Guidance for Industry

Calcium DTPA and Zinc DTPA Drug Products — Submitting a New Drug Application

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2004
Clinical Medical
Revision 1

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist manufacturers wishing to submit new drug applications (NDAs) for pentetate calcium trisodium (Ca-DTPA) and pentetate zinc trisodium (Zn-DTPA) drug products for the treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium. In the *Federal Register* of September 15, 2003 (68 FR 53984), we announced the availability of this guidance, explained in detail our findings regarding safety and effectiveness, and included a list of citations to the literature on which we partially based those findings. Draft product labeling was prepared for Ca-DTPA supplied as 1 g in a 5 mL sterile aqueous solution for administration either by inhalation (with a 1:1 dilution with saline and delivered by nebulization) or intravenous injection. Draft product labeling was also prepared for Zn-DTPA supplied as 1 g in a 5 mL sterile aqueous solution for intravenous injection.

On August 11, 2004, we revised the draft product labeling for Ca-DTPA and Zn-DTPA to incorporate information considered from additional literature citations and other available clinical data. We are revising this guidance to explain our labeling revisions. These labeling revisions reflect our current thinking on (1) routes of administration, (2) duration of therapy, and (3) safety risks reported in patients with severe hemochromatosis who received four times the recommended daily dose of Ca-DTPA by intramuscular injection.

[1] This document was developed in the Division of Medical Imaging and Radiopharmaceutical Drug Products in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in our guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Diethylenetriaminepentaacetate (DTPA) is a ligand that chelates certain transuranium elements. The calcium salt of DTPA is known as pentetate calcium trisodium and is referred to as Ca-DTPA.[2] The zinc salt of DTPA is known as pentetate zinc trisodium and is referred to as Zn-DTPA. For several decades, Ca-DTPA and Zn-DTPA have been used investigationally to enhance the excretion of transuranium elements from the body by means of ion exchange, chelation, and, ultimately, excretion through the urine. The calcium or zinc ions of the Ca-DTPA and Zn-DTPA drugs are readily exchanged for the transuranium elements, and the transuranium-DTPA complex is rapidly excreted in the urine.

Ca-DTPA and Zn-DTPA in sterile aqueous solution have been used under investigational new drug applications (INDs) held by the Radiation Emergency Assistance Center/Training Site (REAC/TS). 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 internal contamination resulting from nuclear power or other industrial accidents.

REAC/TS has retained the medical case reports on 646 individuals treated with Ca-DTPA and Zn-DTPA for radiation contamination during the last 40 years. Data from bioassays measuring urinary radioactive elimination were available for 286 individuals. Of these, 18 had matched pre- and post-chelation therapy urine bioassay results and are considered the *efficacy cases*. To facilitate the development and ultimate approval of Ca-DTPA and Zn-DTPA drug products, we received permission to obtain and review the medical reports on the individuals included in the REAC/TS database. We also reviewed the related available published literature.

After reviewing the REAC/TS database and the published literature, we have concluded that Ca-DPTA and Zn-DTPA drug products, when produced under conditions specified in approved

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[2] For purposes of this notice Ca-DTPA refers only to pentetate calcium trisodium, which has an empirical formula of $Na_3CaC_{14}H_{18}N_3O_{10}$ and the Chemical Abstracts Service (CAS) registry number 12111-24-9. Zn-DTPA refers only to pentetate zinc trisodium, which has an empirical formula of $Na_3ZnC_{14}H_{18}N_3O_{10}$ and the CAS registry number 125833-02-5.

NDAs, can be found to be safe and effective for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination.[3]

III. NDAs SUBMITTED FOR Ca-DTPA AND Zn-DTPA DRUG PRODUCTS

A. Types of NDAs for Ca-DTPA and Zn-DTPA

An NDA for a Ca-DTPA or Zn-DTPA drug product may be either:

- a 505(b)(2) application, which is an NDA in which you rely for approval on studies that you did not conduct, that were not conducted for you, or for which you do not have a right of reference (described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)(2))

or

- a 505(b)(1) application, an NDA that relies exclusively on studies that you conducted, that were conducted for you, or for which you have a right of reference (submitted under section 505(b)(1) of the Act)

After an NDA for a Ca-DTPA or Zn-DTPA drug product has been approved, abbreviated new drug applications (ANDAs) that refer to the approved Ca-DTPA or a Zn-DTPA drug product can be submitted and approved (see 21 CFR part 314, subpart C). Because ANDAs cannot be submitted until an NDA is approved, we primarily discuss 505(b)(1) and 505(b)(2) applications in this guidance.

1. Submitting 505(b)(2) Applications

If you rely on published literature (including the literature we have already reviewed, see the *Federal Register* notice announcing the availability of this guidance) and our evaluation of the REAC/TS data for approval of your application, your NDA will be a 505(b)(2) application.

A 505(b)(2) application could be considered the more direct and, probably, the quickest approach to gaining approval of an NDA for a Ca-DTPA or a Zn-DTPA drug product. A 505(b)(2) application could rely entirely on the published literature that we have already reviewed and our evaluation of the REAC/TS data for the clinical data required for approval of

[3] It is likely that other transuranium elements (e.g., berkelium and californium) could be eliminated by Ca-DTPA or Zn-DTPA. However, there are no clinical effectiveness data to support this recommendation. Elements past americium are very rarely seen in clinical settings and beyond californium, radioactive decay half-lives are so short that accumulation of macroscopic amounts of these materials would not be possible.

an NDA (see the *Federal Register* notice announcing the availability of this guidance). If you took this approach to approval, you would not need to submit copies or summaries of the reports we have cited. The clinical sections of your NDA would only have to cite the *Federal Register* notice, the listed reports we relied on in making our determination of safety and effectiveness. However since the *Federal Register* notice was published, we have become aware of additional published reports of studies regarding Ca-DTPA and Zn-DTPA. You should submit copies of these studies as part of your NDAs. You should contact the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7510 for additional information on submitting reports of these additional studies.

2. Submitting 505(b)(1) Applications

As mentioned above, you can also submit a 505(b)(1) application. This type of NDA relies only on studies that you have conducted, that were conducted for you, or for which you have a right of reference. These NDAs are sometimes called *full NDAs* and are the type of application most frequently used to gain approval for drug products whose active ingredient is not in a previously approved drug product.

We recognize the importance of continuing the development of products, such as Ca-DTPA and Zn-DTPA drug products, to treat or prevent radiation and other types of toxicity. We also recognize that you might not be able to conduct definitive human efficacy studies for Ca-DTPA and Zn-DTPA because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic substance, and new field trials to study Ca-DTPA and Zn-DTPA efficacy after an accidental or hostile exposure to a transuranium radioactive element might be infeasible. We encourage persons who wish to submit 505(b)(1) applications for Ca-DTPA and Zn-DTPA drug products to contact us, before starting any studies, to discuss the development of data to establish safety and effectiveness.

B. Content of NDAs for Ca-DTPA and Zn-DTPA

NDAs submitted to the Agency for approval must include chemistry, manufacturing, and controls information. They must also contain labeling and the appropriate patent information. These requirements are contained primarily in § 314.50.

1. Chemistry, Manufacturing, and Controls Information

In addition to the clinical data discussed in the *Federal Register* notice announcing the availability of this guidance, your NDA must also include a complete chemistry, manufacturing, and controls section describing the composition, manufacture, and specification of the drug substance and drug product (section 355(b)(1) of the Act and § 314.50). You also must meet all other applicable requirements regarding the content of an NDA (section 355(b)(1) of the Act and § 314.50).

2. Labeling for Ca-DTPA and Zn-DTPA

On August 11, 2004, we revised the draft labeling for 1 g of Ca-DTPA in 5 mL of sterile aqueous solution for intravenous or inhalation administration and 1 g of Zn-DTPA in 5 mL of sterile aqueous solution for intravenous administration. We considered information from additional literature citations and other available clinical data and incorporated new recommendations into the draft product labeling for Ca-DTPA and Zn-DTPA, which may be summarized as follows:

- The inhalation route of administration would benefit adults whose internal contamination is by inhalation only. We revised the labeling for Zn-DTPA to add inhalation as a route of administration.[4] FDA believes that availability of Zn-DTPA by the inhalation route will be of particular benefit to the pregnant woman for whom Zn-DTPA is the preferred chelator. The safety and effectiveness of Ca-DTPA and Zn-DTPA administered by inhalation has not been established for pediatric patients.

- We revised the Ca-DTPA and Zn-DTPA labeling to state that the safety and effectiveness of the intramuscular route of administration have not been established.[5]

- We revised the Ca-DTPA and Zn-DTPA labeling to recommend that the duration of chelation therapy depends on the amount of internal radioactive contamination and the individual's response to therapy.[6]

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[4] In the REAC/TS database, an efficacy case internally contaminated with plutonium received three doses of nebulized Zn-DTPA 1 g each, followed by 6 doses of intravenous Zn-DTPA 1 g. Urinary excretion of plutonium after the first nebulized dose of Zn-DTPA was increased by a factor of 45. No pulmonary adverse events were reported for this individual or for 17 other individuals treated with a total of 99 doses of Zn-DTPA via nebulization in the REAC/TS database. The effectiveness of Zn-DTPA by inhalation is supported by the results of a preclinical study in rodents contaminated with aerosolized plutonium and americium as described in Stather, JW, GN Stradling, SA Gray, J Moody, and A Hodgson, "Use of DTPA for Increasing the Rate of elimination of Plutonium-238 and Americium-241 from Rodents After their Inhalation as Nitrates," *Human Toxicology*, 4:573-582, 1985.

[5] The intramuscular route was used in 8 individuals in the REAC/TS database, none of whom were efficacy cases. Three of these experienced injection site pain. There are insufficient safety and effectiveness data to recommend this route.

[6] The previously published draft labeling for Ca-DTPA and Zn-DTPA recommended a minimum of 30 days of chelation therapy. In the REAC/TS database, 72% of individuals who were treated with Ca-DTPA received only one or two doses, while the remaining individuals received 3 or more doses. Among individuals treated with Zn-DTPA, 50% received one or two doses, and the remainder received 3 or more. One individual received 338 doses of Ca-DTPA 1 g over a 6.5-year period, and another individual received 574 doses of Zn-DTPA 1 g over a 3.5-year period. FDA believes that the duration of therapy depends on the amount of internal contamination and the individual's response to therapy and cannot be predicted in advance.

- We revised the labeling for Ca-DTPA to warn about safety risks in patients with severe hemochromatosis who received four times the recommended daily dose of Ca-DTPA by intramuscular injection.[7] Although a causal association between these events and the drug cannot be established, we recommend caution in treating patients with severe hemochromatosis with Ca-DTPA.

You can use this revised draft labeling as part of a 505(b)(2) application for Ca-DTPA or Zn-DTPA drug products. This revised labeling reflects both our conclusions based on the reports cited in the *Federal Register* notice, and our tentative conclusions based on additional reports that we have become aware of since publication of the *Federal Register* notice regarding the potential safety and effectiveness of Ca-DTPA and Zn-DTPA drug products for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium, to increase the rates of elimination.

If you wish to change the draft labeling to include a different or broader indication or different dosage, or if you wish to make any other significant changes to the labeling, you should provide, as part of your 505(b)(2) application, additional literature or other studies to support your requested changes. If you submit a 505(b)(1) application for a Ca-DTPA or Zn-DTPA drug product, you may not use this labeling because it is based on our review of the published literature and the REAC/TS data. If you submit a 505(b)(1) application for Ca-DTPA or Zn-DTPA, your labeling must be based on the data contained in your NDA (section 355(b)(1) of the Act and § 314.50).

The revised draft labeling for 505(b)(2) applications is available on the Internet.[8] You can also contact the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160) for a copy of the labeling.

3. Patent Information

If you submit an NDA (including a 505(b)(2) NDA) for either Ca-DTPA and Zn-DTPA, you must file with your NDA a complete patent declaration form (Form FDA 3542a) for each patent

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[7] FDA is aware of three deaths in patients with severe hemochromatosis who received intramuscular doses of up to 4 g Ca-DTPA per day. One patient became comatose and died after receiving a total of 14 g Ca-DTPA, and the other two died after 2 weeks of daily treatment. See FDA Medical Officer's review dated July 29, 2004 (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). In contrast, the literature contains a report of a patient with a less severe case of hemochromatosis who received a total of 30 g Ca-DTPA by intravenous injection over 12 days and experienced no adverse events. This case is described in Kemble, JVH, "The New Chelating Agent Ca-DTPA in the Treatment of Primary Haemochromatosis," *Guy's Hospital Reports*, 113:68-73, 1964.

[8] See http://www.fda.gov/cder/drug/infopage/dtpa/default.htm.

that is required to be submitted under section 355(b)(1)(F) of the Act and §§ 314.50 and 314.53. You also must submit an additional patent declaration form (Form FDA 3542) within 30 days of approval of your NDA, or, in the case of newly issued patents, within 30 days of issuance of the patent (section 355(c)(2) of the Act and §§ 314.50 and 314.53). If your NDA is approved, we will publish the patent information in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*).

We publish information regarding patents and exclusivity periods for approved drug products in the *Orange Book*. This information is important if you are considering submitting ANDAs or 505(b)(2) applications for Ca-DTPA and Zn-DTPA drug products. If a drug product listed in the *Orange Book* has listed patents, the 505(b)(2) application or ANDA seeking to rely on the finding of safety or effectiveness for that listed drug must contain certifications regarding those patents (see § 314.50(i) for 505(b)(2) applications, and § 314.94(a)(12) for ANDAs).

C. Exclusivity

In addition to the protection provided by patents issued by the U.S. Patent and Trademark Office, Ca-DTPA and Zn-DTPA drug products approved by us may be protected from competition by periods of marketing exclusivity that are administered by us. The Act provides for periods of marketing exclusivity that prevent us from filing or approving 505(b)(2) applications or ANDAs for drug products that contain the same active moiety[9] as certain previously approved drug products. The active moiety of a Ca-DTPA or Zn-DTPA drug product would be the diethylenetriaminepentaacetate (DTPA) ligand.

The following summaries of marketing exclusivity and orphan drug exclusivity are provided solely for the general information of manufacturers considering submitting an NDA for a Ca-DTPA and Zn-DTPA drug product. They should not be read as statements of our general policy regarding marketing exclusivity and orphan drug exclusivity. Our policy can be found in the regulations cited in this guidance.

1. Five-Year Marketing Exclusivity

A 5-year period of marketing exclusivity is provided by section 505(c)(3)(D)(ii) and (j)(5)(D)(ii) of the Act when a sponsor obtains approval of an NDA for which no active moiety has been previously approved by the FDA. The 5-year period of marketing exclusivity generally prohibits us from filing a 505(b)(2) application or receiving an ANDA for a drug product that contains the

[9] *Active moiety* is defined in 21 CFR 314.10(a) as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

same active moiety as the first drug product containing the active moiety to be approved. The 5-year period of marketing exclusivity begins on the approval date of the first NDA approved for a drug product containing the active moiety. Both 505(b)(1) and 505(b)(2) applications may be entitled to benefit from 5-year marketing exclusivity, but only 505(b)(2) applications and ANDAs are blocked by 5-year marketing exclusivity.

Because we have not previously approved a drug product that contains the DTPA ligand as the active moiety, the first NDA approved that contains the DTPA ligand as the active moiety will likely receive 5 years of marketing exclusivity. If an NDA containing the DTPA ligand as the active moiety is entitled to 5-year exclusivity, we cannot file[10] a subsequent 505(b)(2) application for a Ca-DTPA or Zn-DTPA drug product for 5 years after the approval date of that NDA. If you have submitted an essentially complete 505(b)(2) application before we approve the first NDA for a Ca-DTPA or Zn-DTPA drug product, review and approval of your 505(b)(2) application would not be blocked by the marketing exclusivity obtained by the first Ca-DTPA or Zn-DTPA drug product approval (54 FR 28872 at 28901; July 10, 1989). However, after we have approved the first NDA for a Ca-DTPA or Zn-DTPA drug product, 5-year marketing exclusivity would prohibit us from filing your 505(b)(2) application, no matter how soon after the first approval we received your application.

2. Three-Year Exclusivity

A 3-year period of marketing exclusivity may be applicable to Ca-DTPA and Zn-DTPA drug products sometime in the future. Three-year marketing exclusivity is provided by section 505(c)(3)(D)(iii) and (j)(5)(D)(iii) of the Act. Drug products whose active moiety is the same active moiety as that in a previously approved drug product are entitled to 3-year exclusivity if a new clinical study (other than a bioavailabilty or bioequivalence study) is needed for their approval. If a drug product, or change to a drug product, is given 3 years of exclusivity, we are barred for 3 years from approving any 505(b)(2) application or ANDA for the same drug product, or change to the product, that was granted exclusivity. For example, if an applicant obtains 3 years of exclusivity for a new dosage form of Ca-DTPA or Zn-DTPA, FDA may not approve a 505(b)(2) application or an ANDA for that dosage form of Ca-DTPA or Zn-DTPA for 3 years. However, we can approve a 505(b)(2) application or an ANDA for any previously approved dosage form not protected by the exclusivity.

Our regulations in § 314.108 provide more details on marketing exclusivity. If you are interested in how marketing exclusivity could affect your NDA for Ca-DTPA or Zn-DTPA, you are encouraged to discuss the issue with the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products. If you believe your drug product is

[10] Our regulations regarding filing an NDA and receiving an ANDA are found at 21 CFR 314.101.

entitled to marketing exclusivity, you must submit supporting information in your NDA (§ 314.50(j)).

3. Orphan Drug Exclusivity

In addition to 3- or 5-year marketing exclusivity, orphan drug exclusivity may apply to Ca-DTPA or Zn-DTPA drug products approved for orphan indications. Obtaining orphan drug exclusivity is a two-step process. 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. If we designate the drug as an orphan drug and then approve it for the designated indication, the drug will receive orphan drug exclusivity. The issues involved in determining which drug products are entitled to orphan drug exclusivity and which drug products are blocked by orphan drug exclusivity are described in our regulations in part 316 (21 CFR part 316). However, we note that orphan drug exclusivity is for a 7-year period and can prohibit us from approving a 505(b)(1) application, a 505(b)(2) application, or an ANDA for the same active moiety for the same indication during the period of exclusivity. This differs from 5-year marketing exclusivity, which prohibits us from filing a 505(b)(2) application or receiving an ANDA, but would not prohibit us from filing a 505(b)(1) application.

4. Waiver of Exclusivity

If you are entitled to any type of exclusivity for a Ca-DTPA or Zn-DTPA drug product, you may waive that exclusivity after approval of your NDA. Your waiver would allow one or more applicants to submit applications for the product. For example, if you obtain 5-year exclusivity with a 505(b)(2) application for a Ca-DTPA or Zn-DTPA drug product, your complete waiver of such exclusivity would enable other applicants to immediately submit 505(b)(2) applications and ANDAs for drug products containing Ca-DTPA or Zn-DTPA.

D. Innovative Ca-DTPA and Zn-DTPA Drug Products

We encourage the development of drug products containing Ca-DTPA or Zn-DTPA for the treatment of internal contamination with transuranium elements that represent improvements in safety, effectiveness, or convenience. However, your submission of a 505(b)(2) application for such an innovative product may be blocked by marketing exclusivity if the exclusivity is not waived. If the innovative product is clinically superior to the previously approved drug product, its approval might not be blocked by orphan drug exclusivity (see § 316.3(b)(13)). Once approved, an innovative product may qualify for 3-year marketing exclusivity. If a subsequent drug product represents an innovation that presents a commercial advantage over the drug product that enjoys marketing exclusivity, it may be possible to reach an agreement with the person holding the exclusivity to allow marketing of the subsequent drug product.