UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

NOVO NORDISK INC. Plaintiff, v. DCA PHARMACY, Defendant.	Case No. 3:23-cv-668 **AMICUS CURIAE BRIEF** Assigned to the Honorable Judge Waverly D. Crenshaw, Jr.

INTRODUCTION

The Alliance for Pharmacy Compounding ("APC") submits this amicus curiae brief to aid the Court with its understanding of professional pharmacy regulation and practice issues in this case. The APC is recognized as a voice for pharmacy compounding, representing compounding pharmacists and technicians in both state-licensed pharmacies acting under the authority of Section 503A of the Food, Drug & Cosmetic Act ("FDCA") and Outsourcing Facilities acting under the authority of Section 503B of the FDCA. The APC also represents compounding pharmacy stakeholders, including prescribers, educators, patients, and pharmacy suppliers. Including APC partner organizations, the APC represents

approximately 150,000 patients, compounding professionals, prescribers, and others.

The APC does not intend to repeat any party's argument but will provide the Court with a broader perspective on the history, importance, and prevalence of compounding in our health care system. In particular, APC will demonstrate that this case implicates and can have significant impact on basic pharmacy legal principles and practice, and thus on patient access to common medications in the state. Without question, the industry is aware of and following this case because it will impact its ability to continue a patient's care in circumstances where drug manufacturers are unable to supply medications tailored to a specific patient's needs when in the judgment of a prescriber, that compounded medication is needed.

This brief will (1) explain how compounded medications are not manufactured products; (2) explain that, despite the Plaintiff's contention that all products require FDA approval, compounded medications and many manufactured products do not require FDA approval, (3) explain the basics of pharmacy compounding and how state and federal authority and guidance expressly authorize pharmacies to compound "essentially copies," or "identical," versions of commercially manufactured drugs without FDA approval during drug shortages.

ARGUMENT

I. Drug Manufacturing and Compounding Are Distinct Activities from Manufacturing. Not All Manufactured Drugs Require FDA Approval.

Plaintiff's complaint describes the Defendant's actions as participating in the "manufacturing" of a drug that the United States Food & Drug Administration ("FDA") has not approved, which it argues violates Tennessee law. Complaint at 3, ¶ 11 (citing Tenn. Code Ann. § 53-1-110). Plaintiff does not acknowledge, however, that Tennessee also expressly permits compounding (*See* Tenn. Code Ann. § 63-10-216 & Tenn. Comp. R. & Regs. 1140-01-.01) or attempt to harmonize the two laws. *See Lee Medical, Inc. v. Beecher,* 312 S.W.3d 515, 527 (Tenn. 2010). Plaintiff's argument would make it unlawful to sell numerous manufactured drugs, because not all manufactured drugs receive FDA approval. More importantly in this case, compounded drugs also do not require FDA-approval.

Drug manufacturing is strikingly different in practice and in the law than pharmacy compounding. FDA-registered and state-licensed entities manufacture drugs under the authority of the FDCA and its accompanying regulations, known as Current Good Manufacturing Practice ("CGMP"). *See* 21 C.F.R. Part 210, 211, and 314. The CGMP regulations for manufactured drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of drug products. The FDA enforces drug manufacturers' compliance with

CGMP to ensure the quality of mass-produced drug products. The law does not apply CGMP requirements to 503A pharmacy compounding; in fact, it expressly exempts 503A compounding.[1]

Manufactured drugs generally, but not always, undergo an approval process under the FDCA. The approval process for new human drugs starts with a New Drug Application ("NDA"). Human generic drugs undergo an abbreviated approval process that starts with an Abbreviated New Drug Application ("ANDA"). 21 C.F.R. § 314.1 - 314.170. Not all manufactured drugs require an NDA or ANDA. One example is the class of drugs known as biologics, approved through a process outlined in the Public Health Service Act, which starts with a Biologic License Application ("BLA"). 21 C.F.R. § 601.2. Biologics are medications that come from living sources. Humira—a monoclonal antibody used to treat rheumatoid arthritis—is one well-known example. Botox is another.

Another class of drugs known as "Over the Counter" Drugs ("OTCs") can be brought to market without express FDA approval through the OTC Drug Monograph process under Section 505 of the FDCA (21 U.S.C. 355g). An OTC drug monograph establishes conditions for active ingredients, uses, doses, and labeling. In brief, if

[1] *See* FDA, COMPOUNDED DRUG PRODUCTS THAT ARE ESSENTIALLY COPIES OF A COMMERCIALLY AVAILABLE DRUG PRODUCT UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT – GUIDANCE FOR INDUSTRY 3 ("[L]icensed pharmacists and licensed physicians who compound drug products in accordance with section 503A are not required to comply with CGMP requirements.")

an OTC product complies with the monograph, it does not need FDA approval. Common cold medications, antiperspirants, and antacids found on grocery store shelves are a few common examples of such products.

Yet another class of manufactured drugs that do not require NDA or ANDA approval processes relates to products authorized as DESI (Drug Efficacy Study Implementation) or GRASE (Generally Recognized as Safe and Effective). *See* 21 C.F.R. §§ 310.6 and -360fff–3. In brief, these drugs have been "grandfathered" by the FDA, due to their long history of safety and evidence of efficacy prior to FDCA's enactment. Examples of grandfathered drugs in the market include phenobarbital, colchicine, ephedrine sulfate, digitoxin, and hydrocode bitartrate, to name a few.

Whereas Plaintiff's complaint has focused on Tenn. Code Ann. § 53-1-110's prohibition on selling "new drugs" that did not complete NDA, ANDA, or BLA new drug approval processes, the reality is that many drugs marketed in Tennessee are lawful under state and federal law for other reasons.

Medications that pharmacists or physicians compound in compliance with state and federal law are also in this category of medications that federal and state law allow to be prepared and distributed outside of the FDA's NDA, ANDA, or BLA approval processes.

II. The Benefits of Pharmacy Compounding and State and Federal Authority and Guidance Authorizing It.

The science and art of compounding medications can be linked to the origins of pharmacy itself. The first documented chemical processes can be traced as far back as the time of the ancient Egyptians.[2] Drug compounding—the creation of medicines for patients whose clinical needs cannot be met by FDA-approved products or when an FDA-approved product is subject to a national shortage—has long been a part of pharmacy practice. Pharmacy compounding plays an essential role in health and wellbeing of American citizens. In traditional compounding, pharmacists create a customized medication, most often from pure ingredients, for an individual patient pursuant to a prescription written by a practitioner licensed by the state who has a bona fide prescriber-patient relationship. In many cases, this activity is critical to providing effective care. The FDA's published guidance approving compounding in various circumstances states as follows:

> Compounded drug products serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, such as a patient who has an allergy and needs a medication to be made without a certain dye, an elderly patient who cannot swallow a pill and needs a medicine in a liquid form that is not otherwise available, or a child who needs a drug in a strength that is lower than that of the commercially available product.[3]

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[2] Traditional ancient Egyptian medicine: A review, *Saudi J Biol Sci*. 2021 Oct; 28(10): 5823–5832.

[3] FDA, COMPOUNDED DRUG PRODUCTS THAT ARE ESSENTIALLY COPIES OF A COMMERCIALLY AVAILABLE DRUG PRODUCT UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT – GUIDANCE FOR INDUSTRY 2.

In this case, the Defendant is a 503A pharmacy licensed by the state of Tennessee. The FDCA and state law both permit pharmacy compounding. Under Section 503A of the FDCA (21 U.S.C. § 353a). Section 355 (new drugs) does not apply to compounded medications, provided the compounding complies with several requirements, including the following:

(1) an appropriately licensed pharmacist or physician performs the compounding pursuant to a valid prescription order from a licensed prescriber or based on an established history between the prescriber, compounder, and patient (21 U.S.C. § 353a(1)(A) and (B));

(2) compounded medication uses only approved substances (21 U.S.C. § 353b(1)(A), (B), and (C)); and

(3) compounding does not involve producing drug products that are "essentially copies" of commercially available products regularly or in inordinate amounts (21 U.S.C. § 353b(1)(D)).

Under the law, the term "essentially a copy" is defined to exclude compounded drugs where "there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner." 21 U.S.C. § 353b(2). As is discussed below, when a drug is listed as "currently in shortage" by FDA, pharmacies may also compound copies of FDA-approved drugs because they are not "commercially available." The FDCA

therefore expressly permits compounding of drugs that have not received FDA approval. This authority is mirrored in the state.

Plaintiff alleges that a pharmacy's introduction of compounded medications violates Tenn. Code Ann. § 53-1-110, which prohibits the sale of a "new drug unless an application with respect to the drug has become effective under § 505 of the federal act." As noted above, this ignores multiple manufactured drugs that do not receive NDA or ANDA approval under Section 505 of the FDCA, including compounded drugs under Section 503A. More to the point, Tennessee law expressly permits compounding. *See* Tenn. Code Ann. § 63-10-204 and -216; Tenn. Comp. R. & Regs. 1140-01-.01. Under Tenn. Code Ann. § 63-10-204, "Compounding" is defined consistently with Section 503A of the FDCA and requires a valid, patient-specific prescription or established prescribing history. The state licenses sterile and non-sterile compounding pharmacies and regulates the activity to ensure product safety. Tenn. Code Ann. § 63-10-216.

Tennessee law therefore expressly permits and clearly contemplates the sale of compounded medications along with the other classes of drugs that do not receive FDA-approval through NDA and ANDA processes under Section 505 of the FDCA (21 U.S.C. § 355). To give effect to these laws and Tenn. Code Ann. § 53-1-110, the Court must attempt to harmonize them. *See Lee Medical, Inc. v. Beecher,* 312 S.W.3d 515, 527 (Tenn. 2010). In brief, Section 53-1-110 addresses traditional "new drug"

products that would require FDA approval under Section 505 of the FDCA, and is clearly not intended to prohibit the sale of drugs that are otherwise permitted without that approval under state and federal laws.

In this case, the Defendant is a 503A pharmacy licensed by the state of Tennessee. Plaintiff's complaint has not alleged that Defendant has not complied with Section 503A or state law that expressly permits compounding. Instead, Plaintiff has gone much further and alleged—effectively—that all compounding (along with the sale of manufactured drugs that do not receive FDA new drug approval) is unlawful. It is more typically the case that cases such as these are brought under 503A's "essentially a copy" prohibitions, which merit discussion even though it is not the gravamen of Plaintiff's complaint.

In this case and in the act of compounding nationwide, pharmacies do compound drugs that are essentially a copy of commercially available products. That activity is also permitted, however, under both statute and FDA guidance.

III. Pharmacies May Compound Drugs that Are "Essentially Copies of Commercially Available Medications."

Congress passed the Drug Quality & Security Act of 2013. After decades of ambiguity, Congress wrote a clear and rather comprehensive bill affirming the role pharmacy compounding plays in the public health and wellbeing of American citizens. Whereas under 21 U.S.C. § 353a(b)(1)(D), pharmacies registered as Outsourcing Facilities may not compound "essentially copies" of "commercially

available products," Congress authorized compounding copies of commercially manufactured drugs that are, "identical or nearly identical to an approved drug…[if] the drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing." 21 U.S.C. § 353b(a)(2)(A)(ii). In such cases, the FDA notes that "[i]t is important to patients and prescribers that compounded drugs prepared to address a shortage closely resemble the drug in shortage, and for that reason, the statute seeks to allow compounders to compound drugs that are as close as possible to the drug in shortage."[4]

The FDA has also published guidance for 503A pharmacies that mirrors the authority and guidance for 503B Outsourcing Facilities to compound in times of shortage. For 503A compounding, the FDA's guidance states that it "[does] not consider a drug product to be commercially available if . . . the drug product appears on the FDA drug shortage list in effect under section 506E of the FD&C Act."[5] For drugs like semaglutide that are in shortage, a pharmacy that compounds the drug in compliance with Section 503A's other requirements including licensed providers,

[4] *See* FDA, COMPOUNDED DRUG PRODUCTS THAT ARE ESSENTIALLY COPIES OF APPROVED DRUG PRODUCTS UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT – GUIDANCE FOR INDUSTRY 7.

[5] *See* FDA, COMPOUNDED DRUG PRODUCTS THAT ARE ESSENTIALLY COPIES OF A COMMERCIALLY AVAILABLE DRUG PRODUCT UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT – GUIDANCE FOR INDUSTRY 3 ("[L]icensed pharmacists and licensed physicians who compound drug products in accordance with section 503A are not required to comply with CGMP requirements.")

valid patient specific prescriptions, and approved ingredients, does not therefore violate the prohibition on compounding essentially copies. In brief, it is compounding that both federal and state law and guidance expressly permit. As with the other classes of drugs discussed above, NDA and ANDA new drug approval is not required.

Understanding the federal and state authority granted to compounding pharmacies during times of a national drug shortage is, perhaps, the most important fact for the court to consider because semaglutide, the medication discussed at length in the complaint, is and has been listed as "currently in shortage" on the FDA's Drug Shortage List since March 2022. According to news reports and documents that have been made public, there is no reason to believe the national shortage of the branded drugs described in the complaint (Wegovy®, Ozempic®, and Rybelsis®) will be removed from the FDA's shortage list anytime soon. According to Novo Nordisk's own public statements its Brussels-based contract manufacturer responsible for filling syringes with Wegovy® stopped production in December 2021. The production halt was due to adverse FDA inspection observations citing multiple deficiencies in CGMP processes and procedures.[6,7]

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[6] Novo Nordisk Company Announcement, Dec 17, 2021, www.mi-eu.globenewswire.com/resource/download/ /cf92a50b-0b7a-4fe2-9e42-1113ad5840c2. (accessed October 6, 2023)

[7] Food and Drug Administration, Form – 483, re: Catalent Belgium S.A., Issued Oct. 26, 2021.

Whether it is these drugs or others in shortage or to address a patient-specific need, it is critical for the Court to understand that state and federal law and guidance expressly permit compounding. Interpreting the law to allow the sale of only drugs that have gone through NDA and ANDA approval processes would drastically diminish patients' ability to access the drug therapies their physician or other prescriber believe are right for that patient. For some patients taking some drug therapies, that loss of access could be catastrophic.

CONCLUSION

Litigation of this matter may largely turn on legal issues of standing or preemption, which the parties have already raised. It is critical, however, to understand the impact that this case may have on traditional compounding. From ancient Egyptian medicine to the present day, preparing medications tailored to a patient's specific needs has been a foundational element in the practice of pharmacy. This remains true in the age of commercially manufactured drug products, which due to patient-specific needs or product shortages, cannot meet the needs of all patients all the time.

Compounding pharmacies act as a critical safety net when a drug is in shortage. Currently, compounders are helping keep patients with asthma alive by compounding albuterol sulfate solutions for nebulizer machines. They are treating patients (especially children) with epilepsy and other seizure disorders during the

shortage of diazepam gel – so that a caregiver can attend to a person actively seizing while waiting for an ambulance to arrive. They are keeping emergency rooms, air and ground ambulances, and other first responders stocked with epinephrine for injection to treat everything from a severe allergic reaction to cardiac arrest.

Compounding pharmacies and outsourcing facilities are also saving countless lives by providing something as simple as sterile water for injection when it is in shortage. That shortage is in fact due to the lack of adequate manufacturing facilities, precipitated by the exit of one manufacturer from the American market. But that sterile water for injection is used in countless medical interventions every day and is essential for the reconstituting of an untold number of injectable medications that people need and health systems must have.

These are all examples of drugs currently in shortage per the FDA drug shortage list. As the FDA's guidance acknowledges, compounding pharmacies can – and do – fill these potentially life-threatening gaps, and the profession does so under strict state and federal regulation.

The Alliance for Pharmacy Compounding implores the Court to factor into its ultimate decision the need—ancient in its recognition—for patients to have access to medications that pharmacists and physicians compound. For decades this has occurred with tacit and then explicit approval of the FDA. Moreover, a decision that finds that only drugs that have undergone FDA-approval may be marketed in this

state will disregard multiple other paths drugs without FDA-approval take to reach the marketplace and have extreme, unintended consequences on the ability of medical professionals to care for their patients. While it is apparent that Plaintiff and Defendant have a dispute to settle, the implications of this litigation are potentially monumental to drug manufacturing, compounding, and the practices of medicine and pharmacy. Understanding how traditional compounding differs from manufacturing and its essential place in health care is critical to reaching an informed decision.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this ____ day of November, 2023, a true and correct copy of the foregoing _____ was filed electronically. Notice of this filing will be sent by operation of the court's electronic filing system to all parties indicated on the electronic filing receipt. All other parties will be served by regular U. S. Mail. Parties may access this file through the court's electronic filing system.

/s/ Cory R. Miller_____
CORY R. MILLER