

Health Industry Alert: FDA Finalizes Criteria, and First Two Exclusions, for Outsourcing Facility Compounding with Bulk Drug Substances

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Health Industry Alert

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Key Points

- Five years after passage of the DQSA, FDA issued final decisions prohibiting the use of two bulk substances by outsourcing facilities, and finalized criteria for ongoing evaluations of other bulk substances that are currently prohibited but subject to agency enforcement discretion.
- As a result, drug products compounded by outsourcing facilities that contain either of the two prohibited bulk substances, vasopressin and nicardipine hydrochloride, are prohibited and subject to FDA enforcement action.
- Hospitals and other health care providers should review their supply arrangements to evaluate any drug preparations using bulk drug substances and otherwise assess compliance with the DQSA
- Body copy (Body Text style Arial 10.5pt; All body and bullet styles 1.15 line spacing)

On Friday, March 1, 2019, the U.S. Food and Drug Administration (FDA) finalized two long-awaited policies relating to the compounding of bulk drug substances by outsourcing facilities. First, the agency finalized a draft guidance regarding its approach to evaluating clinical need for outsourcing facilities to use bulk drug substances, the raw active ingredients used to make drugs.ⁱ Additionally on Friday, FDA decided to exclude two bulk drug substances—vasopressin and nicardipine hydrochloride—from the list of these substances that outsourcing facilities can use.ⁱⁱ These are the first two final determinations of specific bulk drug substances since enactment of the Drug Quality and Security Act of 2013 (DQSA) more than five years ago.ⁱⁱⁱ As a result, it remains the case that, outside of drug shortages, the use of bulk drug substances by outsourcing facilities is in violation of the Food, Drug, and Cosmetic Act (FDCA) but for some substances is currently subject to the agency's enforcement discretion.

Background

The DQSA created a new category of drug compounders called “outsourcing facilities,” which are permitted to prepare and distribute unapproved drugs without obtaining premarket approval from the FDA or prescriptions for individual patients.^{iv} To qualify, these facilities must register with the FDA, pay fees and submit to inspections against

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good manufacturing practices, and meet other requirements. For more information on the five-year old law, see Akin Gump's report, *The DQSA: Five Years In*.

Unlike traditional pharmacies that compound drugs for individual patients (regulated under Section 503A of the FDCA), Section 503B restricts outsourcing facilities from using bulk drug substances unless one of two conditions is met:

- the substance is used to make a drug that is in shortage
- the substance is on FDA's list of substances for which there is a clinical need.^v

The DQSA requires a public process before approving any bulk substances by including them on the "clinical need" list.^{vi} Beginning shortly after the law's passage, FDA began accepting nominations for bulk drug substances for which there is a clinical need. Since 2016, FDA has exercised enforcement discretion toward an "interim list" of hundreds of these substances for which the agency received a completed nomination.^{vii} To date, FDA has not added any substances to Section 503B's permanent "clinical need list," but on Friday—following a notice-and-comment process required by statute—FDA officially excluded those first two nominated substances from the list.^{viii}

In his appearance before a congressional committee last January, FDA Commissioner Scott Gottlieb promised to issue policies on FDA's approach to evaluating clinical need and to reach a final determination on nominated substances.^{ix} In March 2018, FDA issued draft guidance establishing a detailed two-part test to determine whether there is, in fact, a clinical need for use by outsourcing facilities.^x For substances that are components of FDA-approved drugs, the nomination must show that the FDA-approved drug cannot be used to satisfy the alleged clinical need. For example, FDA states that there would not likely be a clinical need if the approved drug could be diluted to make a lower concentration for a pediatric patient.^{xi} If it does, then FDA weighs four factors to determine whether the potential benefits of the substance's use outweigh its risks. One year later, FDA has finalized this guidance, reaffirming its two-part test.

On the same day, FDA completed the requisite notice-and-comment process for vasopressin and nicardipine hydrochloride, but not for a third substance—bumetanide—that the agency had proposed excluding from the 503B clinical need list in August 2018.^{xii} FDA's review found that these two substances serve no legitimate clinical need that FDA-approved versions of these drugs do not already meet.^{xiii} FDA indicated that bumetanide is still under consideration.

The draft guidance and notice proposing to prohibit the compounding of these three substances were controversial among some stakeholders. Members of Congress wrote at least eight letters to FDA during 2018 regarding these policies, both in support of and raising concern about these proposals. Additionally, the placement of vasopressin on the interim list has been the subject of a lawsuit between the drug's manufacturer and FDA. That lawsuit, which had been stayed until March 15, 2019, may soon end,^{xiv} but could give way to legal action by outsourcing facilities seeking to compound from these two bulk substances.

What does this mean for health care providers?

Effective immediately, drugs compounded from bulk vasopressin and nicardipine hydrochloride will no longer fall under FDA's policy of non-enforcement. Because such

drug preparations are in violation of Section 503B, they would require a new drug approval before being marketed and distributed anywhere in the United States. To ensure they are obtaining and administering lawful drug products, hospitals and health care providers should confirm that they are using FDA-approved versions of these drugs or, alternatively, that preparations received from outsourcing facilities have been compounded from the FDA-approved product rather than bulk drug substances. Outsourcing facilities are able to provide this information.

More broadly, it is important to recognize that except for drugs on the FDA shortage list, there are no lawful uses of bulk substances by outsourcing facilities at this time. Although FDA has not been enforcing this restriction for substances on the interim list, the agency intends to accelerate its review of more substances to determine whether or not there is a clinical need for their use by outsourcing facilities, and will be issuing these notices on a rolling basis.

FDA also announced a process whereby the public can petition FDA to exclude additional substances from the 503B bulks list and it is expected that a range of stakeholders will prompt the agency to review more substances that are components of FDA-approved drugs.^{xv} As hospitals and providers enter into purchasing arrangements, they should assess whether they are purchasing from outsourcing facilities whose drug preparations are in compliance with federal law.

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ⁱ FDA, Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry (Mar. 2019), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM602276.pdf> [hereinafter “Evaluation of Bulk Drug Substances Guidance”].

ⁱⁱ List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 84 Fed. Reg. 7,383 (Mar. 4, 2019).

ⁱⁱⁱ FDA, FDA in Brief: FDA Finalizes Guidance on Evaluating the Clinical Need for Outsourcing Facilities to Compound Drugs with Bulk Drug Substances; Provides Final Decision on Two Substances, <https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm632432.htm> [hereinafter “FDA Bulk Drug Substance Announcement”].

^{iv} See 21 U.S.C. § 353b

^v Id. § 353b(a)(2).

^{vi} Id. § 353b(a)(2)(A)(i)(I) – (III).

^{vii} See FDA, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry (Jan. 2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf>

^{viii} FDA Bulk Drug Substance Announcement, *supra* note 3.

^{ix} Examining Implementation of the Compounding Quality Act: Hearing Before the Subcomm. on Health, H. Comm. On Energy and Commerce, 115th Congr. (Jan. 30, 2018) (statement of Scott Gottlieb, Comm’r, FDA), <https://www.fda.gov/NewsEvents/Testimony/ucm594297.htm>.

^x FDA, Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry; Draft Guidance (Mar. 2018).

^{xi} Evaluation of Bulk Drug Substances Guidance at 14.

^{xii} See FDA Bulk Drug Substance Announcement.

^{xiii} Recently, FDA also addressed compounding with bulk drug substances by pharmacies, issuing a long-awaited final rule regarding bulk drug substances that may be used by pharmacies operating under Section 503A. List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act, 84 Fed. Reg. 4,696 (Feb. 19, 2019). Under Section 503A, compounding pharmacies may compound with bulk drug substances that (1) comply with the standards of an applicable United States Pharmacopoeia (USP) or National Formulary monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if a monograph does not exist, are drug substances that are components of drugs approved by FDA; or (3) if a monograph does not exist and the drug substance is not a component of a drug approved by FDA, that appear on a list developed by FDA through agency issued regulations. 21 U.S.C. § 353a(b)(1)(A).

^{xiv} Endo International plc, Endo Announces FDA Decision Not to Include Vasopressin on 503B Bulks List (Mar. 1, 2019), <http://investor.endo.com/news-releases/news-release-details/endo-announces-fda-decision-not-include-vasopressin-503b-bulks>.

^{xv} Evaluation of Bulk Drug Substances Guidance at 8.