



February 5, 2020

Sidney M. Wolfe, M.D.
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, D.C. 20009

Re: Docket Number FDA-2018-P-2838

Dear Dr. Wolfe:

This letter responds to your citizen petition dated July 23, 2018 (July 2018 Petition). In your petition, you request that the Food and Drug Administration (FDA or we):

(1) immediately issue a determination that dietary supplements containing cesium chloride or any other cesium salt present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, under ordinary conditions of use and require that all such dietary supplements be removed from the market; and

(2) issue an FDA safety communication advising consumers and health care professionals about the harms that can result from supplementation with cesium chloride (CsCl) or any other cesium salt.

(July 2018 Petition at 2).

In accordance with 21 C.F.R. § 10.30(e)(3), we are granting in part and denying in part your July 2018 Petition for the reasons stated in section II of this response.

I. Background

A. Cesium Chloride

1. The December 2017 Petition and Compounding and the 503A Bulks List

FDA appreciates the safety and public health concerns that motivate your request. We note that you raised similar concerns about the use of cesium chloride in the bulk drug compounding context in your December 6, 2017 citizen petition (December 2017 Petition), to which FDA responded on July 23, 2018 (2018 Response).¹ Because the December 2017 Petition is factually

¹ See Docket No. FDA-2017-P-6758.

related to the July 2018 Petition, it is appropriate to provide some brief background information as to that matter.

As explained in our 2018 Response, 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 Federal Food, Drug, and Cosmetic Act (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 certain sections of the FD&C Act. Among these conditions, if a drug is compounded using a bulk drug substance,² that bulk drug substance must be the subject of an applicable United States Pharmacopeia (USP) monograph; if there is no monograph, it must be a component of an FDA-approved drug; and if there is no monograph and the bulk substance is not a component of an FDA approved drug, it must appear on a list developed by the Secretary through regulations. This list of bulk drug substances is sometimes referred to as the 503A bulks list.³ Under section 503A(c)(1) of the FD&C Act, before developing the 503A bulks list through regulation, FDA must convene and consult an advisory committee on compounding. FDA also must consult with USP when promulgating the regulations.⁴

On July 2, 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.⁵ Cesium chloride was nominated for use in combination with other natural substances in treating individuals with numerous types of cancers, by a presumed alkalinizing effect.

On June 23, 2016, FDA held a meeting of the Pharmacy Compounding Advisory Committee (PCAC) to discuss cesium chloride, among other nominated bulk drug substances.⁶ FDA prepared a package of background information for the PCAC.⁷ This package included information regarding cesium chloride and identified serious safety concerns related to its use. (None of the conclusions or recommendations in the background package, however, are final determinations.)⁸ For the reasons discussed in the background package, FDA did not

² A *bulk drug substance* as referenced in section 503A(b)(1)(A) of the FD&C Act 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.” 21 C.F.R. §§ 207.1, 207.3.

³ See section 503A(b)(1)(A)(i) of the FD&C Act.

⁴ Section 503A(c)(2) of the FD&C Act.

⁵ *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations*, 79 Fed. Reg. 37747 (July 2, 2014).

⁶ *Pharmacy Compounding Advisory Committee; Notice of Meeting*, 81 Fed. Reg. 35782 (June 3, 2016).

⁷ *FDA Briefing Document, Pharmacy Compounding Advisory Committee (PCAC) Meeting, June 23, 2016*, available at: <https://www.fda.gov/media/98730/download> (accessed Jan. 10, 2020).

⁸ *Id.* at Tab 2b.

recommend that cesium chloride be included on the list of bulk drug substances that may be used in compounding under section 503A of the FD&C Act.⁹ After discussion, PCAC voted not to recommend that cesium chloride be included on the 503A bulks list.¹⁰

The December 2017 Petition asked, in part, that FDA 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 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*. For the reasons stated in our 2018 Response, FDA granted that request.

Relatedly, on July 23, 2018, we also issued a “compounding risk alert” to warn consumers, patients and health care professionals that the use of cesium chloride and other cesium salts poses significant safety risks (e.g., heart toxicity) and is potentially associated with death. The alert also noted that these events can occur both with oral administration and when cesium chloride is injected into the body.¹¹ In that alert, we further noted that cesium chloride is sometimes taken either by mouth or by injection by cancer patients who seek alternative treatments, notwithstanding that no cesium chloride-containing products have been approved by FDA to treat cancer or other diseases.¹²

More recently, on September 5, 2019, FDA proposed that cesium chloride be identified in Part 216 of Title 21 of the Code of Federal Regulations as having been considered for, but not placed on, the 503A bulks list.¹³ (This rulemaking remains pending.)

2. The July 2018 Petition

The July 2018 Petition, which contains some of the same information presented in the December 2017 Petition, asks FDA to take certain actions regarding dietary supplements that are or contain cesium chloride or any other cesium salt.¹⁴ With respect to dietary supplements, the July 2018 Petition asserts that cesium chloride currently is being marketed to the public in a variety of forms, including aqueous solutions and capsules;¹⁵ that at least one website promotes cesium carbonate (another type of cesium salt) supplementation as a treatment for cancer;¹⁶ and that some dietary supplement products containing cesium chloride are marketed with accompanying

⁹ *Id.*

¹⁰ *Amendments to the List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act*, 84 Fed. Reg. 46688 at 46695 (proposed Sept. 5, 2019) (the 2019 NPRM).

¹¹ *FDA alerts health care professionals of significant safety risks associated with cesium chloride*, dated July 23, 2018, available at: <https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-significant-safety-risks-associated-cesium-chloride> (“2018 Safety Alert”) (accessed Jan. 10, 2020).

¹² *Id.*

¹³ The 2019 NPRM at 46703.

¹⁴ July 2018 Petition at 1. Cesium chloride is a type of cesium salt, with the formula CsCl.

¹⁵ July 2018 Petition at 4.

¹⁶ July 2018 Petition at 5. The petition also discusses other statements that it asserts are promotional in nature. July 2018 Petition at 3-4.

potassium supplements, which the July 2018 Petition asserts indicates manufacturers' awareness of the adverse effects of cesium chloride on serum potassium.¹⁷

B. Applicable Authorities

As amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. No. 103-417, 108 Stat. 4325, the FD&C Act defines the term “dietary supplement” (21 U.S.C. § 321(ff)) and provides FDA with various tools to take action against and protect public health from dietary supplements that are adulterated or misbranded, including products that are unsafe. For example, as noted in the July 2018 Petition,¹⁸ a dietary supplement is deemed to be adulterated under section 402(f)(1)(A) of the FD&C Act (21 U.S.C. § 342(f)(1)(A)) if it is a:

dietary supplement or contains a dietary ingredient that (A) presents a significant or unreasonable risk of illness or injury under (i) conditions of use recommended or suggested in labeling, or (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.

Section 701(a) of the FD&C Act (21 U.S.C. § 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. FDA exercised this authority when we published the *Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk* (the “Ephedrine Alkaloids Final Rule”), which declared dietary supplements containing ephedrine alkaloids to be adulterated under section 402(f)(1)(A) of the FD&C Act because such products presented an “unreasonable risk of illness or injury” under the conditions of use recommended or suggested in labeling or under ordinary conditions of use.¹⁹

Although rulemaking is an important tool FDA can use to help protect the public from adulterated or misbranded dietary supplements, the FD&C Act provides numerous alternatives to address such products. A regulation is not necessary to find that a dietary ingredient or a dietary supplement presents a significant or unreasonable risk,²⁰ nor would rulemaking be needed to establish that a dietary supplement is adulterated or misbranded for another reason. FDA also may seek to enforce the FD&C Act through individual adjudications. For example, FDA may initiate an *in rem* action to seize and forfeit violative products, such as adulterated or misbranded dietary supplements, while in or held for sale after their shipment in interstate commerce, *see* section 304(a)(1) of the FD&C Act (21 U.S.C. § 334(a)(1)); initiate an action to enjoin violations relating to adulterated or misbranded dietary supplements, *see* section 302(a) of the FD&C Act (21 U.S.C. § 332(a)); or order the administrative detention of dietary supplements found during, among other things, an inspection, if an FDA officer or qualified employee has “reason to believe that such article[s] are] adulterated or misbranded,” *see* section 304(h)(1)(A) of the FD&C

¹⁷ July 2018 Petition at 5. As stated in the “compounding risk alert,” cesium chloride is associated with a lower blood level of potassium, which is a mineral that is essential to normal heart function.

¹⁸ Petition at 1.

¹⁹ *Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk*, 69 Fed. Reg. 6788 (Feb. 11, 2004) (codified at 21 C.F.R. § 119.1).

²⁰ *Id.* at 6830. *See also* *Nutraceutical Corp. v. Von Eschenbach*, 459 F.3d 1033 (10th Cir. 2006); *Hi-Tech Pharm., Inc. v. Crawford*, 544 F.3d 1187, 1191 (11th Cir. 2008).

Act (21 U.S.C. § 334(h)(1)(A)). Thus, Congress provided numerous enforcement authorities in the FD&C Act to protect the public health, while leaving the choice of enforcement method to FDA’s discretion on a case-by-case basis.

Moreover, if a product is purportedly marketed as a dietary supplement but is, for example, intended for use in the treatment of disease in man or other animals, then it is a “drug” under the FD&C Act.²¹ Such a product would be subject to all of the requirements and enforcement authorities that pertain to drugs under the FD&C Act. For example, a drug is deemed to be misbranded under section 502(f)(1) of the FD&C Act (21 U.S.C. § 352(f)(1)) if its labeling does not bear adequate directions for use, unless it qualifies for an exemption from that requirement, and under section 502(j) of the FD&C Act (21 U.S.C. § 352(j)) if it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in its labeling. Furthermore, a product that is a “new drug” may not be legally introduced or delivered for introduction into interstate commerce unless it is the subject of an approved new drug application or an effective investigational new drug application, as described in sections 301(d), 505(a), and 505(i) of the FD&C Act (21 U.S.C. §§ 331(d), 355(a)&(i)).

II. Discussion

Your petition asks us to:

- (1) immediately issue a determination that dietary supplements containing cesium chloride or any other cesium salt present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, under ordinary conditions of use and require that all such dietary supplements be removed from the market, and
- (2) issue an FDA safety communication advising consumers and health care professionals about the harms that can result from supplementation with CsCl or any other cesium salt.

We address each of your requests below.

A. Request for FDA to Issue a Safety Communication About the Harms That Can Result from Using Dietary Supplements Containing Cesium Chloride or Any Other Cesium Salt

As noted previously, FDA issued a “compounding risk alert” on July 23, 2018, to warn consumers, patients, and health care professionals that the use of cesium chloride and other cesium salts poses significant safety risks (e.g., heart toxicity) and is potentially associated with death.²² Although the alert focused, in part, on uses of cesium when injected into the body, the alert also identified significant safety concerns associated with cesium when administered orally. These same concerns associated with oral administration apply to products marketed as dietary

²¹ See section 201(g)(1)(B) of the FD&C Act (21 U.S.C. § 321(g)(1)(B)).

²² 2018 Safety Alert, *supra* n.12.

supplements, which by definition are products intended for ingestion.²³ Moreover, since the publication of the July 23, 2018 compounding risk alert, and as part of our review of the July 2018 Petition, we have conducted a comprehensive review of the CFSAN Adverse Event Reporting System (CAERS) database from 2004 to date for events related to cesium chloride or other cesium salts in dietary supplements, and have reviewed FDA's adverse event reporting system (FAERS) database for the same for the sake of comprehensiveness. We also have considered the comments submitted in response to the July 2018 Petition and the 2019 NPRM that referenced cesium chloride.

Based on our review of available information relating to cesium chloride and other cesium salts for ingestion, we agree with the July 2018 Petition that issuing a safety communication about the harms that can result from using dietary supplements containing cesium chloride or any other cesium salt could help protect consumers from serious safety risks. Human intake of cesium chloride is associated with cardiotoxicity.²⁴ Cesium intake by humans has a known negative effect on cardiac conduction and hypokalemia (low serum potassium). These conditions increase the risk for potentially fatal cardiac arrhythmias.²⁵ In addition, FDA notes that Health Canada issued an advisory against any use of unauthorized oral or intravenous stable cesium compounds, including cesium chloride, in September 2009, because of cardiac risks associated with oral or intravenous use.²⁶

Given the public health concerns related to the use of dietary supplements containing cesium chloride and other cesium salts, FDA has concluded that a safety communication is an appropriate action. We have therefore issued on February 5, 2020 a safety communication advising consumers and health care professionals about the harms that can result from ingesting dietary supplements that contain cesium chloride or any other cesium salt.²⁷ Accordingly, your request for us to issue an FDA safety communication advising consumers and health care professionals about the harms that can result from supplementation with cesium chloride and other cesium salts is granted.

²³ See section 201(ff)(2)(A) (21 U.S.C. § 321(ff)(2)(A)).

²⁴ 2018 Safety Alert, *supra* n.12; Lyon, A.W. and W.J. Mayhew, *Cesium toxicity: a case of self-treatment by alternate therapy gone awry*. *Ther Drug Monit*, 2003. 25(1): p. 114-6; Melnikov, P. and L.Z. Zaroni, *Clinical effects of cesium intake*. *Biol Trace Elem Res*, 2010. 135(1-3): p. 1-9.

²⁵ Horn, S., et al., *Cesium-associated hypokalemia successfully treated with amiloride*. *Clin Kidney J*, 2015. 8(3): p. 335-8. Dalal AK, Harding JD, Verdino RJ. Acquired long QT syndrome and monomorphic ventricular tachycardia after alternative treatment with cesium chloride for brain cancer. *Mayo Clin Proc*. 2004; 79: 1065-1069.

²⁶ *Health Canada Warns Canadians of Cardiac Risks Associated with Cesium Chloride*, dated September 10, 2009, available at <https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2009/13329a-eng.php> (accessed Jan. 10, 2020).

²⁷ <https://www.fda.gov/food/dietary-supplement-products-ingredients/public-health-alert-concerning-dietary-supplements-containing-cesium-salts>

B. Request for FDA to Issue a Determination That Dietary Supplements Containing Cesium Chloride or Any Other Cesium Salt Present a Significant or Unreasonable Risk of Illness or Injury and Require the Removal of Such Products from the Market

Although the July 2018 Petition does not specify what type of “determination” is being requested from FDA, it requests that FDA “immediately require the removal from the market of all dietary supplements containing the chemical cesium chloride (CsCl) or any other cesium salt,” and refers to the example of ephedrine alkaloids.²⁸ It is not clear whether this is a request for FDA to proceed by enforcement action or by rulemaking, and, therefore, we address each in turn.

To the extent that you are requesting that FDA take enforcement action, we note that any such action would require the referral of a matter to a United States Attorney, and that such matters are within the exclusive discretion of the Commissioner and are not appropriate for a citizen petition.²⁹ Therefore, to the extent the July 2018 Petition requests enforcement action to remove such products from the market, your request is denied.

To the extent that you are requesting that FDA promulgate a regulation declaring that dietary supplements containing cesium chloride are adulterated under the FD&C Act because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use, that request is also denied. Since receiving the July 2018 Petition, we have searched the market to identify products being sold as dietary supplements that contain cesium chloride or other cesium salts. Our review identified only a very small number of such dietary supplements currently on the market. Furthermore, FDA has searched the relevant databases for adverse events reported to have occurred in individuals following consumption of dietary supplements that contain cesium chloride or other cesium salts. Our review identified only a few such events. As explained above, a regulation is not necessary for FDA to determine that a dietary supplement containing a specific ingredient is adulterated or misbranded, including because it presents a significant or unreasonable risk of illness or injury.³⁰ While rulemaking can be an efficient regulatory mechanism in some circumstances — for example, when, as in the case of ephedrine alkaloids, there are hundreds of different products on the market that contain the same ingredient that presents a risk to the public health³¹ and several hundred reported adverse events³² — rulemaking would not be the most efficient mechanism when the products that would be implicated by such rulemaking, and the reports of serious adverse events, are both few in number, as is the case here.

²⁸ July 2018 Petition at 1.

²⁹ See 21 C.F.R. § 10.30(k) (Section 10.30 “does not apply to the referral of a matter to a United States attorney for the initiation of court enforcement action ...”); see also 21 C.F.R. § 10.3 (excluding from the definition of “Administrative action” “the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral”).

³⁰ See *supra* n.24.

³¹ Ephedrine Alkaloids Final Rule at 6830.

³² *Id.* at 6814.

Given our limited resources, we need to direct those resources as efficiently as possible. As discussed above, a variety of enforcement tools remain available to FDA, including those pertaining to dietary supplements and, where applicable, pertaining to drugs. Therefore, we are denying the request to engage in rulemaking to issue a determination about dietary supplements that contain cesium chloride or other cesium salts at this time.

III. Conclusion

For the reasons stated in section II of this response, your requests are granted in part and denied in part.

Sincerely,

A handwritten signature in black ink, appearing to read "Douglas Stearn". The signature is written in a cursive style with a large, stylized "D" and "S".

Douglas Stearn
Deputy Director for Regulatory Affairs
Center for Food Safety
and Applied Nutrition