IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ATHENEX, INC., ATHENEX PHARMA SOLUTIONS, LLC, and ATHENEX PHARMACEUTICAL DIVISION, LLC, Plaintiffs, v. ALEX M. AZAR II, Secretary of Health and Human Services; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; SCOTT GOTTLIEB, Commissioner of Food and Drugs; and U.S. FOOD AND DRUG ADMINISTRATION, Defendants, and PAR STERILE PRODUCTS, LLC and ENDO PAR INNOVATION COMPANY, LLC, Intervenor-Defendants.	Civil Action No.: 1:19-cv-00603 (APM)

MEMORANDUM IN SUPPORT OF
ATHENEX'S MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

First Issue Presented: Section 102 of the Compounding Quality Act ("CQA") (also referred to as "Section 503B") creates a new category of regulated drug compounders who compound sterile drugs—outsourcing facilities. Section 503B's purpose is to encourage production of sterile compounded drugs from an outsourcing facility whose operations are held to a nationwide quality standard, and not to limit access to quality compounded drugs for providers and patients or regulate the practice of medicine. Section 503B requires outsourcing facilities to meet eleven conditions to produce quality compounded drugs. Some conditions are about the facility, some are about the drug ingredients (active and inactive), and some are about the finished drug product. The condition at issue in this lawsuit—Section 503B(a)(2)—is about active pharmaceutical ingredients, referred to as "bulk drug substances." In relevant part, Section 503B(a)(2) requires the bulk drug substance to (A) appear on a list established by the Secretary, published in the Federal Register following notice and 60-day comment, "identifying bulk drug substances for which there is a clinical need," (B) comply with any official monograph governing its specifications, (C) be sourced from a registered manufacturer; and (D) be accompanied by a certificate of analysis.

The bulk drug substance vasopressin is a polypeptide hormone, also produced naturally by the human body, that contracts vascular and other smooth muscles. It has been used in drug products for nearly a century to treat life-threating and emergency conditions, including vasodilatory shock (e.g., post-cardiotomy or sepsis), diabetes insipidus, and gastrointestinal bleeding. FDA nonetheless excluded vasopressin from the list of "bulk drug substances for which there is a clinical need." 21 U.S.C. § 353b(a)(2)(A)(i)(2013). FDA excluded vasopressin from the 503B Bulks List because a pharmaceutical company is using it to make a branded drug

product (i.e., Vasostrict®[1]) that FDA thinks doctors should choose to use instead of Athenex's compounded vasopressin drug product. In other words, FDA interpreted Congress's directive to determine whether vasopressin meets a clinical need as though Congress had directed FDA to evaluate which drug product made with that substance doctors should choose for their patients—Vasostrict® or Athenex's vasopressin product. FDA rationalized its interpretation of Section 503B(a)(2) by saying it is necessary to protect the integrity of FDA's program for approving branded drug products, even though FDA acknowledges a different statutory condition—Section 503B(a)(6) (prohibiting copies of branded drug products)—already does that. **Should the Court vacate the Vasopressin Decision under *Chevron*?**

Answer: Yes. FDA misinterpreted Congress's plain-language instruction to determine whether a given bulk drug substance (here, vasopressin) is one for which there is a clinical need as directing FDA to decide whether doctors should always choose an existing branded product over any compounded product made with that substance. FDA's interpretation is contrary to the statute's plain language and structure, disturbs Congress's deliberate balancing of interests, and violates Congress's statutory purpose *not* to regulate the practice of medicine or limit the availability of quality compounded products.

Second Issue Presented: Athenex's laboratory and manufacturing facility, located in Clarence, New York, began as a facility that manufactured and tested small-batch, branded

[1] FDA did not approve Vasostrict®, which is manufactured by Intervenor-Defendants Par Sterile Products, LLC and Endo Par Innovation Company, LLC ("Par"), through its process for *new* drugs. FDA approved Vasostrict® in 2014 through its perfunctory Unapproved Drugs Initiative, a process set up in 2006 to quickly process and brand existing, well-established drugs already in use. Vasopressin products have been used for a century, so the clinical effectiveness of vasopressin was long-known before Par brought its particular product to market. FDA 000293-94. FDA's abbreviated, desk-top review of Vasostrict® was essentially a check of already-published literature.

pharmaceuticals for drug companies or researchers. It has been producing sterile drugs in compliance with FDA's stringent current good manufacturing practice ("cGMP") standards for years—the same standards governing manufacturing of branded drugs, like Vasostrict®. This background made Athenex well-suited to operate an outsourcing facility for Section 503B compounding. Accordingly, after Congress enacted the CQA, Athenex registered as a 503B outsourcing facility in 2017—it is one of only about 73 registered 503B facilities nationwide.

After investing millions in its facility and product development, Athenex launched its compounded vasopressin product in August 2018. Athenex developed its vasopressin product as a pre-mixed, ready-to-use intravenous bag that can be easily administered to patients without further manipulations by hospital staff. This attribute is important because vasopressin is one of twelve "high-alert" medicines in the acute care setting, meaning there is high risk for errors in administration that can have devastating outcomes for patients. Hospitals are selecting Athenex's vasopressin product to treat patients every day, especially in emergency rooms, intensive care units, the cardiac catheter laboratory, on crash carts, and for code cases. In stark contrast, Vasostrict® is not a ready-to-use drug. It requires a 16-step process to administer, including admixing (essentially compounding) by nurses or other hospital staff on the fly. Also, unlike Athenex's chlorobutanol-free vasopressin product, the label for every vial of Vasostrict® states: "Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or *chlorobutanol*." FDA 001639-40 (Vasostrict® product label) (emphasis added).

Thus, Athenex's vasopressin product has two attributes that Vasostrict® does not, which the Court should find is a clinical need: (1) it is ready-to-use; and (2) it is not subject to a contraindication for patients allergic to chlorobutanol. FDA, however, disregarded them as such

in its Vasopressin Decision. **Should the Court vacate the Vasopressin Decision as arbitrary and capricious?**

Answer: Yes. Even if FDA's product-based interpretation of Section 503B(a)(2) could survive a *Chevron* analysis, the Vasopressin Decision is arbitrary and capricious because FDA irrationally disregarded clinically significant attributes of Athenex's vasopressin product.

STATEMENT OF FACTS

A. Congress sought to make compounding practices safer without limiting access to compounded drugs or altering the practice of medicine.

In enacting the Drug Quality and Security Act ("DQSA"), Pub. L. No. 113-54, 127 Stat. 587 (2013), which added the Compounding Quality Act ("CQA") to the Federal Food, Drug, and Cosmetic Act ("FFDCA"), Congress sought to create uniform safety controls to address the legacy of unregulated compounding practices *without* limiting provider and patient access to quality compounded drugs: "Nothing in the legislation is intended to limit access to quality compounded drugs for providers and patients or alter the practice of medicine but, rather, create a whole new alternative for safe sources of sterile compounded drugs that are held to a nationwide quality standard." 159 Cong. Rec. S8072 (daily ed. Nov. 18, 2013) (statement of co-sponsor Sen. Alexander); *see also id.* at S8074 (statement of co-sponsor Sen. Warner) (The Act "ensures that patients and providers have access to safe compounded drugs.").

B. Congress established eleven conditions for outsourcing facilities.

Section 102 of the CQA, referred to as Section 503B, creates a new category of regulated drug compounders who compound sterile drugs: "outsourcing facilities."[2] Their drug products

[2] An outsourcing facility is a facility engaged in the compounding of sterile drugs, that has registered with FDA as an "outsourcing facility," and that complies with all the requirements of Section 503B. *See* 21 U.S.C. § 353b(d)(4)(A).

are exempt from the new drug application process if eleven conditions are met. 21 U.S.C. § 353b(a) ("Sections 502(f)(1), 505, and 582, [of the FFDCA] shall not apply to a drug compounded by or under the direct supervision of a licensed pharmacist in a facility that elects to register as an outsourcing facility if each of the following conditions is met [setting forth eleven conditions]."). While this lawsuit is about the second condition, it is important to read the statute as a whole; the eleven conditions, 21 U.S.C. § 353b(a)(1)-(11), can be summarized as follows:

(1) The facility making the drug complies with the registration and reporting requirements of 21 U.S.C. § 353b(b)(5), which include FDA inspections and adverse event reporting.
(2) The drug's active ingredient – i.e., the bulk drug substance – (A) appears on a list established by the Secretary, published in the Federal Register following notice and 60-day comment, "identifying bulk drug substances for which there is a clinical need" (except this requirement shall not apply when the drug being compounded "appears on the drug shortage list in effect under Section 506E"), (B) complies with any official monograph governing its specifications, (C) is sourced from a registered manufacturer; and (D) is accompanied by a certificate of analysis.[3]

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[3] The "official monograph" requirement in § 353b(a)(2)(B) ensures that the bulk ingredients meet uniform standards for identity, quality, purity, strength, packaging and labeling. *See* USP Monographs for Bulk Drug Substances and Other Ingredients, *available at* http://www.usp.org/compounding/bulk-drug-substances-monographs (last visited Mar. 17, 2019).

The "certificate of analysis" obligation in § 353b(a)(2)(D) imposes a number of requirements on the bulk drug substances (or active pharmaceutical ingredient). For example, the Certificate of Analysis must include the name of the ingredient, its grade, batch number, the date of release, any expiry date, and any retest date (if applicable). The certificate must list each test performed, including the acceptance limits and the numerical results obtained. The certificate must be dated and signed by authorized personnel of the quality unit and must show the name, address, and telephone number of the original manufacturer and repacker (if applicable). And, "[i]f new certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached." *See* FDA, Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Aug. 2001), at 29, *available at* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf (last visited Mar. 17, 2019).

(3) The drug's inactive ingredients also comply with any official monograph governing their specifications.
(4) The drug does not appear on the Secretary's list of drugs withdrawn or removed from the market because they are unsafe or not effective.
(5) The drug is not essentially a copy of one more approved drugs.
(6) The drug is not on the Secretary's list of drugs that present demonstrable difficulties for compounding (unless meeting other specified conditions).
(7) The facility follows safety controls under any relevant risk evaluation and mitigation strategy.
(8) The drug is not sold or transferred by an entity other than the outsourcing facility that compounded the drug (i.e., no selling to wholesalers).
(9) The facility has paid all required fees.
(10) The drug meets labeling requirements.
(11) The facility compounds exclusively in accordance with Section 503B.

Notably, some of these conditions are about the outsourcing facility itself (e.g., the first condition, regarding registration), some are about the finished compounded drug product made by the facility (e.g., the fifth condition, prohibiting copies of approved drugs), and some are about the ingredients the facility uses to make the compounded drug product (e.g., the second and third conditions, requiring the active and inactive ingredient to conform to any official monographs for those substances, and requiring the active ingredient to be one for which there is a clinical need, sourced from a registered manufacturer, and accompanied by a certificate of analysis). 21 U.S.C. § 353b(a)(1)-(11).

This lawsuit concerns FDA's interpretation of the second condition, i.e., 503B(a)(2), which is about active pharmaceutical ingredients, also known as "bulk drug substances."[4] 21 U.S.C. § 353b(a)(2). More specifically, it is about one of the four subparts of 503B(a)(2) —

[4] The term "bulk drug substance" is defined as an "active pharmaceutical ingredient"—the two terms are interchangeable. *See* 21 C.F.R. §§ 207.3, 207.1 (2016). 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." 21 C.F.R. § 207.1. It is undisputed that vasopressin is a "bulk drug substance."

subpart A. But again, it is important to read the statute as a whole; the four subparts—A through D—state as follows:

> (A)(i) the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need, by –
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> > (I) publishing a notice in the Federal Register proposing bulk drug substances to be included on the list, including the rationale for such a proposal;
> > (II) providing a period of not less than 60 calendar days for comment on the notice; and
> > (III) publishing a notice in the Federal Register designating bulk drug substances for inclusion on the list; or
> > (ii) the drug compounded from such bulk drug substance appears on the drug shortage list in effect under section 356e of this title at the time of compounding, distribution, and dispensing;
>
> (B) if an applicable monograph exists under the United States Pharmacopeia, the National Formulary, or another compendium or pharmacopeia recognized by the Secretary for purposes of this paragraph, the bulk drug substances each comply with the monograph;
>
> (C) the bulk drug substances are each manufactured by an establishment that is registered under section 360 of this title (including a foreign establishment that is registered under section 360(i) of this title); and
>
> (D) the bulk drug substances are each accompanied by a valid certificate of analysis.

21 U.S.C. § 353b(a)(2)(A)-(D).

Thus, 503B(a)(2) ensures quality standards for the active ingredient by requiring that it (A) meets a clinical need, (B) complies with official specifications, (C) is sourced from a legitimate manufacturer, and (D) is accompanied by a valid certificate of analysis. 21 U.S.C. § 353b(a)(2)(A)-(D).

C. Congress balanced the competing interests of bulk compounding and the new drug approval process by disallowing compounded products that are essentially copies of branded drugs.

Congress struck a deliberate balance between increasing availability of quality compounded drugs with protecting the integrity of the new-drug-approval process by restricting compounding to those compounded products that are not "essentially a copy of one or more approved drugs." 21 U.S.C. § 353b(a)(5). As acknowledged by FDA:

> [S]ection 503B's prohibition on producing a drug product that is essentially a copy of an approved drug product protects the integrity and effectiveness of the new drug and abbreviated new drug application process. Sponsors would be less likely to invest in, and seek approval of, innovative, life-saving medications if an outsourcing facility could, after a drug is approved, compound "substitutes" that may be less expensive because they have not gone through the drug approval process.

See FDA's Essential Copy Guidance, at 4.[5]

D. FDA places vasopressin under its Interim Policy.

In response to FDA's request for nominations[6] of bulk drug substances for the 503B Bulks List, FDA determined that vasopressin was one of only about 300 bulk drug substances potentially eligible for inclusion on the 503B Bulks List based on FDA's interpretation of the statute, nominated with sufficient support, and that did not pose significant safety risks in compounding. *See* FDA 000042-43 (FDA's *Interim Policy on Compounding Using Bulk Drug*

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[5] "Essential Copy Guidance" refers to the following document published on FDA's webpage: *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act, Guidance for the Industry*, Jan. 2018., *available at* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510153.pdf (last visited Feb. 22, 2019).

[6] Baker Hostetler LLP (for Athenex) and QuVa Pharma Inc. separately nominated vasopressin for inclusion on the 503B Bulks List in 2017. *See* FDA 000017-22 (Baker Hostetler request for nomination of vasopressin); FDA 000014-16 (QuVa request for nomination of vasopressin).

Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry (Jan. 2017)); FDA 000009-13 (80 Fed. Reg. 65770 (Oct. 27, 2015)). FDA included vasopressin on a January 2017 "Category 1" List of Substances Nominated for the Bulks List Currently under Evaluation, where it remained until the Vasopressin Decision.[7] For Category 1 substances, to "avoid unnecessary disruption to patient treatment," FDA stated it "does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that does not appear on the 503B bulks list," if the other 503B requirements are still met. FDA 000042-43.

E. FDA takes public comment on its proposal to exclude vasopressin from the 503B Bulks List.

On August 28, 2018, FDA proposed to exclude vasopressin (and two other substances) from the 503B Bulks List based on the information then before the agency. *See* FDA 000105-110 (FDA's List of Bulk Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 83 Fed. Reg. 43877 (Aug. 28, 2018) (FDA's "Vasopressin Proposal")). It opened a 60-day comment period pursuant to 21 U.S.C. § 353b(a)(2)(A)(i)(II). FDA received approximately 30 comments; many supported including vasopressin on the 503B Bulks List.[8] Athenex submitted extensive comments. *See* FDA

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[7] *See* FDA000291 (FDA, *Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Nov. 2018)), *available at* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf (last visited March 3, 2019) (listing vasopressin as a Category 1 substance).

[8] Commenters included: Emory University Hospital, *see* FDA 000252 (excluding vasopressin from the 503B Bulks List will hinder hospital pharmacies' ability to provide timely patient care because of supply issues); the American College of Emergency Physicians, *see* FDA 000253-54 (supply issues should be considered when forming the 503B Bulks List, especially for vasopressin, which is in short supply even though it used to be inexpensive and easy to obtain);

000255-287 (Athenex's Comment Submission); FDA 001505-1512 (Athenex's Reply Comment Submission).

The record evidence establishes vasopressin, a natural hormone also secreted by the human body, has been used for over a century to treat patients, including in unapproved, marketed drugs, FDA 000257; FDA 000293, and FDA officially acknowledged vasopressin is an active pharmaceutical ingredient that meets clinical needs when it approved a branded drug product (Vasostrict®) that uses vasopressin as its active ingredient. The administrative record also shows Athenex's vasopressin product has two clinically important attributes that Vasostrict® does not. First, it is a ready-to-use drug, but Vasostrict® is not and requires a 16-step process to administer. FDA 00256, FDA 000266-68. This attribute is important because out of thousands of medicines vasopressin is one of only twelve designated as a "high-alert" medicine in the acute care setting, meaning there is high risk for errors in administration that can have devastating outcomes for patients. Second, Athenex's vasopressin product is not contraindicated for patients who are allergic to chlorobutanol, but Vasostrict® is. FDA 00259-261; FDA 001639, ¶ 4.

F. FDA excludes vasopressin from the 503B Bulks List.

On March 4, 2019, FDA published its final decision to exclude vasopressin from the 503B Bulks List. FDA 001600-1605 (84 Fed. Reg. 7383). The Vasopressin Decision is FDA's

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the American Society of Health-System Pharmacists, *see* FDA 000241-42 (asking FDA to broaden its definition of clinical need to include supply issues and backorders); two doctors of pharmacy, *see* FDA 000172-74, FDA 000133-34 (vasopressin should be on the 503B Bulks List, given the need for vasopressin in ready-to-use form, supply and access issues, and allergy issues with Vasostrict®); seven outsourcing facilities, *see* FDA 000231-240 (FDA's Vasopressin Decision is tantamount to practicing medicine); and the Outsourcing Facility Association, *see* FDA 000872-880 (noting that FDA's exclusion of vasopressin is tantamount to practicing medicine and a departure from FDA's Good Guidance Practices).

first determination whether to include a bulk drug substance on the "list established by the Secretary identifying bulk drug substances for which there is a clinical need," i.e., the 503B Bulks List. FDA stated: "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… FDA will not place a bulk drug substance on the 503B Bulks list." FDA 001602 (emphasis added). Relying on its interpretation of the statute, FDA decided there is not a clinical need for the compounded vasopressin product given the branded drug product on the market. FDA reasoned: "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." FDA 001601. FDA found there is "no basis to conclude that an attribute of VASOSTRICT makes it medically unsuitable to treat certain patients" and that there is "no basis to conclude that drug products must be compounded using a bulk drug substance rather than the approved drug product." FDA 001604. In other words, if a pharmaceutical company uses a bulk drug substance in one of its branded drug products, FDA will use that fact as a basis to exclude the substance from the 503B Bulks list even though FDA acknowledges the substance is one that meets a clinical need.

ARGUMENT

FDA's Vasopressin Decision violates the APA, which provides that the Court "shall . . . hold unlawful and set aside an agency action" that is "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right," 5 U.S.C. § 706(2)(C), or that is "arbitrary,

capricious, an abuse of discretion, or otherwise not in accordance with law," *id*. § 706(2)(A).[9] Congress directed FDA to include on the 503B Bulks List "bulk drug substances for which there is a clinical need." 21 U.S.C. § 353b(a)(2)(A)(i).[10] FDA interprets this directive as though Congress instructed it to compare a proposed compounded drug product[11] with an existing branded drug product made with the same active pharmaceutical ingredient, decide which product is more medically suitable for doctors to choose for their patients, and then exclude that active pharmaceutical ingredient from the 503B Bulks List if FDA decides doctors should choose the branded drug product—even though both drug products are using that ingredient precisely because it is one "for which there is a clinical need." FDA's interpretation has the agency speaking out of both sides of its mouth—saying an active pharmaceutical ingredient simultaneously is one for which there is a clinical need (for the branded product) and is not (for the compounded product). Indeed, FDA admits that if the bulk drug substance is *not* being used by a pharmaceutical company, it straightforwardly considers the nature of the substance, its safety, effectiveness, and historical use in deciding whether to include it on the 503B Bulks List. *See* FDA 000067.

FDA twisted itself in this knot because the agency's goals are at odds with Congress's clear purpose. Congress says "[n]othing in the legislation is intended to limit access to quality

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[9] It is reviewable final agency action because it is the culmination of FDA's decision-making as to vasopressin's placement on the 503B Bulks List and creates rights and obligations from which legal consequences will flow. *Bennet v. Spear*, 520 U.S. 154, 177-78 (1997).

[10] "Bulk drug substance" is synonymous with active pharmaceutical ingredient. *Supra* at 6 n.4.

[11] This compounded-product-nomination process is not a creature of the statute—FDA invented it in guidance. FDA 000084-104 (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)).

compounded drugs for providers," 159 Cong. Rec. S8072 (daily ed. Nov. 18, 2013) (statement of co-sponsor Sen. Alexander), yet FDA seeks "to limit patient exposure to compounded drug products," FDA 000074. Congress says FDA shall not "alter the practice of medicine," 159 Cong. Rec. S8072, yet FDA seeks to decide which drug products are more "medically suitable" for doctors to choose for their patients, FDA 001603 (asking whether "an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients…"). Congress says to identify "bulk drug *substances* for which there is a clinical need," 21 U.S.C. § 353b(a)(2)(A)(i), yet FDA rejects the plain language and evaluates *products* instead, saying "Patients generally do not have a clinical need for a bulk drug substance … rather, any clinical need will be for a drug product," FDA 000070. Congress deliberately balances its interest in encouraging compounding held to nationwide quality standards with its interest in protecting the integrity of FDA's new drug approval program by prohibiting copies of branded drugs (503B(a)(6)), yet FDA disturbs that balance by using Section 503B(a)(2) to block compounded drugs in the name of protecting the integrity of FDA's new drug approval program.

FDA's Vasopressin Decision should be vacated under *Chevron* step one because FDA's interpretation of the statute is contrary to Congress's unambiguous intent, as demonstrated by the plain language of 503B(a)(2)(i), the structure of 503B(a), Congress's deliberate balancing of interests, and Congress's intent not to regulate the practice of medicine. And, when properly interpreted, it is self-evident that vasopressin is a bulk drug substance for which there is a clinical need, given the long history of doctors' prescribing it for their patients and FDA's own approval of a vasopressin drug product.

FDA's Vasopressin Decision should also be vacated because it is arbitrary and capricious. Even under FDA's misreading of the statute, vasopressin belongs on the 503B Bulks

List because Athenex's vasopressin product has medically important attributes that the branded vasopressin product does not.

I. FDA's Vasopressin Decision is contrary to the DQSA and must be vacated under Section 706(2)(C) of the APA.

Challenges to agency rules under section 706(2)(C) of the APA are subject to the standard of review articulated in *Chevron U.S.A., Inc. v. NRDC*, 467 U.S. 837 (1984), which employs a two-step inquiry. Under *Chevron* step one, the Court uses "traditional tools of statutory construction" to determine if Congress "has directly spoken to the precise question at issue"; if it has, the Court must "give effect to the unambiguously expressed intent of Congress" and the inquiry is over. *Chevron*, 467 U.S. at 842-43, 843 n.9. Only if the statute is silent or ambiguous would this Court move to *Chevron* step two and consider "whether the agency's answer is based on a permissible construction of the statute." *Id.* at 843.[12] The inquiry here begins and ends with *Chevron* step one because the statute is unambiguous: it calls for FDA to include on the 503B Bulks List "bulk drug substances for which there is a clinical need." It does not direct or authorize FDA to exclude such substances because they are used by pharmaceutical companies to make branded drug products. Because Congress "has directly spoken to the precise question at issue," this Court must "give effect to the unambiguously expressed intent of Congress," as determined by the "traditional tools of statutory construction" such as the ordinary

[12] "*Chevron* itself tells us that we must first employ the traditional tools of statutory construction to interpret the statute and to resolve any ambiguities. Only if we are then still left with an ambiguity do we proceed to step two." *District of Columbia v. Dep't of Labor*, 819 F.3d 444, 449 (2016) (internal citation omitted); *see also Robinson v. Shell Oil Co.*, 519 U.S. 337, 340 (1997) (to ascertain congressional intent, courts "determine whether the language at issue has a plain and unambiguous meaning with regard to the particular dispute in the case").

and plain language of the statute, statutory context, and other judicial canons of construction. *Id.* at 842-43, 843 n.9. Traditional tools of construction show FDA committed legal error.

A. FDA's interpretation violates the plain language of 503B(a)(2)(A)(i).

The language of Section 503B(a)(2)(A)(i) is plain. It requires FDA to include vasopressin on the 503B Bulks List if it is a "bulk drug substance[] for which there is a clinical need." But FDA misreads Section 503B(a)(2)(A)(i) as requiring it to decide whether there is a clinical need "for an outsourcing facility" to compound a vasopressin drug "product" given an approved drug product on the market that FDA believes doctors should choose to use instead. FDA 001601-02 (84 Fed. Reg. 7384, 7385). FDA's Vasopressin Decision states: "If a clinical need to compound drug *products* using the drug bulk substance has not been demonstrated, based on the information submitted by the nominator … FDA will not place a bulk drug substance on the 503B Bulks list." *Id.* at FDA 001602 (84 Fed. Reg. 7385). But the plain language of Section 503B(a)(2)(A)(i) makes clear the clinical need determination pertains to the bulk drug substance itself, not the compounded product containing that substance, as FDA's misinterpretation posits. Section 503B states:

> the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need.

21 U.S.C. § 353b(a)(2)(A)(i). This language is unambiguous: the phrase "for which there is a clinical need" modifies the term "bulk drug substance." *See Barnhart v. Thomas*, 540 U.S. 20, 26 (2003) ("[A] limiting clause or phrase … should ordinarily be read as modifying only the noun or phrase that it immediately follows."); *see also* Antonin Scalia & Bryan A. Garner, *Reading Law: The Interpretation of Legal Texts* 148, 152 (2012) (hereinafter, "Reading Law") (a postpositive modifier—i.e., a modifying phrase "'positioned after' what [it] modif[ies]"—"normally applies only to the nearest reasonable referent"). FDA rebels against the statute's

language, refusing to accept it because "[p]atients generally do not have a clinical need for a bulk drug substance … rather, any clinical need will be for a drug product made using the bulk drug substance." FDA 000070. FDA's rewrite violates this "nearest-reasonable-referent" canon of statutory interpretation. Here, the term "bulk drug substance" not only is the "nearest reasonable referent" of the modifying phrase "for which there is a clinical need," it is the only conceivable referent: the only other nouns in the subsection are "Secretary" and "list"—neither of which could be a referent for the modifying phrase "for which there is a clinical need." The language is plain and "[d]isagreeing with Congress's expressly codified policy choices isn't a luxury administrative agencies enjoy." *Cent. United Life Ins. Co. v. Burwell*, 827 F.3d 70, 73 (D.C. Cir. 2016). The plain-language reading is also in accord with how Congress drafted every other subpart of 503B(a)—all eleven conditions specify their respective subject, whether it be the facility, an ingredient (active or inactive), or the finished drug product, *see supra* at 5-6. FDA has not shown why the literal interpretation should not control. *See Del. Dep't of Nat. Res. & Envtl. Control v. EPA*, 895 F.3d 90, 99 (D.C. Cir. 2018) ("Neither Delaware nor EPA has demonstrated why this literal interpretation should not control. To 'avoid a literal interpretation at Chevron step one,' a party 'must show either that, as a matter of historical fact, Congress did not mean what it appears to have said, or that, as a matter of logic and statutory structure, it almost surely could not have meant it.'") (quoting *Engine Mfrs. Ass'n v. EPA*, 88 F.3d 1075, 1089 (D.C. Cir. 1996)).

The plain language of the statutory definition of "bulk drug substance" further confirms the subject of the clinical need inquiry is the active pharmaceutical ingredient and not the finished product. "Bulk drug substance" is defined as "active pharmaceutical ingredient," which means "any substance that is intended for incorporation into a finished drug product." 21 C.F.R.

§§ 207.1, 207.3. Thus, with plain language, Congress directed that the subject of the clinical need inquiry is the active *ingredient,* not the *product*.

Furthermore, FDA's own guidance document admits FDA is rewriting 503B(a)(2)(A)(i). FDA says that when it adds a bulk drug substance to the 503B Bulks List (which it has never done) it will also include any restrictions on which products can be made using that substance.

> [T]he Agency may tailor the entry on the 503B Bulks List to reflect its findings related to clinical need. For example, if the Agency were to find a clinical need for a bulk drug substance to be used to compound a drug product at a specific strength for topical use, it could choose to limit the entry of that bulk drug substances on the 503B Bulks List to use of the substance to compound drug products at a specified strength for topical use.

FDA 000096 (Evaluation of Bulk Drug Substances Guidance); *see also* FDA 000079 ("The Agency…will tailor the listings as appropriate in the context of its evaluation of particular substances."). FDA tries to grant itself this extra-statutory[13] authority to embed further conditions in the 503B List because it refuses to accept the plain language providing that once a bulk drug substance is on the 503B Bulks List outsourcing facilities can use it to make any compounded drug products (provided the other conditions of Section 503B are met). But nothing in Section 503B(a)(2)(A)(i) "suggests that Congress left any leeway for [FDA] to tack on additional criteria." *Cent. United Life Ins. Co.*, 827 F.3d at 73. FDA sees the plain language as a threat to its new drug approval program so it is trying to rewrite the statute as directing it to pick and choose which compounded drug products outsourcing facilities can make using bulk

[13] Where Congress authorized FDA to also include conditions on a list Congress established under the statute it said so expressly. In 503B(a)(6), Congress directed FDA to create a list of drugs presenting demonstrable difficulties for compounding that compounders shall be prohibited from making, unless they do so "in accordance with all applicable conditions identified on the list …." By contrast, 503B(a)(2)(A)(i) does not authorize FDA to include conditions on the 503B Bulks List—just the substances themselves.

drug substances for which there is a clinical need—even though the statute indisputably commands that the 503B Bulks List is a list of ingredients, not of products.

In addition, FDA's interpretation rewrites the statute to turn clinical need into an ephemeral quality that is dependent on which branded drugs exist at the time. An active pharmaceutical ingredient that meets a clinical need today might be one that does not meet a clinical need tomorrow, if a pharmaceutical company starts using it in a branded product. FDA 000073 ("[T]he approval of a new drug product that contains a bulk drug substance on the 503B Bulks List may affect whether there is a clinical need for the bulk drug substance."). But if Congress envisioned the clinical need determination to be transient, it would have written the provision so bulk drug substances could come and go from the 503B Bulks List, as Congress did for the shortage list in 503B(a)(2)(A)(ii), which assesses whether a shortage is in effect "at the time of compounding, distribution, and dispensing." 21 U.S.C. § 353b(a)(2)(A)(i) (drug products come and go from the list depending on conditions in the marketplace). Congress did not—there is no mechanism in 503B(a)(2)(a)(i) to remove a bulk drug substance from the 503B Bulks List.

Finally, Congress's plain-language directive to focus on the ingredient and not the product in Section 503B(a)(2)(A)(i) is supported by sound policy. With this requirement, Congress ensured unproven, fringe ingredients (i.e., those not shown to address a clinical need) are not used in bulk compounding authorized under the statute. In some instances, the clinical need for the bulk drug substance could be obvious, such as if it is already used to make FDA-approved products, as with vasopressin. But bulk drug substances that are not components of FDA-approved drugs could still qualify if their clinical need is shown some other way, such as where they are components of products with long established use, despite not having undergone

FDA approval. This statutory requirement reflects Congress's goal of ensuring access to high-quality, compounded drugs made in FDA-regulated facilities, *without* regulating the practice of medicine. Congress enacted the CQA not to dictate which drug products could be compounded, but rather, to create a new, regulated pathway for large-scale compounders to operate safely under FDA regulations.

> [T]he Drug Quality and Security Act establishes a completely separate and distinct section 503B that authorizes FDA to regulate an optional category for larger compounding facilities. Sterile compounding facilities that do not want to comply with the patchwork of State laws and requirements can choose instead to have FDA regulate their compounding. 503B establishes rigorous quality standards, registration, adverse event reporting, inspections, and fees.

See 159 Cong. Rec. S8072 (daily ed. Nov. 18, 2013) (co-sponsor, Sen. Alexander). The statutory purpose was to encourage more compounded drugs made under nationwide standards for safety controls, not "to limit access to quality compounded drugs for providers and patients or alter the practice of medicine…" *Id*. Doctors will decide which products are most "medically suitable" for their patients; FDA will ensure those products are made under the right standards.

B. FDA's interpretation violates the structure of 503B(a)(2).

FDA's interpretation violates the "whole text" canon, by which the statute must be read "in view of its structure and of the physical and logical relation of its many parts." Reading Law at 167; *see also Del. Dep't of Nat. Res.*, 895 F.3d at 97 (D.C. Cir. 2018) (in analyzing statutory text under Chevron step one, the court must look to the "'language and design of the statute as a whole'") (quoting *K Mart Corp. v. Cartier, Inc*., 486 U.S. 281, 291 (1988)). Section 503B's structure shows that the requirements of the condition in Section 503B(a)(2) are about the bulk drug substance and not the product made with that substance.

Focusing first on the immediate structure of 503B(a)(2), as with subpart A, its three other subparts are also about the *bulk drug substance*:

> (B) if an applicable monograph exists under the United States Pharmacopeia, the National Formulary, or another compendium or pharmacopeia recognized by the Secretary for purposes of this paragraph, *the bulk drug substances* each comply with the monograph;
>
> (C) *the bulk drug substances* are each manufactured by an establishment that is registered under section 360 of this title (including a foreign establishment that is registered under section 360(i) of this title); and
>
> (D) *the bulk drug substances* are each accompanied by a valid certificate of analysis.

21 U.S.C. § 353b(a)(2)(B)-(D) (emphasis added).

The structure of 503B(a)(2) makes its purpose clear. Working together, the four requirements of 503B(a)(2) ensure the legitimacy of the bulk drug substance used by the outsourcing facility – it must be a clinically necessary active ingredient, made by a registered manufacturer of active ingredients, in compliance with official monographs for such substances, and accompanied by a certificate of analysis. These are criteria for the bulk drug substance—ingredient—not drug product.[14] And they have nothing to do with which drug products pharmaceutical companies are selling, which FDA has placed at the center of its flawed clinical-need analysis.

Next, broadening from the immediate structure of 503B(a)(2) to the overall structure of 503B(a) further confirms the plain language interpretation of 503B(a)(2)(A)(i) is correct. As explained above, 503B(a) contains eleven conditions, some about the facility, some about the ingredients, and some about the product. *See supra* at 5-6. Where Congress intended to make a

[14] These are also criteria that ensure the bulk drug ingredient is vetted by FDA: the ingredients must be manufactured by an FDA-registered establishment (21 U.S.C. § 353b(a)(2)(C)), must comply with any applicable USP monograph (*id.* § 353b(a)(2)(B)), and must have a valid certificate of analysis (*id.* § 353b(a)(2)(D)), which confirms that the ingredient has been tested and passed quality control rigors.

condition about the drug product compounded from a bulk drug substance, rather than the bulk drug substance itself, it knew how to do so and did so expressly. A prime example is the condition in 503B(a)(5), wherein Congress required that "*the drug* is not essentially a copy of one or more approved drugs." 21 U.S.C. § 353b(a)(5) (emphasis added).

By ignoring the purposeful distinctions Congress made between drug products and bulk drug substances throughout, FDA's interpretation of 503(B)(a)(2)(A)(i) violates four canons of statutory construction. First, FDA violates the "presumption of consistent usage" canon, by which the use of "one term in one place, and a materially different term in another, [means] that the different term denotes a different idea." Reading Law at 170. "[I]t is a normal rule of statutory construction that identical words used in different parts of the same act are intended to have the same meaning." *Pereira v. Sessions*, 138 S. Ct. 2105, 2115 (2018) (internal quotation marks omitted) (agency interpretation fails *Chevron* step one); *see also Mohasco Corp. v. Silver*, 447 U.S. 807, 826 (1980) (refusing to give the same word "two different meanings in the same section of the statute"). Because Congress specifically defined bulk drug substances to mean active pharmaceutical *ingredient* and used it as such not only in 503B(a)(2)(A) but also 503B(a)(2)(B), (C), and (D), FDA cannot rewrite the statute to focus instead on the drug product. *See, e.g.*, *New York v. EPA*, 413 F.3d 3, 39 (D.C. Cir. 2005). In *New York v. EPA*, the D.C. Circuit explained: "The juxtaposition of the terms 'emit' and 'potential to emit' indicates that when Congress enacted the NSR program in 1977, it was conscious of the distinction between actual and potential emissions, using the term 'emit' to refer to actual emissions and the term 'potential to emit' to refer to potential emissions." 413 F.3d at 39. The same is true here. Congress was conscious of the distinction between *bulk drug substance* and *drug product* and FDA's attempt to revise the statute to the contrary should be rejected.

FDA also violates the canon by which "[c]ourts are required to give effect to Congress' express inclusions and exclusions, not disregard them," *Nat'l Ass'n of Mfrs. v. Dep't of Defense*, 138 S. Ct. 617, 631 (2018). Where "Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." *Russello v. United States*, 464 U.S. 16, 23 (1983) (alteration and citation omitted).[15] Finally, FDA violates both the "omitted-case" canon, by which "nothing is to be added to what the text states or reasonably implies" (Reading Law at 93) and the "negative-implication" canon, by which the expression of one thing implies the exclusion of the other (*id.* at 107): because Congress made the bulk drug substance the subject of the clinical need determination, FDA cannot rewrite the statute to make the drug product (which is omitted from the text) the subject of that determination.

C. FDA's interpretation disturbs the balance Congress deliberately struck.

FDA tries to justify its interpretation of 503B(a)(2)(A)(i) by arguing that it protects the integrity of FDA's new drug approval program, but Congress already made the policy decision of how best to balance that interest with the statute's purpose by including 503B(a)(5).[16]

Congress recognized the importance of drug compounders in our health care system and enacted Section 503B to encourage compounding. *See*, *e.g.*, 159 Cong. Rec. S8071-04 (daily ed. Nov. 18, 2013). Congress also recognized that Section 503B, by authorizing an exception to statutory new drug approval requirements, could threaten the integrity of the new drug approval

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[15] The D.C. Circuit uses this principle to reject agency interpretations under Chevron step one. *See*, *e.g.*, *W. Minn. Mun. Power Agency v. FERC*, 806 F.3d 588, 594-95 (D.C. Cir. 2015); *New York v. EPA*, 413 F.3d 3, 39 (D.C. Cir. 2005).

[16] As discussed *supra* at 2, Vasostrict® did not even go through FDA's traditional new drug approval program.

process. It therefore enacted Section 503B(a)(5) to prohibit outsourcing facilities from making products that are essentially copies of approved drugs.[17] As part of this careful calibration of competing interest, Congress also provided that even this protection for approved drugs shall give way during drug shortages, per Section 503B(a)(2)(A)(ii).

As discussed *supra* at 8, FDA admits in its Essential Copy Guidance that 503B(a)(5) itself protects the integrity of the new drug approval process. Essential Copy Guidance at 4 (stating that the "prohibition on producing a drug product that is an essential copy of an approved drug product protects the integrity and effectiveness of the new drug and abbreviated new drug application process"). Its admission is warranted. Notably, the term "approved drug" is defined in Section 503B(d)(3) and then used only in Section 503B(a)(5) (essential copy provision), not in Section 503B(a)(2) (the clinical need provision). The fact that Congress confined the use of this defined term to Section 503B(a)(5) makes clear the comparison of the compounded drug to an approved drug is exclusively the province of Section 503B(a)(5) and not Section 503B(a)(2)(A)(i).

Thus, Congress weighed and balanced the competing interests of the new drug approval process with the need for compounding and resolved it by including Section 503B(a)(5)—not through Section 503B(a)(2)(A)(i). Yet, FDA's interpretation of 503B(a)(2) makes a comparison to approved drugs the touchstone of the clinical need determination. In so doing, FDA disturbs the balance Congress struck when it made the policy decision of how best to account for the competing interest in encouraging the use of the drug approval process. Where, as here, Congress has struck a balance between competing interests, agencies may not disrupt that

[17] FDA did not make a determination whether Athenex's vasopressin product is essentially a copy of Vasostrict®, which it is not (e.g., the two products use different excipients).

balance. *See Pharm. Research & Manufacturers of Am. v. HHS*, 138 F. Supp. 3d 31, 53 (D.D.C. 2015) (the statutory language "evidences that [Congress] struck a different balance and it is simply not for this Court to rewrite the statute") (internal quotations and court's alterations omitted) (agency interpretation fails *Chevron* step one); *see also White Stallion Energy Center, LLC v. EPA*, 748 F.3d 1222, 1265 (D.C. Cir. 2014) (Kavanaugh, J., dissenting) (EPA's interpretation "upsets Congress's careful balance" and thus, the interpretation was "not what Congress intended or permitted and thus is beyond EPA's authority"), *rev'd sub nom Michigan v. EPA*, 135 S. Ct. 2699 (2015); *Elec. Power Supply Ass'n v. FERC*, 391 F.3d 1255, 1265-66 (D.C. Cir. 2004) (rejecting as "patently wrong" agency's argument that it is "free to strike its *own* balance between its perceived" needs and fairness rules set by Congress); *Nat'l Ass'n of Patients on Hemodialysis & Transplantation, Inc. v. Heckler*, 588 F. Supp. 1108, 1128 (D.D.C. 1984) (agency's interpretation was "a departure from the balance struck by Congress between effective health care delivery and savings to the Medicare program" and was "arbitrary, capricious and not in accordance with law"); *Union of Concerned Scientists v. U.S. Nuclear Regulatory Comm'n*, 735 F.2d 1437, 1446 (D.C. Cir. 1984) (agency rule exceeded its authority when it "upended the balance struck by Congress between efficiency and public participation"); *Shays v. U.S. Fed. Election Comm'n*, 508 F. Supp. 2d 10, 66 n.36 (D.D.C. 2007) (agency's "purported efforts to re-balance the competing policies [set forth by Congress] is particularly misplaced"), *rev'd in part on other grounds*, 528 F.3d 914 (D.C. Cir. 2008).

Furthermore, under FDA's misreading of the statute, there could never be a clinical need for a compounded drug product that is essentially a copy of an approved drug, which makes Section 503B(a)(5) redundant. Any compounded drug that is essentially a copy of an approved drug necessarily is made with a bulk drug substance for which FDA believes there is not a

clinical need because FDA makes differentiation from approved drugs the touchstone for clinical need in the first place. FDA's reading of the statute therefore also violates the canon of statutory construction "that all words in a statute are to be assigned meaning, and that nothing therein is to be construed as surplusage." *Indep. Ins. Agents of Am., Inc. v. Hawke*, 211 F.3d 638, 644 (D.C. Cir. 2000) (internal quotation marks omitted) (agency interpretation fails *Chevron* step one); *see also Del. Dep't of Nat. Res. & Envtl. Control v. EPA*, 895 F.3d 90, 99 (D.C. Cir. 2018) ("[W]e strive to construe statutes so that effect is given to all its provisions ….") (internal quotations omitted); *Winder v. Erste*, 566 F.3d 209, 214 (D.C. Cir. 2009) (rejecting plaintiff's interpretation of a statute that would render it redundant with another statutory provision).

FDA also disturbs the balance Congress struck in another respect, one regarding safety. FDA tries to justify its interpretation of 503B(a)(2)(A)(i) by arguing that its interpretation is rooted in safety, asserting that prohibiting compounded drugs that have an FDA-approved counterpart pushes doctors to choose drugs that are subject to "premarket review by FDA for safety, effectiveness, and quality." FDA 000076, FDA 000089-90. But Congress specifically addressed safety concerns inherent to compounding *specific drug products* in a different condition of Section 503B(a)—Section 503B(a)(6).[18] There, Congress created a "negative list"—i.e., a list of specific drug products for which compounding is prohibited because they present difficulties for compounding safely (unless certain extra conditions are met). FDA's

[18] Section 503B(a)(6), "Drugs presenting demonstrable difficulties for compounding," directs FDA to publish a "list" of "drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients." 21 U.S.C. § 353b(a)(6)(A). It also requires a drug to be "compounded in accordance with all applicable conditions identified on the list described in subparagraph (A) as conditions that are necessary to prevent the drug or category of drugs from presenting the demonstrable difficulties described in subparagraph (A)." *Id.* § 353b(a)(6)(B).

interpretation of 503B(a)(2)(A)(i) has the effect of treating all compounded drugs that have branded counterparts as though they are on the 503B(a)(6) list.

D. FDA's interpretation violates Congress's intention not to regulate the practice of medicine.

In enacting the FFDCA, Congress wanted decisions concerning which medications would treat the patient more suitably be left to the treating physician—not FDA. 78 Cong. Rec. 2728 (1934) (statement of Sen. Copeland) (responding to fears that the proposed legislation would interfere with the "prerogatives of the doctor" by emphasizing that the revised bill "makes certain that the medical practitioner shall not be interfered with in his practice"). Courts have recognized this intent of Congress not to regulate the practice of medicine. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) (recognizing "FDA's mission to regulate in this area without directly interfering with the practice of medicine"); *Chaney v. Heckler*, 718 F.2d 1174, 1179 n.13 (D.C. Cir. 1983) ("the legislative history makes clear that Congress did not want to limit a physician's ability to treat his patients" in enacting FFDCA) (citing S. 5, 74th Cong., 1st Sess. § 201(b), 79 Cong.Rec. 8351 (1935)), *rev'd on other grounds*, 470 U.S. 821 (1985); *see also In re Orthopedic Bone Screw Prods. Liab. Litig.*, MDL No. 1014, 1996 WL 107556, at *3 (E.D. Pa. Mar. 8, 1996) ("FDA does not regulate the practice of medicine").

In adding Section 503B to the FFDCA, Congress was clear once again that "[n]othing in the legislation is intended to limit access to quality compounded drugs for providers and patients *or alter the practice of medicine* …." 159 Cong. Rec. S8072 (daily ed. Nov. 18, 2013) (statement of Sen. Alexander) (emphasis added). However, FDA's clinical need test violates Congress's intent not to regulate the practice of medicine. FDA's interpretation of 503B(a)(2) regulates the practice of medicine by deciding whether a safely made and medically effective drug can be compounded, *based on whether FDA believes physicians should instead choose a*

branded drug on the market—all in the name of protecting the integrity of the drug approval process. But using the drug approval process as an excuse to regulate the practice of medicine is precisely what Congress has made clear FDA shall not do, ever since the advent of the FFDCA and again when it added Section 503B to that statute.

FDA's attempts to assuage fears of its overreach further confirm it *is* practicing medicine, despite its protestations to the contrary. Most tellingly, FDA tries to reassure doctors that they can still have their say in these treatment decisions by making their voices heard by the real decision-makers at FDA. FDA 000070 (asserting medical professionals "have multiple opportunities to advise the Agency" and "FDA is collaborating with the University of Maryland and Johns Hopkins University" to develop the 503B Bulks List). FDA's foray into the practice of medicine—making itself the decisionmaker for whether an approved drug is "medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation" (FDA 001603 (84 Fed. Reg. at 7386))—even makes it a promotor of off-label uses of approved drugs, which is anathema to the agency's role,[19] because FDA's test for clinical need pushes doctors to use an approved drug for off-label purposes by denying them the option to prescribe a compounded product made with the same bulk drug substance. At bottom, FDA's defense is merely a circular argument that comes back to its own misreading of the statute: "When FDA establishes the 503B Bulks list, it is not regulating the practice of medicine, but, rather, fulfilling its statutory mandate of regulating the outsourcing facilities' production and distribution of compounded drug products." FDA 000070.

[19] *See Buckman Co.*, 531 U.S. at 350-51 & n.5 (describing off-label use decisions by physicians as part of the practice of medicine and thus outside FDA regulation).

If Congress had intended to upend more than 80 years of established law and invite FDA to regulate the practice of medicine, it would have said so expressly, not hidden it in 503B(a)(2)(A)(i) using language that would require a cryptic, contra-textual interpretation. *See Gonzales v. Oregon*, 546 U.S. 243, 267 (2006) (holding that the Controlled Substances Act did not authorize the Attorney General to prohibit physicians from prescribing regulated drugs for use in physician-assisted suicide as authorized by Oregon state law and explaining "Congress … does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not, one might say, hide elephants in mouseholes"); *see also FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 160 (2000) ("[W]e are confident that Congress could not have intended to delegate a decision of such economic and political significance to an agency in so cryptic a fashion.").

* * *

For these reasons, FDA's Vasopressin Decision is inconsistent with the unambiguous statutory language. "Where, as here, the canons supply an answer, '*Chevron* leaves the stage.'" *Epic Sys. Corp. v. Lewis*, 138 S. Ct. 1612, 1630 (2018) (citation omitted). Under *Chevron* step one, FDA's decision is "not in accordance with law," and is "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2)(A), (C). It must be set aside.

E. Alternatively, FDA's interpretation fails to survive *Chevron* step two.

Even if a *Chevron* step two analysis were warranted, FDA's interpretation would still be unreasonable. FDA's interpretation would rewrite the statute by adding obligations that are not there (e.g., to show that there is a clinical need for the drug product that can only be met by compounding from bulk drug substance and that the FDA-approved product is not medically suitable). Such an interpretation is unreasonable and therefore is not entitled to *Chevron*

deference. *See*, *e.g.*, *MCI Telecomm. Corp. v. AT&T Co.*, 512 U.S. 218, 229 (1994) ("[A]n agency's interpretation of a statute is not entitled to deference when it goes beyond the meaning that the statute can bear."); *Cent. United Life Ins. Co.*, 827 F.3d at 74 (HHS's "rule was an act of amendment, not interpretation. Accordingly, HHS has no colorable claim to *Chevron* deference."); *Jordan v. Sec'y of Educ.*, 194 F.3d 169, 171-72 (D.C. Cir. 1999) (concluding Department of Education's decision to "add an obligation that is not in the statute ... changed the nature of the statute" and that the "Secretary may not rewrite the statute").

Furthermore, FDA's interpretation is unreasonable because it contravenes Congress's statutory design to encourage *more* quality compounded drugs, not fewer. FDA's clinical need test erodes the ability of outsourcing facilities to compound drugs, doing so in a way that impermissibly curtails patient access to safe, quality, compounded drugs (which 503B is intended to provide) in contravention of Congress's statutory purpose. FDA impermissibly designed its clinical need test to "limit patient exposure to compounded drug products," confusing drug safety with limiting exposure to the very products Congress intended to encourage. 84 Fed. Reg. 7384; *see also* FDA 000074 (same). Its interpretation thus directly contradicts Congress's intent in drafting 503B, to "create a whole new alternative for safe sources of sterile compounded drugs that are held to a nationwide quality standard." 159 Cong. Rec. S8072 (daily ed. Nov. 18, 2013) (statement of Sen. Alexander). Indeed, "[n]othing in the legislation is intended to limit access to quality compounded drugs for providers and patients or alter the practice of medicine." *Id.* Yet FDA's clinical need test does exactly that—it decides for the practitioner that an FDA-branded drug is the more medically suitable option for their patients.

II. FDA's Vasopressin Decision is arbitrary and capricious and should be vacated under Section 706(2)(A) of the APA.

Even if FDA's decision could survive a *Chevron* analysis, it is arbitrary and capricious because it "runs counter to the evidence before the agency," the agency "relied on factors which Congress [did] not intend[the agency] to consider," and the decision is not otherwise the "product of reasoned decisionmaking." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co*., 463 U.S. 29, 43, 52 (1983). In addition to relying on factors which Congress did not intend FDA to consider in its Bulk List determination, *see supra* Part I,[20] FDA's Vasopressin Decision runs counter to the evidence before the agency and is not otherwise the product of reasoned decision-making given two attributes of Athenex's vasopressin product that differentiate it from Vasostrict®: (1) vasopressin is a "high alert" medicine in the acute care setting and only Athenex's vasopressin product is ready-to-use and (2) Vasostrict® is contraindicated *per its label* for chlorobutanol-allergic and Athenex's vasopressin product is not.

A. Vasopressin is a "high alert" medicine in the acute care setting and only Athenex's vasopressin product is ready-to-use.

A ready-to-use vasopressin drug product, like Athenex's, meets a clinical need because vasopressin is a "high alert" medicine in the acute care setting, where time is of the essence and errors in administration are catastrophic. Vasopressin products are commonly used in emergency rooms, intensive care units, the cardiac catheter laboratory, on crash carts, and for code cases, to treat acute conditions where time is critical. FDA 000257, FDA 000252, FDA 000316-17. FDA concludes in broad strokes that ready-to-use is not a clinical need attribute,

[20] Under the lawful interpretation of Section 503B(a)(2)(A)(i), vasopressin would be added to the 503B Bulks List because it is a bulk drug substance for which there is a clinical need, as the administrative record shows. *See supra* Part I.

stating that "improved efficiency for prescribers or healthcare providers" and "address[ing] the possibility that the approved drug might be mishandled by a medical professional" do not meet a clinical need. FDA's knee-jerk disposal of the ready-to-use benefits for a ready-to-use vasopressin product runs counter to the evidence before the agency, which establishes that vasopressin is *a high alert medicine*: of the thousands of medicines used in acute care settings, vasopressin is one of only *twelve* "high alert" medicines specifically identified by the Institute for Safe Medication Practices ("ISMP") as presenting serious risk for patient harm from errors in preparation and administration when not in ready-to-use form. FDA 000464, *ISMP List of High-Alert Medications in Acute Care Settings* (2018). ISMP created and updates this list "[b]ased on error reports submitted to the ISMP National Medication Errors Reporting Program (ISMP MERP), reports of harmful errors in the literature, studies that identify the drugs most often involved in harmful errors, and input from practitioners and safety experts…." *Id.*

FDA ignored this "high alert" designation entirely in its Vasopressin Decision, even though a ready-to-use vasopressin product would address the high alert concerns by giving emergency rooms an option other than a 16-step process (*see* FDA 000266-67) resembling compounding on the fly. Admixing is itself a form of compounding, which further shows the irrationality of FDA's Vasopressin Decision: FDA's interpretation rejects a premixed, ready-to-use vasopressin product that was compounded from quality bulk ingredients in a sterile, cGMP-compliant facility, in favor of a nurse or other medical professional compounding on the spot to create an intravenous bag from a vial under the pressures of exigent circumstances. *See* 21 U.S.C. § 353b(d)(1) (defining compounding as "combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug").

Furthermore, FDA's own guidance recognizes there can be a clinical need for ready-to-use products that do not require further dilution:

> Products should be designed so that foreseeable end users can perform critical tasks using the drug product-user interface without making unintentional medication errors and without being exposed to unnecessary safety hazards. * * * To the extent possible, avoid developing intravenous products already in solution that require a two-step dilution prior to administration. Users might fail to dilute such products because they are already in solution, or they might dilute them incorrectly, leading to medication dosing and administration errors. * * * Products that require further dilution prior to administration should not be packaged in containers that could afford direct administration.

FDA 000346, FDA 000352, FDA 000354 (FDA, Safety Considerations for Product Design to Minimize Medication Errors, Guidance for Industry (2016)); *see also* FDA 00265, FDA 000266 (citing FDA Compliance Policy Sec. 430.100 ("The advantages of unit dose dispensing are that the drug is fully identifiable and the integrity of the dosage form is protected until the actual moment of administration."), *available at* https://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074377.htm (last visited Mar. 17, 2019)).[21]

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[21] The clinical needs met by ready-to-use products, also have been recognized by pharmacy associations, patient safety organizations, other governmental and accrediting bodies. *See*, *e.g.*, FDA 00265 (citing Centers for Medicare and Medicaid Services, Final Rule, Policy and Technical Changes to the Medicare Prescription Drug Benefit, 73 Fed. Reg. 20486, 20496 (April 15, 2008) ("The use of [ready-to-use] drugs or drug classes often results in an earlier hospital discharge and reduced health care costs, and rapid access to these agents is imperative to these health care transitions….)); FDA 000645 (CMS, *CMS Review of Current Standards of Practice for Long-Term Care Pharmacy Services* (Dec. 30, 2004)) ("The standards of practice, however, have evolved to emphasize the use of unit dose systems, particularly in institutional settings."); FDA 000265 (citing Joint Commission Standard MM.03.01.03 (stating that hospital pharmacies should ensure, whenever possible, that emergency medications are available in unit-dose, age-specific, and ready-to-administer forms); Joint Commission Standard MM.05.01.11 (stating that medications should be dispensed in the most ready-to-administer forms)); FDA 000509 (American Society of Hospital-System Pharmacists, *ASHP Guidelines for Preventing Medication Errors in Hospital* 268, 275 (2018)) ("Whenever possible, medications should be available for inpatient use in unit-of-use and ready to administer packaging without further manipulation by the person administering the medication. Every effort should be made to reduce situations where the person administering the medication has to withdraw doses from containers, reconstitute

Given vasopressin's special status (ignored by FDA) as one of twelve medications presenting the highest risks from errors in administration in the acute care setting, and given FDA's admission that ready-to-use attribute can be clinically important, it is arbitrary and capricious for FDA to disregard without a rational basis the clinical need for ready-to-use vasopressin product to reduce this recognized, heightened risk from error in administrating a non-ready-to-use version of the drug. The administrative record shows Athenex's vasopressin product is ready-to-use, meaning it can be administered directly to the patient in the form it is delivered to the medical provider. FDA 000261. This is an important attribute that reduces risk of error in administration and FDA lacks any rational basis to disregard it. FDA takes the option away from emergency rooms to keep office stock of ready to use vasopressin, which interferences with the practice of medicine to the detriment of providers and their patients. FDA also takes decisions away from emergency room doctors who may determine that a ready-to-use drug is preferable for a patient than one requiring a 5-7-minute preparation and a 16-step process prior to administration for a patient who is in shock and could only have a few minutes to live.[22]

Further, FDA's Vasopressin Decision is arbitrary and capricious because it wrongly concludes there is no need to compound vasopressin from bulk, deciding instead that the drug

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powdered drug products, split tablets, or perform other similar manipulations."); and FDA 00263 (citing American Pharmacist Association, *APhA Policy Manual Drug Product Packaging* (2012), *available at* https://www.pharmacist.com/policy-manual (Drug Product Packaging) (advocating need for ready-to-use drug products "to enhance patient safety")).

[22] FDA tries to justify its interpretation of clinical need—to take away the choice of the ready-to-use compounded drug product when FDA decides doctors should choose the branded product instead—by asserting that otherwise "patients lose the assurances associated with using an approved drug …." FDA 001599. That is wrong. Doctors can still choose the branded drug product if the doctor decides it is the more medically suitable choice, so the "assurances" associated with such products are not lost; rather, doctors have the freedom to choose what is medically best for their patients—the branded product or the ready-to-use compounded product.

can be compounded from Vasostrict®. This conclusion lacks factual support and is belied by FDA's own draft guidance and statements from Defendant FDA Commissioner, Dr. Gottlieb, which advocate for fewer manipulations in the act of compounding. For example, FDA's recent guidance states that, as part of current good manufacturing practice in drug compounding:

> In general, processes and procedures at an outsourcing facility should minimize contamination risks posed by, for example, the number and complexity of manipulations, number of simultaneous operations and workstations, and staging of materials used in the process.

FDA, *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, Draft Guidance (Dec. 2018) ("FDA's CGMP Guidance"), *available at* https://www.fda.gov/downloads/drugs/guidances/ucm403496.pdf (last visited on Mar. 17, 2019), at 8. And on December 10, 2018, Defendant Gottlieb issued a statement reiterating that FDA is focused on the importance of ensuring compounded product quality. In the context of that update focused on patient safety, Dr. Gottlieb stated:

> Our aim is to protect patients and see more of the activity that creates the greatest potential for risk be done by compounders that meet CGMP requirements rather than by those that do not. Some of these higher risk activities include compounding done on a large scale, for drugs that must be sterile, and made using many manual manipulations.

See FDA Statement from FDA Commissioner Scott Gottlieb, M.D. and Deputy Commissioner Anna Abram on new efforts to assure the quality of compounded drugs (Dec. 10, 2018), *available at* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628029.htm (last visited Mar. 17, 2019) ("Gottlieb Statement"). The Gottlieb Statement and FDA's CGMP Guidance highlight the well-established principle that with every manipulation of a drug during the compounding process the risk of contamination and error goes up. The more manipulations, the greater the risk for contamination. Yet, FDA's Vasopressin Decision concludes that

vasopressin should be compounded from the branded product, Vasostrict®, FDA 001604, even though doing so requires the manipulation of hundreds to thousands of vials of Vasostrict®, as opposed to one manipulation using the quality and statutorily-regulated bulk drug substance. FDA 000280. FDA is pushing the patient population toward FDA-approved drugs even when doing so means more manipulations of a drug, i.e., increased risk of contamination and error, in violation of its own policies and without any support.

Thus, if the Court were to apply FDA's flawed reading of 503B(a)(2), the Vasopressin Decision is "counter to the evidence before the agency," counter to the agency's own findings with respect to current good manufacturing processes, and at base, is a decision that is not product of reasoned decision-making. *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43.

B. Athenex's Vasopressin Product is not contraindicated for patients allergic to chlorobutanol but Vasostrict® is.

Athenex's vasopressin product has a second attribute that meets a clinical need that Vasostrict® does not: it is chlorobutanol-free whereas Vasostrict® is contraindicated *per its label* for chlorobutanol-allergic patients. FDA 00259-261; FDA 001639, ¶ 4. FDA acknowledges that Vasostrict®'s label states that it is contraindicated for patients allergic to chlorobutanol but asserts that the contraindication does not apply to the single dose (1mL) Vasostrict® vial: "[a]s described in the package insert, the VASOSTRICT 10 mL solution contains chlorobutanol, while the 1 mL solution does not." FDA 001604, n.25. FDA's assertion is contrary to the record evidence and its own regulations regarding contraindication labeling requirements.

Contrary to FDA's assertion, Vasostrict®'s label specifies its chlorobutanol contraindication universally, implicating both the 1ml (single does) and 10ml (multidose) size vials, without exception. FDA 001639, ¶ 4. FDA contends this categorically stated

contraindication should be disregarded for the 1mL vial because the description section of the label does not mention chlorobutanol among the contents of the 1mL vial, but does for the 10mL vial. FDA's invitation for physicians to draw a negative inference from a different part of the label to ignore the express, categorically asserted contraindication violates FDA's own strict regulations about contraindication labeling.[23] FDA regulations state that the contraindication section of a product's label "must describe any situations in which the drug should not be used" and only "[k]nown hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication)." 21 C.F.R. § 201.57(c)(5); *see also* FDA 000373 (FDA, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format: Guidance for Industry* (2011)) ("A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible theoretical benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication."). Thus, whether as a direct additive or from cross-contamination, the labeling of Vasostrict® makes clear that the drug product shall not be used in patients who are allergic to chlorobutanol. FDA ignores its own regulations and the import of the product labeling when it concludes the categorical contraindication statement on the label can be disregarded for the 1mL vial.

[23] FDA's own regulations show that the description section does always identify preservatives. *See* 21 C.F.R. 201.117 ("A harmless drug that is ordinarily used as an inactive ingredient, such as a coloring, emulsifier, excipient, flavoring, lubricant, preservative, or solvent, in the preparation of other drugs shall be exempt from section 502(f)(1) of the act [regarding labeling].").

And FDA's conclusion that doctors and other medical providers should ignore the contraindication on the Vasostrict® label and prescribe it to patients allergic to chlorobutanol *anyway* is tantamount to FDA regulating the practice of medicine, which violates Congressional intent and is not the product of reasoned decisionmaking. Under FDA's rubric, a provider's only option for administering a vasopressin drug product to a patient allergic to chlorobutanol is to prescribe the drug with a label stating it is contraindicated for such patients. This is a medical decision, outside the province of FDA. Other safe, high-quality, and effective vasopressin product options exist on the market and it is not for FDA to pull them off when Congress enacted the CQA to ensure access to them.

* * *

For these reasons, FDA failed to "articulate a satisfactory explanation" and make a "rational connection" between the Vasopressin Decision and the administrative record. *See Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43. To the contrary, FDA's explanations contradict the record evidence and the decision should therefore be vacated.

CONCLUSION

WHEREFORE, Athenex respectfully requests that the Court grant its motion for summary judgment and enter an order vacating FDA's decision to exclude the bulk drug substance vasopressin from the 503B Bulks List.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I HERBY CERTIFY that on this 18th day of March, 2019, a true and exact copy of Athenex's Memorandum in Support of its Motion for Summary Judgment was filed via operation of the ECF system on all counsel of record pursuant to Local Civil Rule 5.4(d).

/s/ Gilbert S. Keteltas
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