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Testimony Before the Food and Drug Administration's Pharmacy Compounding Advisory Committee Regarding Additions to the List of Drug Products Withdrawn or Removed from the Market Because They Have Been Found to be Unsafe or Not Effective

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Comments on Parenteral Neomycin Sulfate

Public Citizen strongly supports the Food and Drug Administration's (FDA's) proposal to add all parenteral drug products containing the aminoglycoside antibiotic neomycin sulfate (except when used for ophthalmic or otic use or in combination with polymyxin B sulfate for irrigation of the intact bladder) to the list of drug products that have been withdrawn or removed from the market because they have been found to be unsafe or not effective and that therefore may not be compounded under the exemptions provided by Section 503A(a) or Section 503B(a) of the Food, Drug, and Cosmetic Act (FDCA) (the Withdrawn or Removed List (codified at 21 C.F.R. § 216.24)). Such action should have been taken by the agency many years ago.

In 1979 — *more than four decades ago* — the FDA first proposed taking regulatory action to remove parenteral neomycin products from the market based on "widespread evidence that the drug's risks outweigh its benefit."[1] At that time, the fact that systemic exposure to neomycin caused serious nephrotoxicity, ototoxicity, and neuromuscular paralysis with respiratory arrest was well-established, and no safe parenteral dosage regimen of the drug had been recognized. Moreover, neomycin was known to be more toxic than other FDA-approved parenteral aminoglycosides.

In 1988 — *more than three decades ago* — the FDA issued a final rule amending the antibiotic drug regulations to revoke the provisions for certification of neomycin in sterile vials for parenteral use and another notice withdrawing the approval of four abbreviated antibiotic drug applications for neomycin in sterile vials for parenteral use because "the risks involved in the parenteral use of neomycin sulfate [were] judged to outweigh any benefits that might be derived from its continued availability."[2,3]

In 1998 — *more than two decades ago* — the FDA appropriately proposed including "all parenteral drug products containing neomycin sulfate" in its proposed rule to establish the initial Withdrawn or Removed List.[4] However, in the final rule establishing the initial list that was issued in 1999, the FDA excluded parenteral neomycin products from the list because the agency

[1] 44 FR 44180-44182.
[2] 53 FR 12658-12661.
[3] 53 FR 48232-49233.
[4] 63 FR 54082-54089.

had failed to take appropriate administrative actions to (1) address pending requests submitted in 1988 for hearings regarding the withdrawal of approval of applications for neomycin sulfate in sterile vials for injection and the withdrawal of approval of the applications for neomycin sulfate for prescription compounding; and (2) respond to four petitions submitted in 1988 to stay these and other agency actions related to neomycin products.[5]

Disturbingly, the straightforward administrative actions for resolving these requests for hearings and petitions for stays of action related to neomycin products were not completed until February 2019, more than 30 years after these requests and petitions had been submitted to the agency.[6]

The FDA's decades-long delay in placing all parenteral drug products containing neomycin sulfate (with the previously noted exceptions) on the Withdrawn or Removed List is unacceptable and borders on regulatory malpractice. The agency now must move swiftly to place parenteral drug products containing neomycin sulfate on the Withdrawn or Removed List given their unacceptable risk-benefit profile.

Comments on the FDA's Process for Updating the Withdrawn or Removed List

While the case of neomycin is an extreme example of unacceptable delays in adding dangerous drugs to the Withdrawn or Removed List, there are many examples over the past decade of drugs not being added to this list until at least several years after the FDA had determined that the drugs had been withdrawn or removed from the market because they had been found to be unsafe or not effective.

Delaying such regulatory action poses unacceptable and avoidable risks to patients and public health. Therefore, on April 13, 2021, Public Citizen petitioned the FDA to take the following actions:

(1) Promptly amend, through notice and comment rulemaking, the Withdrawn or Removed List to include (a) all drug products containing lorcaserin hydrochloride and (b) all parenteral drug products containing the antibiotic 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 a notice of proposed rulemaking (NPRM) proposing to amend the Withdrawn or Removed List.[7]

Regarding lorcaserin hydrochloride, on March 4, 2021, the FDA announced in the Federal Register that the agency had determined that lorcaserin hydrochloride tablets marketed under the

[5] 64 FR 10944-10947.
[6] Food and Drug Administration. FDA briefing document, Pharmacy Compounding Advisory Committee (PCAC) meeting, June 9, 2021. https://www.fda.gov/media/149084/download. Accessed June 8, 2021. PDF p. 1103.
[7] Public Citizen. Citizen Petition to the FDA to amend the list of drug products that were withdrawn or removed from the market because they were deemed unsafe of ineffective. April 13, 2021. https://mkus3lurbh3lbztg254fzode-wpengine.netdna-ssl.com/wp-content/uploads/2576.pdf. Accessed June 8, 2021.

brand names Belviq and Belviq XR for weight loss 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.[8] The FDA noted in its notice that results of a required post-market trial to evaluate the risk of cardiovascular problems suggested an imbalance in cancer in humans. The FDA further stated the following:

> 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 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.

Regarding parenteral drug products containing bacitracin, on March 12, 2021, the FDA announced in the Federal Register that the agency was withdrawing approval of five ANDAs for bacitracin for injection from multiple holders.[9] The FDA noted the following in its notice:

> Bacitracin for injection is an antibiotic for intramuscular administration, the use of which is limited to the treatment of infants with 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.
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> 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…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.

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.

Moving forward, the FDA should not delay initiating the rulemaking process for amending the Withdrawn or Removed List 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

[8] 86 FR 12697-12698.
[9] 86 FR 14127-14128.

announces such a determination, it simultaneously should issue an NPRM proposing to amend the Withdrawn or Removed List to include that drug product. Such simultaneous action could shorten the rulemaking process for amending the Withdrawn or Removed List by several months to years.

Although section 503A(c)(1) of the FDCA stipulates that the FDA must convene and consult with an advisory committee before implementing changes to the Withdrawn or Removed List, it allows the agency to issue such 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 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 was withdrawn or removed from the market because it was ineffective. Nevertheless, if the agency feels it must seek advice from this committee before issuing a final rule amending the Withdrawn or Removed List, the agency could schedule a meeting of the advisory committee for shortly after the NPRM proposing to amend the list is published.

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.