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Citizen Petition

Date: December 6, 2017

On behalf of Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, and Public Citizen's Health Research Group, the undersigned submits this petition under Section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) and under Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to immediately (1) add cesium chloride to the list of bulk drug substances that present significant safety risks (the 503A Category 2 list) and, therefore, may not be compounded under the agency's January 2017 *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act - Guidance for Industry* and (2) promulgate a rule that excludes cesium chloride from the list of bulk drug substances that, although they are neither the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs, can be used to compound drug products under section 503A of the FDCA (the 503A bulks list). Such action is necessary because FDA staff determined more than 18 months ago that cesium chloride presents "serious safety concerns" and is "not safe for human use." Any further failure by the FDA to immediately add cesium chloride to the 503A Category 2 list clearly would constitute a dangerous and unreasonable delay.

A. ACTION REQUESTED

Immediately (1) add cesium chloride to the list of bulk drug substances that raise significant safety risks (the 503A Category 2 list) and, therefore, may not be compounded under the agency's January 2017 *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act - Guidance for Industry* and (2) promulgate a rule that excludes cesium chloride from the list of bulk drug substances that, although they are neither the subject of an applicable USP or NF monograph nor components of FDA-approved drugs, can be used to compound drug products under section 503A of the FDCA.

B. STATEMENT OF GROUNDS

1. Background

Statutory requirements

Section 503A of the FDCA describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FDCA: section 505 (concerning the approval of drugs under new drug applications or abbreviated new drug applications), section 502(f)(1) (concerning the labeling of drugs with adequate directions for use), and section 501(a)(2)(B) (concerning current good manufacturing practice requirements).

One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503A is that a licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that:

(1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding;
(2) if such a monograph does not exist, are components of drugs approved by the Secretary; or
(3) if such a monograph does not exist and the drug substances are not components of any drug approved by the Secretary, appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A (hereafter referred to as the 503A bulks list).

The FDA's interim policy

On June 10, 2016, the FDA issued its *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act - Guidance for Industry*.[1] Under this policy — which was revised in January 2017 — until a substance has been evaluated and is identified in a final rule as being included or not included on the 503A bulks list, the FDA does not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not a component of an FDA-approved drug product and that is not the subject of an applicable USP or NF monograph, provided that the following conditions are met:[2]

(1) The bulk drug substance appears on the 503A Category 1 list (*Bulk Drug Substances Under Evaluation*) on the FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf, which was last updated on July 1, 2017. A bulk drug substance is included on the Category 1 list if it may be eligible for inclusion on the 503A bulks list, was nominated with sufficient supporting information for the FDA to evaluate it, and has *not* been identified by the FDA as a substance that presents a significant safety risk in compounding (the 503A Category 2 list) prior to the publication of a final rule to include or not include the substance on the 503A bulks list;

(2) The original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under section 510 (including foreign establishments that are registered under section 510(i) of the FDCA);

(3) The bulk drug substance is accompanied by a valid certificate of analysis; and

[1] 81 FR 37502.
[2] Food and Drug Administration. Interim policy on compounding using bulk drug substances under section 503A of the Federal Food, Drug, and Cosmetic Act- Guidance for Industry. January 2017 (revision 1). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf. Accessed December 5, 2017.

(4) The drug product compounded using the bulk drug substance is compounded in compliance with all other conditions of section 503A of the FDCA.

Therefore, under the agency's interim policy, a State-licensed pharmacy, Federal facility, or licensed physician may *not* compound a drug product using a bulk drug substance that appears on either of the following lists (or does not appear on the 503A Category 1 list):[3]

(1) The 503A Category 2 list of bulk drug substances identified by the FDA as presenting a significant safety risk in compounding. This list, which was last updated on July 1, 2017, includes only three items: domperidone, quinacrine hydrochloride for intrauterine administration, and germanium sesquioxide.[4]

(2) The 503A Category 3 list of bulk drug substances nominated for the 503A bulks list that may be eligible for inclusion on the list, but that the FDA is unable to evaluate for inclusion on the list at this time because the substances were nominated with insufficient supporting evidence for the FDA to evaluate them. This list also was last updated on July 1, 2017.[5]

2. FDA evaluation of industry nomination of cesium chloride for pharmacy compounding

Nominations for inclusion on the 503A bulks list

On September 30, 2014, the American Association of Naturopathic Physicians, Alliance for Natural Health USA, Integrative Medicine Consortium, and McGuff Compounding Pharmacy Services, Inc., nominated cesium chloride for inclusion on the 503A bulks list for use in combination with other natural substances in treating individuals with numerous types of cancer, by a presumed alkalinizing effect.[6] The proposed route of administration of compounded cesium chloride for this use is intravenous infusion. There is no applicable USP or NF monograph for cesium chloride, and it is not a component of any FDA-approved drug product.

Current status under the FDA's interim policy

Cesium chloride is listed on the 503A Category 1 list on the FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf. Therefore, under the FDA's *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act* -

[3] *Ibid*.
[4] Food and Drug Administration. Bulk drug substances nominated for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act. July 1, 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf. Accessed December 5, 2017.
[5] *Ibid*.
[6] Food and Drug Administration. FDA briefing document, Pharmacy Compounding Advisory Committee (PCAC) meeting. June 23, 2016. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM505041.pdf. Accessed December 5, 2017.

Guidance for Industry, a State-licensed pharmacy, Federal facility, or licensed physician may compound a drug product using the bulk drug substance cesium chloride.

FDA reviewers identify significant safety risks with compounding cesium chloride

The FDA's Pharmacy Compounding Advisory Committee (PCAC) considered the nomination of cesium chloride on June 23, 2016.[7] In a May 31, 2016, review of cesium chloride, FDA reviewers did not recommend adding cesium chloride to the 503A bulks list, in part because there are "serious safety concerns related to the use of cesium chloride."[8]

In their discussion of the safety of cesium chloride for use in compounding, FDA reviewers noted the following in their nonclinical assessment of the drug:[9]

> b. Safety pharmacology
>
> In rabbits and dogs, cesium chloride administration, either as intravenous bolus injections (1 mmol/kg) or intravenous infusion (0.018 – 0.1 mmol/kg/min), has been **shown to cause ventricular tachycardia** (Takahashi et al., 1998; Nayebpour et al., 1989; Senges et al., 2000). The finding in dogs was associated with **early and delayed afterdepolarizations** (Patterson et al., 1990). In canine cardiac Purkinje fibers, cesium chloride treatment (5 mM) resulted in **prolongation of action potential duration and bradycardia-dependent early afterdepolarizations** (Kinnaird et al., 1991).
>
> c. Acute toxicity
>
> … In mice, single-dose administration with cesium chloride caused **decreased motor activity** and Straub tail in a dose-dependent manner. Clinical signs included **autonomic disturbance, diarrhea, and salivation** (Bose et al., 1984). …
>
> f. Developmental and reproductive toxicity
>
> The effect of pre- and postnatal maternal ingestion of cesium chloride on neonatal growth and development was evaluated in albino mice. In this study, cesium chloride was administered in drinking water at conception and during gestation, lactation, and throughout the 21 days of breast-feeding during weaning. Maternal exposure to cesium chloride **caused a sex-dependent decrease of weanling's body weight**. Decreased brain and testis weights and increased spleen weights were noted when compared to control (Messiha, 1988; Messiha, 1994). Similarly, in a separate study in mice, maternal exposure to 1mEq CsCl solution from birth and through weaning of offspring, resulted in decreased body, kidney, and brain weights in the offspring, which were breastfed until weaning (Messiha, 1998). …

[7] *Ibid*.
[8] *Ibid.* Tab 2b, PDF pages 61-73.
[9] *Ibid.* PDF pages 65-66.

> **Conclusions: Nonclinical studies in mice, rats, and dogs identified the cardiovascular and central nervous systems as the major target organ systems of toxicity**. **Major toxicity findings included ventricular tachycardia, decreased motor activities, autonomic disturbances, and salivation**. Genetic toxicology studies with cesium chloride have yielded equivocal results; however, some studies have shown that cesium chloride can cause chromosomal aberration in mouse bone marrow cells. Reproductive studies in mice have shown that exposure of offspring through breastfeeding by mothers administered cesium chloride in the drinking water caused decreased body and organ weights (e.g., brain, kidney, spleen, and testis) in the offspring. **The toxicity profile of cesium chloride in animal studies weighs against its inclusion on the 503A list**.
>
> [Emphasis added]

Regarding human safety data on cesium chloride, FDA reviewers reported the following:[10]

> a. Reported adverse reactions
>
> Cesium blocks potassium rectifier channels on atrial and ventricular myocytes, **resulting in prolongation of the QT interval, which can lead to arrhythmias, including torsade de pointes** (Chan et al., 2009, Dalal et al., 2004, Jones et al, 2001, Himeshkumar et al., 2006, Lyon and Mayhew 2003, O'Brien et al., 2008, Pinter et al., 2002, Sessions et al., 2013, Sohn and Vassale, 1995, Wiens et al., 2009.) Because of the long half-life of cesium, it takes approximately 200 days of daily dosing to reach a steady state. It is therefore not surprising that FAERS and CAERS case reports describe arrhythmias occurring after weeks to months of therapy with cesium chloride. **Several case reports describe serious toxicities resulting from cesium chloride ingested as an alternative therapy for cancer, including hypokalemia, seizures, ventricular arrhythmias, syncope, and death**. …
>
> **Conclusions: The limited information available about the safety of cesium chloride gives rise to significant concern about its use in compounding. The evidence of cesium chloride causing hypokalemia, seizures, QT prolongation, and cardiac arrhythmias is particularly concerning.** There are numerous FDA-approved agents that have demonstrated safety and efficacy for the treatment of patients with various cancers.
>
> [Emphasis added]

It is also notable that the FDA reviewers concluded the following regarding the efficacy of cesium chloride for the treatment of cancer:[11]

> Cesium chloride has **not been shown to be efficacious for the prevention or treatment of any form of cancer**. … evidence of clinical benefit from cesium in human cancer is limited to one case series published in 1984 by Sartori. That case series had major flaws

[10] *Ibid.* PDF page 67-68.
[11] *Ibid*. PDF page 68.

> including its uncontrolled nature, retrospective design and probable case selection bias. Therefore, the results cannot be considered reliable.

In their recommendation regarding whether cesium chloride should be included on the 503A bulks list, FDA reviewers stated the following:[12]

> **III. RECOMMENDATION**
>
> We have evaluated cesium chloride as a candidate for the list of bulk drug substances under section 503A of the FD&C Act and **do not recommend** it be included on the list of bulk drug substances allowed for use in compounding [Emphasis in original]. …
>
> **There are serious safety concerns related to the use of cesium chloride indicated by the results of both non-clinical and clinical studies**. Non-clinical studies show significant cardiac and central nervous system toxicity including ventricular tachycardia, decreased motor activities, and autonomic disturbances. In addition, studies in mice show reproductive effects of decreased body and organ weights in offspring. **Clinically, numerous reports of serious toxicity following cesium chloride use for the treatment of cancer have been made with effects including hypokalemia seizures, ventricular arrhythmias, syncope, and death.** … [Emphasis added]
>
> **Cesium chloride is not safe for human use and there is no evidence it is effective for the treatment of any cancer. Relying on this type of treatment may have serious health consequences, including ventricular arrhythmias and cardiac arrest.** In addition, use of cesium chloride may cause a patient to delay the use of treatments that have been found to be safe and effective for treating cancer. Based on a balancing of the four evaluation criteria, we find that cesium chloride is not a suitable substance for the bulk drug substance list under 503A of the FD&C Act. [Emphasis added]

PCAC deliberations and recommendation

On June 23, 2016, the FDA's PCAC discussed and voted on whether cesium chloride should be included on the 503A bulks list. During the meeting, Dr. Michael Brave, Clinical Reviewer in the Division of Oncology Products 1, Office of Hematology and Oncology Products, presented the FDA's review of the drug. His presentation affirmed the assessment presented in the FDA's May 31, 2016, review of cesium chloride. During his presentation, Dr. Brave noted the following:[13]

> Published literature indicates that cesium chloride used in the treatment of cancer has been taking place since at least the 1980s. Currently, oral cesium chloride is advertised by a number of compounding pharmacies.

[12] *Ibid*. PDF pages 69-70.

[13] Food and Drug Administration. Transcript of Pharmacy Compounding Advisory Committee (PCAC). June 23, 2016, morning session. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM563843.pdf. Accessed December 5, 2017. PDF page 75.

When asked by PCAC member Dr. Michael Carome, Director of Public Citizen's Health Research Group, whether it would be fair to say that the FDA has concluded that cesium chloride raises serious safety concerns, Dr. Brave answered affirmatively.[14]

PCAC member Dr. John DiGiovanna, Senior Research Physician in the DNA Repair Section, Dermatology Branch, Center for Cancer Research, National Cancer Institute, offered the following comments during the discussion of cesium chloride:[15]

> This substance is a little bit different than the others, I think, that we've discussed in that its indication seems to be for patients who are at end-of-life scenarios because of malignancy.
>
> It occurs to me that these patients are a very vulnerable group that are easily manipulated by anything that offers them hope. I think in that scenario, my perception is that potentially toxic compounds really need to be studied in a controlled environment under an IND [investigational new drug application] to determine if there's any evidence that they offer benefit comparable to the toxicity that they offer. This particular compound raises some concerns to me that the others didn't.

PCAC Chairperson Dr. Jurgen Venitz, Associate Professor at Virginia Commonwealth University School of Pharmacy, Department of Pharmaceutics, noted the following during the discussion of cesium chloride:[16]

> So even if you state the point that the efficacy [of cesium chloride] is not demonstrated, it has a major safety issue, and safe doses have not been established, forget the fact that we know nothing about effective doses.

By a unanimous vote of 11 to 0 (with no abstentions), the PCAC recommended that the FDA **not** place cesium chloride on the 503A bulks list.[17] All members cited concerns about the safety of the drug as a reason for their votes.[18]

3. Conclusions

Given the conclusion of FDA reviewers more than 18 months ago that cesium chloride presents "serious safety concerns" and is "not safe for human use," followed shortly thereafter by the PCAC's unanimous recommendation that cesium chloride not be included on the 503A bulks list, we are astonished that the FDA has not yet taken action to prevent pharmacy compounding of cesium chloride by placing it on the 503A Category 2 list of bulk drug substances identified by the FDA as presenting a significant safety risk in compounding. The failure to take such action represents an unreasonable delay that has threatened patient safety.

[14] *Ibid*. PDF page 77.
[15] *Ibid*. PDF page 99.
[16] *Ibid*. PDF page 100.
[17] *Ibid*. PDF page 102.
[18] *Ibid*. PDF pages 102-104.

For the reasons stated above, we hereby petition the FDA, pursuant to section 503A of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 10.30, to immediately (1) add cesium chloride to the list of bulk drug substances that present significant safety risks (the 503A Category 2 list) and, therefore, may not be compounded under the agency's January 2017 *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act - Guidance for Industry* and (2) promulgate a rule that excludes cesium chloride from the 503A bulks list.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

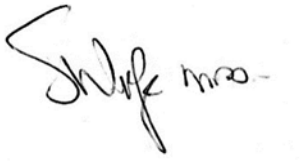
D. ECONOMIC IMPACT

Will be submitted upon request.

E. CERTIFICATION

I certify that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,



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