

the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

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SUPPLEMENTARY INFORMATION:

I. Background

A. Cesium

Cesium-137, a radioactive isotope of cesium, was discovered in 1941 by Glenn T. Seaborg and Margaret Melhase. Cesium-137 is a product of fusion and is found in the fallout from the detonation of nuclear weapons and the waste from nuclear power plants. Cesium-137 is one of the most common radioisotopes used in industry. It is used in various measuring devices, such as moisture-density gauges. Cesium-137 is also widely used as a source of gamma radiation for treatment of various forms of cancer. Cesium-137 has a half-life of 30.07 years.

Contamination with cesium-137 can cause serious illness or death, depending upon the dose, and has been associated with the development of cancer long after exposure. In addition to concerns about exposure to cesium-137 in industrial and medical environments, cesium-137 contamination is of particular concern because it has been mentioned as a potential component of 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, such as cesium-137. An RDD is not a nuclear bomb and does not involve a nuclear explosion.

B. Thallium

Thallium occurs naturally in several minerals and ores. It was discovered independently by both William Crookes and Claude Auguste Lamy in the early 1860s. Thallium is very toxic, and thallium sulfate has been used as a rat and ant poison in the past. Other thallium compounds are used in the manufacture of semiconductors, photocells, optical glass, and other items. Thallium-201, a radioactive isotope of thallium, is widely used in very small doses as an approved radioimaging drug. Thallium-201 has a half-life of 72.912 hours.

Acute exposure to high dose radioactive or nonradioactive thallium is generally characterized by severe

gastrointestinal symptoms followed by neurological symptoms, which may lead to death. The toxicity resulting from chronic exposure to thallium is characterized by various neurological symptoms. Thallium-201 has also been mentioned as a potential component of a dirty bomb.

There are no approved treatments for internal contamination with thallium or radioactive cesium.

C. Prussian Blue

Prussian blue was first synthesized in 1704 by a Berlin color maker named Diesbach. It has been used as an industrial and artists' pigment ever since. The chemical name for prussian blue is ferric hexacyanoferrate(II).

Since the 1960s, prussian blue has been used investigatively as an orally ingested drug to enhance the excretion of isotopes of cesium and thallium from the body by means of ion exchange. However, there is currently no approved NDA for prussian blue. Prussian blue has a very high affinity for cesium and thallium. Cesium and thallium ions are ordinarily excreted into the intestine, reabsorbed from there into the bile, and then excreted again into the gastrointestinal tract. Orally administered prussian blue traps thallium or cesium in the intestine, interrupts its reabsorption from the gastrointestinal tract, and thereby increases fecal excretion of thallium and cesium. Prussian blue itself is not absorbed across the intestinal wall in significant amounts.

Prussian blue, in 500-milligram (mg) capsules, has been distributed by the Radiation Emergency Assistance Center/ Training Site (REAC/TS) under investigational new drug application (IND) number 51,700. 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. ORISE owns the IND for prussian blue. The 500-mg capsules used under the IND are manufactured by HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG (HEYL). HEYL uses the trade name Radiogardase-Cs for its 500-mg capsules of prussian blue.

II. Safety and Effectiveness of Prussian Blue Drug Products

We have concluded that prussian blue, when produced under conditions specified in approved NDAs, can be found to be safe and effective for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. As described in the following

paragraphs, our conclusion is based upon our review of published information.

We encourage the submission of NDAs for prussian blue drug products. If you are interested in submitting an NDA for this product, please contact us. We also recommend that you consult the guidance "Prussian Blue Drug Products—Submitting a New Drug Application," which is being made available with this notice.

A. Basis for Finding of Safety and Effectiveness

We have reviewed the published literature and have determined that 500-mg prussian blue capsules, when produced under conditions specified in an approved NDA, can be found to be safe and effective for the treatment of patients with known or suspected internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. Prussian blue increases the rate of elimination of thallium or radioactive cesium. Administration of prussian blue decreases the risk of death and major morbidity after exposure to radioactive thallium, nonradioactive thallium, or radioactive cesium.

In reaching our determination on the effectiveness of prussian blue, we evaluated published reports of a 1987 incident in Goiânia, Brazil, where approximately 250 people were contaminated with cesium-137 that had been abandoned after use in a cancer clinic (see International Atomic Energy Agency, 1998). Forty-six patients with heavy internal contamination were treated with prussian blue. Data on the whole-body effective half-life of cesium-137 during treatment and after treatment with prussian blue was completed on 33 of the 46 patients. The untreated mean whole-body effective half-life of cesium-137 is 80 days in adults, 62 days in adolescents, and 42 days in children. Prussian blue reduced the mean whole-body effective half-life of cesium-137 by 69 per cent in adults, by 46 per cent in adolescents, and by 43 per cent in children (see International Atomic Energy Agency, 1998). Data from additional literature articles, including a study of 7 human volunteers contaminated with trace doses of cesium-137 and reports on 19 patients contaminated with cesium-137 in other incidents, show a similar reduction in whole-body effective half-life after administration of prussian blue (see Madhus, 1968 and National Council on Radiation Protection and Measurement, 1979).

We also evaluated reports in the literature that describe 33 patients who