DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Food and Drug Administration
Rockville MD 20857

NDA 20-484/S-002

Bristol-Myers Squibb Pharma Company
Attention: Mr. David Silberstein
Associate Director, Regulatory Affairs
Room D2.245 (Mail stop D22-05
P.O. Box 4000
Princeton, New Jersey

Dear Mr. Silberstein:

Please refer to your supplemental new drug application dated August 8, 2001, received August 9, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Innohep® (tinzaparin sodium injection).

This "Changes Being Effected in 30 days" supplemental new drug application provides for revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert to add or strengthen safety information.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. In the PRECAUTIONS section, the “Pregnancy, Teratogenic Effects” subsection, the first sentence of the second paragraph, should be revised to read as follows:

   Cases of teratogenic effects that include cleft palate, optic nerve hypoplasia, and trisomy 21 (Down’s) syndrome, and cutis aplasia of the scalp have been reported in infants of women who received INNOHEP during pregnancy.

2. In the ADVERSE REACTIONS section, the “Ongoing Safety Surveillance” subsection, the last paragraph should be revised to read as follows:

   Spinal epidural hematoma with INNOHEP administered at a therapeutic dose has been reported in at least one patient who had not received neuraxial anesthesia or spinal puncture.

The final print labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the patient package insert submitted August 8, 2001, and must be formatted in accordance with the requirements of 21 CFR 201.66. Marketing the product with FPL that is not identical to the approved labeling text and "Drug Facts" format, may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please mount individually ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submission in electronic Format – NDAs (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-484/S-002. Approval of this submission by FDA is not required before the labeling is used.

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 submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

Victor F. C. Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick
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