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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 not to Include Bumetanide, Nicardipine Hydrochloride, and Vasopressin 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
Docket No. FDA-2018-N-3240

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments with regard to 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 August 28, 2018 (Docket No. FDA-2018-N-3240).[1]

Public Citizen strongly supports the Food and Drug Administration's (FDA's) proposal *not* to include bumetanide, nicardipine hydrochloride, and vasopressin 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 the nominated bulk drugs is a component of one or more FDA-approved drug products. In each case, the nominators have failed to demonstrate that (a) the drug products proposed to be compounded at a lower concentration than the FDA-approved product(s) must be compounded using a bulk drug substance rather than the approved drug product and (b) there is a clinical need for an outsourcing facility to compound a drug product using the nominated bulk drug substances. In addition, for vasopressin, the nominators failed to demonstrate that an attribute of the FDA-approved product makes it medically unsuitable to treat patients such that patients would need a concentration higher than the FDA-approved vasopressin product.

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 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

[1] 83 FR 43877.

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.

The FDA appropriately notes in its notice that compounded drugs pose a higher risk to patients than FDA-approved drugs.[2] In particular, 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 three nominated products discussed in the FDA notice

A. Bumetanide

QuVa Pharma nominated bumetanide for the 503B Bulks List to compound drugs for management of edema associated with congestive heart failure, cirrhosis, and renal disease.[3] The nominator proposed that this bulk drug substance would be used to compound drugs for intravenous infusion at a strength of 0.1 milligrams/milliliter (mg/mL).

Two FDA-approved generic bumetanide products are available at a strength of 0.25 mg/mL for either intravenous or intramuscular injection.

The FDA noted the following regarding QuVa Pharma's nomination of bumetanide:

> The nomination does not provide a basis to conclude that a bulk drug substance must be used to prepare a drug product containing bumetanide at concentrations below the concentration of the FDA-approved drug product (0.25 mg/mL). The nomination states that it may not be safer to prepare a drug product at such concentrations by starting with the approved drug; however, the nomination also recognizes that doing so would only

[2] *Ibid*.
[3] QuVa Pharma. Letter to Docket No. FDA-2015-N-3469 for bulk drug substances that can be used to compound drug products in accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act; establishment of a public docket. June 21, 2017. https://www.regulations.gov/document?D=FDA-2015-N-3469-0013. Accessed October 29, 2018.

> require a dilution. It does not take the position or provide support for a position that a bulk drug substance must be used to prepare these concentrations of bumetanide.[4]

Accordingly, FDA found no basis to conclude that (a) "the drug products proposed to be compounded at a lower concentration than FDA-approved bumetanide must be compounded using a bulk drug substance rather than the approved drug product" or (b) "there is a clinical need for an outsourcing facility to compound a drug product using the bulk drug substance bumetanide."[5] Therefore, the agency proposed to not include bumetanide on the 503B Bulks List.

We strongly endorse the agency's proposal to exclude bumetanide from the 503B Bulks List. Preparing bumetanide drug products that have a concentration lower than 0.25 mg/mL by diluting one of the FDA-approved sterile bumetanide products clearly would pose less risk to patients than compounding such products from the bulk drug substance bumetanide.

B. Nicardipine hydrochloride.

Cantrell Drug Company nominated nicardipine hydrochloride for the 503B Bulks List to compound drugs for unspecified uses.[6] The nominator proposed that this bulk drug substance would be used to compound drugs for intravenous injection at a strength of 0.1-2.5 mg/mL.

The FDA has approved nicardipine hydrochloride products as 0.1 mg/mL and 0.2 mg/mL ready-to-use solutions for intravenous administration and as a 2.5 mg/mL single-dose vial that must be diluted prior to infusion. These products are indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable.[7]

In assessing this nomination, the FDA noted the following:

> The nomination does not provide a basis to conclude that a bulk drug substance must be used to prepare drug products containing nicardipine hydrochloride at concentrations at or below the concentrations of the FDA-approved products (0.1, 0.2, and 2.5 mg/mL) and for the same route of administration (intravenous) as that described in the approved drug product labeling. Initially, we note that two nicardipine drug products are approved in ready-to-administer form (*e.g.*, no further dilutions needed) at concentrations within the range described in the nominations. The nomination does not present a reason to compound a drug product from a bulk drug substance at these concentrations. With respect to other concentrations, the nomination asserts, without support, that it would be safer to use a bulk drug substance than to start with the approved drug product. However,

[4] 83 FR 43877.
[5] *Ibid*.
[6] Cantrell Drug Company. Comments to Docket No. FDA-2015-N-3469 for bulk drug substances that can be used to compound drug products in accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act; establishment of a public docket. https://www.regulations.gov/document?D=FDA-2015-N-3469-0002. Accessed October 29, 2018.
[7] Wockhardt USA. Label: nicardipine hydrochloride injection. December 2017. https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=e61159ba-ff6b-4696-a642-4f64c79c4708&type=pdf&name=e61159ba-ff6b-4696-a642-4f64c79c4708. Accessed October 29, 2018.

> the nomination does not take the position or provide support for the position that a bulk drug substance must be used to prepare these concentrations of nicardipine hydrochloride. In fact, the approved labeling of another nicardipine hydrochloride drug product directs the drug product to be diluted to a concentration within that range.[8]

Accordingly, FDA found no basis to conclude that (a) "the drug products proposed to be compounded at a lower concentration than FDA-approved nicardipine hydrochloride must be compounded using a bulk drug substance rather than the approved drug product" or (b) "there is a clinical need for an outsourcing facility to compound a drug product using the bulk drug substance nicardipine hydrochloride."[9] Therefore, the agency proposed to not include nicardipine hydrochloride on the 503B Bulks List.

We strongly endorse the agency's proposal to exclude nicardipine hydrochloride from the 503B Bulks List. Preparing nicardipine hydrochloride drug products by diluting one of the FDA-approved sterile nicardipine hydrochloride products clearly would pose less risk to patients than compounding such products from the bulk drug substance nicardipine hydrochloride.

C. Vasopressin

QuVa Pharma nominated vasopressin for the 503B Bulks List to compound drugs for management of septic shock, post-cardiotomy shock, diabetes insipidus, and hypotension.[10] The nominator proposed that this bulk drug substance would be used to compound drugs for intravenous infusion at strengths of 0.1, 0.2, 0.4, and 1.0 units (U)/mL.

BakerHostetler also nominated vasopressin for the 503B Bulks List to compound drugs for treating adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.[11] The nominator proposed that this bulk drug substance would be used to compound drugs for intravenous infusion at a concentration of 1.0 U/mL, as well as concentrations above that of the FDA-approved drug product without identifying any specific concentration.

The FDA has approved vasopressin under the brand name VASOSTRICT at a concentration of 20 U/mL for intravenous infusion. The product is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines.[12] The FDA-

[8] 83 FR 43877.
[9] *Ibid*.
[10] QuVa Pharma. Letter to Docket No. FDA-2015-N-3469 for bulk drug substances that can be used to compound drug products in accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act; establishment of a public docket. April 19, 2017. https://www.regulations.gov/document?D=FDA-2015-N-3469-0012. Accessed October 29, 2018.
[11] BakerHostetler. Letter to Docket No. FDA-2015-N-3469 for bulk drug substances that can be used to compound drug products in accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act; establishment of a public docket. July 27, 2017. https://www.regulations.gov/searchResults?rpp=25&po=0&s=FDA%E2%80%932015%E2%80%93N%E2%80%933469%E2%80%930023&fp=true&ns=true. Accessed October 29, 2018.
[12] Par Pharmaceutical Company. Label: vasopressin (VASOSTRICT). December 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204485s004lbl.pdf. Accessed October 29, 2018.

approved product should be diluted with normal saline or 5-percent dextrose in water to either 0.1 U/mL or 1 U/mL for intravenous administration.

Regarding the nomination from BakerHostetler, the FDA noted the following:

> The [nomination] proposes vasopressin for the 503B Bulks List so that it can be used to compound a drug product whose concentration of vasopressin is higher than undiluted VASOSTRICT. The nomination does not identify an attribute of VASOSTRICT that makes it medically unsuitable for patients and that such high-concentration products are intended to address. The nomination does not identify any data or information as to the need for a higher concentration than the approved product, nor does the nomination identify specific higher concentrations it proposes to compound. In addition, the information provided in the nomination does not identify patients for whom a concentration at or below 20 U/mL is medically unsuitable and who would therefore require a higher concentration, and FDA is not aware of patients who would need concentrations above 20 U/mL.[13]

Regarding both nominations, the FDA further stated the following:

> Both nominations propose vasopressin for the 503B Bulks List so that it can be used to compound drug products whose concentrations of vasopressin are lower than undiluted VASOSTRICT. The nominations do not provide a basis to conclude that a bulk drug substance must be used to prepare a drug product that contains vasopressin at concentrations below the concentration of VASOSTRICT (20 U/mL) and uses the same diluents (dextrose and sodium chloride) and the same route of administration (intravenous) as that described in the approved product labeling. The nominations do not take the position or provide support for the position that a bulk drug substance rather than the FDA-approved drug product must be used to prepare these lower concentrations of vasopressin. In fact, VASOSTRICT's approved labeling directs VASOSTRICT to be diluted using the diluents described in the nominations to concentrations within which the drug products proposed to be compounded fall.[14]

Accordingly, the FDA found no basis to conclude that (a) "an attribute of VASOSTRICT makes it medically unsuitable to treat patients such that patients would need a…concentration higher than that of VASOSTRICT;" (b) "the drug product proposed to be compounded at a lower concentration than VASOSTRICT must be compounded using a bulk drug substance rather than the approved drug;" or (c) "there is a clinical need for an outsourcing facility to compound using the bulk drug substance vasopressin."[15] Therefore, the agency proposed to not include vasopressin on the 503B Bulks List.

We strongly endorse the agency's proposal to exclude vasopressin from the 503B Bulks List. Preparing vasopressin drug products by diluting the FDA-approved vasopressin product clearly

[13] 83 FR 43877.
[14] *Ibid.*
[15] *Ibid.*

would pose less risk to patients than compounding such products from the bulk drug substance vasopressin.

III. Conclusions

To protect public health, we urge the FDA to expeditiously issue a final notice that excludes bumetanide, nicardipine hydrochloride, and vasopressin from the 503B Bulks List

Thank you for the opportunity to comment on this important public health matter.

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