Health Industry Alert

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District Court Affirms FDA Policy on Compounding with Bulk Drug Substances—Bringing Much Needed Clarity for the Outsourcing Facility Industry

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On August 1, 2019, the U.S. District Court for the District of Columbia affirmed the U.S. Food and Drug Administration's (FDA's) decision to exclude the bulk drug substance vasopressin from the agency's List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B ("503B Bulks List") in *Athenex Pharma Solutions, LLC et al. v. Azar, II et al.*[1]

Although the court affirmed FDA's decision regarding the fate of a single bulk drug substance, vasopressin, the court's decision endorses FDA's approach to reviewing all bulk drug substances for use by outsourcing facilities based on a clinical need. Thus, the decision gives the agency a green light to move forward in reviewing—and excluding—more substances from compounding under Section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA). Given the *Athenex* ruling, health care providers and others using compounded drugs should ensure they are only prepared from bulk drug substances in accordance with FDA policies, and prepare for FDA to move more expeditiously in evaluating individual substances based on the "clinical need" analysis previously announced by the agency

Background

On March 4, 2019, Athenex Pharma Solutions, LLC and Athenex Pharmaceutical Division LLC (Athenex) sued the U.S. Department of Health and Human Services (HHS), alleging that FDA's decision to exclude the company's compounded vasopressin product from the agency's 503B Bulks List was contrary to the FDCA.[2] Bulk drug substances, or the raw active ingredients from which drugs are prepared, may only be used by 503B-registered outsourcing facilities if they appear on the 503B Bulks List or are used to prepare drugs that are currently in shortage.[3]

Par Sterile Products, LLC and Endo Par Innovation Company, LLC (Endo Par), the maker of Vasostrict, the branded version of vasopressin, filed a motion to intervene as defendants, which the court granted on March 11, 2019.[4] Following prompts by Endo Par, on March 1, 2019, FDA issued a notice excluding bulk vasopressin from the 503B Bulks List as well as guidance outlining its standards for evaluating bulk drug

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substances, and Athenex filed suit the next business day. FDA agreed not to initiate enforcement action against Athenex "based solely on Athenex's use of the bulk drug substance [vasopressin] to compound drugs" until the court issued a decision on the merits of the case.[5]

Decision

The court granted summary judgment in favor of FDA and intervenor Endo Par, finding that FDA's method of determining clinical need for a bulk drug substance was supported by the plain language of Section 503B and gave effect to the expressed intent of Congress. Further, the court found that FDA's interpretation of clinical need was reasonable.

Athenex had argued that FDA incorrectly applied the clinical need requirement for bulk drug substances to be added to the 503B Bulks List under the Drug Quality and Security Act (DQSA).[6] The company claimed that because vasopressin is the active ingredient of an FDA-approved drug, its therapeutic value had already been confirmed by the agency. The court rejected this line of argument, positing that "reading 'clinical need' this way does not create a category of active pharmaceutical ingredients for which there is not a 'clinical need.'"[7] The court found that "Congress plainly thought that there are some bulk drug substances for which there is a 'clinical need' and others for which there is not."

The court also dismissed Athenex's contention that Congress had intended for clinical need to be determined by medical practitioners and that FDA was erroneously usurping that role as a mischaracterization of FDA's role in evaluating clinical need. The court underscored that FDA's decision does not interfere with a physician's decision to administer Vasostrict, or even a compounded version of the drug; rather, the agency is simply deciding on "the type of drug that reaches the marketplace."[8]

The court agreed with FDA that Athenex's interpretation of clinical need would open the floodgates to outsourcing facilities compounding with every bulk substance contained within FDA-approved drugs, a point accentuated by Endo Par, whose attorneys had printed out the entire Orange Book of Approved Drug Products with Therapeutic Equivalence Evaluations and brought it to oral argument. The court observed that "no good purpose is served by requiring FDA to certify hundreds, if not thousands, of bulk drug substances already contained in approved drugs."[9]

Athenex had argued that Section 503B contained independent provisions to safeguard the drug approval system, with the statute prohibiting 503B-registered outsourcing facilities from compounding what is "essentially a copy" of one or more FDA-approved drugs.[10] The court disagreed, finding that the essentially a copy prohibition complemented, rather than duplicated, the clinical need evaluation, as implemented by FDA.[11]

Judge Mehta agreed with FDA that its interpretation should receive deference from the court, and found that the agency's method for determining clinical need is supported by the text, structure and purpose of the statute.[12] The court recognized the need to protect the premarket approval process for new drug products from unfair competition by bulk-compounded drugs. It found persuasive FDA's argument that Congress deliberately cabined the use of bulk drug substances in part to protect against the economic incentives for outsourcing facilities routinely to compound from bulk drug substances. The opinion differentiates "sterile-to-sterile" compounding—which involves

compounding an approved drug—from compounding from bulk drug substances, describing the latter as "an exception within an exception."[13] This represents an important victory for FDA, with the agency having asserted the importance and benefits of compounding from approved drug products whenever possible. Specifically, in addition to safeguarding the drug approval process, FDA has asserted approved products benefit from FDA oversight, including premarket assessment of quality standards, specifications, and controls, and inspections of manufacturing operations, in contrast to bulk drug substances.[14]

Following Thursday's decision in favor of FDA, Athenex announced that the company plans to appeal the ruling and seek a stay pending appeal.[15]

What does the *Athenex* decision mean for health care providers, outsourcing facilities and drug manufacturers?

As a result of the district court's order, it is likely that:

- FDA will reinvigorate its evaluation of bulk drug substances nominated to the 503B Bulks List, applying the framework established in its final guidance, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (March 2019). This means for nominated bulk drug substances that are components of FDA-approved drug products, FDA will continue to consider (1) if there is an attribute of the FDA-approved drug product that makes it medically unsuitable for certain patients and (2) if the proposed compounded drug product must be produced from a bulk drug substance. Nominated bulk drug substances that do not affirmatively meet both threshold criteria will not be evaluated any further by FDA for clinical need, and thus will forego a second-step inquiry that balances various additional factors.
  - As noted during oral argument, the agency has not currently approved any bulk drug substance to the 503B Bulks List, though it has excluded two bulk drug substances from the list (vasopressin and nicardipine hydrochloride).[16] Given that FDA is currently exercising enforcement discretion over the compounding of scores of substances under its Interim Policy on Compounding Using Bulk Drug Substance Under Section 503B, it is expected that most of FDA's determinations will result in *excluding* substances, rather than adding them to, the 503B Bulks List. FDA has been collaborating with the University of Maryland and Johns Hopkins University to gather and analyze information intended to inform FDA's review of a number of bulk drug substances.
- FDA will no longer exercise enforcement discretion regarding use of vasopressin in bulk drug substance form by outsourcing facilities, although the company has stated that it plans to seek a stay of the District Court's ruling.[17]
- Hospitals and other health care providers should closely review their supply arrangements to evaluate any drug preparations that include vasopressin or nicardipine hydrochloride—both excluded from the 503B Bulks List—to ensure they are sourced from FDA-approved drugs rather than bulk ingredients.
- In light of this court decision and its anticipated effects, health care providers using compounded drugs prepared from bulk drug substances should closely track FDA's actions relating to the 503B Bulks List to assess compliance with the DQSA and prepare for further restrictions on the use of bulk drug substances.

[1.] Athenex Pharma Solutions, LLC v. Azar, No. 1:19-cv-00603, 019 WL 3501811 (D.D.C. Aug. 1, 2019).

[2.] A related case, *Par Sterile Products, LLC et al v. Hargan et al*., was filed in October of 2017 by Endo Par against FDA. No. 1:17-cv-02221 (D.D.C. filed Oct. 26, 2017). Endo Par alleged that the agency failed to implement Drug Quality and Security Act (DQSA) requirements by allowing outsourcing facilities to compound unapproved vasopressin that is essentially a copy of Vasostrict.

[3.] 21 U.S.C. § 353b(a)(2).

[4.] Scheduling Order at 1, *Athenex*, No. 1:19-cv-00603.

[5.] Joint Motion to Enter Scheduling Order at 1-2, *Athenex*, No. 1:19-cv-00603.

[6.] *See* 21 U.S.C. § 353b(a)(2).

[7.] *Athenex*, No. 1:19-cv-00603, slip op. at 13.

[8.] *Id*. at 25.

[9.] *Id*. at 20.

[10.] *See* 21 U.S.C. § 353b(a)(5).

[11.] *Athenex*, No. 1:19-cv-00603, slip op. at 24-25.

[12.] *Id*. at 28.

[13.] *Id*. at 15.

[14.] 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 (Final), at 5-6 (Mar. 2019).

[15.] Athenex, Inc., Athenex Provides an Update Regarding the Vasopressin Case (Aug. 2, 2019), http://ir.athenex.com/news-releases/news-release-details/athenex-provides-update-regarding-vasopressin-case.

[16.] 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).

[17.] Athenex, Inc., Athenex Provides an Update Regarding the Vasopressin Case (Aug. 2, 2019), http://ir.athenex.com/news-releases/news-release-details/athenex-provides-update-regarding-vasopressin-case.