DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-749
NDA 21-751

Hameln Pharmaceuticals GmbH
c/o B & H Consulting Services, Inc.
Attention: Helen M. Ribbans, President
55 North Gaston Avenue
Somerville, NJ 08876

Dear Ms. Ribbans:

Please refer to your new drug applications (NDAs) dated April 1 and 5, 2004, received April 28, 2004, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pentetate zinc trisodium injection and Pentetate calcium trisodium injection, respectively.

We acknowledge receipt of your submissions dated April 20 and 28, May 14, June 11, 17 and 28, July 9, August 10 and 11, 2004.

These new drug applications provide for the use of Pentetate zinc trisodium injection and for Pentetate calcium trisodium injection for treatment of internal contamination with plutonium, americium or curium.

We completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels) and submitted labeling (package insert submitted August 11, 2004, immediate container and carton labels submitted August 10, 2004). Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDA 21-749"** or **"FPL for approved NDA 21-751**." Approval of these submissions by FDA is not required before the labeling is used.

If you choose to use a proprietary name for these products, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

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. We note that the requirement has been fulfilled for the intravenous route of administration by referencing the Federal Register /Vol. 68, No. 178/ Monday, September 15, 2003, page 53984, Docket No. 2003D-0399. We are deferring submission of your pediatric study for the inhalation route of administration for ages 0 to 16 years until August 11, 2008.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment, included in your submission dated August 10, 2004, is listed below.

Human pharmacokinetic study in pediatric subjects to compare and evaluate the absorption, distribution and elimination of Ca and Zn-DTPA via inhalation using a commonly available jet type nebulizer (FDA approved model to be selected by the sponsor) with the intravenous route. Data/information on dose delivered and the particle size distribution obtained from the specified nebulizer shall be provided.

a. Protocol submission: Within 6 months of the date of final approval of these applications
b. Study start: Within 6 months of agreement to the protocol
c. Final study report submission: Within 12 months of initiation of the study.

We remind you of your postmarketing study commitments in your submission dated August 10, 2004. These commitments are listed below.

1. Longitudinal studies involving follow up of Patient Treatment Data Forms and placement of data into a registry for periodic analyses related to post-marketing drug safety and uses.
   a. Protocol submission: Within 6 months of the date of final approval of these applications
   b. Study start (i.e., the date the database will be ready to accept patient data, should it be necessary): Within 6 months of agreement to the protocol
   c. Agree to submit annual reports of ongoing longitudinal studies beginning one year from study initiation.

2. Human pharmacokinetic study in adult subjects to compare and evaluate the absorption, distribution and elimination of Ca and Zn-DTPA via inhalation using a commonly available jet type nebulizer (FDA approved model to be selected by the sponsor) with the intravenous route. Data/information on dose delivered and the particle size distribution obtained from the specified nebulizer shall be provided.
   a. Protocol submission: Within 6 months of the date of final approval of these applications
   b. Study start: Within 6 months of agreement to the protocol
   c. Final study report submission: Within 12 months of initiation of the study.

Submit clinical protocols to an IND for these products. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your NDAs. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to your NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual

report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products 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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for your products. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Patricia A. Stewart, Regulatory Project Manager, at (301) 827-7496.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Julie Beitz

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