

to be safe and effective for the treatment of internal contamination with plutonium, americium, or curium to increase the rates of elimination. We encourage the submission of NDAs for Ca-DTPA and Zn-DTPA drug products. We are also announcing the availability of a guidance for industry entitled "Calcium-DTPA and Zinc-DTPA Drug Products—Submitting a New Drug Application." This guidance is intended to assist manufacturers who plan to submit NDAs for Ca-DTPA and Zn-DTPA.

ADDRESSES: Submit NDAs to the Food and Drug Administration, Center for Drug Evaluation and Research, Central Document Room, 12229 Wilkins Ave., Rockville, MD 20857. Submit requests for copies of draft labeling to the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7510. Copies of the reports referred to in this document will be on display at the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written requests for single copies of the guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Division of Dockets Management (address given previously). Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Kyong Kang, Center for Drug Evaluation and Research (HFD-160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7510.

SUPPLEMENTARY INFORMATION:

I. Background

A. Plutonium, Americium, and Curium

Plutonium, americium, and curium are transuranium radioactive elements of the actinide series. They are products of nuclear bombardment and are found in the fallout from the detonation of nuclear weapons and the waste from nuclear power plants. These elements are used in various types of research.

All isotopes of plutonium, americium, and curium are radioactive.

Contamination with plutonium, americium, or curium can occur through a variety of routes including ingestion, inhalation, and/or wounds. Contamination can cause serious illness or death when high radiation absorbed doses are delivered to critical organs. Lower doses have been associated with the development of cancer long after exposure. In addition to concerns about exposure to plutonium, americium, or curium in industrial and research environments, contamination by radioactive elements such as these, is of particular concern because of their potential use in a radiological dispersal device (RDD), commonly called a "dirty bomb." An RDD is a conventional explosive or bomb containing radioactive material. The conventional bomb is used as a means to spread radioactive material. An RDD is not a nuclear weapon and does not involve a nuclear explosion. Significant amounts of radioactive material, particularly plutonium, could also be spread by the detonation of an improvised nuclear device by terrorists. The extemporized design and construction of such a terrorist weapon could lead to an incident where only a small portion of the weapon's plutonium is consumed in the atomic reaction, and the rest of the plutonium is spread through the air by the explosion of the device. There are currently no approved treatments for internal contamination with plutonium, americium, or curium.

B. Ca-DTPA and Zn-DTPA

Diethylenetriaminepentaacetate (DTPA) is a ligand that acts as a chelator with a very high affinity for plutonium, americium, and curium. The calcium salt of DTPA is known as pentetate calcium trisodium and is referred to as Ca-DTPA. The zinc salt of DTPA is known as pentetate zinc trisodium and is referred to as Zn-DTPA.¹

For several decades, Ca-DTPA and Zn-DTPA have been used investigational to enhance the excretion of plutonium, americium, and curium from the body by means of ion exchange, chelation, and, ultimately, excretion through the urine. Because DTPA has a very high affinity for these transuranium elements, when it comes in contact with such elements, the

calcium or zinc ions of Ca-DTPA and Zn-DTPA drugs are readily exchanged for the transuranium elements. The transuranium-DTPA complex is then rapidly excreted in the urine. There are currently no approved NDAs for drug products containing Ca-DTPA or Zn-DTPA.

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 under a contract with the Department of Energy. The INDs are for treatment of contamination resulting from nuclear power or other industrial accidents.

Traditional clinical trials have not been conducted because it would be unethical to deliberately expose patients to radiation; it would also be unethical to withhold potential beneficial medications from patients who have been accidentally exposed. Instead, under these INDs, accidentally exposed patients were treated empirically and the findings were reported in the literature as observational studies.

REAC/TS has retained the medical case reports on 646 patients treated with Ca-DTPA and Zn-DTPA for radiation contamination during the last 40 years. To facilitate the development and ultimate approval of Ca-DTPA and Zn-DTPA drug products, we have reviewed the medical reports on the patients in the REAC/TS database and reviewed the available published literature. This notice announces our conclusions about the safety and effectiveness of Ca-DTPA and Zn-DTPA drug products, and it is addressed primarily to persons interested in submitting NDAs for Ca-DTPA or Zn-DTPA drug products.

II. Safety and Effectiveness of Ca-DTPA and Zn-DTPA Drug Products

We have concluded that Ca-DTPA and Zn-DTPA drug products, when produced under conditions specified in approved NDAs, can be found to be safe and effective for the treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. As described in section II.A of this document, our conclusion is based on our review of medical reports in the REAC/TS database.

We encourage the submission of NDAs for both Ca-DTPA and Zn-DTPA drug products. If you are interested in submitting NDAs for these products, please contact the Center for Drug

¹ For purposes of this document Ca-DTPA refers only to pentetate calcium trisodium, which has an empirical formula of $\text{Na}_3\text{CaC}_{14}\text{H}_{18}\text{N}_3\text{O}_{10}$ 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 $\text{Na}_3\text{ZnC}_{14}\text{H}_{18}\text{N}_3\text{O}_{10}$ and the CAS registry number 125833-02-5.