/22/00*

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CLASS 1 RESUBMISSION ACKNOWLEDGEMENT (AC)  
(DDR: Update the user fee goal date based on the class of resubmission.)

DISCIPLINE REVIEW LETTER

DuPont Pharmaceuticals Company  
Attention: James L. Gaskill, R.Ph.  
Chestnut Run Plaza, MR 2146  
974 Centre Road  
Wilmington, DE 19805

FEB 28 2000

Dear Mr. Gaskill:

Please refer to your June 30, 1999 new drug application for innohep® (tinzaparin sodium injection).

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Tinzaparin polysaccharide chains carry unsaturated groups at the non-reducing end, which can be easily detected and quantitated using \_\_\_\_\_ system equipped with UV detector (232nm). Provide molecular weight distribution profile of various tinzaparin batches (peak pattern) which correspond to various polysaccharide chains. This information can be used for characterization of tinzaparin and for monitoring batch to batch consistency.
2. With respect to characterization and proof of structure of the drug substance: in order to demonstrate the equivalence of the drug substance manufactured at \_\_\_\_\_ head-to-head comparison should be performed on these two materials using the same analytical tools (testing methods) performed under similar conditions.
3. Provide components/composition for the \_\_\_\_\_ used in the manufacturing process of \_\_\_\_\_
4. Provide the manufacturing details of the Tinzaparin Reference Standards (T51 and S43).
5. Provide any testing performed on the powder of the drug substance before its formulation.
6. Provide details of the UV method, including data, and its specificity to tinzaparin sodium.
7. Include the free sulfate test in the specification section and provide details of the sampling plan used in the regulatory analytical methods of the drug substance, tinzaparin.
8. Provide tabulated format for all the tinzaparin sodium batches used in pre-clinical, clinical, and stability studies.

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10. Specify the time interval for each manufacturing step used in manufacturing the drug product.
  11. Provide the details of the sampling plan used in the regulatory specification and methods for the drug product.
  12. Based on the submitted primary stability data, your proposed expiration dating for the drug product is not acceptable.

In addition, on February 24, 2000, the Agency issued deficiency letters to \_\_\_\_\_ Products Ltd. A/S regarding their DMFs \_\_\_\_\_ referenced as supportive documentation in your NDA 20-484 application for innohep® (tinzaparin sodium injection).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Karen Oliver, Regulatory Health Project Manager, at (301) 827-7457.

Sincerely,

*JS/*  
Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal and Coagulation Drug  
Products, (HFD-180)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

NDA 20-484

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cc:

Archival NDA 20-484

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Zhou

HFD-180/A.Al-Hakim

HFD-820/DNDC Division Director - only for CMC related issues

DISTRICT OFFICE

Drafted by: KO/February 28, 2000

Initialed by: A.Al-Hakim 02/28/00

L.Zhou 02/28/00

151

02/28/00

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DISCIPLINE REVIEW LETTER (DR)

DUJER

NDA 20-484

**DISCIPLINE REVIEW LETTER**

DuPont Pharmaceuticals Company  
Attention: James L. Gaskill, R.Ph.  
Chestnut Run Plaza, MR 2146  
974 Centre Road  
Wilmington, DE 19805

JAN 21 2000

Dear Mr. Gaskill:

Please refer to your June 30, 1999 new drug application for innohep® (tinzaparin sodium injection).

Our review of the proprietary name, innohep®, is complete, and we have concluded that the name is unacceptable.

There are currently 3 approved products with significant look-alike/sound-alike conflicts with innohep including Innovar, Inocor, and Innogel. Innovar and Inocor have more confusion potential due to the following: (1) they are parenteral, prescription products that may be stored in close proximity to innohep, making it possible for dispensing errors to occur; (2) the usual doses for these drugs are patient dependent (i.e., weight-based); and (3) medication errors involving these three drugs can be serious because of their indications for use (Inocor is an inotropic agent for treatment of congestive heart failure; innohep is an anticoagulant for the proposed indications of prophylaxis and treatment of DVT; and Innovar is an anesthetic).

Further, the spelling of "innohep" with a lower case "i" violates the grammatical rule that proper names should be capitalized. Further, it could potentially lead to confusion between the tradename and generic name.

Please submit a new proprietary name for review and evaluation.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Karen Oliver, Regulatory Health Project Manager,  
at (301) 827-7457.

Sincerely,

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-484  
HFD-180/Div. Files  
HFD-180/K.Oliver  
HFD-180/L.Talarico  
HFD-180/K.Robie-Suh  
HFD-180/R.He  
HFD-180/L.Zhou  
HFD-180/A.Al-Hakim  
HFD-180/J.Choudary  
HFD-870/S.Al-Fayoumi  
HFD-715/P.Flyer  
HFD-715/M.Fan  
HFD-400 L. Lee  
HFD-400/J.Phillips  
HFD-820/DNDC Division Director  
DISTRICT OFFICE

Drafted by: KO/January 19, 2000

Initialed by: L.Talarico 01/20/00

Initialed by: K.Johnson 01/21/00

*jpsl 01/21/00*

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DISCIPLINE REVIEW LETTER (DR)

NDA 20-484

JUL - 8 1999

DuPont Pharmaceuticals Company  
Attention: Mary Buesing, M.D.  
Chestnut Run Plaza  
MR 2152  
974 Centre Road  
Wilmington, Delaware 19805

Dear Dr. Buesing:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: innohep<sup>®</sup> (tinzaparin sodium injection)

Therapeutic Classification: Standard (S)

Date of Application: June 30, 1999

Date of Receipt: June 30, 1999

Our Reference Number: NDA 20-484

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 29, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 30, 2000 and the secondary user fee goal date will be June 30, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

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

U.S. Postal/Courier/Overnight Mail:

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

