Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO X

- Does the submission contain an accurate comprehensive index? YES X NO
- Was form 356h included with an authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? YES NO
- Is it an electronic CTD? YES NO X
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES NO X
- Exclusivity requested? YES, ___7____years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES X NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: NA

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) __12/10/03_____
  NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES X NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES X NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  NA YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
  If no, did applicant submit a complete environmental assessment? YES NO

If EA submitted, consulted to Nancy Sager (HFD-357)?	YES		NO
• Establishment Evaluation Request (EER) submitted to DMPQ?	YES	X	NO
• If a parenteral product, consulted to Microbiology Team (HFD-805)?	YES	X	NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: N/A

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). N/A

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO X

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO X

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO X

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  __X__ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES X NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    NA YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    NA YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES X NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    N/A IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES X NO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: April 21, 2004	**DESIRED COMPLETION DATE:** May 21, 2004	**ODS CONSULTS #:** 04-0142

TO: George Mills, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

THROUGH: Patricia Stewart
Project Manager
HFD-160

PRODUCT NAME: ~~~~ (Pentetate Zinc Trisodium Injection) 1 g/5 mL **NDA: 21-751**	**NDA SPONSOR:** Hameln Pharmaceuticals

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name ~~~~. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

2. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.

3. DDMAC finds the proprietary name ~~~~ acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 26, 2004

NDA # 21-751

NAME OF DRUG: ———
(Pentetate Zinc Trisoidum Injection) 1 g/5 mL

NDA HOLDER: Hameln Pharmaceuticals

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products, to review the proprietary name ——— regarding potential name confusion with other proprietary and established drug names. Labels and labeling have been submitted for review and comment.

PRODUCT INFORMATION

——— (pentetate zinc trisodium injection) is indicated for the treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. ——— therapy is recommended on day 2 of exposure with ———*** (pentetate calcium trisodium injection) injected on day 1. The recommended dose of ——— is 1 gram by slow intravenous push over a period of 3 to 4 minutes or by intravenous infusion diluted in 100 to 250 mL of D5W, Ringers Lactate or Normal Saline. ——— will be supplied in ampules containing 1 gram per 5 mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to ——— to a degree where potential confusion between drug names could occur

*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[4] An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written inpatient prescription studies and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name [redacted] Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three proprietary names as having the potential for confusion with [redacted] These products are listed in Table 1 (see below), along with the dosage forms and usual dosage.

2. DDMAC did not have concerns about the name [redacted] with regard to promotional claims.

Table 1
Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s), Strength	Usual dose*	Other**
[redacted]	Pentetate Calcium Trisodium Injection 1 g/5 mL	A single dose of 1 gram by slow intravenous push or intravenous infusion.	
Lipitor	Atorvastatin Tablets 10 mg, 20 mg, 40 mg, and 80 mg	10 mg to 80 mg given once daily.	LA
Dipentum	Olsalazine Capsules 250 mg	1 g per day in two divided doses.	SA
Timentin	Ticarcillin and Clavulanate Potassium Injection Solution 3 g/0.1 g per 100 mL Powder for Injection 3 g/0.1 g per vial	Gynecologic infections: 200 mg to 300 mg/kg every 4 to 6 hours intravenously for 10 to 14 days. Systemic and urinary tract infections: 3.1 g every 4 to 6 hours intravenously for 10 to 14 days.	LA,SA

* Frequently used, not all-inclusive.
** L/A (look-alike), S/A (sound-alike)

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs though the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The results from the [redacted] query identified one

[4] WWW location http://www.uspto.gov/main/trademarks.htm

additional drug name that has a strong orthographic similarity to [redacted]. This product is listed in Table 2 (see below), along with the dosage forms and usual dosage.

Table 2
Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name*	Established name, Dosage form(s), Strength	Usual dose*	Other**
[redacted]	Pentetate Calcium Trisodium Injection 1gg/5 mL	A single dose of 1 gram by slow intravenous push or intravenous infusion.	
Zarontin	Ethosuximide Capsules 250 mg Syrup 250 mg/5 mL	250 mg to 500 mg per day.	LA

* Frequently used, not all-inclusive.
** L/A (look-alike), S/A (sound-alike)

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for each proposed proprietary name to determine the degree of confusion of [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 121 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written for each name, each consisting of a combination of marketed and unapproved drug products and a prescription for [redacted] (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: [redacted]	[redacted] Give in clinic today.
Inpatient RX: Continue [redacted]	

2. Results:

One participant from the verbal prescription study interpreted ——— as the currently marketed drug product Dipentum while three participants from the verbal prescription study provided similar interpretations "Dipenten" and "Dipentin". Additionally, in the verbal prescription study, one participant interpreted the proposed name as "Litensin" which is similar to Lotensin while a second participated provided the interpretation Zytensin which is similar to the currently marketed Wytensin. The remaining responses were phonetic/misspelled interpretations of the proposed drug name. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name ——— the primary concerns raised were related to potential confusion with the currently marketed products Lipitor, Dipentum, Timentin and Zarontin.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that ——— could be confused with Dipentum. One participant from the verbal prescription study interpreted ——— as the currently marketed drug product Dipentum while three participants from the verbal prescription study provided similar phonetic interpretations "Dipenten" and "Dipentin". A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Although the interpretations "Litensin" and "Zytensin", gathered from the verbal prescription study, are similar to the currently marketed products "Lotensin" and "Wytensin" respectively, DMETS did not further review these names due differences in dosage form, route of administration, strength, usual dose and a lack of convincing sound-alike potential. Additionally, differences in product usage and patient monitoring for will further minimize the potential for confusion.

a. Lipitor was identified as having look-alike similarity to ——— Lipitor contains atorvastatin and is indicated for use as an antihyperlipidemic agent. The first letter "L" in Lipitor may look similar to the first letter ——— when scripted (see below). The middle letters "ipi" vs. "ipe" and "tor" vs. "ten" in Lipitor and ——— respectively, share similar scripted characteristics. Lipitor and ——— share numerically similar strengths and dose (10 mg vs. 1 g). The products differ in dosage form (oral vs. injection), route of administration (oral vs. intravenous), duration of use (chronic vs. 30 days) and monitoring. Patients on therapy are closely monitored upon initiation of treatment and periodically thereafter. Although the names look similar, differences in dosage form, product usage and patient monitoring will minimize the potential for confusion.

Lipitor ———

b. Dipentum and ——— may look similar when scripted and sound similar when spoken. Dipentum contains olsalazine sodium and is indicated for maintenance of remission of ulcerative colitis in patients intolerant of sulfasalazine. With exception to the first letter in

each name, Dipentum and [redacted] are phonetically and orthographically similar. However, the first letter in each name "D" vs. [redacted] helps to distinguish one name from the other. Dipentum and [redacted] differ in dosage form (capsules vs. injection), route of administration (oral vs. intravenous), strength (250 mg vs. 1 g), dose (500 mg vs. 1 g), dosing regimen (twice daily vs. once daily) and duration of use (chronic vs. 30 days). Patients on [redacted] therapy are closely monitored upon initiation of treatment and periodically thereafter. Given the lack of convincing sound-alike potential as well as differences in use, product characteristics and patient monitoring of [redacted] the potential for confusion between Dipentum and [redacted] is minimal.

c. Timentin and [redacted] were thought to have both look-alike and sound-alike potential. Timentin contains ticarcillin and clavulanate and is indicated for the treatment of infections caused by designated organisms. The "Ti" in Timentin versus the [redacted] have the potential to look similar as do the ending letters "entin" vs. [redacted] The letter "m" vs. "p" in Timentin and [redacted] respectively, are somewhat distinguishable if the down stroke of the letter "p" is prominent. Otherwise, the names are very similar in script. The products share an overlapping dosage form (injection) and route of administration (intravenous). Dipentum and [redacted] differ in duration of treatment (10 to 14 days vs. 30 days), usual dose and dosing regimen (every 4 to 6 hours vs. once daily). The usual dose of Dipentum is based on body weight whereas the usual dose of [redacted] is 1 gram. Additionally, patients on [redacted] therapy are closely monitored upon initiation of treatment and periodically thereafter. Given product differences as well as differences in use and patient monitoring of [redacted] the potential for confusion between Timentin and [redacted] is minimal.

Timentin [redacted]

d. [redacted] were identified as having the potential to look similar. [redacted] contains ethosuximide and is indicated for the management of petit mal seizures. [redacted] and [redacted] owe their look-alike proprieties to the shared letter [redacted] and similarly scripted ending "ontin" vs. [redacted] " However, the scripted letter "r" in [redacted] is distinguishable from the letter "p" in [redacted] The products differ in dosage form (capsules and syrup vs. injection), route of administration (oral vs. intravenous), strength and usual dose. Additionally, patients on [redacted] therapy are closely monitored upon initiation of treatment and periodically thereafter. Given product differences as well as differences in product usage and patient monitoring of [redacted] the potential for confusion between [redacted] and [redacted] is minimal.

[redacted]

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

In the review of the draft container label as well as carton and insert labeling of [redacted], DMETS has

attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. The package insert expresses the strength and dose in grams (1 g) yet the container label and carton labeling express the strength in milligrams (1000 mg). In order to avoid any misinterpretation, cite the strength and dose consistently on labels and labeling.

2. We note that there is no U.S. contact on the label. Since this product is manufactured in Europe, it would be difficult to contact the sponsor for information or to report product problems. Additionally, the place of business is required to include a city, state and zip code,

B. CONTAINER LABEL

1.

2.

3.

4.

C. CARTON LABELING

1.

2.

D. PACKAGE INSERT

III. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name ——— We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product.

C. DDMAC finds the proprietary name ——— acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Alina R. Mahmud, R.Ph.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Alina Mahmud
6/25/04 09:56:03 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/25/04 03:56:17 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: April 21, 2004	**DESIRED COMPLETION DATE:** May 21, 2004	**ODS CONSULTS #:** 04-0141

TO: George Mills, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

THROUGH: Patricia Stewart
Project Manager
HFD-160

PRODUCT NAME: ~~~~ (Pentetate Calcium Trisodium Injection) 1 g/5 mL **NDA: 21-749**	**NDA SPONSOR:** Hameln Pharmaceuticals

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

RECOMMENDATIONS:

1. DMETS has does not recommend the use of the proprietary name ~~~~
2. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.
3. DDMAC finds the proprietary name ~~~~ acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 26, 2004

NDA # 21-749

NAME OF DRUG: [redacted]
(Pentetate Calcium Trisoidum Injection) 1g/5 mL

NDA HOLDER: Hameln Pharmaceuticals

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products, to review the proprietary name [redacted] regarding potential name confusion with other proprietary and established drug names. Labels and labeling have been submitted for review and comment.

PRODUCT INFORMATION

[redacted] (pentetate calcium trisodium injection) is indicated for the treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. The recommended dose on the first day is 1 gram loaded intravenously or by inhalation. A maintenance dose on the second day with Zipentin*** is recommended. [redacted] will be supplied in ampules containing 1 gram per 5 mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to ' [redacted] ' to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

and Trademark Office's Text and Image Database was also conducted.[4] An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written inpatient prescription studies and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name ——— Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three proprietary names as having the potential for confusion with ——— These products are listed in Table 1 (see below), along with the dosage forms and usual dosage.

2. DDMAC did not have concerns about the name ——— with regard to promotional claims.

Table 1
Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
———	Pentetate Calcium Trisodium Injection 1gm/5 mL	A single dose of 1 gram intravenously or by inhalation	N/A
Cogentin	Benztropine Tablets 0.5 mg, 1 mg, and 2 mg Injection: 1 mg/mL	Parkinsons: 1 to 2 mg per day Drug Induced Extrapyramidal disorder: 1 to 4 mg per day.	LA
Cenestin	Synthetic Conjugated Estrogens Tablets 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg	0.625 to 1.25 mg once daily.	LA
Capoten	Captopril Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg	25 to 50 mg two to three times daily.	LA,SA

* Frequently used, not all-inclusive.
** L/A (look-alike), S/A (sound-alike)

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs though the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The results from the ——— query did not indicate any additional product names that had strong phonetic or orthographic similarities to ———

[4] WWW location http://www.uspto.gov/main/trademarks.htm

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for each proposed proprietary name to determine the degree of confusion of [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 121 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written for each name, each consisting of a combination of marketed and unapproved drug products and a prescription for [redacted] (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: [redacted] to be given in clinic today #1	[redacted] Give in clinic today.
Inpatient RX: [redacted]	

2. Results:

Four participants from the outpatient prescription study provided the interpretation "Capoten" which is currently marketed drug product. The remaining responses were phonetic/misspelled interpretations of the proposed drug name. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name [redacted] the primary concerns raised were related to potential confusion with the currently marketed products Cogentin, Capoten and Cenestin.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that [redacted] could be confused with Capoten. Four respondents misinterpreted the name as Capoten in the written outpatient prescription study. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

a. Capoten was identified as having look-alike and sound-alike similarity to [redacted]. Capoten contains Captopril and is indicated for use in the treatment of hypertension, heart failure, left ventricular dysfunction post myocardial infarction and diabetic neuropathy. Capoten and [redacted] begin with the letters [redacted]. The middle of the names differ (o vs. en), however this difference is virtually indistinguishable in script and sound. Capoten and [redacted] differ in dosage form, dose, and dosing frequency. The drug products share an overlapping route of administration (oral) and numerically similar strengths (100 mg vs.1000 mg). Despite the limited use of [redacted] as a counter terrorism product which will most likely be stored separate in specialized pharmacies until notified by public health officials, DMETS believes that errors and confusion may arise between [redacted] and Capoten during this time. For example, during a crisis requiring [redacted] orders for either drug product may be delayed or incorrectly dispensed due to the similarity of the drug product characteristics and name.

b. Cogentin and [redacted] may look similar when scripted. Cogentin contains benztropine and is indicated for use as an adjunct in the therapy of all forms of parkinsonism. Cogentin may also be used in the control of extrapyramidal disorders. Cogentin and [redacted] are identical in script as they begin with the letter "C", share the similarly scripted letters [redacted] and [redacted]. The drug products share an overlapping dosage form (injection), route of administration (intravenously), and dosing frequency (once per day). The products also share similar numerals in their strengths (1 mg vs. 1g) and daily dose (1 mg vs. 1 g). Although the dosage units differ (mg vs. g), this minor difference can easily be overlooked. Despite the limited use of [redacted] as a counter terrorism product which will most likely e stored separate in specialized pharmacies until notified by public health officials, DMETS believes that errors and confusion may arise between [redacted] and Cogentin during this time. For example, during a crisis requiring [redacted] orders for either drug product may be delayed or incorrectly dispensed due to the similarity of the drug product characteristics and name.

c. Cenestin and [redacted] may look similar when scripted. Cenestin contains synthetic conjugated estrogens and is indicated for use in menopause and vulvar or vaginal atrophy. Cenestin and [redacted] begin with the letter "C" and end with the similar endings "tin" vs. [redacted] Additionally, the names appear similar if the down stroke of the letter "p" in [redacted] is not prominent. The letter "s" in Cenestin may also look similar to the letter "n" when [redacted] is scripted (see below). The drug products differ in dosage form (tablets vs. injection), strength, and dose. Given these differences, the likelihood for confusion between Cenestin and [redacted] is reduced.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

In the review of the draft container label as well as carton and insert labeling of [redacted] DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. The package insert expresses the strength and dose in grams (1 g) yet the container label and carton labeling express the strength in milligrams (1000 mg). In order to avoid any misinterpretation, cite the strength and dose consistently on labels and labeling.

2. We note that there is no U.S. contact on the label. Since this product is manufactured in Europe, it would be difficult to contact the sponsor for information or product problems. Additionally, the place of business is required to include a city, state and zip code,

B. CONTAINER LABEL

1.

2. [redacted]

3. [redacted]

4.

C. CARTON LABELING

1. [redacted]

2.

D. PACKAGE INSERT

1.

2. [redacted]

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name (———)

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product.

C. DDMAC finds the proprietary name ——— acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Alina R. Mahmud, R.Ph.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Alina Mahmud
6/4/04 02:06:27 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/4/04 02:09:52 PM
DRUG SAFETY OFFICE REVIEWER

hameln pharmaceuticals gmbh
PO Box 10 08 63, 31758 Hameln, Germany
Langes Feld 13, 31789 Hameln, Germany
http://www.hameln-pharmaceuticals.com

14 May 2004

NDA 21-749 –
Ca-DTPA (Pentetate Calcium Trisodium injection)

Application under 21 CFR § 25
Claim for Categorical Exclusion

hameln pharmaceuticals gmbh is claiming a categorical exclusion from requirements that it conduct an environmental assessment. hameln pharmaceuticals gmbh claims the exclusion under 21 CFR 25.31(b), which states that approval will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

To the applicants knowledge extraordinary circumstances indicating that the approval of this application may significantly affect the quality of the human environment do not exist.

Dr. Mathias Dewald
Head of Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-751

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

Dear Ms. Ribbans:

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:	——— Zn-DTPA (pentetate zinc trisodium injection)
Review Priority Classification:	Priority (P)
Date of Application:	April 1, 2004
Receipt Date of User Fees:	April 28, 2004
Our Reference Number:	NDA 21-751

This application was considered incomplete and was not accepted for filing because all fees owed for this application, products, establishments, or previous applications were not paid. Subsequently, we received a letter granting orphan-drug designation dated April 28, 2004 exempting the user fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the above 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 June 28, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 28, 2004.

Under 21 CFR 314.102(c), 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 ultimate approvability of the application. Alternatively, you may choose to receive 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 Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Kyong Kang, PharmD
Chief, Project Management Staff
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Kyong Kang
4/29/04 09:12:33 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-749

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

Dear Ms. Ribbans:

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:	——— Ca-DTPA (pentetate calcium trisodium injection)
Review Priority Classification:	Priority (P)
Date of Application:	April 5, 2004
Receipt Date of User Fees:	April 28, 2004
Our Reference Number:	NDA 21-749

This application was considered incomplete and was not accepted for filing because all fees owed for this application, products, establishments, or previous applications were not paid. Subsequently, we received a letter granting orphan-drug designation dated April 28, 2004 exempting the user fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the above 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 June 28, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 28, 2004.

Under 21 CFR 314.102(c), 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 ultimate approvability of the application. Alternatively, you may choose to receive 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 Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Kyong Kang, PharmD
Chief, Project Management Staff
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Kyong Kang
4/29/04 09:13:44 AM

COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

April 28, 2004

B & H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, NJ 08876

Attention: Elizabeth N. Dupras
Associate Project Manager

Re: Designation Request # 04-1868

Dear Ms. Dupras:

Reference is made to your request, submitted on behalf of Hameln Pharmaceuticals gmbh, for orphan-drug designation dated March 22, 2004, of diethylenetriaminepentaacetic acid (DPTA) for the treatment of patient known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. Reference is made to our acknowledgement letter dated April 7, 2004.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan drug designation of diethylenetriaminepentaacetic acid is granted for *treatment of known or suspected internal contamination with plutonium, americium or curium.* Please be advised that it is diethylenetriaminepentaacetic acid and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

Hameln Pharmaceutical gmbh

If you need further assistance in the clinical development of your drug, please feel free to contact Henry H. Startzman III, M.D., at (301) 827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Hameln Pharmaceutical gmbh

cc:

HF-35/OP File # 04-1802
HF-35/Chron
HF-35/HStartzman
JFritsch 4/28/04
APPROVAL

MEMORANDUM OF TELECON

DATE: April 27, 2004

APPLICATION NUMBER: NDA 21-751, Zn-DTPA (pentetate zinc trisodium)
NDA 21-749, Ca-DTPA (pentetate calcium trisodium)

BETWEEN:

Name:
Hameln Pharmaceuticals gmbh
Dr. Mathias Dewald, Head of Regulatory Affairs
Britta Borchard, Head of Pharmaceutical Development
Arne Brechmann, Regulatory Affairs Manager
Dr. Kim Goldenstein, Regulatory Affairs Team Leader

B&H Consulting Services, Inc.
Elizabeth Dupras, Associate Project Manager
Stanley Rodgers, Senior Project Manager

Phone: 888-476-3762 #470316
Representing: Hameln Pharmaceuticals gmbh

AND

Name:
FDA:
Eric Duffy, Ph.D, Director of New Drug Chemistry II
Eldon Leutzinger, Ph.D., Chemistry Team Leader
Ravindra kasliwal, Ph.D., Chemistry Reviewer
Patricia A. Stewart, Regulatory Health Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: The meeting request dated April 20, 2004 from Hameln Pharmaceuticals to discuss the Information Requests faxed to Hameln April 16, 21 and 22, 2004 by the FDA chemistry reviewer.

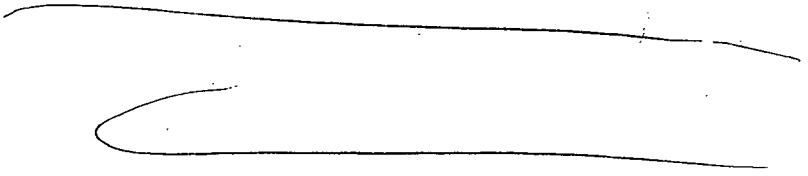
DISCUSSION:

Following brief introduction of all the participants, the teleconference began with discussion/clarification of the comments faxed by the Agency and Hameln's proposed responses. The comments that the FDA chemistry reviewer faxed are in **bold**.

April 16, 2004 fax:

1. **Provide a retest date for pentetic acid.**

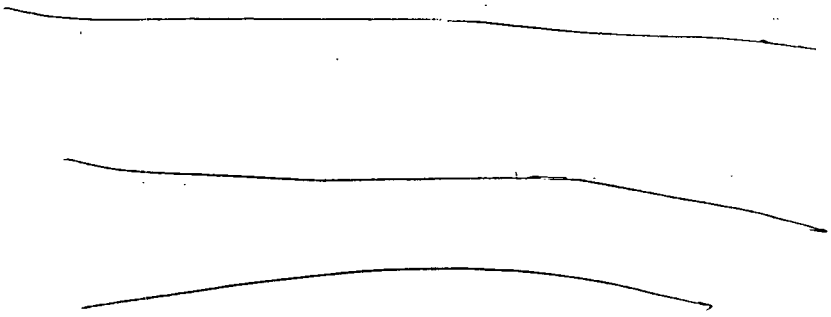
2. **Do you have any evidence that your manufacturing process yields pentetate zinc (or calcium) trisodium from pentetic acid, ZnO and NaOH under the conditions of manufacture? Describe how do you intend to assure the identity and quality of the pentetate zinc (or calcium) trisodium in manufactured batches of the drug product?**



<u>April 21, 2004 fax:</u>

3. **You are performing the content uniformity test on DTPA (apparently DTPA assay). Since this is a solution product, we recommend that the content uniformity should either be performed on the basis of weight variation or fill volume. Provide appropriately amended content uniformity test procedure and the acceptance criteria.**

4.



5. **We recommend that an identity test for Calcium (or Zinc)in the finished drug product should also be performed. Provided updated finished product specifications that include this test.**

Hameln will perform the [redacted] test to confirm identity.

A typographical error will be corrected to state the [redacted] method will be used for the assay.

April 22, 2004 fax:

1. **Please submit the drug product stability data. In addition to the data from formal stability studies currently underway, you may also send us supporting stability data from any other developmental batches / literature, etc.**

The [redacted] stability data should be available in [redacted] and Hameln will provide the data as soon as it is available. Hameln will also provide the stability data on [redacted] development batches and compatibility data as soon as possible. An amendment is needed to include a post approval stability protocol. The last paragraph in the NDA, section 3.2 P.8.2 needs to be amended to indicate that the after approval the expiry will be extended beyond the approved NDA expiration dating periods instead of the current [redacted] period.

2. **Your claim for categorical exclusion from the preparation from EA statement under 21 CFR 25.31(a) is not justified since this a new drug product and its indicated use may increase the use of the active moiety. We recommend that you evaluate and submit a claim for categorical exclusion from the preparation of EA under 21CFR 25.31 (b) or under 21 CFR 25.31 (c).**

The FDA clarified that the EA statement under 21 CFR 25.31(a) was not acceptable and suggested Hameln submit a categorical exclusion claim under 25.31 (b) or (c).

4. [redacted]

Additional discussion points:

1. The PDUFA user fee dates have been changed to reflect a new PDUFA clock starting date based on the date of the letter granting orphan product designation since the user fees were not received with in 5 days of receiving the applications. The new PDUFA user fee goal date will be October 28, 2004.

2. The FDA inquired about the timeline with regards to readiness for the inspections. Hameln responded that they had initially proposed the first week in [redacted] to Linda Adams, the FDA inspection coordinator, but now were looking at [redacted] The Agency indicated that they would like to see the inspections scheduled at the earliest possible date and would try to facilitate the process. Hameln will inform the project manager of the earliest date that they will be ready for inspection and provide the name of the contact person at Merck KGaA.

Minutes recorded by Patricia A. Stewart, Regulatory Project Manager

---

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/s/

Patricia Stewart
5/7/04 05:13:22 PM

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 22, 2004

BACKGROUND: The Agency did a review of literature and analyzed the REAC/TS database and published the findings of safety and efficacy in the Federal Register /Vol. 68, No. 178/ Monday, September 15, 2003, page 53984, Docket No. 2003D-0399 and encouraged manufacturers to submit NDAs.

ATTENDEES: Patricia Stewart, Eldon Leutzinger, Eric Duffy, Ravi Kasliwal, Julie Beitz, Sally Loewke

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	N/A
Secondary Medical:	
Statistical:	N/A
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	Ravi Kasliwal
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	Brian Riley
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	Patricia Stewart
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL N/A FILE _____ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A _____ FILE _____ REFUSE TO FILE _____

STATISTICS N/A FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS N/A FILE _____ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE _____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __X____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO X
- Microbiology YES X NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__X_____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Regulatory Project Manager, HFD-

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/s/

Patricia Stewart
4/26/04 05:17:02 PM
CSO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 22, 2004

BACKGROUND: The Agency did a review of literature and analyzed the REAC/TS database and published the findings of safety and efficacy in the Federal Register /Vol. 68, No. 178/ Monday, September 15, 2003, page 53984, Docket No. 2003D-0399 and encouraged manufacturers to submit NDAs.

ATTENDEES: Patricia Stewart, Eldon Leutzinger, Eric Duffy, Ravi Kasliwal, Julie Beitz, Sally Loewke

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	N/A
Secondary Medical:	
Statistical:	N/A
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	Ravi Kasliwal
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	Brian Riley
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	Patricia Stewart
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL N/A FILE _____ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A _____ FILE _____ REFUSE TO FILE _____

STATISTICS N/A FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS N/A FILE _____ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE _____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __X____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO X
- Microbiology YES X NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__X_____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Regulatory Project Manager, HFD-

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/s/

Patricia Stewart
4/26/04 05:18:09 PM
CSO

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

6 Number of Pages (including cover sheet) **Date**: April 21, 2004

To: Beth Dupras

Fax Number: 908-704-1693 **Voice Number**: 908-704-1691 X-223

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7496

Message: Request for Information from Hemeln NDAs 21-749 and 21-751 Ca & Zn-DTPA

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.
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.

NDA 21-749 (——— ™ Injection)

Date: 20-Apr-2004

Request for information:

1. ———————————————————————

2. *Clarify whether Hameln or the respective excipient manufacturer performs the release testing for each excipient as per their respective USP or NF monograph? What are Hameln procedures for accepting each excipient?*

3. *You are performing the content uniformity test on DTPA (apparently DTPA assay). Since this is a solution product, we recommend that the content uniformity should either be performed on the basis of weight variation or fill volume. Provide appropriately amended content uniformity test procedure and the acceptance criteria.*

4. *The limit of ——————— in the finished product is high and should be significantly reduced. Do you have any analytical data concerning the amount of ——— found in the batches? Provided ——— specifications based on the actual data/ significantly reduced acceptance criteria.*

5. *We recommend that an identity test for Calcium in the finished drug product should also be performed. Provided updated finished product specifications that include this test.*

6. *You did not provide a sample testing plan, i.e., did not indicate how many ampoules will be used for each test attribute. Provide a tabular sampling plan.*

7. *While the COA for the container closure system (ampoule) does indicate that the test for dimensional conformance, including the external and stem diameter, and test for forced required for ——— the ampoule was performed, it is not clear to us whether these tests will be routinely performed for each lot release. Please clarify that these tests as well as the tests listed in the submitted COA for the ampoules are performed routinely to release each lot for use in production.*

NDA 21-751 (——— \™ Injection)

Date: 20-Apr-2004

Request for information:

3. ———————————————————

4. *Clarify whether Hameln or the respective excipient manufacturer performs the release testing for each excipient as per their respective USP or NF monograph? What are Hameln procedures for accepting each excipient?*

3. *You are performing the content uniformity test on DTPA (apparently DTPA assay). Since this is a solution product, we recommend that the content uniformity should either be performed on the basis of weight variation or fill volume. Provide appropriately amended content uniformity test procedure and the acceptance criteria.*

4. *The limit of ——————— in the finished product is high and should be significantly reduced. Do you have any analytical data concerning the amount of ——— found in the batches? Provided ——— specifications based on the actual data/ significantly reduced acceptance criteria.*

5. *We recommend that an identity test for zinc in the finished drug product should also be performed. Provided updated finished product specifications that include this test.*

7. *You did not provide a sample testing plan, i.e., did not indicate how many ampoules will be used for each test attribute. Provide a tabular sampling plan.*

7. *While the COA for the container closure system (ampoule) does indicate that the test for dimensional conformance, including the external and stem diameter, and test for forced required for ——— the ampoule was performed, it is not clear to us whether these tests will be routinely performed for each lot release. Please clarify that these tests as well as the tests listed in the submitted COA for the ampoules are performed routinely to release each lot for use in production.*

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/s/

Patricia Stewart
4/21/04 11:36:08 AM

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

3 Number of Pages (including cover sheet) **Date**: April 16, 2004

To: Beth Dupras

Fax Number: 908-704-1693 **Voice Number**: 908-704-1691 X-223

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7496

Message: Request for Information from Hemeln NDAs 21-749 and 21-751 Ca & Zn-DTPA

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

NDA 21-751
Zn-DTPA

Date: 14-Apr-2004

REQUEST FOR INFORMATION:

1. Provide a retest date for pentetic acid.

2. Do you have any evidence that your manufacturing process yields pentetate zinc trisodium from pentetic acid, ZnO and NaOH under the conditions of manufacture? Describe how do you intend to assure the identity and quality of the pentetate zinc trisodium in manufactured batches of the drug product?