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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comments on the Food and Drug Administration's Notice Proposing 19 Exclusions and Four Inclusions for the List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act
Docket No. FDA-2018-N-3240

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments regarding the notice "List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act," which was published in the *Federal Register* on July 31, 2020 (Docket No. FDA-2018-N-3240).[1]

Public Citizen strongly supports the Food and Drug Administration's (FDA's) proposal *not* to include diazepam, dobutamine hydrochloride (HCl), dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium thiosulfate, and verapamil HCl on the list of bulk drug substances for which there is a clinical need under Section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) (hereafter, the 503B Bulks List). Each of these nominated bulk drug substances is a component of one or more FDA-approved drug products. In each case, the nominators failed to either explain or provide support for why an attribute of the FDA-approved drug(s) makes them unsuitable to treat certain patients and that the proposed compounded drug products are intended to address.

We take no position regarding the FDA's proposal to include diphenylcyclopropenone, glycolic acid, squaric acid dibutyl ester, and trichloroacetic acid on the 503B Bulks List to compound drug products for topical use.

I. Background

Section 503B of the FDCA, which was enacted under the Drug Quality and Security Act in 2013, stipulates the conditions that must be satisfied for human drug products compounded by an

[1] 85 FR 46126-46141.

outsourcing facility to be exempt from the FDCA requirements concerning (a) the approval of drugs under new drug applications or abbreviated new drug applications, (b) the labeling of drugs with adequate directions for use, and (c) drug supply-chain security. Drug products compounded under the conditions in section 503B are not exempt from Current Good Manufacturing Practice requirements and must satisfy other requirements.

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B is that the outsourcing facility may not compound a drug using a bulk drug substance unless (a) the bulk drug substance appears on the 503B Bulks List or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing.

Previously, the FDA appropriately has noted that compounded drugs pose a higher risk to patients than FDA-approved drugs. The agency once again reaffirmed that position in its July 31, 2020, notice by emphasizing that compounded drugs produced by outsourcing facilities have not undergone FDA premarket review for safety, effectiveness, and quality. In addition, these drugs have not been determined to be safe or effective for conditions of use reflected in drug product labeling and lack a premarket inspection and finding of manufacturing quality. We agree with the FDA that because compounded drug products are subject to a lower regulatory standard than FDA-approved drug products, they should be used only by patients whose medical needs cannot be met by an FDA-approved drug product.

II. Comments about the 19 nominated bulk drug substances that the FDA proposes to exclude from the 503B Bulks List

For each of the 19 bulk drug substances — diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium thiosulfate, and verapamil HCl — the FDA noted that the nominated bulk drug substance is a component of one or more FDA-approved drugs available at concentrations that in nearly all cases are the same as the specifically proposed concentrations of the proposed compounded drug products to be produced from the nominated bulk drug substance. In each case, the nominators failed to either explain or provide support for why an attribute of the FDA-approved drug(s) makes them unsuitable to treat certain patients and that the proposed compounded drug products are intended to address. The FDA therefore appropriately found in each case that there is no basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable to treat certain patients for a condition that the FDA (or nominator) has identified for evaluation and that a proposed compounded product is intended to address.

We therefore strongly endorse the agency's proposal to exclude diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium

thiosulfate, and verapamil HCl from the 503B Bulks List. To protect public health, we urge the FDA to expeditiously issue a final notice that excludes these 19 drugs from the 503B Bulks List.

III. The FDA needs to rescind its January 2017 *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*

It is readily apparent that the basis for nominating the bulk drug substances referenced in the FDA's July 31 notice and many other bulk drug substances to the 503B Bulks List was not to ensure that unmet clinical needs are satisfied but rather to meet the commercial goals of the nominators.

There is no dispute that (a) compounded drugs pose a higher risk to patients than FDA-approved drugs; (b) the FDA has evaluated and taken final action on only a small fraction of the bulk drug substances nominated for inclusion on the 503B Bulks List; and (c) for every nominated bulk drug substance that the agency has evaluated so far, the agency concluded that the bulk drug substance should not be placed on the 503B Bulks List. Thus, maintaining the FDA's January 2017 *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* is indefensible, reckless, and a threat to public health. In particular, it is unacceptable to allow outsourcing facilities to continue compounding drugs using the approximately 250 bulk drug substances that were nominated with sufficient supporting information for the FDA to evaluate them but have not yet either been identified as raising significant safety concerns or been excluded from the 503B Bulks List.

We therefore urge the FDA to announce that, within a specified time period (for example, six months), it will rescind its January 2017 interim policy, begin enforcing all requirements of 503B, and not allow outsourcing facilities to produce drugs from bulk drug substances unless those substances appear on either the 503B Bulks List or the agency's drug shortage list.

Thank you for the opportunity to comment on these important public health matters.

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