

NDA 21-749
Ca-DTPA

Date: 14-Apr-2004

REQUEST FOR INFORMATION:

3. Provide a retest date for pentetic acid.
4. Do you have any evidence that your manufacturing process yields pentetate calcium trisodium from pentetic acid, calcium carbonate and NaOH under the conditions of manufacture? Describe how do you intend to assure the identity and quality of the pentetate calcium trisodium in manufactured batches of the drug product?

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/s/

Patricia Stewart
4/16/04 05:12:52 PM

MEMORANDUM

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

DATE: April 10, 2003
FROM: Florence Houn MD MPH
SUBJECT: Office Director Memo
TO: Administrative File for Ca- and Zn-DTPA

This memo documents my concurrence with the Division of Medical Imaging and Radiopharmaceutical's findings that Ca- and Zn-DTPA are safe and effective for treatment of radiation contamination by plutonium, americium, or curium. This indication is specific to the elements listed for which we have data to base effectiveness. There is a chemical basis for predictable binding affinity with other elements in the periodic table next to curium.

and this is noted in the CLINICAL PHARMACOLOGY section of the label. The basis of the findings is review and evaluation of the human registry data provided by the Radiation Emergency Assistance Center/Training Site (REAC/TS) and of the published literature. These data were obtained with the permission of IND holder and its US Department contracting Agency, the Department of Energy. Because radiation contamination is infrequent and it is unethical to conduct trials in humans knowingly exposing subjects to radiation or knowingly withholding these agents, FDA is making the determination of safety and efficacy using these historical data. There is some comparative data over time within the database that demonstrate the effectiveness of the agents. The safety monitoring after agents were given also provided data to base safety.

Inhalation route

Inhalation use of Ca- and Zn-DTPA does not need phase 4 studies to confirm effectiveness. Urine rates of radiation elimination are documented and are increased. Inhalation route will be labeled as an alternative for patients with inhalation contamination only. Inhalation of the initial dose can be followed by IV maintenance of Ca-DTPA until Zn-DTPA is available.

Unstable binding affinity of other transuranium elements (neptunium and uranium, etc.)

There is no need to study binding affinity of uranium and neptunium as a phase 4 study. The labeling has information that less stable chelates form with these elements and the elements are not part of the indication. The animal data showing toxicity of use of DTPA with neptunium and uranium by increasing incorporation of neptunium and uranium into inaccessible areas for chelation and excretion, such as animal bone, is noted in the CLINICAL PHARMACOLOGY section of the label.

Duration of Treatment

Treatment duration is based on the need to lower radiation contamination. The whole body effective half-life of a radioactive contaminant helps guide treatment duration, as well as the level of contamination. There are no hard data on what should be recommended for treatment duration, unlike for Prussian blue, where the average whole body effective half life for cesium-137 was reduced from 90 days to 30 days with 30 days of treatment. One patient with urinary concentration of radioactivity measured is reported by Volf's review article as having a non-treatment effective half life of 75 days and this was reduced to 35 days under treatment with Ca-DTPA. Treatment duration with DTPAs has been individualized from days to years. However, FDA would like to recommend a standard time of duration to minimize confusion in situations where individual tailoring of duration is not practical, especially if radioactivity monitoring is infeasible. In a controlled setting, careful count monitoring can dictate treatment, but as a guide post,

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/s/

Florence Houn

7/30/04 10:42:50 AM

MEDICAL OFFICER

This review was finalized on 4-10-03 to support the
FR notice findings of S and E for
Ca and Zn DTPA of Sept. 15, 2003.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2004

To: Mathias Dewald	From: Lynn Panholzer
Company: Hameln Pharmaceuticals GmbH	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 49-5151-581-581	Fax number: 301-480-6036
Phone number: 49-5151-581-214	Phone number: 301-827-3247
Subject: IND is Ca-DTPA and Zn-DTPA: Meeting minutes of December 10, 2003 pre-NDA meeting	

Total no. of pages including cover: 48

Comments: Please call me if you have any questions.

Document to be mailed: YES NO

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AGENDA: The purpose of this meeting was to discuss the possible submission of New Drug Applications (NDAs) for Calcium-DTPA and Zinc-DTPA. Hameln Pharmaceuticals GmbH requested this meeting in response to a call for submission of NDAs for these products in a Federal Register notice (Vol. 68, No. 178) dated September 15, 2003.

The meeting began with the introduction of meeting participants. The sponsor then presented an overview of Hameln Pharmaceuticals and of chemistry, manufacturing and controls issues related to its production of Ca-DTPA and Zn-DTPA (see Appendices 1 and 2).

The following points were discussed during the overview:

- The sponsor is currently in discussion with _____ to be the supplier of the drug substance.
- _____
- The sponsor presented release specifications for the DTPAs that were based on a _____ (DTPA) whose source was not _____. The specification for appearance was listed as _____ without visible _____. The sponsor expressed uncertainty as to whether this was problematic, but stated that it expected the acceptance criteria for appearance to change for the better when the _____ product was used.
- The sponsor noted that there are no compendial standards for the salts. The FDA stated that the sponsor will need to establish its own reference standards as well as a procedure for re-qualifying the standards as needed.
- The FDA stated that USP standards are minimum standards, and that the sponsor may need to establish additional specifications, such as for impurities, if needed.
- The sponsor stated that it has performed photostability studies on the drug product and that the product is stable.
- The sponsor stated that it used _____ for stability testing instead of _____ because ICH guidelines allow a choice, and other countries require that studies be performed at _____.
- The sponsor may be able to submit NDAs in April 2004 with _____ months of stability data.

A discussion of the sponsor's meeting questions followed. A handout containing the FDA responses to those questions and additional FDA comments was distributed to the meeting participants at the beginning of the meeting (Appendix 3). All FDA responses and comments were reviewed during the meeting. Questions for which there was additional discussion appear below, with the additional discussion identified and bolded beneath the question to which it applies.

Labeling: Immediate container and carton labels; package insert (see *Guidance for Industry: Calcium DTPA and Zinc DTPA Drug Products; Submitting a New Drug Application*); Patient Treatment Data Forms (see **Additional FDA Comments** below).

Patent declaration: Patent information, as described under 21 CFR 314.53 (submit on Form FDA 3542a); patent certification, as described under 21 CFR 314.50(i) [See *Guidance for Industry: Calcium DTPA and Zinc DTPA Drug Products- Submitting a New Drug Application*]

Additional discussion:

- **Labeling**: The FDA advised the sponsor to submit 3 full copies of the NDA at the time of submission, along with 15 copies of the labeling and 2 copies of the methods validation package.
 - **Stability data**: The FDA stated that it could be flexible with how much stability data is needed at the time of NDA submission. Some stability data should be submitted by the 60-day filing date, and further data could be submitted during the 6 month review period.
10. *Can a review plan (time scale) be fixed at this moment? Could this product fall under the procedure of "fast track" according "Guidance for Industry Fast Track Drug Development Programs-Designation, Development, and Application Review"?*

FDA Response:

No clinical development is needed since the safety and efficacy of the DTPAs have been published in the FR notice; therefore, there is no apparent benefit to the designation of Ca-DTPA or Zn-DTPA products as "fast track" products.

Fast track designation is not required for priority review of an NDA. A new drug application is classified as a priority review application if the drug product, if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. NDAs for Ca-DTPA and Zn-DTPA products are expected to qualify at the time of filing for priority review. The classification of a new drug application (NDA) as a priority review application imposes a 6-month review clock on the application.

Additional discussion: The FDA referred to its current pilot program for **Continuous Marketing Applications (CMA)**, in which a sponsor can submit portions of an NDA for a fast track product in advance of the complete NDA. The sponsor must apply to the Division to be part of this program. The FDA stated that the benefits of this program to Hameln Pharmaceuticals would be minimal given that (1) NDAs for the DTPA products will consist of only one major portion (chemistry, manufacturing and controls), and (2) the review clock does not begin until receipt of the complete NDA.

12. *What types of fees-regulations according to the Federal Food, Drug and Cosmetic Act, Chapter VII-General Authority Subchapter C-Fees will come into force?*

Types of fees

- §736(a)(1) *Human drug application and supplement fee*
- §736(a)(2) *Prescription drug establishment fee*
- §736(a)(3) *Prescription drug product fee*

Fee amounts

- §736(b)(1) *Application and supplement fees (full/other fees)*
- §736(b)(2) *Total fee revenues for establishment fees*
- §736(b)(3) *Total fee revenues for product fees*

Fee adjustment

- §736(c)(1) *Inflation adjustment*
- §736(c)(2) *Annual fee adjustment*

Fee waiver or reduction

- §736(d)(1) *General*
- §736(d)(2) *Use of standard costs*
- §736(d)(3) *Rules relating to small business (<500 employees)*
 - First application (no fee)*

FDA Response:

In general, we would expect an application for both salts and we would expect a 1/2 fee for each application (because the clinical data required for approval is by reference to the Federal Register notice). Fee payment would be expected at the time of submission. The current fee for an application in which the clinical data is by reference is \$286,750. The applicant may be eligible for a waiver of the application fees (e.g., small business, public health).

Once approved, the applicant may be eligible for the yearly product and establishment fees. Currently the yearly product fee is \$36,080 and the yearly establishment fee is \$226,800.

For a full description on how the fees were calculated for FY 2004 please see the FR notice of August 1, 2003, available on the internet at <http://www.fda.gov/cder/pdufa/default.htm> under Federal Register documents.

For a full discussion of user fees regarding your situation, including criteria for waivers, how to ask for waivers, and how products and establishments are billed, it is recommended that you speak with Michael Jones, Office Of Regulatory Policy, at 301-594-2041.

Additional discussion: The FDA provided the following additional guidance with regard to fees-

- **The sponsor can apply for a small business waiver of the application fee for its, or its affiliates, first human drug application if the company, including affiliates, employs less than 500 people.**
- **The sponsor could also make a credible argument for waivers based on protection of public health or barrier to innovation. However, the public health and barrier to innovation waiver includes a financial test. With _____ in annual revenue, Hameln Pharmaceuticals should not expect to be able to receive a waiver.**
- **The sponsor may receive an exemption of application fees for both Ca-DTPA and Zn-DTPA applications if orphan drug status is granted to the active ingredient for the indication proposed. If the application includes indications other than orphan designated indications, then an exemption would not be granted.**
- **The sponsor may be able to get a small business waiver for one of the applications, and an orphan drug exemption for the other salt application.**
- **If orphan drug status is applied for but not granted prior to NDA submission, the sponsor must submit the application fee and request reimbursement. If orphan status is granted, FDA would then refund the application fee.**
- **See 21 CFR 316.20 for the content and format of a request for orphan drug designation. This request can be submitted up until the time of NDA submission. The granting of orphan status is public information, which may be taken into consideration by a company deciding when to submit the request.**
- **Receiving orphan designation is not competitive.**
- **If FDA refuses to file an application for which an application fee was paid, only 75% of the fee is reimbursed to the applicant.**
- **Once approved, an applicant would be responsible for the annual product and establishment fees.**
- **The establishment fee is shared by the number of applicants that have user fee liable products made there. It is the number of applicants and not the number of products which determines the establishment fee split.**
- **Once an applicant's products have generic competition, its products and establishments would be exempt from the annual fees.**

Additional FDA Comments

1. The FDA will seek agreement/commitment from applicants to the following post-marketing studies prior to approval of NDAs for Ca-DTPA and Zn-DTPA:
 - a) 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.**

- b) Clinical pharmacology studies to provide data about absorption of drug and tolerability of injection sites for routes of administration : _____

Additional discussion:

- The FDA stated a change would be made to item 1.a) above (the revised portion has been bolded).
 - The FDA stated that the sponsor can enter into a contractual arrangement with a contract research organization for performance of these post-marketing studies.
3. All manufacturing facilities should be ready for inspection at the time of NDA submission.

Additional discussion: The FDA stated that it can arrange an inspection as soon as the sponsor is ready.

At the conclusion of the meeting, FDA reiterated its recommendation that the sponsor obtain a consultant to provide legal and technical advice.

ACTION ITEM

The FDA Project Manager will prepare minutes of this meeting and fax them to the sponsor by January 9, 2004.

Meeting minutes recorded by Lynn Panholzer, Pharm.D., Project Manager, HFD-160.

APPENDIX 1

**Presentation of information about Hameln Pharmaceuticals GmbH
Christoph Kerstein (General Manager)**

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

APPENDIX 3

**FDA Responses to Meeting Questions
(Handout provided at beginning of meeting)**

**DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG
PRODUCTS**

**Calcium-DTPA and Zinc-DTPA (Hameln Pharmaceuticals GmbH)
Pre-NDA Meeting
December 10, 2003**

FDA Responses to Meeting Questions

CMC-Related Questions

1. We considered DTPA according to USP as the active ingredient (drug substance). Nevertheless, the complex pentetate calcium trisodium is present in the finished product.

Is the submitted drug substance documentation sufficient provided that DTPA should be considered as the active ingredient?

FDA Response:

No. The DTPA must be manufactured in accordance to GMP's in a facility that is currently in GMP compliance. Also, your qualification of the source of DTPA should include independent testing of three different batches of DTPA from the proposed source against the criteria specified in the USP monograph for DTPA.

You must have procedures for acceptance of DTPA from its manufacturer, consisting of testing for conformity with the established specifications [21 CFR 211.84 (d)(2)]. However, in lieu of full testing, the procedures can include receipt of an acceptable certificate of analysis, along with performance of at least one identity test and confirmatory full testing at appropriate intervals.

2. The sodium salt of calcium DTPA is formed in ~~in~~ in the bulk (see B.5.a & b).

Are the used excipients and the process of manufacture acceptable?

FDA Response:

Yes. However, you must have procedures for their acceptance from the supplier(s) that include appropriate testing [21 CFR 211.84 (d)(2)]. In lieu of full testing, the procedures can include receipt of an acceptable certificate of analysis, along with performance of at least one identity test and confirmatory full testing at appropriate intervals.

3. We considered a bulk size of — sufficient for — ampoules 5ml. We have to perform a process validation on three batches. The best case is to validate on production scale batches.

What could be the yearly consumption in the market to plan the optimal bulk size and capabilities of the filling line?

FDA Response:

The FDA does not consider yearly consumption in the market when determining the approvability of an NDA for a product, and therefore cannot provide this information. Additionally, the FDA does not procure product for the U.S. government or make decisions regarding procurement. If we become aware of further information in this regard, we will contact you. You may call Nicki Pesik, M.D., Senior Medical Consultant for the Strategic National Stockpile Program, at 404-639-5976, or Richard Hatchett, M.D., Senior Health Advisor, Office of the Assistant Secretary for Public Health Emergency Preparedness (OASPHEP), Department of Health and Human Services (DHHS), at 202-401-4862, if you have additional questions.

4. *Is the extent of process validation (see part B.5.c.) acceptable?*

FDA Response:

Yes for CMC, but you need to provide batch records for one executed batch and analytical data for that batch.

Yes for microbiology, but you must provide the data as described in the Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

5. *Are the indicated test parameters and the specifications for release of the finished product acceptable?*

Which test parameters should be added?

FDA Response:

Yes. However, several procedures in the specification sheet (B.6.b) are indicated as "in-house." All analytical procedures, other than those in the USP, need to be fully described. Also, you have denoted single unknown and total unknown impurities as "to be defined." All "to be defined" entries in the specification sheet must be resolved and analytical procedures described at the time of submission of the NDA.

6. *Is the stability plan for the finished product acceptable?*

FDA Response: Yes.

7. *Is the proposed time line for pharmaceutical development, preparation of documentation and submission of application acceptable (see part 11, under "Brief Summary of CMC, development Status, Time Line")?*

FDA Response: Yes.

Submission of NDA

We recommend that you consider obtaining a consultant to guide you through the New Drug Application process. Also, if you do not reside or have a place of business within the United States, 21 CFR 314.50(a)(5) requires that the application contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

8. *What documents are essential for NDA application in regards to*
- *Pharmaceutical development (critical steps of production)*
 - *Validation of testing methods*
 - *Impurity profile*
 - *Stability data*
 - *Labeling*
 - *Patent declaration*

FDA Response:

Pharmaceutical development: As listed in Section P.2 of CTD-Q (components of the drug product; drug substance; excipients; drug product; formulation development; overages; physicochemical and biological properties; manufacturing process development; container closure system; microbiological attributes; compatibility)

Validation of testing methods: Consult FDA web page (ICH Q2A/Q2B). Generally, information includes statement of principle of the analytical procedure; performance characteristics validated; description of procedures used in the validation; validation data; discussion of the results.

Impurity profile: Consult FDA web page (ICH Q3AR and Q3BR). Data to support impurity specification.

Stability data: Stability testing protocol; stability tests; data. Include photostability (ICH Q1B)

Labeling: Immediate container and carton labels; package insert (see *Guidance for Industry: Calcium DTPA and Zinc DTPA Drug Products; Submitting a New Drug Application*); Patient Treatment Data Forms (see **Additional FDA Comments** below).

Patent declaration: Patent information, as described under 21 CFR 314.53 (submit on Form FDA 3542a); patent certification, as described under 21 CFR 314.50(i) [See *Guidance for Industry: Calcium DTPA and Zinc DTPA Drug Products- Submitting a New Drug Application*]

9. *What are the US specific requirements for module 3.2.R Regional Information of the CTD?*

FDA Response:

As per CTD-Q Module 3.2 Body of Data. Executed batch record and methods validation package are required.

10. *Can a review plan (time scale) be fixed at this moment? Could this product fall under the procedure of "fast track" according "Guidance for Industry Fast Track Drug Development Programs-Designation, Development, and Application Review"?*

FDA Response:

No clinical development is needed since the safety and efficacy of the DTPAs have been published in the FR notice; therefore, there is no apparent benefit to the designation of Ca-DTPA or Zn-DTPA products as "fast track" products.

Fast track designation is not required for priority review of an NDA. A new drug application is classified as a priority review application if the drug product, if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. NDAs for Ca-DTPA and Zn-DTPA products are expected to qualify at the time of filing for priority review. The classification of a new drug application (NDA) as a priority review application imposes a 6-month review clock on the application.

11. *Is an electronic submission of the application required by the FDA?*

FDA Response:

An electronic submission is encouraged but not required.

12. *What types of fees-regulations according to the Federal Food, Drug and Cosmetic Act, Chapter VII-General Authority Subchapter C-Fees will come into force?*

Types of fees

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- §736(d)(1) *General*
- §736(d)(2) *Use of standard costs*
- §736(d)(3) *Rules relating to small business (<500 employees)*
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In general, we would expect an application for both salts and we would expect a 1/2 fee for each application (because the clinical data required for approval is by reference to the Federal Register notice). Fee payment would be expected at the time of submission. The current fee for an application in which the clinical data is by reference is \$286,750. The applicant may be eligible for a waiver of the application fees (e.g., small business, public health).

Once approved, the applicant may be eligible for the yearly product and establishment fees. Currently the yearly product fee is \$36,080 and the yearly establishment fee is \$226,800.

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For a full discussion of user fees regarding your situation, including criteria for waivers, how to ask for waivers, and how products and establishments are billed, it is recommended that you speak with Michael Jones, Office Of Regulatory Policy, at 301-594-2041.

13. *When have the fees be paid?*

See FDA response to Question 12.

14. *What are the circumstances of receiving a market exclusivity?*

FDA Response:

Ca-DTPA and Zn-DTPA products could be eligible for the following types of exclusivity (see *Guidance for Industry: Calcium DTPA and Zinc DTPA Drug Products- Submitting a New Drug Application*):

- a) **Five-Year Marketing Exclusivity-** This exclusivity is provided when a sponsor obtains approval of an NDA for which no active moiety has been previously approved by the FDA. FDA has identified the DTPA ligand as the active moiety in Ca-DTPA and Zn-DTPA products. The first Ca- or Zn-DTPA NDA approved will be eligible to receive 5-year marketing exclusivity. This exclusivity does not block the review and approval of another Ca-DTPA or Zn-DTPA NDA that was submitted and essentially complete prior to the approval of the first Ca-DTPA or Zn-DTPA product.
- b) **Orphan Drug Exclusivity-** Orphan drug exclusivity is for a 7-year period and can prohibit FDA from approving a 505(b)(1), a 505(b)(2), or an ANDA for the same active moiety for the same indication during the period of exclusivity. The regulations require that you seek orphan drug designation for the active moiety of your drug product for an orphan indication **before** you submit an NDA.

Additional FDA Comments

1. The FDA will seek agreement/commitment from applicants to the following post-marketing studies prior to approval of NDAs for Ca-DTPA and Zn-DTPA:
 - a) Longitudinal studies involving follow up of patient treatment data forms and placement of data into a registry for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness.
 - b) Clinical pharmacology studies to provide data about absorption of drug and tolerability of injection sites for routes of administration
2. For the purpose of obtaining follow up data as described in 1.a. above, Patient Treatment Data Forms should be submitted in the NDA with the labeling for the products. A short version of this form should be attached to the end of the Package Insert. A long version should be made available on an internet site. Please see the approved labeling for Radiogardase™ (insoluble Prussian blue) 0.5gm capsules, available at www.fda.gov/cder/foi/label/2003/0216261bl.pdf, for examples of the type of information that should be included on these forms.
3. All manufacturing facilities should be ready for inspection at the time of NDA submission.

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/s/

Lynn Panholzer
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MEMORANDUM

Date: 03/03/03

To: Patricia Love, MD, MBA, Division Director
Division of Medical Imaging and Radiopharmaceutic Drug Products (HFD160)

Through: Hank Malinowski, Ph.D., Division Director
Division of Pharmaceutical Evaluation (HFD870)
Office of Clinical Pharmacology and Biopharmaceutics

From: Young Moon Choi, Ph.D.
Team Leader
Office of Clinical Pharmacology and Biopharmaceutics

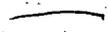
CC: Florence Houn, MD, MPH., Office Director, Office of New Drug III

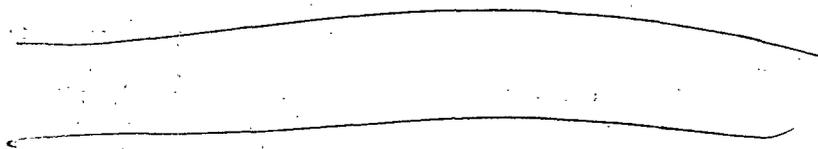
Lawrence Lesko, Ph.D., Office Director, Office of Clinical Pharmacology and Biopharmaceutics

Shiew-Mei Huang, Ph.D., Deputy Director, Office of Clinical Pharmacology and Biopharmaceutics

Alfredo R. Sancho, Ph.D. , Expert Regulatory Scientist, Office of Clinical Pharmacology and Biopharmaceutics

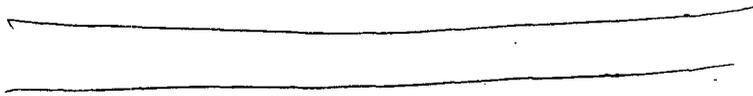
RE: Office of Clinical Pharmacology and Biopharmaceutics (OCPB) comments on Radioprotectants.

On 17 December 2002, senior OCPB staff (Lawrence Lesko, Ph.D. Office Director and Shiew Mei Huang, Ph.D., Deputy Director) were briefed on the status of the three radioprotectants reviewed to date by HFD160 co-locates, Prussian blue, , Ca-DTPA (IND 4,041), and Zn-DTPA (IND 14,603). The following is a summary of the issues discussed and OCPB's recommendations:

1. 

2. The inhalation route of administration of Zn-DTPA and Ca-DTPA has limited supporting data and/or information. The data from peer reviewed articles and case report studies state that a large percentage (~40%) of the standard administered dose, 1 gm, remained within the nebulizer apparatus used for the study. There is no data from clinical trials and/or reviewed articles that would support a different dose than the presently recommended 1 gm dose for either product. Moreover, most of the human data from nebulizer administration was with Ca-DTPA, as the first dose of a protracted chelator therapy regimen. It is recommended that this method of administration should be used for those patients which their main route of contamination was through the lungs and the time from radio-contaminant exposure was less than 24 hours. If the sponsor wishes to change the recommended dose of either product to be given via inhalation, the sponsor needs to study a new dose in comparison with the recommended dose in a well controlled study.

3.



4. Co-administration of all three radioprotectants to radio-contaminant exposed patients is likely and suggested in the label. Prussian blue (PO) is not absorbed from the gastrointestinal track and the chelators are both given IV but sequentially (1 dose of Ca-DTPA, followed by several daily doses of Zn-DTPA). The major route of elimination of the chelators is via the urine, while for Prussian blue is via the feces. Drug-Drug interaction is not viewed as a safety issue for these three products.

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/s/

Patricia Stewart

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CSO

Memo originally signed by Dr. Choi 3/3/03

DIVISION DIRECTOR INTERIM MEMO TO THE FILE

NDA: Pending
DRUG: Ca-DTPA
Zn-DTPA
ROUTE: Intravenous and Inhalation
MODALITY: T Therapeutic
INDICATION: Radiation decontamination (elimination)
SPONSOR: Pending
SUBMITTED: Pending
COMPLETED: January 27, 2003

RELATED REVIEWS:

Chemistry: David Place, PhD; 11/26/02 (preliminary)
Clinical: Robert Yaes, MD, DSc; 11/31/02
Mitchell Mathis, MD 01/29/03
Clinical Pharmacology: Alfredo Sancho, PhD; 01/14/03
Microbiology: David Hussong, PhD; 05/09/02 (preliminary)
Pharmacology: Adebayo Laniyonu, PhD; 01/27/03
Project Manager: Patricia Stewart, PhD

BACKGROUND:

Radiation exposure to elements from nuclear reactions (plant emergencies or nuclear weapons) is known to be associated with immediate and delayed radiation toxicity. There are a limited number of FDA marketed drugs to treat or minimize the complications of radiation. Potassium iodide, prevents the uptake of iodide in the thyroid and, thereby, decreases the risk of thyroid complications. A few products (aluminum chloride, intravenous fluids) been used to increase the rate of renal elimination of diagnostic or therapeutic radioactive drugs; however, they have limited effect on radioactive elements that have distributed out of the vascular system. Also, while these products that have acute benefit in clinical radiation therapy, their usefulness against a broad spectrum of nuclear elements is limited. Two drugs (calcium-DTPA and zinc-DTPA) that have been used for several decades under INDs held by REAC/TS (Radiation Emergency Assistance Center/Training Site) and are the subjects of this memo. REAC/TS is part of the Oak Ridge Associated Universities (ORAU). ORAU operates the Oak Ridge Institute for Science and Education (ORISE) under a contract with the Department of Energy. The INDs are for treatment of nuclear power or weapons plant emergencies. The drugs are manufactured by _____

_____ Traditional clinical trials were not done because it is considered to be unethical to expose patients to radiation and it is unethical to withhold potential beneficial medications. In part because of the anticipated limited market, a traditional commercial sponsor did not emerge to champion the development of these drugs. Instead, under these INDs, patients were treated empirically and were reported in the literature as observational studies. REAC/TS retained the medical case reports on 687

patients who had radiation contamination over the last 40+ years. To facilitate the development and ultimate approval of these drugs, FDA requested the medical reports on the patients in the REAC/TS database and reviewed the available published literature.

The REAC/TS database review identified 18 patients with a pre-treatment baseline and follow-up data, and 3 patients with an early post-treatment data that could serve as a baseline and follow-up data. The remaining patients had insufficient data to analyze comprehensively because of missing baseline information, missing follow-up data, or insufficient information to correlate the timing of the dosing and laboratory data. The literature provided reasonable information in 16 clinical articles. Of these, 14 articles discussed 1 to 6 patients, 1 article summarized 60 patients and 1 summarized 485 patients. Overall, with the exception of one recent case report, these articles were published from 1960- 1989. As such, the articles discussed many of the early, exploratory treatment regimens. There was limited information on the current regimen. Based on the patient descriptors and the fact that the use of these drugs in this country was under these INDs, double reporting of patients in the literature and REAC/TS database is quite probable. There are separate medical reviews for the literature and REAC/TS data. Hence, there are subtle differences in the review conclusions. After assessing all recommendations, the REAC/TS database is accepted as a reflection of the true total number of patients who received these drugs after radiation contamination. Likewise, the REAC/TS treatment regimens were evaluated for the dosing and administration recommendations. Based upon these data and animal literature data, the reviewers¹ recommend approval of Calcium-DTPA as a loading dose and Zinc-DTPA as maintenance treatment for radiation decontamination. In essence I agree with this recommendation. Salient points that effect labeling and final assessments are addressed in this memo.

At the time of this writing, the manufacturing sites of current producer _____ for the IND have been inspected. Although several sponsors, including _____ have expressed interest in submitting an NDA, an NDA has not been submitted and a confirmed NDA holder has not been identified.

CALCIUM-DTPA and ZINC-DTPA

DTPA (diethylenetriaminepentaacetate) is a chelator that has been used in many drug products to form stable complexes with heavy metals and to link them to other compounds. DTPA is considered to be the key active ingredient, but the manner in which it is administered is critical. Salts of DTPA are used in approved medical imaging drugs and _____ labeled Ca-DTPA itself is approved for imaging of the brain, heart, renal perfusion and glomerular function rate. In the presence of metals that are heavier than Ca^{+2} or Zn^{+2} , an ion exchange will occur. Transuranic radioactive elements found in nuclear reactions (i.e., those heavier than uranium) will rapidly exchange with Ca^{+2} or Zn^{+2} and will form very stable complexes with DTPA that are rapidly eliminated in the

¹ Two clinical reviews were completed: one for the literature prepared by Dr. Robert Yaes and one for the REAC/TS database (prepared by Dr. Mitchell Mathis in conjunction with Dr. Micheal Welch, statistician):

urine. As an adverse effect, this beneficial binding can lead to the depletion of nutritional elements of the body (e.g., zinc, manganese, and magnesium).

Dr. Yaes' medical review described the evolution of the investigational use from Ca-DTPA, to Zn-DTPA, to a combination of Ca-DTPA for the initial dose and Zn-DTPA for maintenance. For both drugs the recommended daily dose for adults and adolescents is a single 1 gram IV bolus (or slow infusion) once a day. For pediatrics, the dose is 14 mg/kg. The dose should not be split because it was associated with more rapid elimination of the body's essential metals. The two drugs should not be used simultaneously for prolonged periods of time because of the depletion of nutritional cations. Instead, as soon as possible after contamination, patients should receive one dose of Ca-DTPA. The next day, Ca-DTPA should be stopped and Zn-DTPA should be started. If Ca-DTPA is not available, treatment should begin with Zn-DTPA. If Zn-DTPA is not available, Ca-DTPA may be continued, but the patient should be carefully observed for nutritional element depletion.

In part, these recommendations are based on the acceptance of the rate of radiation elimination as a clinically meaningful endpoint for a decreased risk of (or delayed onset of) in radiation toxicity related adverse events. Actual whole-body radiation dosimetry data were not available. In dog studies after exposure to plutonium, untreated dogs died of osteosarcoma at ~1429 days. In these dogs, treatment with Zn-DTPA decreased organ radiation burden and doubled the dog's survival time. Also, in dogs the rate of non-malignant liver lesions decreased.

Clinical and pharmacology literature findings (discussed in the medical and pharmacology reviews) showed that divided daily doses of DTPA were associated with increased toxicity from nutritional depletion. In these data in comparable dosing regimens, in comparison to Zn-DTPA, Ca-DTPA caused 3 x more likely to be associated with depletion related adverse events. But Ca-DTPA as a loading dose more rapidly eliminates radioactivity before it has time to bind to the bone or to distribute to other organs. Once the radioactivity has redistributed out of the plasma, the rate of decontamination is comparable for both Ca- and Zn-DTPA. Dose recommendations in pediatrics are based on the fact that the mechanism of action is the same in adults and pediatrics, and plasma volume and organ size scales with weight. The youngest patient treated was 16 years of age. In this patient the Ca-DTPA treatment began 12 years after exposure to radiation. The skeletal elimination was ~3-4 fold higher than that of an adult relative with the same delay in treatment. Similar results were reported in immature and adult baboons. The increased benefit was seen in the immature skeleton because the continued bone growth allowed for increased vascular access to the bone.

REAC/TS DATABASE ASSESSMENTS

Efficacy:

REAC/TS provided raw data case report forms (CRFs) for FDA data entry and analysis. Overall, the CRFs reflected data collected on 646 patients with 685 exposure events. Of

these, 435 (63.5%) had primary inhalation exposure, 127 (18.5%) had primary wound exposure, 42 (10.%) had other routes, 81 (11.8%) had unknown or unreported routes of exposure. The majority of the patients (532, 77.7%) were exposed to Plutonium. The remainders were exposed to a range of radioactive elements (americium, curium, cesium, uranium, californium, neptunium and yttrium). Patients received at least one dose of either Ca-DTPA or Zn-DTPA. Of these for details of the database, demographics and analysis, Dr. Mathis' comprehensive review should be read. Several salient features of his review will be discussed in this memo.

Before the FDA data analysis began, it was determined that the 24-hour urine radiation elimination rate would be measured. The analyzed unit would be the EER (excretion enhancement ratio; i.e., the ratio of post-treatment to pre-treatment radiation). Higher EER values indicate greater radiation elimination. For patients that did not have a pre-treatment urine, the first available urine that was available 5 days after treatment was used as original value. For the analysis, patients had to have at least 1 day of post-treatment 24-hour urine data.

Based on the above, of the 646 patient case report forms, 18 met the pre-treatment and post treatment criteria and will be termed the core dataset. Three (3) additional patients met the first available urine criteria. The remaining 613 patients had either single dose without follow-up or unclear timing between dosing and follow-up data. In the 18 patient core dataset, all had Ca-DTPA as their first dose (10 by inhalation, 8 by intravenous injection). As shown on in Dr. Mathis' review, page 16 and reproduced in this memo in attachment 1, page 12), the mean EER for the IV route was 21.25 (SD =31.68, range = 0.45 – 80). For the IH route, the mean EER was 23.46 (SD=28.21; range =1.14 – 93.54, with one outlier of _____). Overall, there is consistent variability in both groups. Regardless of the route of administration, the urine rate of radiation elimination increased. This suggests that the product delivered by the inhaled route is bioavailable. Detailed PK data are not available to document the relationship of the inhaled and intravenous routes.

Route of administration:

Ca-DTPA and Zn-DTPA are provided in single 1-gram ampules. Typically, the drug was administered intravenously. The intravenous route has the obvious advantage of immediate systemic availability to begin elimination of the circulating contaminants. If given immediately, this route should limit the amount of contaminants that distribute to other tissues.

The literature and REAC/TS database identified patients that received other routes of administration; e.g., inhalation (via 1:1 saline dilution in a standard nebulizer), intramuscular injection, and as wash or infiltrate of the wound site.

- Inhalation: Ca-DTPA inhalation is administered as a 1:1 dilution with water or saline in a standard nebulization device. Overall, Ca-DTPA nebulization was given to 326 (28%) REAC/TS patients. Literature references indicate the inhaled route may be

selected in patients who were presumed to have only inhaled contamination; e.g., industrial workers exposed when the ventilation containment area was breached. Nebulization may remove pulmonary surface contaminants and, conceptually, decrease the systemic exposure. Confirmatory data for the decrease in systemic exposure or decrease in local pulmonary toxicity were not identified.

- Intravenous: The intravenous route was used in 293 REAC/TS patients
- Intramuscular: The intramuscular route was used in 8 REAC/TS patients). None of these were in the core dataset. These data are not sufficient to recommend this route.
- Wound wash or infiltration: The literature describes patients that received topical washing with chelators. None of the 18 patients with comprehensive data received a wound wash/infiltration. Data are not available to document systemic bioavailability. Likewise data are not available on the relationship of chelator topical decontamination in relationship to soap, water, and saline wash.

What this above information on the routes of administration suggests is that under emergency circumstances, a number of routes of administration may be plausible and necessary. However, data are not sufficient to recommend the intramuscular route or the topical wash.

Data are sufficient to recommend the intravenous route of administration and the primary route. It provides immediate systemic availability and provides the best chance of minimizing tissue uptake of the radiation.

For the inhalation route, data are less compelling but empirically based on the patients that responded to treatment. Thus, it is reasonable to support the inhalation route of administration for patients known to have only pulmonary exposure within a few hours. (For example, patients contaminated in a controlled industrial environment.) Labeling should note that this route is associated with respiratory/allergic adverse events. If systemic contamination is possible, the intravenous route should be used initially.

Note: During early investigation with prolonged co-administration of both the Ca-DTPA and Zn-DTPA there was increased depletion of essential metals and metalloproteinases. Thus, empirically, investigators began to use the current regimen of Ca-DTPA first followed by Zn-DTPA 24 hours later. It is conceivable that a one-day dose of both inhaled and intravenous Ca-DTPA may be able to provide both systemic and topical pulmonary chelation. However, at this time safety data are not sufficient to support this approach.

Zn-DTPA Maintenance: Within the REAC/TS database patients received various mixed treatment regimens. The basis for the drug selection is not evident in the CRFs. On page 21-24 of Dr. Mathis' review, examples of mixed regimens are presented. (These are reproduced in attachment 2 (pages 13-15) for ease of reference. The y-axis shows the amount of EER radiation in the 24-hour urine. The x-axis shows the date, the drug and

route of administration.) The graphic spikes represent a bolus in radiation elimination after each treatment. On page 13, case 495, shows the elimination results in a patient treated with 14 doses of Ca-DTPA followed by 11 doses of Zn-DTPA. Both regimens show a similar slopes in radiation elimination. On page 14, case 327 shows the results of a patient that received Zn-DTPA by both inhalation and intravenous injection. On page 15, case 27 shows the results of a patient contaminated with plutonium and americium. Treatment began with Ca-DTPA IV, then changed to Ca-DTPA IH, then to Zn-DTPA IV. Within patients the slope trends appear to be similar for all treatments.

Uranium and Neptunium: The review team recommended contraindication for treatment with Uranium and Neptunium. This recommendation was based on an animal study that showed that neptunium does not form a stable chelate with DTPA. The instability allowed free neptunium to circulate and deposit in the bone. The complex itself did not contribute to the deposition; instead the instability of the complex resulted in limited benefit. Hence, treatment is not contraindicated, but there may be limited effectiveness of Ca-DTPA or Zn-DTPA. The complex instability should be noted in labeling.

In the REAC/TS database there were 4 patients with Uranium exposure and 2 with neptunium exposure. Each had 1 dose of Ca or Zn-DTPA, however, there are not sufficient follow-up data to determine the chelation benefit. As per Dr. Mathis, in case 422, after uranium exposure, there was an increase in uranium elimination in the 1st 24 hours after Ca-DTPA nebulization treatment. (See attachment, page 16). Subsequent treatment is not recorded. Over the next 9 days, the elimination rate decreased. Such decrease is expected without repeat treatment. Thus, this one case suggests that there is the potential for DTPA chelation with uranium. Therefore, as discussed for neptunium, the use in uranium is not a contraindication.

Overall, in the REAC/TS database 62 patients received Zn-DTPA. Of the 18 patients in the core dataset, 6 patients had Zn-DTPA as part of their treatment regimen. But, none of these patients had the specific currently recommended regimen (i.e., only one loading dose with Ca-DTPA and the next day beginning Zn-DTPA). Regardless of drug, these data and the animal data, however, do demonstrate similarity in the maintenance radiation elimination rates. Also, as discussed below, Zn-DTPA has a better safety profile. Based on this the overall treatment experience in the REAC/TS database, Zn-DTPA is preferred for maintenance treatment. Patients should be treated until radiation is no longer detected in the urine or feces.

Safety

Animal data revealed that in rats after inhaled doses of Ca-DTPA 0.035 mmol/kg (0.2 x MHD) in 3 every other day doses there was transient vesicular emphysema sacrifice at 3 weeks. In another study in rats that received inhalation for 30 min/day for 5 days (56 mg/kg (x0.64 MHD BSA per day), pulmonary epithelia atypia was reported. These data suggest that in-patients prolonged inhaled Ca-DTPA may be associated with pulmonary toxicity.

Based on the REAC/TS database 646 patients were treated with at least one dose of either Ca-DTPA or Zn-DTPA. Of these, 632 received Ca-DTPA and 62 received Zn-DTPA. For the 632 patients that received Ca-DTPA, 326 patients were dosed by inhalation, 293 by intravenous injection, and 60 by other or unknown routes of administration. For the 62 patients received Zn-DTPA, 48 patients were dosed by inhalation, 18 intravenous injection, and 8 by other or unknown routes of administration². Most patients 416 (64%) received only one dose of DTPA (Ca-DTPA, n=393; Zn-DTPA n=23). The largest number of dosing treatments for Ca-DTPA was 338 and for Zn-DTPA was 574 doses over > 3 years. In the core dataset of 18 patients, the maximum number of doses was 17 for Ca-DTPA and 9 for Zn-DTPA.

Overall, the presence or absence of adverse events was recorded in 310/645 REAC/TS patients. Of these 18 (6.1%) had a reported event and 290 (93%) had a statement that adverse events did not occur (“No AE”). The following table identifies summarizes the types of adverse events in these 18 patients (derived from Dr. Mathis’ listings in Appendix A, page 32 of his review). Three patients had more than one adverse event.

Number of Adverse Events in Patients with Recorded Data ⁽¹⁾			
	Number of Patients (n)*		% of Total Patients with Recorded AE Data; (n = 310)
Total number of patients with at least one AE recorded	18		6.77
Type of event	Ca-DTPA	Zn-DTPA	
Headache	3	1	
Injection site pain	3		2.58
Cough paroxysm, wheezing	2		
Hives / itching	2		
Nausea, nausea and diarrhea	2		
Lightheadedness	1	1	
Chest pain	1		
Dermatitis/delayed beard growth	1		
Fatigue	1		
Metallic taste	1		
Rapid pulse	1		
Tenderness in bladder		1	
Recorded as “No AE”	290		93.9
Patient information not available = 376 / 645 (58%)			
(1) Adapted from Mathis listings in Appendix A, page 32 of his review			

² [Note: the sum of these patients is greater than the denominator because many patients received both drugs.]

Overall by drug and route, the number of events (not number of patients) are distributed as follows:

Number of Adverse Events by Drug and Route of Administration				
Ca-DTPA				Zn-DTPA
IV*	IH*	IM*	Unknown	IV
8	3	3	5	1
*IV = intravenous, IH = nebulized inhalation, IM = intramuscular				
For Ca-DTDPA:				
<ul style="list-style-type: none"> • The 2 patients with cough/wheeze/allergic events received the IH route. • The 3 patients with injection site pain had the IM route • The one patient with delayed dermatitis had 28 days of Ca-DTPA IV. • Lightheadedness and dizziness was reported in the patients that received both the IV and IH routes. 				
For both drugs				
<ul style="list-style-type: none"> • 1 patient received both drugs; the route and time relationships were not identified. 				

These results are consistent with the animal data and literature reports that suggest that the Ca-DTPA is associated with a higher adverse event rate. However, of the 17 events, the IV route is associated with most events. The IM route was associated with local injection site pain. The IH route is associated with allergic events. The most clinically significant events appear to be the allergic events. It is difficult to determine the exact rate of these occurrences. Of the 326 patients that received Ca-DTPA by inhalation, 2 (0.6%) had recorded cough/wheeze or anaphylaxis.

Laboratory events: Of the 231 patients with laboratory data, 131 patients had normal laboratory data, and 100 had at least one laboratory abnormality. The details are listed in Mathis' review (page 27 and page 32 attachment A). The abnormalities included urinalyses (hematuria, proteinuria, pyuria, glucosuria), electrolytes (potassium) metabolites (uricemia, hypoglycemia), and leukocytosis. These events were transient and data are not sufficient to allow for a comprehensive determination the relationship to the treatment, radiation toxicity or underlying disorders. However, most of the laboratory abnormalities reflect renal or urinary dysfunction. Both the radiation and DTPA are eliminated through the kidney. Whether these abnormalities reflect therapeutic drug responses, radiation toxicity, or underlying disorders can not be determined.

Vital signs: Overall, (as per Dr. Mathis' review page 28 and related attachments) vital signs were reported in 42 to 81 patients, depending upon the time point. Of these 4 had transient hypertension (i.e., 3 patients had an increase of 20-30 mmHg systolic during or just after infusion. Of these, one had a 10 mmHg increase in diastolic. The other patient had a transient 12 beats

DTPA should be used for the initial loading dose and Zn-DTPA for maintenance. Treatment should continue as long as there is measurable radiation in the urine.

There appears to be similar efficacy with Ca-DTPA by both the intravenous and inhalation loading doses. However, conceptually there may be alternative benefits based on the route of administration. The IH route is considered to topically chelate radioactive particles. When expectorated, this could decrease the amount of radiation available for systemic absorption. Likewise, it may decrease the likelihood of local pulmonary radiation fibrosis. Controlled studies are not available to confirm these hypotheses; however, empirical treatment with the IH route was given in 50% of patients in the total database and 55% of the core dataset.

The intravenous route is considered critical in multiple routes of administration when immediate systemic radiation exposure is expected. The goal of treatment in this case is to rapidly eliminate circulating radiation to prevent tissue deposition. Interestingly, the 24-hour urine radiation elimination data reveal comparable mean, median, SD, and range data for both routes of administration. The actual early time point data are not available.

Because of the possibility of acute respiratory allergic events associated with the IH route, the IV route is the preferred route of administration. However, the IH route may have additional benefit in patients who have known contamination through the inhaled route only and are within a few hours of contamination. Additionally, this route should be available to patients in whom vascular access is difficult (e.g., burns or other trauma). Therefore, the IH route should be included in labeling for selected patients. Warnings of respiratory adverse events should be prominent.

In approving Ca-DTPA and Zn-DTPA there are some uncertainties. Specifically, the dosing regimen are based largely on empiric development, clinical case studies, expected body size relationships in pediatrics, and the need to rapidly decontaminate patients while ensuring patient compliance. Specific data to establish linear contamination and dose requirements are not available. Likewise, the radiation principles that are included in the package insert, reflect commonly accepted emergency medicine approaches. They have not been tested in controlled clinical trials.

Radiologic emergencies may expose patients to contaminants from elements other than those tested. There are insufficient and inconsistent data on uranium and neptunium. The literature suggests that an unstable DTPA complex forms and thus, the expected elimination is uncertain. However, in REAC/TS database one patient with uranium contamination had evidence of increased elimination at 24 hours. Additional animal and, or in vitro studies are needed to evaluate the benefit in other radioactive elements.

Because of the limitations in the current database, ongoing drug development should include the following:

1. ~~_____~~ longitudinal follow-up of patients treated with Ca-DTPA or Zn-DTPA is needed to assist in determining how long patients should be treated. These data should be in the form of a patient registry that follows patients for life. This registry should be maintained and analyzed by the NDA holder.

2. ~~_____~~

3. ~~_____~~

4. ~~_____~~

5. ~~_____~~

ACTION: Anticipate approval of safety and efficacy database after demonstration of adequate chemistry, manufacturing controls and sterility assurance.

The results of the ongoing development items listed above are not needed before approval, but these should begin as soon as possible (i.e., before or after approval)

Attachment 1: Summary of Effective Elimination Ratio Data in the 18 patient core dataset.
 Reproduced from Dr. Mathis' table 6, page 16 of his review.

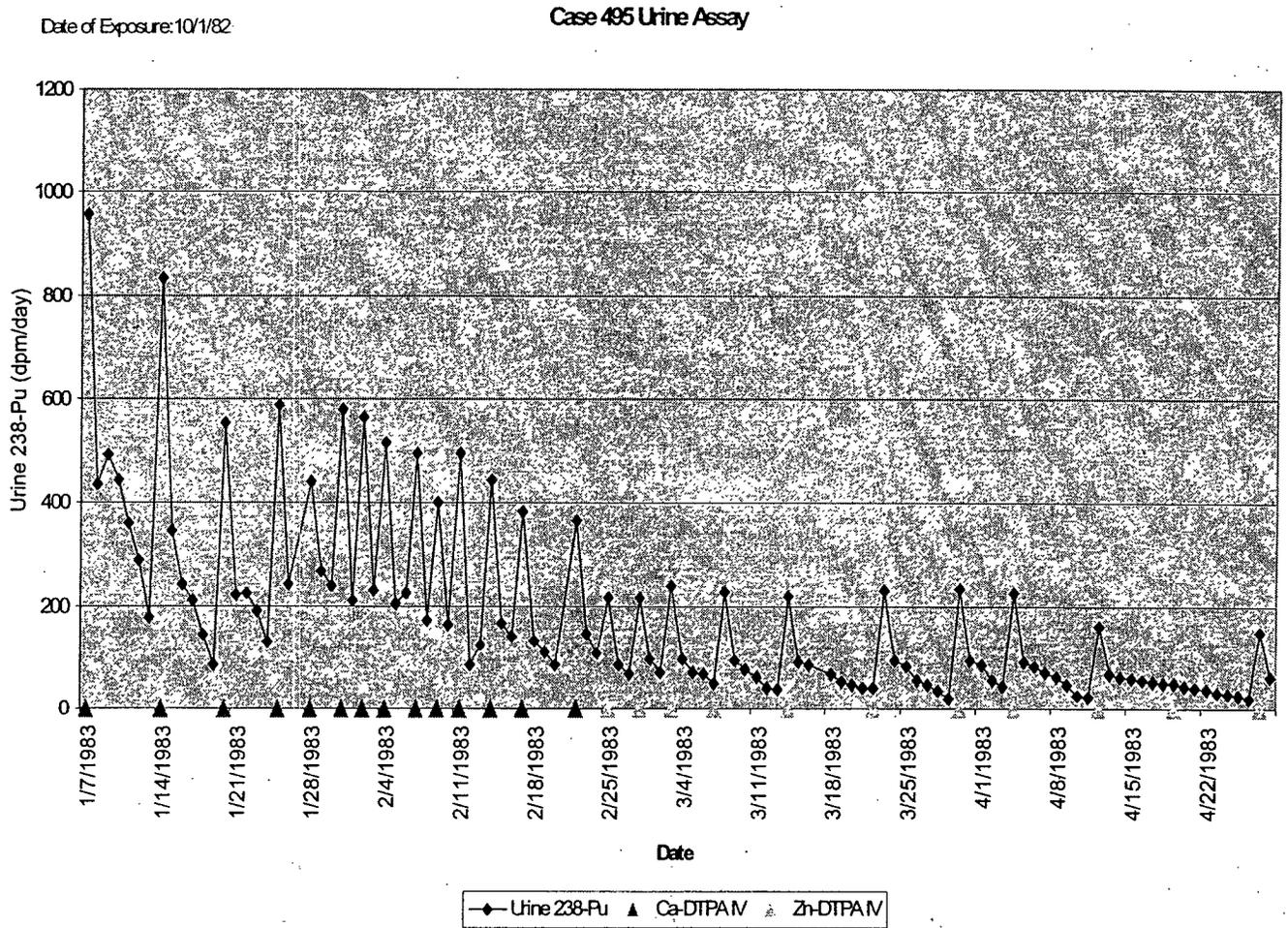
Urine Activity Ratio Calculations					
Case Number	Radionuclide(s)	First Chelator Dose	Urine Activity Prior to First Dose of Chelator Ψ	Urine Activity After first Dose of Chelator Φ	Ratio of Post to Pre Urine Activity (EEF)*
12	239-Pu	Ca-DTPA I.V.	7.58E-05 dpm/ml	7.09E-03 dpm/ml	93.54
	241-Am	Ca-DTPA I.V.	2.55E-04 dpm/ml	1.01E-01 dpm/ml	396.08
13	239-Pu	Ca-DTPA I.V.	6.37E-05 dpm/ml	9.52E-04 dpm/ml	14.94
	241-Am	Ca-DTPA I.V.	5.38E-04 dpm/ml	6.55E-03 dpm/ml	12.17
27	238-Pu	Ca-DTPA I.V.	2.63E-05 nCi/ml	1.96E-03 nCi/ml	74.52
	239-Pu	Ca-DTPA I.V.	2.63E-04 nCi/ml	1.64E-02 nCi/ml	8.37
	241-Am	Ca-DTPA I.V.	1.04E-02 nCi/ml	1.68E-02 nCi/ml	1.62
44	238,239-Pu	Ca-DTPA I.V.	20 dpm/L	32 dpm/L	1.6
261	239-Pu	Ca-DTPA Neb	2 dpm/1.5L	3 dpm/1.5L	1.5
	241-Am	Ca-DTPA Neb	0.6 dpm/1.5L	0.5 dpm/1.5L	0.83
263	238-Pu	Ca-DTPA Neb	0.2 dpm/day	5.3 dpm/day	26.5
264	238-Pu	Ca-DTPA Neb	0.4 dpm/day	7.7 dpm/day	19.25
265	238-Pu	Ca-DTPA Neb	0.2 dpm/day	16 dpm/day	80
327	238-Pu	Zn-DTPA Neb	7.1 dpm/day	320 dpm/day	45.07
495	238-Pu	Ca-DTPA I.V.	85 dpm/day	553 dpm/day	6.51
516	238-Pu	Ca-DTPA Neb	0.5 dpm/L	31 dpm/L	62.00
519	238-Pu	Ca-DTPA I.V.	0.5 dpm/L	6.4 dpm/L	12.8
568	238-Pu	Ca-DTPA I.V.	85 dpm/1.5L	553 dpm/1.5L	6.51
578	244-Cm	Ca-DTPA I.V.	0.7 dpm/1.5L	0.8 dpm/1.5L	1.14
621	238-Pu	Ca-DTPA Neb	3 dpm/1.5L	3.2 dpm/1.5L	1.07
622	239-Pu	Ca-DTPA Neb	0.1dpm/1.5L	3.6 dpm/1.5L	36.00
626	UNKNOWN	Ca-DTPA Neb	0.1dpm/1.5L	0.7 dpm/1.5L	7.00
669	238-Pu	Ca-DTPA Neb	4.4 dpm/1.5L	2.0 dpm/1.5L	0.45

Ψ dpm = decays per minute *EEF = Excretion Enhancement Factor

Summary Statistics for Ratio Data	
Mean	39.29
Median	10.27
SD	84.68
Range	0.45-396.08
N**	17
** Omits case 327	

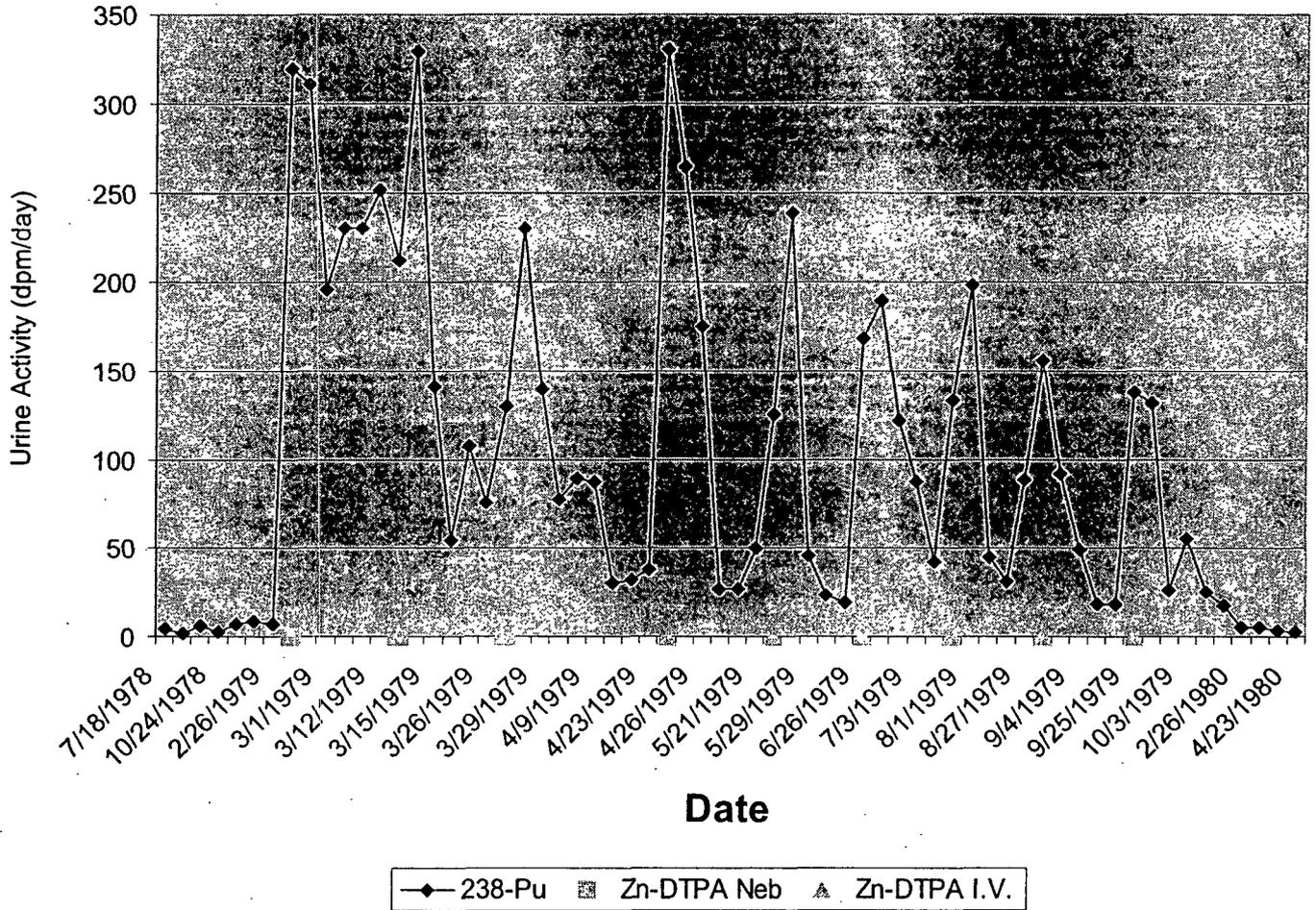
Attachment 2: Sample figures reproduced from Dr. Mathis' Review pages 21-24.

For each figure, the y-axis shows the amount of radiation per 24-hour urine. The x-axis shows the date, the treatment drug and route of administration.



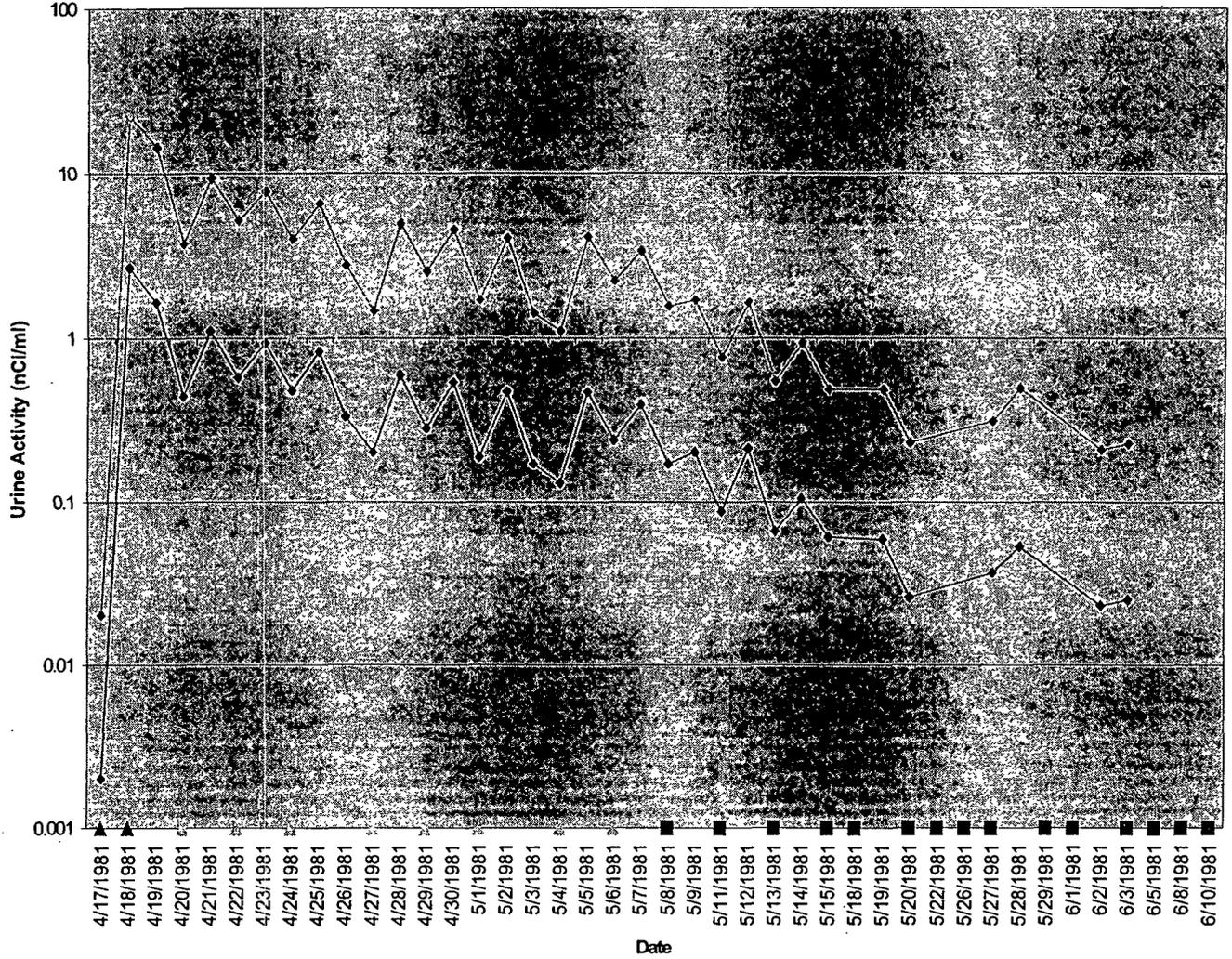
Date of Exposure: 4/28/77

Case 327 Urine Assay



Case 27 Urine Assay

Date of Exposure: 4/17/81



◆ 238-Pu ◆ 239-Pu ◆ 241-Am ▲ Ca-DTPA IV ■ Ca-DTPA Neb ▲ Zn-DTPA IV

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

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

/s/

Patricia Stewart
8/9/04 03:20:53 PM
CSO

Originally signed by Patricia Love, M.D. 1-27-03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDAs 21-749/21-751	Efficacy Supplement Type SE-	Supplement Number
Drugs: Pentetate calcium trisodium injection Pentetate zinc trisodium injection		Applicant: Hameln Pharmaceutical, GmbH
RPM: Patricia A. Stewart	HFD-160	Phone # 301-827-7496
<p>Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>() Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s): Federal Register /Vol. 68, No. 178/ Monday, September 15, 2003, page 53984, Docket No. 2003D-0399</p>	
❖ Application Classifications:		
• Review priority	() Standard (X) Priority	
• Chem class (NDAs only)	1P	
• Other (e.g., orphan, OTC)	Orphan	
❖ User Fee Goal Dates		
10/28/04		
❖ Special programs (indicate all that apply)		
(X) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2		
❖ User Fee Information		
• User Fee	() Paid UF ID number	
• User Fee waiver	(X) Small business (N21-751) () Public health () Barrier-to-Innovation () Other (specify)	
• User Fee exception	(X) Orphan designation (both) () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	() Yes (X) No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Orphan
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	8/10/04

General Information	
Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> Press Release <input checked="" type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	X 12/10/03
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Federal Register /Vol. 68, No. 178/ Monday, September 15, 2003, page 53984, Docket No. 2003D- 0399

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	X 7/30/04, 8/9/04, 8/11/04
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	X 8/10/04,
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X 8/10/04
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	X 8/6/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	X 8/11/04, 7/22/04
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	X 7/22/04
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	X 6/30/04
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	X 7/30/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).