Sidney M. Wolfe, M.D.
Public Citizen's Health Research Group
1600 20th Street, N.W.
Washington, DC 20009

JUL 23 2018

RE: Docket No. FDA-2017-P-6758

Dear Dr. Wolfe:

This letter responds to your citizen petition received on December 6, 2017 (Petition). In your Petition, you request that the Food and Drug Administration (FDA or the Agency):

> immediately (1) add cesium chloride to the list of bulk drug substances that present significant safety risks . . . and, therefore, may not be compounded under the [A]gency'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* [Interim Policy Guidance] and (2) promulgate a rule that excludes cesium chloride from the list of bulk drug substances that . . . can be used to compound drug products under section 503A of the [Federal Food, Drug, and Cosmetic Act (FD&C Act)] (the 503A bulks list).

Petition at 1.

FDA has considered the information submitted in the Petition and other relevant data. Based on our review of this information and for the reasons described below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Compounding and the 503A Bulks List

Pharmacy compounding is generally a practice in which a licensed pharmacist or licensed physician combines, mixes, or alters the ingredients of a drug to create a medication tailored to the needs of an individual patient. Compounded drug products have traditionally been prescribed where an FDA-approved drug product is not medically suitable for a particular patient, for example, where the patient is unable to swallow a capsule or tablet or is allergic to one of the inactive ingredients in the approved product. Compounded drug products are not FDA-approved.

Section 503A of the FD&C Act (21 U.S.C. 353a) 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 FD&C Act: section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and section 501(a)(2)(B) (21 U.S.C. 351(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 these exemptions is that a licensed pharmacist or licensed physician who compounds the drug product using bulk drug substances[1] must use bulk drug substances that: (1) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A of the FD&C Act (the 503A bulks list).[2]

Under section 503A(c)(1), before developing this list through regulation, FDA must convene and consult an advisory committee on compounding unless FDA determines that the issuance of such regulation before consulting the advisory committee is necessary to protect the public health. FDA must also consult with USP when promulgating the regulations.[3] The criteria for determining which bulk drug substances should appear on the section 503A bulks list "shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify."[4]

B. Interim Policy for Nominations for the 503A Bulks List

In July 2014, FDA published a notice in the *Federal Register* inviting all interested persons to nominate bulk drug substances for inclusion on the 503A bulks list (79 FR 37742). Approximately 740 unique substances were nominated in response to this request. FDA is in the process of evaluating approximately 65 substances that were nominated with adequate support, in consultation with the Pharmacy Compounding Advisory Committee (PCAC) and USP, and is addressing the substances in rulemaking (e.g., 81 FR 91071 (Dec. 16, 2016)) on a rolling basis.

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[1] A *bulk drug substance* as referenced in section 503A(b)(1)(A) means the same as "active pharmaceutical ingredient," which is defined as "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body," but the term "does not include intermediates used in the synthesis of the substance" (see section 503A(b)(1)(A) and 21 CFR 207.1 and 207.3).

[2] See section 503A(b)(1)(A)(i) of the FD&C Act.

[3] Section 503A(c)(2) of the FD&C Act.

[4] Id.

As described in the Interim Policy Guidance,[5] FDA has placed the substances nominated for the 503A bulks list into the following categories, listed on its website:[6]

- **503A Category 1 – Substances Nominated for the Bulks List Currently Under Evaluation**: These substances may be eligible for inclusion on the 503A bulks list, were nominated with sufficient supporting information for FDA to evaluate them, and do not appear on any other list.

- **503A Category 2 – Substances Nominated for the Bulks List That Raise Significant Safety Risks**: These substances were nominated with sufficient supporting information to permit FDA to evaluate them and they may be eligible for inclusion on the 503A bulks list. However, FDA has identified significant safety risks relating to the use of these substances in compounding.

- **503A Category 3 – Substances Nominated for the Bulks List Without Adequate Support**: These substances may be eligible for inclusion on the 503A bulks list, but were nominated with insufficient supporting information for FDA to evaluate them.

As further described in the Interim Policy Guidance, FDA generally does not intend to take regulatory action (e.g., issuance of a warning letter, seizure of product, injunction, and/or criminal prosecution) against a state-licensed pharmacy, federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product if that substance appears in Category 1, provided that the other conditions in the Interim Policy Guidance and in section 503A of the FD&C Act are met, until the substance is addressed in a final rule. However, FDA is not applying this interim policy to a nominated substance if the Agency has identified the substance as posing a significant safety risk (Category 2),[7] or if the substance was nominated without adequate support (Category 3).

Also, as stated in the Interim Policy Guidance, FDA intends to give notice to the public before removing any nominated bulk drug substances from Category 1 or 2. If the Agency adds a substance to Category 2, it intends to publish a public communication (e.g., a safety alert) describing the safety risks and to post the communication on FDA's human drug compounding

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[5] See guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act - Guidance for Industry* (January 2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] "Bulk Drug Substances Nominated for Use in Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf.

[7] This is not a determination regarding whether the substances will be added to the 503A bulks list. FDA intends to make that determination after notice and comment rulemaking.

website,[8] advising that the substance has been added to Category 2 and is no longer eligible for the policies that apply to substances in Category 1.

C. Cesium Chloride

Cesium chloride, an inorganic chloride salt, was nominated for inclusion on the 503A bulks list[9] by the American Association of Naturopathic Physicians, Alliance for Natural Health USA, Integrative Medicine Consortium, and McGuff Compounding Pharmacy. It was nominated with sufficient information for evaluation and placed in Category 1. FDA evaluated cesium chloride for use in the treatment of cancer and presented its recommendation regarding that substance at a PCAC meeting held on June 23, 2016. Based on an evaluation of cesium chloride's physical and chemical characteristics, safety when used in compounded drug products, effectiveness for the proposed use, and historical use in compounded drug products, FDA recommended that cesium chloride not be included on the 503A bulks list.

Regarding the safety of cesium chloride, FDA stated the following in the briefing materials presented to the PCAC:[10]

> 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 [FDA Adverse Event Reporting System] and CAERS [Center for Food Safety and Applied Nutrition Adverse Event Reporting System] 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.

FDA's review also stated that 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

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[8] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

[9] Cesium chloride has not been nominated for the list of bulk drug substances that can be used in compounded drug products under section 503B of the FD&C Act.

[10] "Briefing Information for the June 23, 2016 Meeting of the Pharmacy Compounding Advisory Committee (PCAC)," available at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm505040.htm.

concerning."[11] The PCAC voted unanimously not to include cesium chloride on the 503A bulks list.[12]

In addition to the data discussed with the PCAC in June 2016, FDA recently conducted a comprehensive review of the FDA Adverse Events Reporting System (FAERS), Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS), and medical literature for all adverse events related to cesium chloride and other cesium salts through June 30, 2018. Our current findings support our previous conclusions from the 2016 PCAC. Since 2016, there have been three more published case reports related to cesium chloride that describe life-threatening neurologic and cardiac toxicity (e.g., QT prolongation), which further increases our concern about the risks of cesium chloride.[13, 14, 15]

The available data indicate that the use of cesium chloride is associated with serious adverse events and potentially associated with fatalities.

II. DISCUSSION

Your Petition asks FDA to (1) immediately move cesium chloride to Category 2, as described in the Interim Policy Guidance, and (2) promulgate a rule that excludes cesium chloride from the list of bulk drug substances that can be used to compound drug products under section 503A of the FD&C Act. In support of these requests, you discuss FDA's May 31, 2016, review of cesium chloride and quote pertinent information about the safety of that substance as stated in that review, including its pharmacology, acute toxicity, developmental and reproductive toxicity, and reported adverse reactions. You also discuss FDA's presentation on that substance to the PCAC at its June 23, 2016, meeting and statements made by PCAC members regarding their concerns about the safety of cesium chloride in compounded drug products.

We address each of your requests below.

A. Request to Move Cesium Chloride to Category 2 Described in the Interim Policy Guidance

As stated above and explained in the Interim Policy Guidance, FDA will place nominated substances in Category 2 if it has identified significant safety risks relating to the use of these substances in compounding. Based on FDA's evaluation of cesium chloride as presented to the PCAC in June 2016, and the comprehensive review of FAERS, CAERS, and medical literature

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[11] Id. at 68.

[12] Transcript available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM563843.pdf.

[13] Patel, P.R., Rathod, J.. "Life Threatening Neurologic and Cardiac Toxicity Due to Cesium Chloride Used for the Holistic Treatment," *Am J Respir Crit Care Med*, 2018:197:A6906.

[14] Rodriguez, F.F., Liroff, K.G., "Cesium chloride: Prolonging QTC intervals, not life expectancy," *J of Gen Int Med*, 2018:33;490.

[15] Mahida H., Maludum O., Ugoeke N., Gharia B., Calderon D., Litsky J., Patel A., "Cesium induced acquired long QT syndrome leading to torsades de pointes", *Journal of the American College of Cardiology*, 2018:71 (11); A2612.

conducted in June 2018, FDA has determined that there are significant safety risks related to the use of cesium chloride in compounding and, therefore, moving this substance from Category 1 to Category 2 is appropriate. We note that placement in Category 2 is an interim step intended to protect the public health until cesium chloride is addressed in rulemaking and is not a final determination regarding whether the substance will be eligible for use in compounded drug products. As required by section 503A of the FD&C Act, whether cesium chloride will be included on the 503A bulks list will be the subject of notice and comment rulemaking.

As described above, FDA gives notice to the public when it intends to move any nominated substances out of Category 1 or Category 2. As the first step in implementing the movement of cesium chloride to Category 2, and concurrent with the issuance of this response, FDA today provided the public 7-days' notice of its intent to move cesium chloride to Category 2. See https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf (updates at page 7). Upon conclusion of that notice period, FDA will move cesium chloride to Category 2.

Accordingly, your request to move cesium chloride to Category 2 is granted.

B. Request to Promulgate Rulemaking Excluding Cesium Chloride from the 503A Bulks List

As stated above, FDA is engaged in rulemaking to establish the 503A bulks list and intends to address substances in proposed rules on a rolling basis. As required by section 503A of the FD&C Act, FDA will determine whether to include cesium chloride on the 503A bulks list through notice and comment rulemaking. To date, however, FDA has not issued a proposed rule addressing cesium chloride. When FDA publishes a Notice of Proposed Rulemaking addressing cesium chloride, the public will have an opportunity to comment on the proposal to include or not include this substance on the list. If you opt to comment on the proposed rule that addresses cesium chloride, once published, we will consider your feedback when determining whether to include cesium chloride on the 503A bulks list in a final rule.

For the foregoing reasons, your request that FDA promulgate a regulation that excludes cesium chloride from the 503A bulks list cannot be granted at this time.

III. CONCLUSION

For the reasons described above, your Petition is granted in part and denied in part.

Sincerely,

Julie Dohm
for

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research