

TABLE 1—ESTIMATED ANNUAL RECORDKEEPING BURDEN ¹—Continued

21 CFR section	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeper	Total hours
Controls to Prevent Adulteration Due to Automatic (Mechanical or Electronic) Equipment—106.35(c) and 106.100(f)(5).	3	52	156	520	81,120
Controls to Prevent Adulteration Due to Automatic (Mechanical or Electronic) Equipment—106.35(c) and 106.100(f)(5).	3	2	6	640	3,840
Controls to Prevent Adulteration Caused by Ingredients, Containers, and Closures—106.40(g) and 106.100(f)(6).	3	52	156	0.17 (10 minutes) ...	26.52
Controls to Prevent Adulteration During Manufacturing—106.50 and 106.100(e).	3	52	156	0.23 (14 minutes) ...	35.88
Controls to Prevent Adulteration From Microorganisms—106.55(d), 106.100(e)(5)(ii), and 106.100(f)(7).	3	52	156	0.25 (15 minutes) ...	39
Controls to Prevent Adulteration During Packaging and Labeling of Infant Formula—106.60(c).	1	12	12	0.25 (15 minutes) ..	3
General Quality Control Testing—106.91(b)(1)–(3).	2	1	2	2	4
General Quality Control—106.91(b)(1), 106.91(d), and 106.100(e)(5)(i).	2	52	104	0.15 (9 minutes)	15.6
General Quality Control—106.91(b)(2), 106.91(d), and 106.100(e)(5)(i).	2	52	104	0.15 (9 minutes)	15.6
General Quality Control—106.91(b)(3), 106.91(d), and 106.100(e)(5)(i).	2	52	104	0.15 (9 minutes)	15.6
Audit Plans and Procedures—106.94; Ongoing Review and Updating of Audits.	3	1	3	8	24
Audit Plans and Procedures—106.94; Regular Audits.	3	52	156	4	624
Total Recurring Recordkeeping Burden	85,889.64
Total Recordkeeping Burden	105,209.64

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Based on a review of the information collection, we made a correction since the last OMB approval. While the one-time estimated recordkeeping burden remains as 19,320 hours, we increased the annual estimated recurring recordkeeping burden to 85,889.64 hours due to a calculation error (a 79,561.58 hour increase) for a total recordkeeping burden of 105,209.64 hours.

Dated: February 27, 2019.

Lowell J. Schiller,

Acting Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-3240]

List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is evaluating substances that have been nominated for inclusion on a list of bulk drug substances (active pharmaceutical ingredients) for which there is a clinical need (the 503B Bulks List). Drug products that outsourcing facilities compound using bulk drug substances on the 503B Bulks List can qualify for certain exemptions from the Federal Food, Drug, and Cosmetic Act (FD&C Act) provided certain conditions are met. This notice identifies two bulk drug substances that FDA has

considered and is not including on the list at this time: Nicardipine hydrochloride and vasopressin. Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of future notices.

DATES: The announcement of the notice is published in the **Federal Register** on March 4, 2019.

ADDRESSES: Submit electronic comments on bulk drug substances nominated for the 503B Bulks List to Docket No. FDA-2015-N-3469. Submit written comments on bulk drug substances nominated for the 503B Bulks List to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Elizabeth Hankla, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5216,

Silver Spring, MD 20993, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

A. Drug Compounding

Compounded drug products can serve an important role for patients for whom an FDA-approved drug product is not appropriate, such as patients who have an allergy and need a medication to be made without a certain dye or hospital inpatients who need infusions of a drug combined with a particular diluent not specified in the approved product labeling. However, they also pose a higher risk to patients than FDA-approved drugs. In 2012, contaminated injectable drug products that a State-licensed compounding pharmacy shipped to patients and healthcare practitioners across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection.¹ This was the most serious of a long history of outbreaks and other serious adverse events associated with contaminated, superpotent, or otherwise poor quality compounded drugs.

In response to this outbreak, Congress enacted the Drug Quality and Security Act (Pub. L. 113-54), which, among other things, added new section 503B to the FD&C Act (21 U.S.C. 353b) and created a new category of compounders known as outsourcing facilities.² Drug products compounded by outsourcing facilities in accordance with the conditions of section 503B are exempt from the following three sections of the FD&C Act: Section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)); section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and section 582 (21 U.S.C. 360eee-1)

¹ See <https://www.cdc.gov/HAI/outbreaks/meningitis.html>.

² See Public Law 113-54, section 102(a), 127 Stat. 587, 587-588 (2013). Other compounders, which are not the subject of this notice, are regulated under section 503A of the FD&C Act (21 U.S.C. 353a). These include licensed pharmacists in State-licensed pharmacies or Federal facilities, and licensed physicians, who have not registered an outsourcing facility with FDA. Drug products compounded by section 503A compounders are exempt from sections 505 (new drug approval requirements), 502(f)(1) (labeling with adequate directions for use), and 501(a)(2)(B) (CGMP requirements) if the conditions of section 503A are met, including that compounding is based on the receipt of valid prescriptions for identified individual patients (section 503A(a)). In general, section 503A compounders do not register with and are not routinely inspected by FDA and are primarily overseen by the States.

(concerning drug supply chain security requirements).³

Drug products compounded under the conditions in section 503B are not exempt from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).⁴ Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.⁵ Outsourcing facilities may or may not obtain prescriptions for identified individual patients and may, therefore, distribute compounded drugs to healthcare practitioners for “office stock” to hold in their offices in advance of patient need.⁶

Because compounded drug products are not FDA-approved, they have not undergone FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities must comply with CGMP requirements and are inspected by FDA according to a risk-based schedule, their drug products have not been determined to be safe or effective for the conditions of use reflected in drug product labeling and have not been subjected to a premarket inspection or associated with a finding of manufacturing quality, all of which are part of the drug approval process. Because compounded drug products are subject to a lower regulatory standard than FDA-approved drug products, they should only be used by patients who could not use an FDA-approved drug product.

When a compounded drug is appropriate for a patient, outsourcing facilities may be able to prepare that drug using an FDA-approved drug product as the starting material. On other occasions it may be necessary to compound the drug from a bulk drug substance.⁷ Section 503B limits the bulk drug substances that outsourcing facilities can use in compounding to those that are used to compound drugs

³ Section 503B(a) of the FD&C Act.

⁴ Compare section 503A(a) of the FD&C Act (exempting drugs compounded in accordance with section 503A from CGMP requirements) with section 503B(a) of the FD&C Act (not exempting drugs compounded in accordance with section 503B from CGMP requirements).

⁵ Section 503B(b)(4) and (5) of the FD&C Act.

⁶ Section 503B(d)(4)(C) of the FD&C Act.

⁷ For a fuller discussion of these issues, see FDA’s guidance for industry entitled “Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act” (503B Bulks Evaluation Guidance), particularly sections II.B. and C., available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM602276.pdf>.

in shortage or that appear on a list developed by FDA of bulk drug substances for which there is a clinical need. Section 503B includes this limitation, among others, to help prevent outsourcing facilities from growing into conventional manufacturing operations making unapproved new drug products. Allowing outsourcing facilities to compound a drug product from a bulk drug substance that is a component of an FDA-approved drug product because of, for instance, economic incentives, when a patient’s clinical needs could be met by the approved drug product or a drug product compounded from the approved drug product would reduce the incentive for applicants to seek FDA approval of drug products and to continue to market them. The drug approval process is critical to ensure pharmaceuticals meet regulatory standards established for quality, safety, and effectiveness. In addition, when it is feasible to compound a drug product by starting with an approved drug product, there are certain benefits of doing so over starting with a bulk drug substance, including benefits relating to the assurances associated with premarket review by FDA for safety, effectiveness, and quality.

In sum, section 503B’s limitation on the 503B Bulks List to bulk drug substances for which there is a clinical need serves important public health functions. First, it helps to limit patient exposure to compounded drug products, which have not been demonstrated to be safe and effective, to those situations in which the compounded drug product is necessary for patient treatment. Second, it preserves the incentives for applicants to invest in the research and testing required to obtain FDA approval and to continue to manufacture FDA-approved drug products, thereby helping to maintain a supply of high-quality, safe, and effective drugs.

B. Statutory and Regulatory Background

Section 503B of the FD&C Act describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from the approval, labeling, and drug supply chain security requirements cited above.⁸ 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 the bulk drug substance appears on a list established by the Secretary of Health and Human

⁸ Section 503B(a) of the FD&C Act.

Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List); or the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act (FDA's drug shortage list) (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.⁹

Section 503B directs FDA to establish the 503B Bulks List by (1) publishing a notice in the **Federal Register** proposing bulk drug substances to be included on the list, including the rationale for such proposal; (2) providing a period of not less than 60 calendar days for comment on the notice; and (3) publishing a notice in the **Federal Register** designating bulk drug substances for inclusion on the list.¹⁰

For purposes of section 503B, *bulk drug substance* means an active pharmaceutical ingredient as defined in 21 CFR 207.1(b).¹¹ *Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, but the term does not include intermediates used in the synthesis of the substance.^{12 13}

II. Methodology for Developing the 503B Bulks List

A. Process for Developing the List

In the **Federal Register** of December 4, 2013 (78 FR 72838), FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List. In response to that request, interested groups and individuals nominated a wide variety of substances. However, many of those nominations were not for substances used in compounding as active pharmaceutical ingredients or did not include sufficient information to allow FDA to evaluate the nominated substance. To improve the efficiency of the process for the development of the

list of bulk drug substances, FDA reopened the nomination process in the **Federal Register** of July 2, 2014 (79 FR 37750) and provided more detailed information on what it needs to evaluate nominations for the list. On October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA-2015-N-3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances or to renominate substances with sufficient information.

As FDA evaluates bulk drug substances, it intends to publish notices for public comment in the **Federal Register** that describe its proposed position on each substance along with the rationale for that position.¹⁴ After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA intends to consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making its determination, and if so, it will seek PCAC input.¹⁵ Depending on its review of the docket comments and other relevant information before the Agency, FDA may finalize its proposed determination without change, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need. FDA will then publish in the **Federal Register** a final determination identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that final determination. FDA will also publish in the **Federal Register** a final determination regarding those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this decision.

FDA intends to maintain a current list of all bulk drug substances it has evaluated on its website, with separate lists for bulk drug substances it has placed on the 503B Bulks List and those it has decided not to place on the 503B Bulks List. FDA will only place a bulk drug substance on the 503B Bulks List where it has determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to

compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and any other information considered by the Agency, FDA will not place a bulk drug substance on the 503B Bulks List.

FDA intends to evaluate the bulk drug substances nominated for the 503B Bulks List on a rolling basis. FDA will evaluate and publish in the **Federal Register** its proposed and final determinations in groups of bulk drug substances until all nominated substances that were sufficiently supported have been evaluated and either placed on the 503B Bulks List or identified as bulk drug substances that were considered but determined not to be appropriate for inclusion on the 503B Bulks List.¹⁶

B. Analysis of Substances Nominated for the List

As noted above, section 503B(a)(2)(A)(i) provides that the 503B Bulks List is to include "bulk drug substances for which there is a clinical need." The Agency is evaluating bulk drug substances that were nominated for inclusion on the 503B Bulks List, proceeding case by case, under the standard provided by the statute.¹⁷ In applying this standard to make determinations regarding the substances set forth in this notice, FDA interprets the phrase "bulk drug substances for which there is a clinical need" to mean that the 503B Bulks List may include a bulk drug substance if: (1) There is a clinical need for an outsourcing facility to compound a drug product, and (2) the drug product must be compounded using the bulk drug substance. FDA is not interpreting supply issues, such as backorders, to be within the meaning of "clinical need" for compounding with a bulk drug substance. Section 503B separately provides for compounding from bulk drug substances under the exemptions from the FD&C Act discussed above if the drug product compounded from the bulk drug

¹⁶ On June 10, 2016 (81 FR 37502), FDA announced the availability of a guidance for industry (revised January 2017) entitled "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act"; available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf>. This guidance provides additional information regarding FDA's policies for bulk drug substances nominated for the 503B Bulks List pending our review of nominated substances under the "clinical need" standard.

¹⁷ See 503B Bulks Evaluation Guidance, *supra* n.7 (describing FDA's policies for developing the 503B Bulks List, including the interpretation of the phrase "bulk drug substances for which there is a clinical need," as it is used in section 503B).

⁹ Section 503B(a)(2)(A) of the FD&C Act.

¹⁰ Section 503B(a)(2)(A)(i)(I) to (III) of the FD&C Act.

¹¹ 21 CFR 207.3.

¹² Section 503B(a)(2) of the FD&C Act and 21 CFR 207.1.

¹³ Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable United States Pharmacopeia or National Formulary monograph, if a monograph exists.

¹⁴ This is consistent with procedures set forth in section 503B(a)(2)(A)(i). Although the statute only directs FDA to issue a **Federal Register** notice and seek public comment when it proposes to include bulk drug substances on the 503B Bulks List, we intend to seek comment when the Agency has evaluated a nominated substance and proposes either to include or not to include the substance on the list.

¹⁵ Section 503B does not require FDA to consult the PCAC before developing a 503B Bulks List.

substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing.

Additionally, we are not considering cost of the compounded drug product as compared with an FDA-approved drug product when assessing “clinical need.”

The bulk drug substances that we are addressing in this notice are components of FDA-approved drug products, and we evaluated them by asking the following questions:

(1) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (a) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (b) the drug product proposed to be compounded is intended to address that attribute?

(2) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?

The reason for question (1) is that unless an attribute of the FDA-approved drug is medically unsuitable for certain patients, and the drug product to be compounded is intended to address that attribute, we do not expect that there will be a clinical need for a patient to use a compounded drug product. Rather, such compounding would unnecessarily expose patients to the risks associated with drug products that have not been shown to meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. The reason for question (2) is that to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance* rather than starting with an FDA-approved drug product.

If the answer to both of these questions is “yes,” there may be clinical need for outsourcing facilities to compound using the bulk drug substance, and we would analyze the question further.¹⁸ If the answer to either of these questions is “no,” there generally would not be a basis to

¹⁸ Under the analysis described in FDA’s 503B Bulks Evaluation Guidance, the additional analysis would consist of the consideration of four additional factors. We did not answer “yes” to both of the threshold questions for nicardipine hydrochloride or vasopressin, so we did not consider these additional factors in our determination not to include nicardipine hydrochloride or vasopressin on the 503B Bulks List.

conclude that there is a clinical need to compound drug products using the bulk drug substance instead of administering or starting with an approved drug product, and we would generally not include the bulk drug substance on the 503B Bulks List.

III. Substances Proposed for the 503B Bulks List

In August 2018, the Agency issued a **Federal Register** notice in which it evaluated three nominated bulk drug substances under the statutory standard—bumetanide, nicardipine hydrochloride, and vasopressin—and proposed not to include them on the 503B Bulks List (the August notice). In this notice, after review of the comments submitted to the docket for the August notice, FDA is making its final determination with regard to nicardipine hydrochloride and vasopressin. At this time, FDA is not making a final determination regarding bumetanide. This substance remains under consideration by FDA.

1. Nicardipine Hydrochloride

Nicardipine hydrochloride has been nominated for inclusion on the 503B Bulks List.¹⁹ The proposed route of administration is intravenous, the proposed dosage form is injection, and the proposed strength is 0.1 to 2.5 milligrams per milliliter (mg/mL). This nominated bulk drug substance is a component of FDA-approved drug products (e.g., NDAs 022276 and 019734). FDA has approved nicardipine hydrochloride drug products as 0.1 mg/mL and 0.2 mg/mL solutions ready for intravenous administration (or “ready to use”) and as a 2.5 mg/mL single-dose vial that must be diluted prior to infusion.^{20 21} The single dose vial (NDA 022276) contains an excipient, benzoic acid; the ready-to-use solutions (NDA 019734) do not contain benzoic acid.

Because nicardipine hydrochloride is a component of FDA-approved drug products, we considered whether (1) there is a basis to conclude that an attribute of each FDA-approved drug product makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the nicardipine

¹⁹ See Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0002.

²⁰ See, e.g., labeling available as of the date of this notice at <https://www.accessdata.fda.gov/spl/data/32756b4e-a977-47ac-9620-0c1ed74d7606/32756b4e-a977-47ac-9620-0c1ed74d7606.xml> (ready-to-use) and <https://www.accessdata.fda.gov/spl/data/5444784f-feje-4352-afd1-b4c487165f3a/5444784f-feje-4352-afd1-b4c487165f3a.xml> (for dilution).

²¹ Nicardipine hydrochloride is also approved as an oral capsule. See, e.g., ANDA 074642.

hydrochloride drug product proposed to be compounded is intended to address that attribute in each FDA-approved drug product; and (2) whether the drug product proposed to be compounded must be compounded using a bulk drug substance.

a. Suitability of FDA-Approved Drug Products.

The nomination proposed to include on the list nicardipine hydrochloride injection compounded to concentrations of 0.1 mg/mL through 2.5 mg/mL. The nomination does not identify attributes of the approved nicardipine hydrochloride products that make them medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address. Specifically, the nomination did not explain why ready-to-use nicardipine hydrochloride injection at 0.1 mg/mL and 0.2 mg/mL, and the 2.5 mg/mL single dose vial (for dilution) are medically unsuitable for certain patients.

A commenter on FDA’s proposal not to include nicardipine hydrochloride on the 503B Bulks List indicated that an attribute of approved nicardipine hydrochloride injections, the presence of the excipient benzoic acid, makes those approved drug products medically unsuitable for patients who have an allergy to benzoic acid and that drug products would be compounded from the bulk drug substance nicardipine hydrochloride without benzoic acid. However, the commenter did not acknowledge the availability of FDA-approved benzoic acid-free nicardipine hydrochloride ready-to-use solutions for intravenous administration or explain why these approved drug products would be medically unsuitable for patients who have an allergy to benzoic acid.²²

Accordingly, with respect to the nicardipine hydrochloride drug products proposed to be compounded, FDA finds no basis to conclude that an attribute of each of the approved drug products makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

The nomination provided no basis to conclude that drug products containing nicardipine hydrochloride must be compounded using a bulk drug substance rather than using an FDA-approved drug product. The nomination

²² See NDAs 022276 and 019734.

and a related comment assert that it would be preferable to compound a drug product using a bulk drug substance than using an approved drug product that requires dilution. However, the nomination and comment do not take the position or provide support for the position that a bulk drug substance must be used to prepare the proposed concentrations of nicardipine hydrochloride. For example, the nomination does not indicate that the desired concentrations of nicardipine hydrochloride could not be prepared by diluting the approved drug product in a form that is suitable for patient administration. Nor is FDA aware of data or information suggesting this cannot be done. We note that the approved labeling of a nicardipine hydrochloride drug product directs the drug product to be diluted to a concentration within that range. We do not consider whether a benzoic acid-free nicardipine hydrochloride drug product must be compounded using the bulk drug substance because benzoic acid-free nicardipine hydrochloride product is FDA-approved at concentrations of 0.1 mg/mL and 0.2 mg/mL and because patients for whom these FDA-approved drug products may be medically unsuitable were not identified in section III.1.a. In sum, FDA finds no basis to conclude that drug products must be compounded using a bulk drug substance rather than the approved drug product.

2. Vasopressin

Vasopressin was nominated for inclusion on the 503B Bulks List to compound drug products that treat septic shock, post-cardiotomy shock, diabetes insipidus, and hypotension.²³ The proposed route of administration is intravenous; the proposed dosage form is injection. The nominators proposed a range of specific concentrations (0.1, 0.2, 0.4, and 1 units/mL (U/mL)) and concentrations above that range without identifying any specific concentration. This nominated bulk drug substance is the active ingredient of the FDA-approved drug VASOSTRICT (NDA 204485). VASOSTRICT is approved as a 20 U/mL intravenous infusion that, per its labeling, 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.²⁴

VASOSTRICT is available in a multidose vial that contains the

preservative agent chlorobutanol and in a single dose vial that does not contain chlorobutanol. The VASOSTRICT labeling includes a contraindication regarding chlorobutanol that applies to the chlorobutanol-containing product.²⁵ Because vasopressin is a component of an FDA-approved drug product, we considered whether (1) there is a basis to conclude that an attribute of each FDA-approved drug product containing vasopressin makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the vasopressin drug product proposed to be compounded is intended to address that attribute; and (2) whether the drug product proposed to be compounded must be compounded using a bulk drug substance.

a. Suitability of FDA-Approved Drug Product

The nominations propose vasopressin for the 503B Bulks List so that it can be used to compound drug product at various concentrations, some lower than undiluted VASOSTRICT and others higher. However, the nominations and the comments do not identify an attribute of VASOSTRICT that makes it medically unsuitable for patients and that the compounded products are intended to address.

The nomination that refers to products with a higher concentration than VASOSTRICT 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 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.

Both nominations also propose to compound vasopressin at specific concentrations lower than undiluted VASOSTRICT. However, the proposed concentrations are within the range described in the labeling for the FDA-approved drug product, and the proposed route of administration (intravenous) is the same as that of

VASOSTRICT. The nominations do not identify an attribute of the approved drug product that would make it medically unsuitable for patients or show that the compounded drug product would address that attribute.

Commenters on FDA's proposal not to include vasopressin on the 503B Bulks List assert that an attribute of VASOSTRICT that makes it medically unsuitable to treat patients is that it contains a preservative, chlorobutanol. Chlorobutanol-containing VASOSTRICT is contraindicated in patients who have an allergy or hypersensitivity to this excipient. However, the commenters fail to acknowledge that the preservative-free formulation of VASOSTRICT is also marketed and fail to explain why that formulation would be medically unsuitable for patients who have an allergy to chlorobutanol.

Accordingly, with respect to the vasopressin drug products proposed to be compounded, FDA finds no basis to conclude that an attribute of VASOSTRICT makes it medically unsuitable to treat certain patients.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

As noted previously, the nominations propose to compound drug products containing vasopressin at concentrations that are lower than undiluted VASOSTRICT, but that are within the range of VASOSTRICT's final, post-dilution concentrations. 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. For example, the nominations do not explain, or even suggest, that the desired concentration of vasopressin cannot be prepared by diluting the approved drug product.²⁶ We do not consider whether a chlorobutanol-free vasopressin drug product must be compounded using the bulk drug substance because a chlorobutanol-free vasopressin product is FDA-approved and because patients for whom this FDA-approved drug product may be medically unsuitable were not identified in section III.2.a. In addition, in light of the analysis in section III.2.a. above, we do not

²³ See Docket No. FDA-2015-N-3469, documents No. FDA-2015-N-3469-0012 and -0023.

²⁴ The labeling as of the date of this notice is available at <https://www.accessdata.fda.gov/spl/data/4166e423-659e-4fe4-8a3c-2394434d00dd/4166e423-659e-4fe4-8a3c-2394434d00dd.xml>.

²⁵ The labeling states that VASOSTRICT is "contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol." However, this contraindication is not applicable to the formulation of VASOSTRICT marketed without chlorobutanol. As described in the package insert, the VASOSTRICT 10 mL solution contains chlorobutanol, while the 1 mL solution does not.

²⁶ For example, the nomination does not take the position or provide support for a position that a drug product prepared by starting with the approved drug product would be unsuitable for patient administration. We also note that outsourcing facilities often prepare ready-to-use forms of drug products for healthcare practitioners by compounding (e.g., diluting) approved drug products, including VASOSTRICT.

consider whether a bulk drug substance must be used to compound a vasopressin drug product at concentrations higher than 20 U/mL. In sum, FDA finds no basis to conclude that drug products must be compounded using a bulk drug substance rather than the approved drug product.

IV. Other Issues Raised in Nominations and Comments

The nominations for nicardipine hydrochloride and vasopressin and some comments state that there could be a benefit in the availability of drug products containing each of these bulk drug substances that do not require dilution prior to administration. We note first, with respect to nicardipine hydrochloride, that two ready-to-use nicardipine drug products are FDA-approved, and the comments do not identify patients for whom these products are medically unsuitable. More broadly, as explained above, when a bulk drug substance is a component of an approved drug, FDA asks whether there is a basis to conclude that an attribute of each approved drug product makes each one medically unsuitable to treat certain patients for their condition, an interpretation that protects patients and the integrity of the drug approval process. The nominations and comments do not show that the approved drug product, when not manufactured in the ready-to-use form, is medically unsuitable for certain patients. Nor do the nominations and comments establish that drug products in the relevant concentrations, including ready-to-use products, cannot be prepared from the approved nicardipine and vasopressin drug products.²⁷ Rather, they propose to compound a ready-to-use product from bulk drug substances to seek improved efficiency for prescribers or healthcare providers, or to address the possibility that the approved drug might be mishandled by a medical professional. That is not clinical need to compound a drug product using a bulk drug substance.

The nominations for nicardipine hydrochloride and vasopressin and some comments also include statements that these substances should be added to the 503B Bulks List because compounding from the bulk drug substance could help outsourcing facilities to address drug shortages and disruptions in supply of approved drugs intended for injection. As noted above, section 503B contains a separate provision for compounding from bulk drug substances to address a drug shortage, and we do not interpret the other price- and supply-related issues advanced by the nomination to be within the meaning of “clinical need” for compounding with a bulk drug substance.

V. Conclusion

For the reasons stated above, we find no clinical need for an outsourcing facility to compound using the bulk drug substances nicardipine hydrochloride and vasopressin and, therefore, we are not including nicardipine hydrochloride and vasopressin on the 503B Bulks List.

Dated: February 26, 2019.
Lowell J. Schiller,
Acting Associate Commissioner for Policy.
 [FR Doc. 2019-03810 Filed 3-1-19; 8:45 am]
BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-N-0280]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Financial Disclosure by Clinical Investigators

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing that a proposed collection

of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by April 3, 2019.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or emailed to *oira_submission@omb.eop.gov*. All comments should be identified with the OMB control number 0910-0396. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Amber Sanford, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-8867, *PRAStaff@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Financial Disclosure by Clinical Investigators

OMB Control Number 0910-0396—Extension

Respondents to this collection are sponsors of marketing applications that contain clinical data from studies covered by the regulations. These sponsors represent pharmaceutical, biologic, and medical device firms. Respondents are also clinical investigators who provide financial information to the sponsors of marketing applications.

Table 1 of this document shows information that is the basis of the estimated number of respondents in tables 2 through 4.

TABLE 1—ESTIMATED NUMBER OF APPLICATIONS, CLINICAL TRIALS, AND INVESTIGATORS SUBJECT TO THE REGULATION BY TYPE OF APPLICATION ¹

Application type	Total number of applications	Number of applications affected	Number of trials	Number of investigators
Drugs:				

²⁷ With respect to vasopressin specifically, a comment states that vasopressin cannot be produced in ready-to-use form because the approved drug product is labeled with an in-use time of 18 hours room temperature or 24 hours

refrigerated once diluted. In contrast, the commenter says that it could compound a “pre-diluted” drug product from bulk vasopressin with a beyond-use-date (BUD) of 60 days. We note that, in accordance with CGMP provisions, outsourcing

facilities can conduct stability studies on vasopressin compounded using the approved drug product to assign a BUD based on data.