May 6, 2022

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group
1600 20th Street, N.W.
Washington, DC 20009

Re: Docket No. FDA-2021-P-0378

Dear Dr. Carome:

This letter responds to the citizen petition submitted on behalf of Public Citizen to the Food and Drug Administration (FDA or Agency), received on April 13, 2021 (Petition). The Petition requests that FDA:

> (1) Promptly amend, through notice and comment rulemaking, FDA regulations at 21 C.F.R. § 216.24 — the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness and that therefore may not be compounded under the exemptions provided by Section 503A(a) or Section 503B(a) of the [Federal Food, Drug and Cosmetic Act (FD&C Act)] — to include (a) all drug products containing lorcaserin hydrochloride and (b) all parenteral drug products containing bacitracin.
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> (2) Promptly implement a policy stipulating that whenever the FDA issues a notice announcing a determination that a drug product was withdrawn from sale for reasons of safety or effectiveness, the agency simultaneously will issue an NPRM [notice of proposed rulemaking] proposing to amend FDA regulations at 21 C.F.R. § 216.24 to include that drug product on the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness and that therefore may not be compounded under the exemptions provided by Section 503A(a) or Section 503B(a) of the [FD&C Act].[1]

We have carefully considered the Petition. For the reasons described in this response, the Petition is denied.

I. BACKGROUND

A. Lorcaserin Hydrochloride

Belviq (lorcaserin hydrochloride) tablets, 10 milligrams (mg), were the subject of new drug application (NDA) 022529, and Belviq XR (lorcaserin hydrochloride) extended-release tablets, 20 mg, were the subject of NDA 208524, both held by Eisai Inc. (Eisai), and initially approved

[1] Petition at 1-2.

on June 27, 2012, and July 15, 2016, respectively.[2] Belviq and Belviq XR were indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of:

- 30 kilograms per square meter (kg/m^2) or greater (obese); or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipedemia, type 2 diabetes).[3]

In 2012, FDA required the application holder to conduct a clinical trial to evaluate the risk of cardiovascular problems associated with lorcaserin hydrochloride.[4] Analysis of the results of that trial, which was conducted over five years, suggested an imbalance in cancer in humans.[5] On January 14, 2020, FDA issued a Drug Safety Communication alerting the public that the results of the clinical trial assessing the risk of heart-related problems showed a possible increased risk of cancer with Belviq and Belviq XR.[6] After being asked by FDA to voluntarily withdraw Belviq and Belviq XR for the U.S. market, Eisai submitted a request to FDA on February 13, 2020, to withdraw approval for NDA 022529 for Belviq and NDA 208524 for Belviq XR under 21 CFR 314.150(d) and waived its opportunity for a hearing.[7] On September 17, 2020, FDA issued a *Federal Register* notice withdrawing approval of these NDAs.[8] On March 4, 2021, FDA issued a *Federal Register* notice announcing its determination that Belviq and Belviq XR were withdrawn from sale for reasons of safety and effectiveness.[9]

B. Bacitracin for Injection

Bacitracin for injection is an antibiotic for intramuscular administration with an approved indication limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug.[10] In April 2019, FDA's Antimicrobial Drugs Advisory Committee discussed the safety and effectiveness of bacitracin for injection and voted almost unanimously, with one abstention, that its benefits do not outweigh its risks, which include nephrotoxicity and anaphylactic reactions, for the drug's only approved indication.[11] On January 31, 2020, FDA asked six application holders for bacitracin for injection to voluntarily

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[2] See 86 FR 12697, March 4, 2021.

[3] Id.

[4] Id.

[5] Id.

[6] Safety clinical trial shows possible increased risk of cancer with weight-loss medicine Belviq, Belviq XR (lorcaserin), available at https://www.fda.gov/drugs/drug-safety-and-availability/safety-clinical-trial-shows-possible-increased-risk-cancer-weight-loss-medicine-belviq-belviq-xr.

[7] See 86 FR 12697.

[8] 85 FR 58063, September 17, 2020.

[9] 86 FR 12697.

[10] See 86 FR 14127, March 12, 2021.

[11] Id.

request withdrawal of approval of their applications under 21 CFR 314.150(d). On March 12, 2021, FDA announced the withdrawal of five abbreviated new drug applications (ANDAs) from multiple application holders who requested voluntary withdrawal of their applications and waived the opportunity for a hearing.[12]

Xellia Pharmaceuticals ApS (Xellia), the holder of the remaining ANDA for a marketed bacitracin for injection drug product (ANDA 203177), did not initially request withdrawal of its application. However, in response to further communication from FDA, Xellia requested withdrawal of ANDA 203177 and waived the opportunity for a hearing on June 14, 2021.

C. Applicable Statutory and Regulatory Framework

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions under which a human drug product compounded by a licensed pharmacist or licensed physician for an identified individual patient based on a prescription is exempt from three sections of the FD&C Act: (1) section 501(a)(2)(B) (concerning current good manufacturing practice); (2) section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (concerning the approval of new drugs under NDAs or ANDAs).[13] One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that the licensed pharmacist or licensed physician does not compound a drug product that appears on a list published by the Secretary in the *Federal Register* of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (see section 503A(b)(1)(C) of the FD&C Act). Section 503A(c)(1) of the FD&C Act also states that the Secretary shall issue regulations to implement section 503A, and that before issuing regulations to implement section 503A(b)(1)(C) pertaining to the withdrawn or removed list, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health.

Section 503B of the FD&C Act (21 U.S.C. 353b) describes the conditions under which human drugs compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility are exempt from three sections of the FD&C Act: (1) section 502(f)(1); (2) section 505; and (3) section 582 (concerning drug supply chain security requirements).[14] One of the conditions in section 503B of the FD&C Act that must be satisfied to qualify for the exemptions is that the drug does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (see section 503B(a)(4)). To be eligible for the exemptions in section 503B, a drug must be compounded in an outsourcing facility in which the compounding of drugs occurs only in accordance with section 503B, including as provided in section 503B(a)(4) of the FD&C Act.

[12] Id.

[13] Section 503A(a) of the FD&C Act.

[14] Section 503B(a) of the FD&C Act.

Given that nearly identical criteria are described in section 503A(b)(1)(C) and section 503B(a)(4) of the FD&C Act, these conditions have been implemented through the publication of a single list in the *Federal Register* of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.[15] This list (referred to as ''the Withdrawn or Removed List'' or ''the List''), which has been developed through the notice and comment rulemaking process, is codified in 21 CFR § 216.24.

Regulations are issued from time to time to revise the Withdrawn or Removed List.[16] Before regulations to amend the Withdrawn or Removed List are issued, the Pharmacy Compounding Advisory Committee (PCAC) is convened and consulted, unless a determination is made that the issuance of such regulations before consultation is necessary to protect the public health.[17] A *Federal Register* notice is published to announce the intention to convene and consult the PCAC to discuss proposed inclusion of specific drug products on the Withdrawn or Removed List.[18] As announced in the *Federal Register* notice, interested persons are invited to present data, information, or views in writing on issues pending before the committee. All electronic and written submissions can be made at the addresses listed in the *Federal Register* notice. Additionally, interested parties have the opportunity to present relevant data, information, or views orally during a portion of the advisory committee meeting referred to as the "open public hearing." The *Federal Register* notice also provides instructions on how interested parties can request time during the open public hearing to deliver a formal oral presentation to the PCAC.

The notice and comment rulemaking process provides an additional opportunity for public participation, allowing interested parties to comment on a proposal to add drug products to the Withdrawn or Removed List. Comments received are reviewed and considered before the issuance of a final rule revising the Withdrawn or Removed List.

After soliciting public comments and consulting with the PCAC, entries may be added to the List in § 216.24 of drug products that have been withdrawn or removed from the market because the drug products or components of such drug products have been found to be unsafe or not effective.

D. Upcoming PCAC Meeting

As announced in today's *Federal Register*, a public meeting of the PCAC is scheduled to be held on June 8, 2022. The committee will discuss whether to amend the List to add lorcaserin hydrochloride. As explained in the *Federal Register* of July 2, 2014, the List may specify that a drug may not be compounded in any form, or, alternatively, may expressly exclude a particular

[15] See sections 503A(b)(1)(C) and 503B(a)(4) of the FD&C Act; see also 81 FR 69668 at 69669-70, November 7, 2016; 83 FR 63569 at 63570, December 11, 2018.

[16] See, e.g., 83 FR 63569, December 11, 2018.

[17] See section 503A(c)(1) of the FD&C Act.

[18] See, e.g., 80 FR 29717, May 22, 2015.

formulation, indication, dosage form, or route of administration from an entry on the List.[19] Further, a drug may be listed only with regard to certain formulations, indications, routes of administration, or dosage forms because it has been found to be unsafe or not effective in those particular formulations, indications, routes of administration, or dosage forms.[20] At the upcoming meeting, FDA plans to seek the committee's advice concerning whether to include lorcaserin hydrochloride on the List, as well as the appropriate scope of any entry.

II. DISCUSSION

A. Inclusion of Lorcaserin Hydrochloride on the Withdrawn or Removed List

The Petition requests that the Agency "promptly amend FDA regulations at 21 C.F.R. § 216.24 to include all drug products containing lorcaserin hydrochloride" in light of the "determinations that Belviq (lorcaserin hydrochloride) tablets, 10 mg, and Belviq XR (lorcaserin hydrochloride) extended-release tablets, 20 mg, were withdrawn from sale for reasons of safety or effectiveness."[21]

As described above, a notice in today's *Federal Register* established a public docket and announced a forthcoming PCAC meeting where the potential inclusion of lorcaserin hydrochloride on the Withdrawn or Removed List will be discussed. The *Federal Register* notice invites interested persons to comment on issues pending before the PCAC and describes how to notify FDA of a desire to make a formal oral presentation at the meeting. Because public comments and participation can help shape the PCAC's analysis, as well as FDA's decision regarding whether to propose including certain drug products on the Withdrawn or Removed List in a proposed rule,[22] we decline to address here the substance of your Petition's request regarding the addition of lorcaserin hydrochloride to the List. Instead, you should direct your input regarding the inclusion of lorcaserin hydrochloride on the List to the docket opened for the PCAC meeting and to notify FDA if you would like to make a formal oral presentation at the meeting. Please note the deadlines set out in the *Federal Register* notice announcing the upcoming PCAC meeting for providing comments or notifying FDA of your interest in making a presentation. Our decision to answer the Petition's request in this manner will permit FDA to efficiently reach a determination regarding the proposed addition to the Withdrawn or Removed List while taking into consideration all comments and information provided by the public, as well as the PCAC's recommendations. Accordingly, your request regarding the addition of drug products containing lorcaserin hydrochloride to the Withdrawn or Removed List is denied.

[19] 79 FR 37687 at 37689-90.

[20] Id.

[21] Petition at 5.

[22] As noted above, if FDA determines that it is appropriate to issue a proposed rule to add lorcaserin hydrochloride to the List, an NPRM will be published in the *Federal Register*, and the public will have the opportunity to submit written or electronic comments on FDA's proposal.

B. Inclusion of Bacitracin for Injection on the Withdrawn or Removed List

The Petition also asks that FDA "promptly amend FDA regulations at 21 C.F.R. § 216.24 to include all parenteral drug products containing bacitracin," given the "FDA's March 12, 2021, notice announcing that it had requested that all holders of ANDAs for bacitracin for injection voluntarily request withdrawal of approval of their applications specifically because the agency had determined the drug was unsafe."[23]

The Petition correctly observes that FDA requested the voluntary withdrawal of marketing applications for bacitracin for injection because of its serious risks, as well as the availability of other effective FDA-approved treatments that do not have these risks.[24] However, as explained in greater detail below, broader considerations inform whether to include a drug product on the Withdrawn or Removed List. We are continuing to consider issues relevant to whether bacitracin for injection should be included on the Withdrawn or Removed List and will take further action if appropriate. If the Agency decides to discuss with the PCAC whether to add bacitracin for injection to the Withdrawn or Removed List, you will have the opportunity to submit comments to the docket for such PCAC meeting and to notify FDA if you would like to make a formal oral presentation at the meeting. At the present time, however, the Petition's request that we add bacitracin for injection to the Withdrawn or Removed List is denied.

C. Procedure for Updating the Withdrawn or Removed List

As noted above, the Petition requests that FDA "[p]romptly implement a policy stipulating that whenever the FDA issues a notice announcing a determination that a drug product was withdrawn from sale for reasons of safety or effectiveness, the agency simultaneously will issue an NPRM proposing to amend [the Withdrawn or Removed List] to include that drug product . . . ."[25] The Petition further asserts that FDA would not be required to convene and consult an advisory committee prior to amending the Withdrawn or Removed List in this circumstance. According to the Petition, section 503A(c)(1) of the FD&C Act permits FDA to issue regulations revising the Withdrawn or Removed List "before consultation with an advisory committee if it determines that doing so is necessary to protect the public health."[26] This determination, the Petition states, could "be made in all cases in which the FDA has determined that a drug product was withdrawn or removed from the market because it was unsafe" and "in most cases in which the FDA has determined that a drug product was withdrawn or removed from the market because it was ineffective."[27] In cases where the Agency would like to seek the advice of the PCAC before issuing a final rule amending § 216.24, the Petition suggests that "the agency could schedule a meeting of the advisory committee for shortly after the NPRM is

[23] Petition at 5.

[24] See 86 FR 14127, March 12, 2021.

[25] Petition at 2.

[26] Id. at 6 (emphasis omitted).

[27] Id.

published in the Federal Register."[28] Finally, the Petition states that FDA also should aim to amend the Withdrawn or Removed List within six months of publishing the NPRM proposing such amendment.[29]

According to the Petition, the "expeditious regulatory action" that it suggests "would minimize the period during which patients could be potentially harmed by exposure to compounded formulations of drug products that were determined to have been withdrawn or removed from the market for reasons of safety or effectiveness."[30] It contends that "[d]elaying such regulatory action poses unacceptable and avoidable risks to patients and public health."[31]

For the reasons explained below, however, FDA does not agree that it should "implement a policy stipulating that whenever the FDA issues a notice announcing a determination that a drug product was withdrawn from sale for reasons of safety or effectiveness, the agency simultaneously will issue an NPRM proposing to amend FDA regulations at 21 C.F.R. § 216.24 to include that drug product."[32]

The inclusion of an entry on the Withdrawn or Removed List prevents all compounding of human drug products that fall within that entry. Such a bar on compounding human drug products might not be appropriate in every instance in which FDA determines that an FDA-approved drug product was withdrawn from sale for reasons of safety or effectiveness. Compounded drug products are not FDA approved, but they can serve an important role for patients whose medical needs cannot be met by an FDA-approved drug product. FDA's determination that an FDA-approved drug product was withdrawn from the market for reasons of safety or effectiveness does not consider compounded drug products, including those that contain components of the drug whose approval was withdrawn. Compounded drug products may raise different considerations that necessitate separate and thorough analysis through FDA's process for considering potential entries for the Withdrawn or Removed List. For example, compounded drug products may differ from the approved product in various ways such as formulation, concentration, indication, route of administration, or dosage form. These differences are not considered in FDA's determinations regarding whether FDA-approved drug products were withdrawn from the market for reasons of safety or effectiveness. Because this separate analysis is a critical step in FDA's decisionmaking process on whether to add an entry to the Withdrawn or Removed List, it could be premature for FDA to propose amending the List whenever it issues a determination that an FDA-approved drug product was withdrawn from sale for reasons of safety or effectiveness.

Moreover, section 503A of the FD&C Act describes a consultation and rulemaking process by which FDA may add an entry to the Withdrawn or Removed List. Specifically, section

[28] Id.

[29] Id.

[30] Id.

[31] Id.

[32] Id. at 2.

503A(c)(1) of the FD&C Act states that "[b]efore issuing regulations to implement subsection[] . . . (b)(1)(C) [pertaining to the Withdrawn or Removed List] . . . , the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health." FDA recognizes that adding drug products to the Withdrawn or Removed List would limit their availability to patients and providers. Consulting the PCAC and soliciting input from the public in connection with this consultation provide FDA with important information that factors into its consideration of whether to include drug products on the Withdrawn or Removed List and the appropriate scope of such an inclusion.

In making determinations regarding potential additions to the Withdrawn or Removed List, the FDA benefits from the recommendations of the PCAC, which is composed of subject matter experts. The PCAC consists of a core of twelve voting members, including the Chair. Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of pharmaceutical compounding, pharmaceutical manufacturing, pharmacy, medicine, and related specialties. These members include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.[33] The PCAC provides advice on scientific, technical, and medical issues concerning human drug compounding under sections 503A and 503B of the FD&C Act, and, as required, any other product for which FDA has regulatory responsibility, and makes appropriate recommendations to the Commissioner of Food and Drugs.[34]

Further, PCAC meetings can provide an opportunity for the public to contribute to the process of revising the List and an opportunity for FDA to obtain information that may impact the position that FDA will propose in the rulemaking.[35] In many cases, FDA believes the public benefits from being able to consider the PCAC's prior expert input during the comment period of a proposed rule, which can promote efficiency in the rulemaking process. Thus, FDA believes implementing the petition's proposed policy that would favor consulting with the PCAC after issuing a proposed rule could deny FDA and the public the benefit of having a full informational foundation to support informed decisionmaking. PCAC meetings are open to the public except as determined otherwise by the Commissioner or designee in accordance with the Government in the Sunshine Act (5 U.S.C. 552b(c)) and the Federal Advisory Committee Act. Notice of all meetings is given to the public by publication of a notice in the *Federal Register*, and interested parties may submit comments to a docket associated with the notice. During the PCAC meeting,

[33] See sections 503A(c)(1) and 503B(c)(2) of the FD&C Act.

[34] See FDA's PCAC website for more information at https://www.fda.gov/advisory-committees/human-drug-advisory-committees/pharmacy-compounding-advisory-committee.

[35] Although it is not the case with respect to lorcaserin hydrochloride, FDA sometimes issues an NPRM proposing to amend the List prior to consulting the PCAC. As FDA has previously explained, the order of the PCAC meeting and issuance of a proposed rule "will depend on the timing of the Advisory Committee meetings, the priority of matters that may be brought before the Advisory Committee, and the status of other compounding-related rulemakings." 81 FR 69668 at 69671, October 7, 2016.

representatives from FDA, industry, and sometimes members of the public present information on the subjects being discussed at the meeting, and the PCAC members have an opportunity to ask questions and vote on the subjects being discussed.

FDA does not agree with the Petition's suggestion that, "in all cases in which the FDA has determined that a drug product was withdrawn or removed from the market because it is unsafe and . . . in most cases in which the FDA has determined that a drug product was withdrawn or removed from the market because it was ineffective," FDA would not be required to consult an advisory committee prior to amending § 216.24 to include the drug product because FDA could reasonably determine that updating § 216.24 "is necessary to protect public health."[36] FDA recognizes that section 503A provides a more expedited path to amend the Withdrawn or Removed List in cases where FDA determines that issuance of regulations amending the List before the PCAC consultation is necessary to protect the public health. Based on FDA's experience to date, however, we generally expect to use this expedited pathway in rare circumstances and that instead, it is generally appropriate to consult the advisory committee before proposing to add a drug product to the Withdrawn or Removed List. FDA has also found that the PCAC consultation and the notice and comment rulemaking processes have not caused delays that created unacceptable risks to patients and public health.[37]

FDA's compounding program aims to protect patients from unsafe, ineffective, and poor quality compounded drugs, while preserving access to lawfully marketed compounded drugs for patients who have a medical need for them. Protecting patient safety and the public health are among FDA's highest priorities, and, for the reasons described above, FDA believes its current process for updating the List best serves these aims. Thus, the Petition's request that FDA implement the proposed policy for adding drug products to the Withdrawn or Removed List is denied.

[36] Petition at 6.

[37] FDA has previously considered altering its approach to amending the Withdrawn or Removed List. As explained in the *Federal Register* on October 7, 2016 (81 FR 69668), FDA solicited public comment on the appropriate procedure for updating the Withdrawn or Removed List in the July 2, 2014 *Federal Register* (79 FR 37687) and specifically considered that consulting with the advisory committee and completing the rulemaking process are likely to contribute to delay in updating the List to reflect current safety information. After consideration of the comments submitted on the July 2014 proposed rule, however, FDA declined to alter its process for amending the Withdrawn or Removed List, stressing, among other things, the importance of public participation in the process of amending the List.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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Date: 2022.05.06 13:34:20 -04'00'

Patrizia Cavazzoni, M.D.
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