IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PUBLIC CITIZEN, INC., and PUBLIC CITIZEN'S HEALTH RESEARCH GROUP, 1600 20th Street NW Washington, DC 20009, Plaintiffs, v. FOOD AND DRUG ADMINISTRATION, 10903 New Hampshire Avenue Silver Spring, MD 20993, Defendant.	)	Civil Action No. 18-1712

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

1. Plaintiffs Public Citizen and Public Citizen's Health Research Group (collectively, Public Citizen) bring this action pursuant to the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, and the Administrative Procedure Act (APA), 5 U.S.C. §§ 702 and 706, to compel the Food and Drug Administration (FDA) to act on Public Citizen's petition requesting that the FDA (1) add cesium chloride to the 503A Category 2 list of bulk drug substances that present significant safety risks 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* (2017 FDA Guidance),[1] 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 or National Formulary monograph

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf.

nor components of FDA-approved drugs, can be used to compound human drug products under section 503A of the FDCA, 21 U.S.C. § 353a.

2. Pursuant to 21 C.F.R. § 10.30, Public Citizen petitioned the FDA on December 6, 2017, to take these actions. Although the FDA reviewers determined more than two years ago that cesium chloride presents "serious safety concerns" and is "not safe for human use," the FDA has failed to respond to Public Citizen's petition. Therefore, to protect public safety and forestall preventable death and injury, Public Citizen seeks a declaration that the FDA has acted unlawfully by withholding action on Public Citizen's petition and an order requiring the FDA to act on the petition.

PARTIES

3. Plaintiff Public Citizen, Inc., a non-profit, public-interest research, litigation, and advocacy organization based in Washington, D.C., with members and supporters in all 50 states, advocates before Congress, regulatory agencies, and in the courts to advance the interests of its members on a wide range of consumer-protection issues. Plaintiff Public Citizen's Health Research Group (HRG) promotes research-based, system-wide changes in health care policy and provides oversight concerning drugs, medical devices, doctors, hospitals, and occupational health. HRG works to ban or relabel unsafe or ineffective drugs and publishes "Worst Pills, Best Pills News," a consumer guide to avoiding drug-induced death or illness. Public Citizen submitted the citizen petition at issue in this suit. And as long as the FDA does not take action on its own determination that cesium chloride presents "serious safety concerns" and is "not safe for human use," Public Citizen members are at risk of suffering the adverse effects of drug products containing this bulk drug substance, including death and severe injury.

4. Defendant FDA is a component of the Department of Health and Human Services, an agency of the federal government. The FDA is responsible for administration of the FDCA. In particular, the FDA is responsible for regulating the bulk drug substances compounded in human drug products by licensed pharmacists and physicians.

JURISDICTION

5. This Court has jurisdiction pursuant to 28 U.S.C. § 1331.

FACTS

Regulatory Background

6. Section 503A of the FDCA, 21 U.S.C. § 353a, addresses certain compounding of human drugs by licensed pharmacists and physicians. It describes the requirements for such compounding by a licensed pharmacist in a state-licensed pharmacy or a federal facility, or by a licensed physician.

7. Drugs compounded in accordance with all the requirements of section 503A are exempt from certain FDCA requirements regarding the approval of new drugs, 21 U.S.C. § 355, the labeling of drugs with adequate directions for use, *id.* § 352(f)(1), and current good manufacturing practice, *id.* § 351(a)(2)(B). *See id.* § 353a(a).

8. By regulation, a bulk drug substance 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." 21 C.F.R. §§ 207.1, 207.3.

9. For a bulk drug substance to be used in compounding under section 503A, it must either (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 no such monograph exists, be a component of a drug already approved by the FDA; or (3) if no monograph exists and the drug substance is not a component of an FDA-approved drug, "appear on a list developed by the [FDA] through regulations," referred to as the 503A Bulks List. 21 U.S.C. § 353a(b)(1)(A)(i); *see* 2017 FDA Guidance at 2.

10. In response to a 2014 Federal Register notice, the FDA received nominations for the 503A Bulks List. *See* 2017 FDA Guidance at 5. In evaluating the bulk drug substances nominated to be included on the 503A Bulks List, the FDA balances criteria established in 2015 by the FDA in consultation with the agency's Pharmacy Compounding Advisory Committee. Those criteria are: (1) "[t]he physical and chemical characterization of the substance"; (2) "safety issues raised by use of the substance in compounded drug products"; (3) "[h]istorical use of the substance in compounded drug products, including information about the medical condition(s) the substance has previously been used to treat and any references in peer-reviewed medical literature"; and (4) "available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance." 2017 FDA Guidance at 8.

11. The FDA maintains lists of three categories of nominated bulk drug substances that may be eligible for inclusion on the 503A Bulks List (and thus for use in compounding under section 503A), but that have not yet been identified in a final FDA rule as being included or not included on the 503A Bulks List. *See* 2017 FDA Guidance at 7–9.

12. First, the 503A Category 1 list, titled *Bulk Drug Substances Under Evaluation*,[2] includes bulk drug substances that were "nominated with sufficient supporting information for

[2] FDA, *Bulk Drug Substances Nominated for Use in Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act* 1 (updated July 1, 2017), http://www.fda.gov/

FDA to evaluate [them] and [have] not been identified by the FDA as a substance that presents a significant safety risk in compounding prior to the publication of a final [503A Bulks List] rule." 2017 FDA Guidance at 9–10. The FDA has stated that it will not take action against state-licensed pharmacies, federal facilities, or licensed physicians for compounding using such a bulk drug substance, provided the following conditions are met:

(1) "The original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under [21 U.S.C. § 360] (including foreign establishments registered under [21 U.S.C. § 360(i)])";

(2) "The bulk drug substance is accompanied by a valid [certificate of analysis]"; and

(3) "The drug product compounded using the bulk drug substance is compounded in compliance with all other conditions of [21 U.S.C. § 353a]."

Id.

13. Second, the 503A Category 2 list, titled *Bulk Drug Substances that Raise Significant Safety Risks*,[3] also contains bulk drug substances that "were nominated with sufficient supporting information to permit FDA to evaluate them." 2017 FDA Guidance at 7. As to these items, however, the FDA has identified "significant safety risks related to [their] use … in compounding." *Id.* A bulk drug substance included on the Category 2 list may not be used in compounding under section 503A, unless the FDA later publishes a final rule authorizing its use under that section. *See* 2017 FDA Guidance at 7, 9.

downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf.

[3] *Id.* at 2.

14. The Category 2 list, last updated on July 1, 2017, currently includes three items: domperidone, quinacrine hydrochloride for intrauterine administration, and germanium sesquioxide.

15. Third, the 503A Category 3 list, titled *Bulk Drug Substances Nominated Without Adequate Support*,[4] includes bulk drug substances as to which the FDA currently has insufficient supporting information to evaluate. A bulk drug substance included on the Category 3 list may not be used in compounding under section 503A, although it could be renominated and, if sufficient information is provided, placed in a different category at that time. *See* 2017 FDA Guidance at 7–10.

Cesium Chloride

16. Cesium chloride is a bulk drug substance presently used in compounding of human drug products by some pharmacists in state-licensed pharmacies or federal facilities, and by some licensed physicians.

17. Cesium chloride is not an FDA-approved drug and is not a component of any FDA-approved drug. There are no USP or NF monographs for cesium chloride.

18. According to the FDA's clinical reviewer, "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."[5] However, "[n]umerous case reports

[4] *Id.* at 3–6.

[5] Transcript of Pharmacy Compounding Advisory Committee (PCAC), Morning Session, Thursday, June 23, 2016, at 75 (testimony of Dr. Michael Brave), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM563843.pdf (last visited July 18, 2018) (hereinafter "June 2016 Transcript").

describe serious toxicities resulting from cesium chloride ingested as an alternative treatment for cancer, including hypokalemia, seizures, ventricular arrhythmias, syncope, and death."[6]

19. On or about 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 substances in treating individuals with certain types of cancer, through intravenous infusion.[7]

20. In a May 31, 2016, evaluation of cesium chloride, FDA reviewers flagged "serious safety concerns related to the use of cesium chloride."[8] Discussing the safety issues raised by animal studies involving cesium chloride, the FDA reviewers observed, among other findings, that "[n]onclinical studies in mice, rats, and dogs identified the cardiovascular and central nervous systems as the major target organ systems of toxicity [from cesium chloride]. Major toxicity findings included ventricular tachycardia, decreased motor activities, autonomic disturbances, and salivation."[9] The FDA reviewers concluded that "[t]he toxicity profile of cesium chloride in animal studies weighs against its inclusion on the [503A Bulks List]."[10]

21. Additionally, the FDA reviewers' evaluation of human safety data recognized that "[s]everal case reports describe serious toxicities resulting from cesium chloride ingested as an

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[6] *Id.*

[7] *See* FDA, *FDA Briefing Document: Pharmacy Compounding Advisory Committee (PCAC) Meeting, June 23, 2016*, at Tab 2a, https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM505041.pdf (last visited July 18, 2018) (hereinafter "June 2016 Briefing Document").

[8] *Id.* at Tab 2b, p. 9.

[9] *Id.* at Tab 2b, p. 5.

[10] *Id.*

alternative therapy for cancer, including hypokalemia, seizures, ventricular arrhythmias, syncope, and death."[11] The FDA reviewers concluded that "[t]he limited information available about the safety of cesium chloride gives rise to significant concern about its use in compounding."[12]

22. In addition to identifying serious safety issues, the FDA reviewers found that "[c]esium chloride has not been shown to be efficacious for the prevention or treatment of any form of cancer" and that no reliable evidence showed any clinical benefit from cesium chloride in human cancer treatment.[13]

23. The FDA reviewers concluded, in sum, that "[c]esium 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."[14]

24. On June 23, 2016, the FDA's Pharmacy Compounding Advisory Committee considered the nomination of cesium chloride to the 503A Bulks List. The advisory committee recommended, by a unanimous vote of eleven to zero (with no abstentions), that the FDA should not place cesium chloride on the 503A Bulks List, due to safety and other concerns.[15]

25. Although more than two years have passed since the FDA reviewers concluded that cesium chloride presents "serious safety concerns" and is "not safe for human use," and an FDA advisory committee unanimously recommended that cesium chloride not be included on the 503A Bulks List, the FDA has not yet taken action to prevent section 503A compounding using cesium

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[11] *Id.* at Tab 2b, p. 6.

[12] *Id.* at Tab 2b, p. 7.

[13] *Id*.

[14] *Id.* at Tab 2b, p. 9.

[15] June 2016 Transcript, *supra* note 5, at 98–102.

chloride. Rather, cesium chloride remains on the permissive 503A Category 1 list on the FDA's website. Therefore, under the 2017 FDA Guidance, a pharmacist in a state-licensed pharmacy or federal facility, or licensed physician may still use cesium chloride in section 503A compounding without any threat of action by the FDA.

Public Citizen's Citizen Petition

26. On December 6, 2017, Public Citizen submitted a citizen petition to the FDA asking the FDA to (1) immediately 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 2017 FDA Guidance, and (2) promulgate a rule that formally excludes cesium chloride from the 503A Bulks List.

27. Public Citizen's petition provides sufficient grounds for the FDA to take the actions that Public Citizen requested.

28. Public Citizen is entitled to a decision on its citizen petition. *See* 21 C.F.R. § 10.30(e)(1).

29. On or about June 4, 2018, the FDA provided an "interim" response to Public Citizen's petition. The FDA stated that it had not reached a decision on the petition because the petition "raises complex issues requiring extensive review and analysis by Agency officials."

30. To date, despite its own reviewers' and advisory committee's recognition of the safety issues associated with using cesium chloride in the compounding of human drug products, the FDA has not issued a decision on Public Citizen's petition, has not given any indication on when it will respond substantively to the petition, and has not taken either of the actions that Public Citizen requested to prevent section 503A compounding using cesium chloride.

31. The considerable danger to public health occasioned by the FDA's failure to act on Public Citizen's petition regarding the status of cesium chloride counsels in favor of expeditious action. The FDA's decisional process is lagging unreasonably in light of the nature and extent of the public health interests addressed in the petition and harmed by the FDA's delay.

CLAIMS FOR RELIEF

32. The FDA's failure to act on Public Citizen's petition constitutes agency action unlawfully withheld or unreasonably delayed under the APA, 5 U.S.C. § 706(1).

33. The FDA's failure to act on Public Citizen's petition is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, under the APA, 5 U.S.C. § 706(2)(A).

WHEREFORE, Plaintiff requests that this Court

A. Declare unlawful the FDA's failure to act on Public Citizen's petition;

B. Order the FDA to issue a decision on Public Citizen's petition within 30 days of the Court's order;

C. Award Public Citizen its reasonable costs and attorney's fees under 28 U.S.C. § 2412; and

D. Grant all other appropriate relief.

Dated: July 23, 2018

Respectfully submitted,

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