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Citizen Petition

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and Public Citizen's Health Research Group, the undersigned submit this petition under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §§ 353a and 353b) and under Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to promptly amend FDA regulations at 21 C.F.R. § 216.24 — the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness and therefore may not be compounded under the exemptions provided by Sections 503A(a) or Section 503B(a) of the FDCA — to include all drug products containing lorcaserin hydrochloride and all parenteral drug products containing bacitracin.

Furthermore, we request that the Commissioner 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implement a policy stipulating that whenever the FDA issues a notice announcing a determination that a drug product was withdrawn from sale for reasons of safety or effectiveness, that agency simultaneously will issue a notice of proposed rulemaking (NPRM) proposing to amend FDA regulations at 21 C.F.R. § 216.24 to include that drug product. Such an agency policy would minimize the period during which patients could be potentially harmed by exposure to compounded formulations of FDA-approved drug products previously marketed by traditional drug manufacturers that were determined by the agency to have been withdrawn or removed from the market because they were unsafe or ineffective. Delaying such regulatory action poses unacceptable and avoidable risks to patients and public health.

A. ACTION REQUESTED

- (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through notice and comment rulemaking, FDA regulations at 21 C.F.R. § 216.24 — the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness and that therefore may not be compounded under the exemptions provided by Section 503A(a) or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 FDCA — to include (a) all drug products containing lorcaserin hydrochloride and (b) all parenteral drug products containing bacitracin.

- (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 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 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 requirements of 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 may not compound a drug product that appears on a list published by the Secretary of Health and Human Services 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 (section 503A(b)(1)(c)). Section 503A(c)(1) stipulates that the FDA must convene and consult with an advisory committee on compounding before issuing regulations to implement the list of drug products established under section 503A(b)(1)(c) *unless the agency determines that the issuance of such regulations before consultation the advisory committee is necessary to protect the public health.*

Section 503B of the FDCA describes the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the requirements of the following three sections of the FDCA: section 505, section 502(f)(1), and section (21 U.S.C. § 360eee-1) of Part H (concerning pharmaceutical distribution supply chain requirements). One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503B is that a registered outsourcing facility may not compound a drug product that appears on a list published by the Secretary of Health and Human Services 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 (section 503B(a)(4)).

21 C.F.R. § 216.24 – Drug products withdrawn or removed from the market for reasons of safety or effectiveness

FDA regulations at 21 C.F.R. § 216.24 currently list 85 drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness.

The initial final rule establishing the list of drug products under FDA regulations at 21 C.F.R. § 216.24 was published on March 8, 1999 and included 59 drug products.¹

On July 2, 2014, the FDA proposed adding 24 drug products to the list of drug products under FDA regulations at 21 C.F.R. § 216.24 and amending the description of one drug product that was already on the list.² In most cases, the determination that the drug products proposed for inclusion on the list had been withdrawn or removed from the market for reasons of safety or effectiveness had been made at least several years earlier. On October 7, 2016 — more than two years after the issuing the proposed rule — the FDA finally issued a final rule adding the 24 drug products to the list of drug products under FDA regulations at 21 C.F.R. § 216.24.³

The list was last updated on December 11, 2018, to include all drug products containing bromocriptine mesylate for prevention of physiological lactation and all intravenous drug products containing greater than a 16-milligram (mg) single dose of ondansetron hydrochloride.⁴ In both cases, the determination that the drug product proposed for inclusion on the list had been withdrawn or removed from the market for reasons of safety or effectiveness had been made at least several years earlier.

The list of drug products under FDA regulations at 21 C.F.R. § 216.24 currently does not include all drug products containing lorcaserin hydrochloride or all parenteral drug products containing bacitracin, nor has the FDA issued an NPRM proposing to include these drug products on the list.

2. FDA determination regarding Belviq (lorcaserin hydrochloride)

On March 4, 2021, the FDA published a notice in the Federal Register announcing that the agency had determined 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 and that the agency would not accept or approve abbreviated new drug applications (ANDAs) for lorcaserin hydrochloride tablets, 10 mg and 20 mg.⁵

The following excerpts from the FDA's notice indicates that these lorcaserin hydrochloride products were withdrawn from sale specifically for reasons of safety:

In 2012, the Agency required the drug manufacturer to conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the risk of cardiovascular problems. The Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients--Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) clinical trial was conducted to fulfill this requirement. An analysis of the CAMELLIA-TIMI 61 trial results suggests an imbalance in cancer in humans. Although chance effect cannot be ruled out, the imbalance persisted throughout multiple analysis approaches. The clinical findings corroborated by the evidence from the animal models informed the Agency's

¹ 64 FR 10944-10947.

² 79 FR 37687-37696.

³ 81 FR 69668-69677.

⁴ 83 FR 63569-63574.

⁵ 86 FR 12697-12698.

assessment that the risk outweighs any potential benefits for the current indications. These findings were considered clinically meaningful and could not be adequately addressed through labeling. Additional evidence would be necessary to investigate this signal; however, the Agency has determined that it is unlikely that the necessary safety endpoints (i.e., cancer and reproductive safety) can be readily or ethically investigated in a clinical trial. Because preclinical or clinical studies would first need to be conducted to address these concerns, the Agency has determined that this drug product would not be considered safe and effective if it were reintroduced to the market.

FDA issued a Drug Safety Communication on January 14, 2020, alerting the public that results from a clinical trial assessing the risk of heart-related problems show a possible increased risk of cancer with BELVIQ and BELVIQ XR (see <https://www.fda.gov/drugs/drug-safety-and-availability/safety-clinical-trial-shows-possible-increased-risk-cancer-weight-loss-medicine-belviq-belviq-xr>). On February 13, 2020, FDA announced it had asked Eisai to voluntarily withdraw BELVIQ and BELVIQ XR from the U.S. market (see <https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market>). On February 13, 2020, Eisai submitted a request to FDA to withdraw approval of NDA 022529 for BELVIQ and NDA 208524 for BELVIQ XR under 21 CFR 314.150(d) and waived its opportunity for a hearing. As requested by Eisai, the Agency issued a Federal Register notice on September 17, 2020 (85 FR 58063), withdrawing approval of the applications for BELVIQ (lorcaserin hydrochloride) tablets, 10 mg, and BELVIQ XR (lorcaserin hydrochloride) extended-release tablets, 20 mg, effective September 17, 2020.

Accordingly, the Agency will remove BELVIQ (lorcaserin hydrochloride) tablets, 10 mg, and BELVIQ XR (lorcaserin hydrochloride) extended-release tablets, 20 mg, from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product.

3. FDA withdrawal of approval of five ANDAs for bacitracin for injection

On March 12, 2021, the FDA published a notice in the Federal Register announcing that the agency was withdrawing approval of five ANDAs for bacitracin for injection from multiple holders.⁶ The ANDAs were withdrawn from approval at the request of Akorn Inc. (Akorn), Mylan ASI LLC (Mylan), Pfizer Inc. (Pfizer), X-GEN Pharmaceuticals, Inc. (X-GEN), and Fresenius Kabi USA, LLC (Fresenius), all of which waived their opportunity for a hearing.

The following excerpts from the FDA's notice indicate that the agency had requested that all application holders of bacitracin for injection voluntarily request withdrawal of approval of their applications specifically because the agency had determined the drug was unsafe:

On January 31, 2020, FDA requested that all application holders of bacitracin for injection voluntarily request withdrawal of approval of their applications under Sec. 314.150(d) (21 CFR 314.150(d)). Bacitracin for injection is an antibiotic for intramuscular administration, the use of which is limited to the treatment of infants with

⁶ 86 FR 14127-14128.

pneumonia and empyema caused by staphylococci shown to be susceptible to the drug. Bacitracin for injection poses serious risks, including nephrotoxicity and anaphylactic reactions. Healthcare professionals generally no longer use bacitracin for injection to treat infants with pneumonia and empyema because other effective FDA-approved treatments are available that do not have these risks.

In April 2019, FDA's Antimicrobial Drugs Advisory Committee met and discussed the safety and effectiveness of bacitracin for injection. The advisory committee voted almost unanimously, with one abstention, that the benefits of bacitracin for intramuscular injection do not outweigh its risks, including nephrotoxicity and anaphylactic reactions, for the drug's only approved indication. Based on FDA's review of currently available data and information, the Agency believes that the potential problems associated with bacitracin for injection are sufficiently serious that the drug should be removed from the market...

Therefore, for the reasons discussed above, which the applicants do not dispute in their letters requesting withdrawal of approval under Sec. 314.150(d), FDA's approval of ANDAs 206719, 090211, 060733, 064153, 065116, and all amendments and supplements thereto, is withdrawn (see DATES). Distribution of Akorn's bacitracin for injection (50,000 units/vial), Mylan's bacitracin for injection (50,000 units/vial), Pfizer's bacitracin for injection (10,000 units/vial and 50,000 units/vial), X-GEN's bacitracin for injection (50,000 units/vial), or Fresenius's bacitracin for injection (50,000 units/vial) into interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(a) and 331(d))).

The FDA's notice reasonably can be read as a determination by the agency that bacitracin for injection was withdrawn from sale for reasons of safety or effectiveness.

4. Conclusions

Given the FDA's March 4, 2021, 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, the agency should promptly amend FDA regulations at 21 C.F.R. § 216.24 to include all drug products containing lorcaserin hydrochloride.

Likewise, 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, the agency should promptly amend FDA regulations at 21 C.F.R. § 216.24 to include all parenteral drug products containing bacitracin.

Moreover, moving forward, the FDA should not delay initiating the notice and comment rulemaking process for amending FDA regulations at 21 C.F.R. § 216.24 once the agency has published a determination that a drug product was withdrawn from sale for reasons of safety or effectiveness. Instead, whenever the FDA issues a notice announcing such a determination, the

agency simultaneously should issue an NPRM proposing to amend FDA regulations at 21 C.F.R. § 216.24 to include that drug product. Such simultaneous action could shorten the rulemaking process for amending these regulations by several months to years.

Although the FDA has always convened and consulted with an advisory committee on compounding before implementing changes to FDA regulations at 21 C.F.R. § 216.24, section 503A(c)(1) of the FDCA allows the agency to issue such revised regulations *before consultation with an advisory committee if it determines that doing so is necessary to protect public health*. Such a determination certainly could reasonably 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 likely could reasonably be made in most cases in which the FDA has determined that a drug product was withdrawn or removed from the market because it was ineffective. Nevertheless, if the agency feels it needs to seek advice from its Pharmacy Compounding Advisory Committee before issuing a final rule amending FDA regulations at 21 C.F.R. § 216.24 to include a particular drug product, the agency could schedule a meeting of the advisory committee for shortly after the NPRM is published in the Federal Register.

Finally, given the simplicity of proposed rules that would amend FDA regulations at 21 C.F.R. § 216.24 each time the FDA publishes a determination that a particular drug product was withdrawn from sale for reasons of safety or effectiveness, the FDA also should strive to issue a final rule amending FDA regulations at 21 C.F.R. § 216.24 to include that drug product within six months of publishing the NPRM.

Such expeditious regulatory action 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. Delaying such regulatory action poses unacceptable and avoidable risks to patients and public health.

For the reasons stated above, we hereby petition the FDA, pursuant to Sections 503A and 503B of the FDCA and FDA regulations at 21 C.F.R. § 10.30, to take the following actions:

- (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 FDCA — to include (a) all drug products containing lorcaserin hydrochloride and (b) all parenteral drug products containing bacitracin.
- (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, that agency simultaneously will issue an NPRM 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 FDCA.

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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