Opportunities to Improve the Compounding Quality Act

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ABSTRACT

Pharmaceutical manufacturers produce and distribute medicines by seeking approval from the U.S. Food and Drug Administration (FDA) pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA). The FDCA and FDA regulations set quality standards for production and require medicines to be safe and effective as demonstrated by animal and human testing prior to sale. Compounding pharmacies, regulated by states, produce medicines for patients intolerant to FDA-approved, manufactured products or for patients for whom no FDA-approved medicine exists. While medicines produced by compounding pharmacies are technically covered within the FDCA, enforcement of all the FDCA's requirements on compounding pharmacies would be prohibitively expensive considering the small market of patients requiring these compounded medicines. These compounded products have no FDA premarket approval and are not required to be demonstrated as safe and effective prior to being dispensed to a patient. A proper regulatory framework must allow access for patients who need compounded medicines, but also protect the new drug approval process for pharmaceutical manufacturers because of the safety and medical advancements created by pharmaceutical manufacturers. Congress and FDA have struggled to strike a balance between safety and access along with drawing clear lines between what power belongs to the federal government and what power belongs to the states. In 2012, a compounding pharmacy's contaminated compounded sterile drug gave rise to a fungal meningitis outbreak that killed sixty-four people and injured hundreds more, spurring Congress to pass the Compounding Quality Act (CQA or the Act). The CQA attempts to delineate federal and state power along with creating an entirely new type of drug-producing entity called an outsourcing facility. Among pharmaceutical manufacturers, outsourcing facilities, and compounding pharmacies, each has strengths and weaknesses. The CQA is still in the process of being implemented. Outsourcing facilities face considerable ongoing regulatory uncertainty. This paper explains the regulatory framework and offers suggestions to improve or amend the Compounding Quality Act and the overall regulation of compounded medicines.

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INTRODUCTION

The origin of many federal laws related to pharmaceuticals can be traced to tragedies.[1] The Pure Food and Drug Act of 1906,[2] which established labeling requirements for food and drugs, became law partly due to public outrage over pharmaceutical-related poisonings and deaths.[3] The Pure Food and Drug Act is regarded as the beginning of the federal consumer protections that would come to be overseen by the agency known today as the U.S. Food and Drug Administration (FDA).[4] Several decades later, Congress passed the Federal Food, Drug, and Cosmetic Act (FDCA) of 1938[5] in reaction to the death of over 100 people, including children, after ingesting a new formulation of Elixir Sulfanilamide, which the manufacturer had created using diethylene glycol, commonly used today in antifreeze.[6] At the time, no toxicity or safety testing for pharmaceuticals was required. Diethylene glycol is toxic to the body in relatively small quantities and causes abnormalities of multiple systems, including gastrointestinal, renal, and neurological, leading to death.[7] In the modern era, the FDCA now generally requires, among other things, that evidence of a drug's safety be submitted to FDA for review prior to the drug's sale in interstate commerce.[8]

Similarly, in the 1960s, the drug thalidomide was approved by the European drug approval agency to treat morning sickness in pregnant women but was not approved for marketing in the United States.[9] The teratogenic effect of thalidomide is phocomelia, a shortening, deformation, or outright lack of development of hands or arms of the fetus.[10] Reports of birth defects from embryological exposure to thalidomide in Europe led to U.S. public support for stronger drug regulation.[11] The Kefauver–Harris Drug Amendments of 1962[12] amended the 1938 law and authorized FDA to require proof of a drug's efficacy determined through clinical trials—along

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[1] K.T. Patel & N.P Chotai, *Pharmaceutical GMP: Past, Present, and Future—A Review*, 63 PHARMAZIE 251, 251–55 (2008).

[2] Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906) (amended 1938).

[3] John P. Swann, *How Chemists Pushed for Consumer Protection: The Food and Drugs Act of 1906*, 24 CHEM. HERITAGE 6, 6–11 (2006).

[4] Alexander Nasr, Thomas J. Lauterio & Matthew W. Davis, *Unapproved Drugs in the United States and the Food and Drug Administration*, 28 ADVANCES THERAPY, 842, 842–45 (2011).

[5] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (1938).

[6] Caroline Ballentine, *Sulfanilamide Disaster*, FDA CONSUMER, June 1981, at 1.

[7] Leo J. Schep, Robin J. Slaughter, Wayne A. Temple & D. Michael G. Beasley, *Diethylene Glycol Poisoning*, 47 CLINICAL TOXICOLOGY 525, 525–35 (2009) (stating that the mean lethal dose of diethylene glycol is 1mL/kg).

[8] 21 U.S.C. § 355(b)(1)(A)(i).

[9] Anthony J. Perri III & Sylvia Hsu, *A Review of Thalidomide's History and Current Dermatological Applications*, 9 DERMATOLOGY ONLINE J. 5, 5 (2003).

[10] Neil Vargesson, *Thalidomide-Induced Teratogenesis: History and Mechanisms*, 105 BIRTH DEFECTS RSCH. 140, 142 (2015).

[11] *Milestones in U.S. Food and Drug Law*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law (last visited Oct. 23, 2023).

[12] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

with the existing 1938 requirement of safety—prior to approving a new drug.[13] These amendments also added requirements for adequate controls in the manufacture of pharmaceuticals by mandating conformity with "current good manufacturing practice (cGMP)."[14]

As shocking as the lack of requirements for safety and efficacy of pharmaceuticals from decades ago may seem today, issues relating to drug safety are not relegated to the Twentieth Century. In September 2012, the Centers for Disease Control and Prevention (CDC), FDA, and various state health authorities began investigating an outbreak of fungal meningitis in multiple states. The epidemiological commonality among the fungal infections was that patients had received an injection into their spines or joints of a drug called methylprednisolone acetate to treat inflammation. The drug had been prepared by a compounding pharmacy, the New England Compounding Center (NECC), in Framingham, Massachusetts.[15] In 2012, the law governing compounded products was unclear. Compounded products, that is, products made by a compounding pharmacy rather than a pharmaceutical manufacturer, do not require FDA approval prior to marketing—there was little federal oversight of safety or efficacy.[16] The NECC injectables were contaminated as a result of insanitary production facilities and practices.[17] The compounding pharmacy's injectable product was associated with 753 infections, resulting in sixty-four deaths, in twenty states.[18]

The Compounding Quality Act (CQA or the Act), which was signed into law in November 2013 in response to this fungal meningitis outbreak, is still being implemented.[19] The CQA is embedded, as title I, into a larger act called the Drug Quality and Security Act (DQSA) of which the Drug Supply Chain Security Act is title II.[20]

This paper begins, in Part I, by reviewing the history of pharmaceutical manufacturing as a business, and of pharmacists as a profession, along with the difference in function and regulatory oversight of a drug manufacturer as compared to a compounding pharmacy prior to the enactment of the CQA. As the focus of this paper is on the CQA and compounding pharmacies, discussion of drug manufacturers is limited to knowledge required to distinguish them from

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[13] Jeremy A. Greene & Scott H. Podolsky, *Reform, Regulation, and Pharmaceuticals—The Kefauver–Harris Amendments at 50*, 367 NEW ENG. J. MED. 1481, 1481–83 (2012).

[14] Drug Amendments of 1962, *supra* note 12.

[15] *Multistate Outbreak of Fungal Meningitis and Other Infections*, CTRS. FOR DISEASE CONTROL & PREVENTION (Oct. 30, 2015), https://www.cdc.gov/hai/outbreaks/meningitis.html.

[16] T.R. Goldman, *Health Policy Brief: Regulating Compounding Pharmacies*, HEALTH AFFS., 2014, at 3.

[17] Press Release, U.S. Food & Drug Admin., Owner and Four Former Employees of New England Compounding Center Convicted Following Trial (Dec. 13, 2018) (on file with FDA).

[18] *Multistate Outbreak of Fungal Meningitis and Other Infections – Case Count*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/hai/outbreaks/meningitis-map-large.html (last visited Oct. 20, 2023).

[19] Nabeel Qureshi, Laurie Wesolowicz, Trish Stievater & Alexandra Tungol Lin, *Sterile Compounding: Clinical, Legal, and Regulatory Implications for Patient Safety*, 20 J. MANAGED CARE & SPECIALTY PHARMACY 1183, 1185 (2014).

[20] Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013) (amending 21 U.S.C. § 351 et seq.).

compounders or understand policy suggestions to improve the CQA. Part II explains the effect of the CQA on the compounding pharmacy industry through its creation of 503B outsourcing facilities while also examining legislative history to determine legislative intent of the CQA. Part III examines gaps and controversies within the Act offering legislative and policy suggestions to improve the safety of compounded medications and ensure patient access to needed medications, all while preserving the integrity of the new drug approval process.

I. PHARMACEUTICAL MANUFACTURERS AND COMPOUNDING PHARMACIES PRIOR TO CQA

As of November 2021, FDA-regulated products represented twenty cents of every dollar U.S. consumers spent. FDA has granted approval to over 20,000 prescription drugs. FDA's office overseeing the approval of human drugs represented over $2 billion of the agency's $6.1 billion appropriated budget in 2021.[21] Aggregate pharmaceutical and biotechnology company revenue from drug sales was $775 billion in 2015.[22] Manufactured and FDA-approved pharmaceuticals, however, do not exist for every patient's need.

Common rationales for compounding pharmacies is that they produce medications for patients who are allergic to commonly used excipients, those who are unable to swallow solid dosage forms and require a liquid formulation of a drug only manufactured in a solid dosage form, or those whose physicians determine they need a dosage not commercially available.[23] Less frequently heard, but importantly, compounding pharmacies produce medicines for large segments of patients for which there is no comparable FDA approved product.[24] For example, 90,000 radical prostatectomies are performed annually in the United States following a prostate cancer diagnosis.[25] Erectile dysfunction following radical prostatectomy is common, and the rates of failure of FDA-approved drugs range widely from 20% to 80%,

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[21] *FDA at a Glance*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance (last visited Oct. 20, 2023).

[22] U.S. GOV'T ACCOUNTABILITY OFF., GAO-18-40, DRUG INDUSTRY: PROFITS, RESEARCH AND DEVELOPMENT SPENDING, AND MERGER AND ACQUISITION DEALS 16 (2017), https://www.gao.gov/assets/gao-18-40.pdf.

[23] Maria Carvalho & Isabel F. Almeida, *The Role of Pharmaceutical Compounding in Promoting Medical Adherence*, 15 PHARMACEUTICALS 1091, 1097–98 (2022).

[24] *See* Adam Parker, Matthew Bruha, Oluwaseun Akinola, & Charles Welliver, *A Summary of the Controversy Surrounding Off-Label Medications in Men's Health*, 5 TRANSLATIONAL ANDROLOGY & UROLOGY, 201, 201–06 (2016) (Alprostadil alone, for intracavernosal injection, is FDA-approved, indicated for the treatment of erectile dysfunction. American Urological Association guidelines for the treatment of erectile dysfunction state combinations of medications (alprostadil, papaverine, phentolamine) are also used [from compounding pharmacies]). *See also* Arthur L. Burnett, Ajay Nehra, Rodney H. Breau, Daniel J. Culkin, Martha M. Faraday, Lawrence S. Hakim, Joel Heidelbaugh, Mohit Khera, Kevin T. McVary, Martin M. Miner, Christian J. Nelson, Hossein Sadeghi-Nejad, Allen D. Seftel & Alan W. Shindel, *Erectile Dysfunction: AUA Guideline*, 200 J. UROLOGY 633, 637 (2018).

[25] William T. Lowrance, James A. Eastham, Caroline Savage, A. C. Maschino, Vincent P. Laudone, Christopher B. Dechet, Robert A. Stephenson, Peter T. Scardino & Jaspreet S Sandhu, *Contemporary Open and Robotic Radical Prostatectomy Practice Patterns Among Urologists in the United States*, 187 J. UROLOGY 2087, 2087–92 (2012).

leaving many patients with a compounded product as their next treatment option.[26] Mainstream medical treatment in other therapeutic areas also involves products from compounding pharmacies. For example, total parenteral nutrition (TPN) is compounded by mixing FDA-approved products together into an intravenous solution for a patient. More than 20,000 patients annually receive TPN in the United States.[27] Yet each of these examples of a compounded product, from one needed for a patient who cannot swallow, to a treatment for erectile dysfunction, to TPN, are produced through different compounding practices that carry varying levels of safety risk and, therefore, require different types of regulation to promote product quality and protect patients. Finally, another rationale is that compounded drugs provide another source in the event of a drug shortage.

The business of present-day pharmaceutical manufacturers is composed of research, development, and intellectual property protection.[28] The evolution of this model from small chemical companies supplying raw ingredients to physicians and pharmacists to its modern iteration is beyond the scope of this Article, but many factors encouraged this development. This evolution was caused by various factors, including increased demands of changing legal and regulatory frameworks, the industrial revolution in both Europe and the United States, and scientific and medical advancements.[29]

Changes in federal regulation as well as to the scope and volume of large-scale pharmaceutical manufacture led to functional changes in the state-regulated practice of pharmacy. Where previously a physician would ask a pharmacist to compound medicine for a patient with a specific active pharmaceutical ingredient (API) in a certain dosage form (e.g., tablet, capsule, or ointment), now mass-manufactured, finished dosage forms were commonplace. In 1930, 75% of prescriptions dispensed by a pharmacist were compounded. By 1950 that number shrank to 25%.[30] By 1960, only 4% of prescriptions dispensed by pharmacists were compounded by them, the rest of the pharmaceuticals were mass produced and FDA approved.[31]

There is a tension between the competing priorities of patient access to compounded medications and the overall integrity of the FDA approval process. The financial figures referenced above are indicative of the tremendous financial interests that are also at play. Powerful groups representing both the medical establishment and the pharmaceutical and compounding industries have been actively involved in the evolution of related regulations. For example, the American Medical Association opposed the Kefauver–Harris Amendments' imposition of demonstrated efficacy prior to approval, while others criticized these same amendments for the delay the approval process would cause for access to pharmaceuticals, as well as the increased

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[26] Zachary Hamilton & Moben Mirza, *Post-Prostatectomy Erectile Dysfunction: Contemporary Approaches from a US Perspective*, 6 RSCH. & REPS. UROLOGY 35, 36 (2014).

[27] Jason John & Ali Seifi, *Total Parenteral Nutrition Usage Trends in the United States*, 40 J. CRITICAL CARE 312, 312–13 (2017).

[28] Arthur Daemmrich, *Pharmaceutical Manufacturing in America: A Brief History*, 59 PHARMACY HIST. 63 (2017).

[29] Greene & Podolsky, *supra* note 13, at 1483.

[30] Daemmrich, *supra* note 28, at 67.

[31] *Id.*

cost.[32] The question remains as to what the proper balance between access, safety, and efficacy might be and what regulatory framework produces that balance.

A. Pharmaceutical Manufacturers

The FDCA prohibits, among other things, the introduction into interstate commerce of any drug that is adulterated or misbranded.[33] As an example, a drug is deemed adulterated if it is not manufactured under current Good Manufacturing Practices (cGMP).[34]A drug is deemed misbranded if, among other possibilities, its labeling[35] does not contain adequate directions for use. An indication must be supported by "substantial evidence of effectiveness based on adequate and well-controlled studies" and the indications and usage section of a label must state the disease or condition treated, prevented, mitigated, cured, or diagnosed by the drug and the population (age group) in which the safety and efficacy data applies.[36]

Since the passage of the FDCA in 1938, "new drugs"[37] must have a New Drug Application (NDA) approved by FDA prior to commercialization and shipment into interstate commerce. The NDA is the pathway by which drug sponsors—typically, manufacturers—submit to FDA a proposal to approve a drug.[38] Broadly, the NDA process allows FDA to determine if the drug is safe and effective for its proposed use; if the labeling proposed by the manufacturer has all of the required information; and if the material, methods, and facility used to manufacture the drug are sufficient to assure quality standards like identity, purity, and strength of the finished product.[39]

Numerous FDA-issued guidance documents exist to help a manufacturer through the NDA compilation and submission. A brief look at just a few steps shows the sheer complexity of the data required for a submission. The guidance titled "Container Closure Systems for Packing Human Drugs" provides the specifications for the package, i.e., the packaging must not interact with the finished product in a

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[32] Greene & Podolsky, *supra* note 13, at 1482.

[33] 21 U.S.C. § 331(a).

[34] *Id.* § 351(a)(2)(B). cGMP regulations promulgated by FDA contain requirements for methods, facilities, and controls used in the manufacture of drugs. 21 C.F.R. §§ 210–211; *see Current Good Manufacturing Practice (CGMP) Regulations*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations (last visited Oct. 20, 2023).

[35] 21 U.S.C. § 321(m) (defining the term "labeling" to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article").

[36] U.S. FOOD & DRUG ADMIN., INDICATIONS AND USAGE SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT: GUIDANCE FOR INDUSTRY (2018), https://www.fda.gov/media/114443/download.

[37] "New drug" means "[a]ny drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use . . . ." 21 U.S.C. § 321(p)(1).

[38] *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/types-applications/new-drug-application-nda (last visited Oct. 20, 2023); 21 U.S.C. § 355(a).

[39] 21 U.S.C. § 355(b)(1)(A).

way that changes its quality.[40] This guidance also explains the possible requirement of the package protecting the pharmaceutical from degradation by light, or in the case of sterile products, for the package to prevent microbial contamination.[41] The "Guideline for the Format and Content of the Clinical and Statistical Section of an Application" explains how to summarize the clinical trial results that purport to demonstrate safety and efficacy of the drug as well as the statistical analysis of those results compared to placebo.[42] Another FDA guidance explains how to summarize the pharmacokinetic and bioavailability sections of the NDA, i.e., the absorption of a drug after ingestion, distribution to its intended site of action, in what tissues or organs it concentrates, how the drug is metabolized, and how the drug is eliminated from the body.[43]

The Prescription Drug User Fee Act of 1992 (PDUFA)[44] focuses on expediting FDA's review of the various applications submitted to it and grants permission for FDA to collect application fees to help defray the cost of its review. For example, FDA uses the money collected to hire, support, and maintain staff for NDA evaluation and review.[45] For FY 2023, the NDA application fee for a submission including clinical data is $3,242,026.[46] While FDA retains complete authority over the review process and approval determination, PDUFA also established performance goals for FDA with NDA approval or rejection determinations set at ten months following FDA acceptance of an application.[47]

In addition to these safety and efficacy trials, manufacturers must demonstrate their ability to scale-up production from the smaller batch sizes needed for clinical trials to those required for manufacturing and marketing the product after FDA approves it.

From 2009 to 2018, FDA approved 355 new drugs.[48] The cost for a pharmaceutical manufacturer, as the sponsor of an NDA, to bring a new drug to the U.S. market in this time period was estimated at $1.1 billion.[49] Other cost estimates

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[40] U.S. FOOD & DRUG ADMIN., CONTAINER CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY (May 1999), https://www.fda.gov/media/70788/download.

[41] *Id.*

[42] U.S. FOOD & DRUG ADMIN., GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION (July 1988), https://www.fda.gov/media/71436/download.

[43] U.S. FOOD & DRUG ADMIN., GUIDELINE FOR THE FORMAT AND CONTENT OF THE HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION OF AN APPLICATION (Feb. 1987), https://www.fda.gov/media/71286/download.

[44] Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992) (codified at 21 U.S.C. § 379).

[45] *Prescription Drug User Fee Amendments*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments (last visited Oct. 20, 2023).

[46] *Id.*

[47] U.S. FOOD & DRUG ADMIN., PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022, https://www.fda.gov/media/99140/download (last visited Oct. 20, 2023).

[48] Olivier J. Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018*, 323 JAMA 844, 850 (2020).

[49] *Id.* at 844.

from research and development to approval are as high as $2.6 billion.[50] This figure includes the cost of failures, as it has been reported that out of 100 drugs that begin clinical trials, ninety fail somewhere in the process of attempting approval.[51]

Drug manufacturers protect their products from competition the same way as many other industries—with patents. In the United States, a patent term is twenty years from the date of filing of an application to the United States Patent and Trademark Office.[52] Of note, to protect its potential product, a manufacturer generally submits a patent application at the earlier stage of molecular discovery, long before the required preclinical and clinical trials and regulatory filings have begun. The time period for a drug from patent filing to regulatory approval, for one lucky enough to make it, is estimated on average to be ten years[53] with other estimates showing fifteen years.[54] This development time erodes into the patent exclusivity period, which limits return on investment for the manufacturer. In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch–Waxman Act,[55] to return some of the time lost developing the product and awaiting FDA approval to a patent holder.[56] Under this law, patent term restoration requires several conditions to be met, and a maximum of five years can be restored.[57]

Beyond the protections offered by patent law, exclusivity is another pathway used by drug manufacturers to stall or delay competition by restricting entry of a competitive product to the market. The provision of exclusivity was made possible by the Hatch–Waxman Act.[58] Depending on the type of exclusivity granted by FDA to a manufacturer, the agency may, for a period established by the Hatch–Waxman Act, be prevented from approving a drug containing the same active moiety (generally, the core molecule of a drug) or from approving a drug that relies on the information supporting the approval of a drug, among other restrictions. The type of exclusivity similarly determines the duration of the exclusivity, which can range from 180 days to seven years.[59]

The Hatch–Waxman Act also offered modifications to the law intended to support the generic market. After all, regulation of the drug development and approval

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[50] PHRMA, BIOPHARMACEUTICAL RESEARCH & DEVELOPMENT: THE PROCESS BEHIND NEW MEDICINES, https://invivobiosystems.com/wp-content/uploads/2022/09/rd_brochure_022307.pdf (last visited Oct. 20, 2023).

[51] Duxin Sun, Wei Gao, Hongxiang Hu & Simon Zhou, *Why 90% of Clinical Drug Development Fails and How to Improve It?*, 12 ACTA PHARMACEUTICA SINICA B, 3049, 3049–62 (2022).

[52] Himanshu Gupta, Suresh Kumar, Saroj Kumar Roy & R. S. Gaud, *Patent Protection Strategies*, 2 J. PHARMACY & BIOALLIED SCIS. 2, 3 (2010).

[53] PHRMA, *supra* note 50.

[54] Holly Matthews, James Hanison & Niroshini Nirmalan, *"Omics"-Informed Drug and Biomarker Discovery: Opportunities, Challenges and Future Perspectives*, 4 PROTEOMES (2016).

[55] Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[56] Natalie Peelish, Note, *Antitrust and Authorized Generics: A New Predation Analysis*, 72 STAN. L. REV. 791, 800 (2020).

[57] *Id.*

[58] *Id.*

[59] Renu Lal, *Patents and Exclusivity*, FDA/CDER SBIA CHRONICLES, May 19, 2015, at 3, https://www.fda.gov/media/92548/download.

process must balance incentives for innovation against costs to the U.S. healthcare system. Prior to the enactment of the Hatch–Waxman Act, when an innovative manufacturer's brand name drug patent expired, a generic drug manufacturer would generally have to file an entire NDA before being able to market a cheaper generic alternative. This regulatory hurdle limited generic competition and supported high drug prices.[60] The Hatch–Waxman Act expanded the existing Abbreviated New Drug Application (ANDA) process to allow generic competition to enter the market faster by relying in part on the brand manufacturer's NDA data.

Plainly, innovation—that is, new treatments for diseases—depends on a pharmaceutical manufacturer's ability to derive a return on its investment in research and development. But competition in a free market is needed to, in theory, lower costs to the U.S. healthcare system. Ideally, federal and state policy strikes a sufficient balance to support innovation while fostering sufficient competition to curtail drug prices, thereby improving access.[61] A similar challenge exists related to access to needed medications and the overall regulation of safety and efficacy of medications, as applied to compounding pharmacies and pharmaceutical manufacturers.

B. Compounding Pharmacies

Most of the FDA-approved medications dispensed by pharmacists today are commercially available in their finished dosage forms. But when drugs of that nature are not available, or a patient is intolerant of an ingredient in a finished drug product, a pharmacist may compound an alternative. FDA defines compounding as "combining, mixing, or altering the ingredients of a drug to create a medication tailored to a patient."[62] FDA considers compounded medication to be a "new drug," distinct from its approved, finished-dose counterpart. In other words, the compounded "new drug" does not have an approved NDA, does not have an approved label bearing its indications for use, and was not produced under the provisions of cGMP. As such, these compounded medications are not FDA-approved.[63]

The practice of pharmacy is regulated primarily by the states.[64] Since passage of the FDCA in 1938, FDA largely deferred to the states for the regulation of compounding.[65] But FDA became concerned that pharmacists were using

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[60] Holly Soehnge, *The Drug Price Competition and Patent Term Restoration Act of 1984: Fine-Tuning the Balance Between the Interests of Pioneer and Generic Drug Manufacturers*, 58 FOOD & DRUG L.J. 51 (2003).

[61] Rena Conti, Richard G. Frank & Jonathan Gruber, *Addressing the Trade-Off Between Lower Drug Prices and Incentives for Pharmaceutical Innovation*, BROOKINGS INST. (Nov. 15, 2021), https://www.brookings.edu/essay/addressing-the-trade-off-between-lower-drug-prices-and-incentives-for-pharmaceutical-innovation/.

[62] James Quertermous, Seemal Desai, Julie Harper, Mark Lebwohl, Abel Torres & Leon H Kircik, *The Practice of Compounding, Associated Compounding Regulations, and the Impact on Dermatologists*, 17 J. DRUGS DERMATOLOGY s17, s17 (2018).

[63] *The Special Risks of Pharmacy Compounding*, U.S. FOOD & DRUG ADMIN., (Dec. 2012), http://wayback.archive-it.org/7993/20170111235218/http:/www.fda.gov/ForConsumers/ConsumerUpdates/ucm107836.htm.

[64] *About Us*, NAT'L ASS'N OF BDS. OF PHARMACY, https://nabp.pharmacy/about/ (last visited Oct. 12, 2023).

[65] Thompson v. W. States Med. Ctr., 535 U.S. 357, 362 (2002).

compounding as a pretext to manufacture and sell drugs, thereby subverting the FDCA.[66] In 1992, FDA published Compliance Policy Guide (CPG) 7132.16, explaining that while it would allow pharmacists to compound "very limited quantities" of drugs following receipt of a prescription or in anticipation of a prescription, it would exercise its enforcement discretion when compounding activities "raise[d] 'the kinds of concerns normally associated with a manufacturer.'"[67] With this announcement, FDA was attempting to allow access to unique, extemporaneously compounded medications for those who truly need them, while maintaining the integrity of the drug approval process to ensure safety and efficacy. Recall the sulfanilamide disaster leading to the passage of the original FDCA where an untested excipient led to deaths. If FDA were to require that all marketed drug products be approved, with no exception, then it could put an end to the practice of compounding. However, this would deprive some patients of access to the medication or medications that fits their therapeutic needs.

In 1997, Congress enacted the Food and Drug Administration Modernization Act (FDAMA)[68] codifying some of FDA's 1992 CPG as section 503A of the FDCA. Section 503A exempted compounders from cGMP production requirements, certain labeling requirements, and the NDA process if certain conditions were met.[69] These conditions include that the compounding must be in response to or in anticipation of a prescription, that the pharmacist use APIs satisfying certain standards, that they avoid compounding copies of FDA-approved finished products, and that the prescription must be unsolicited—that is, the pharmacist must not have advertised or promoted a particular compounded formulation.[70]

A group of compounding pharmacies using promotional materials to market their compounds to physicians sued in the U.S. District Court for the District of Nevada seeking a Temporary Restraining Order (TRO) and Preliminary Injunction asking the court to enjoin the government from enforcement of the promotion prohibition as an unconstitutional violation of the First Amendment's free speech clause.[71] On December 18, 1998, the court granted the TRO, and the parties stipulated to extend the order awaiting resolution of motions for summary judgement.[72] The parties agreed the speech in question is commercial speech,[73] and the district court applied the Central Hudson test.[74] The district court ruled the speech-related prohibitions

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66 *Id.*

67 *Id.* (quoting U.S. Food & Drug Admin., Compliance Policy Guide No. 7132.16 (Mar. 1992)).

68 Food and Drug Administration Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

69 FOOD AND DRUG ADMINISTRATION § 13:142. (4th ed. 2022); *see also* 21 U.S.C. §§ 351(a)(2)(B), 352(f)(1), 355.

70 *W. States Med. Ctr.*, 535 U.S. at 363–64.

71 W. States Med. Ctr. v. Shalala, 69 F. Supp. 2d 1288, 1293 (D. Nev. 1999), *aff'd in part, rev'd in part*, 238 F.3d 1090 (9th Cir. 2001), *aff'd sub nom.*, Thompson v. W. States Med. Ctr., 535 U.S. 357 (2002).

72 *Id.*

73 "[E]xpression related solely to the economic interests of the speaker and its audience," *see* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 561 (1980), that "does no more than propose a commercial transaction," Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 776 (1976).

74 "In commercial speech cases, then, a four-part analysis has developed. At the outset, we must determine whether the expression is protected by the First Amendment. For commercial speech to come

within 503A unconstitutional and severed them from FDAMA, leaving the rest of 503A intact in an opinion dated September 16, 1999.[75]

The U.S. Court of Appeals for the Ninth Circuit reviewed the decision and issued an opinion on February 6, 2001, affirming the district court's decision on the unconstitutionality of the commercial speech restrictions but reversing the lower court's finding with regard to severability, thereby invalidating the entirety of the new section 503A of the FDCA.[76] The government's petition for certiorari to the Supreme Court challenged only the constitutionality determination of the Ninth Circuit, not the severability. The Supreme Court accepted review, affirming the Ninth Circuit's ruling on April 29, 2002.[77]

In a May 2002 Guidance for Industry, FDA summarized the court actions concluding that "all of section 503A is now invalid."[78] As such, compounding was, in FDA's view, again subject to the FDCA without exemption, but the agency stated that it would defer to state authorities regarding minor violations[79] related to pharmacy compounding.[80] FDA went on to identify nine factors it would use to distinguish compounding from manufacturing, thereby triggering its enforcement discretion. These factors included compounding before receipt of a prescription (except in limited quantities), using API from a facility not registered with FDA, using commercial scale manufacturing equipment, compounding drugs for third parties to resell, compounding copies of FDA-approved drugs, and failing to follow state law.[81]

Subsequently, a group of pharmacies sued in the U.S. District Court for the Western District of Texas, challenging FDA's authority to regulate compounding at all. On August 30, 2006, the district court held compounds are "new drugs" under the FDCA but that the exemptions in section 503A were severable from the unconstitutional prohibition on advertising.[82] On July 28, 2008, the Fifth Circuit Court of Appeals affirmed that compounds are new drugs, and that with the unconstitutional prohibition on advertising severed, section 503A remained in

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within that provision, it at least must concern lawful activity and not be misleading. Next, we ask whether the asserted governmental interest is substantial. If both inquiries yield positive answers, we must determine whether the regulation directly advances the governmental interest asserted, and whether it is not more extensive than is necessary to serve that interest." *Cent. Hudson*, 447 U.S. at 566.

75 *Shalala*, 69 F. Supp. 2d at 1293, 1308–10.

76 W. States Med. Ctr. v. Shalala, 238 F.3d 1090, 1098 (9th Cir. 2001), *aff'd sub nom.*, Thompson v. W. States Med. Ctr., 535 U.S. 357.

77 *W. States Med. Ctr*., 535 U.S. at 360.

78 U.S. FOOD & DRUG ADMIN., GUIDANCE FOR FDA STAFF AND INDUSTRY, IMPORTATION OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIS) REQUIREMENTS CPG 460.200 PHARMACY COMPOUNDING COMPLIANCE POLICY GUIDES MANUAL (TAB M) 3 (2002), https://www.ipqpubs.com/wpcontent/uploads/2012/10/CPG_pharmacy_compounding.pdf [hereinafter FDA, IMPORTATION OF API REQUIREMENTS].

79 Minor violations meaning essentially the mere act of compounding as this inherently violates 21 U.S.C. §§ 351(a)(2)(B), 352(f)(1), and 355 of the FDCA.

80 FDA, IMPORTATION OF API REQUIREMENTS, *supra* note 78, at 4.

81 *Id.* at 4–5.

82 Med. Ctr. Pharmacy v. Gonzales, 451 F. Supp. 2d 854, 865 (W.D. Tex. 2006), *vacated in part sub nom*, Med. Ctr. Pharmacy v. Mukasey, 536 F.3d 383 (5th Cir. 2008).

force.[83] This circuit split remained until the passage of the CQA in 2013 in response to the NECC fungal meningitis outbreak.[84]

Before addressing the changes to compounding regulations caused by the CQA, it is important to understand the different types of compounding and the levels of risk to patient safety and public health involved. Many states, through their Boards of Pharmacy, regulate pharmacy compounding by incorporating standards set by the United States Pharmacopeia (USP) into their statutes and regulations.[85]Although USP is an independent, scientific, nonprofit organization, the Pure Food and Drug Act of 1906 recognized USP as the standards-setting organization for strength, quality, and purity of drugs in the United States.[86] Indeed, section 503A of the FDCA requires compounders to use API that conforms with USP standards, meaning that both federal standards for manufacturing and compounding, as well as state standards for compounding, rely on USP.[87]

1. Non-Sterile Compounding

Non-sterile compounding is the process for production of compounded drugs that do not require sterility for safety. This includes many topical and oral products. Usually, the skin is a sufficient barrier to provide protection from the ubiquitous microbial contamination encountered in the environment. Similarly, the pH of the stomach serves as its own protection from much microbial contamination. For these reasons, compounded products taken orally or applied topically do not have to be produced in a buffer room or demonstrate sterility of the final product.[88] To be clear, this does not mean there are no controls related to the production environment or final product when it comes to non-sterile compounding, just that the requirements are less stringent.[89]

Because of the body's own protections, sterility risks are nearly nonexistent in non-sterile compounding. This largely limits safety risks for non-sterile products to excipients, or potency, which can also be an efficacy concern. Potency refers to the amount of API contained in the product. A non-sterile product containing too much API can cause toxicity or side effects greater than those usually associated with a particular treatment. A non-sterile product containing too little API may not have the desired effect. Recall, though, that because no clinical trials are required for

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[83] *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 408 (5th Cir. 2008). Recall that in *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002), the Supreme Court only reviewed the unconstitutionality determination but not severability because the government failed to appeal that determination.

[84] Qureshi et al., *supra* note 19, at 1185.

[85] *See, e.g.*, OR. ADMIN. R. 855-045-0200 (2023); *see also Recognition of USP Compounding Standards*, U.S. PHARMACOPEIA, https://www.usp.org/compounding/legal-considerations (last visited Oct. 17, 2023).

[86] Pub. L. No. 59-384, 34 Stat. 768 (repealed 1938) (Pure Food and Drug Act); *About the U.S. Pharmacopeia (USP)*, U.S. PHARMACOPEIA, https://www.usp.org/about (last visited Oct. 17, 2023) (about USP); *Building Trust for Over 200 Years: A Timeline of USP*, U.S. PHARMACOPEIA, https://www.usp.org/200-anniversary/usp-timeline (last visited Oct. 17, 2023) (recognition as standard setting organization).

[87] *See Recognition of USP Compounding Standards*, *supra* note 85.

[88] U.S. PHARMACOPEIA, <795>. PHARMACEUTICAL COMPOUNDING - NONSTERILE PREPARATIONS § 1 (2014).

[89] *Id.* § 6.

compounded products, data on the absorption of an active ingredient in its compounded form is limited.

Non-sterile compounds may be prepared from ingredients that are FDA-approved, commercially available, finished pharmaceuticals, or may be made exclusively from API, or some combination of both.[90]

2. Sterile Compounding

Sterile compounding is the process for production of compounded preparations that require sterility. Examples of these products include injectable drugs and eye drops.[91] An injectable preparation meant to be administered subcutaneously, intramuscularly, or intravenously bypasses the body's protective skin barrier and GI tract, going directly to areas of the body ordinarily free from microbial contamination. For this reason, injectable compounded products have to be produced under more strict environmental conditions.[92] Similarly, eye drops require sterile production because of the sensitive and internalized nature of the eye.

i. Sterile to Sterile

Sterile to sterile compounding is the process of beginning with an FDA approved sterile dosage form and manipulating it to change the product while maintaining the existing sterility.[93] The manipulations are performed in a primary engineering control, e.g. laminar airflow hood, that provides an ISO-class 5 environment, in a buffer room with a scrubbed and garbed operator using aseptic technique to maintain sterility.[94]

As for safety concerns, sterile compounds produced from a sterile to sterile technique are not without a sterility safety risk as sterility may have been compromised during manipulation, though this risk is lower than non-sterile to sterile preparation.[95] Sterile to sterile compounding also carries similar potency risks as described above for nonsterile compounding, that is, too much or too little of the active ingredient as well as potential chemical incompatibilities between ingredients.[96]

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[90] "Magic mouthwash" is an example of a non-sterile compound product and, although typically produced by combining FDA-approved finished dosage forms, compounding from APIs is also possible. See Karthik Giridhar, *Magic Mouthwash: Effective for Chemotherapy Mouth Sores?*, MAYO CLINIC https://www.mayoclinic.org/tests-procedures/chemotherapy/expert-answers/magic-mouthwash/faq-20058071 (last visited Oct. 18, 2023).

[91] U.S. PHARMACOPEIA, USP GENERAL CHAPTER <797>. PHARMACEUTICAL COMPOUNDING - STERILE PREPARATIONS §§ 1, 1.1 (2019).

[92] *Id.* § 4.1.

[93] *Id.* § 1.5.

[94] *Id.* § 4.1.

[95] *Id.*

[96] *See* Davide Zenoni & Stefano Loiacono, *Experience of Compounding Total Parenteral Nutrition Admixtures for Preterm Infants in a Hospital Pharmacy: Evidence of Calcium and Phosphate Compatibility Problem*, 25 EUR. J. HOSP. PHARMACY 38, 41 (2018). TPN is an example of a product commonly compounded using a sterile to sterile technique.

ii. Nonsterile to sterile

Nonsterile to sterile compounding is the process of beginning with a bulk drug substance, an API, typically a powder, which by its nature is nonsterile, often dissolving it in a solvent then sterilizing the final solution.[97] Sterilization can be performed by filtration or terminal sterilization techniques like heat or irradiation. As with sterile to sterile, these manipulations are performed in a primary engineering control located in a buffer room with a scrubbed and garbed operator using aseptic technique to achieve sterility.[98]

Lack of sterility as a safety concern with nonsterile to sterile products is the greatest risk for this type of compounded preparation. This type of sterile compounding also carries the potency risks described above in both nonsterile and sterile to sterile compounding.

II. THE COMPOUNDING QUALITY ACT

The previously mentioned fungal meningitis outbreak in September 2012 was caused by NECC compounding using the API methylprednisolone acetate to produce a preservative-free version[99] of the FDA-approved drug branded as Depo Medrol.[100] Both FDA's 1992 CPG and section 503A of the FDCA prohibited producing inordinate amounts of compounds that were essentially copies of commercially available pharmaceuticals. Federal regulations prohibited the production of large quantities of an approved drug as well as limited the production of compounds prior to receipt of a valid prescription (anticipatory compounding).[101] NECC did not have valid patient-specific prescriptions for all of their compounded preparations.[102] Hundreds of patients were injured and dozens died from infections associated with the products.

A July 2013 report from the Government Accountability Office (GAO) in response to the fungal meningitis outbreak found that FDA authority to regulate compounding was unclear, citing, in part, the circuit split relating to the severability of the speech prohibition in section 503A. Further, GAO cited a lack of consensus on when exactly large-scale, anticipatory compounding and shipping of drugs across state lines shifted from pharmacy compounding to manufacturing.[103] Testimony from

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[97] U.S. PHARMACOPEIA, *supra* note 91, at § 1.5.

[98] *Id.* § 4.1. The combinations of alprostadil, papaverine, and phentolamine, commonly known as Trimix, for the treatment of erectile dysfunction is an example of a compounded product typically produced from non-sterile to sterile compounding. *See* Tobias Kohler, *Erectile Dysfunction*, MAYO CLINIC, https://www.mayoclinic.org/diseases-conditions/erectile-dysfunction/diagnosis-treatment/drc-20355782 (last visited Oct. 18, 2023).

[99] *See* Kevin Outterson, *Regulating Compounding Pharmacies After NECC*, 367 NEW ENG. J. MED. 1969 (2012).

[100] *Depo-Medrol (Methylprednisolone Acetate Injectable Suspension, USP)*, PFIZER (2021), https://labeling.pfizer.com/showlabeling.aspx?format=PDF&id=550.

[101] Recall FDA, in response to the Supreme Court's decision in *Western States*, stated section 503A was a nullity and would defer to states to regulate traditional compounding. *See Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 362 (2002).

[102] Outterson, *supra* note 99, at 1970.

[103] *See* U.S. GOV'T ACCOUNTABILITY OFF., GAO-13-702, DRUG COMPOUNDING: CLEAR AUTHORITY AND MORE RELIABLE DATA NEEDED TO STRENGTHEN FDA OVERSIGHT (2013).

a November 14, 2012, House Committee hearing titled, "The Fungal Meningitis Outbreak: Could it have been Prevented?" provides context for the development of the Compounding Quality Act, which would be passed approximately one year later.[104] Even in the face of this tragedy, the testimony shows the tension between access, safety, and efficacy to pharmaceuticals as well as concerns for the concept of federalism—which rights belong to the states and which belong to the federal government.[105] The FDA Commissioner's testimony introduces the idea of segmenting compounding by risk into traditional compounding, which would remain regulated under the state's practice of pharmacy, and non-traditional compounding, which would be regulated federally.[106]

Illustrating the trouble with drawing the line between compounding and manufacturing, Congressman Dingell asked FDA Commissioner Hamburg, "[NECC] sold over 17,000 doses in . . . 23 States. Don't you have the authority to define who is a manufacturer and who is a compounder?"[107] Further statements showed there was even doubt over the existence of a true legal gap in regulating the distinctions between manufacturing and compounding and suggested increased collaboration between federal and state regulatory authorities may hold the solution.[108] The hearing also made clear that FDA lacked data on the number of state-regulated compounders and the activities they engaged in.[109] Concern about possible federal overreaction in

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[104] *The Fungal Meningitis Outbreak: Could It Have Been Prevented?: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Com.*, 112th Cong. (2012).

[105] "We recognize that traditional compounding provides an important service for patients who, for example, can't swallow a pill or are allergic to an ingredient in a drug product. But the industry has evolved well beyond the neighborhood pharmacist. In particular, the movement by many hospitals to outsource pharmacy compounding has created a market for compounding operations that produce drugs that reach far larger numbers of patients. When these facilities operate well, they may serve an important function in terms of safety and efficiency. However, when they fail to follow safety and quality standards, many patients may be harmed." *Id.* at 21 (statement of Margaret A. Hamburg, Comm'r, U.S. Food & Drug Administration). "I am committed to working with Congress and other stakeholders to design a system of rational, risk-based regulation that takes into account both the Federal and the State roles." *Id.* at 22 (statement of Margaret A. Hamburg, Comm'r, U.S. Food & Drug Administration).

[106] *See id.* at 22 (statement of Margaret A. Hamburg, Comm'r, U.S. Food & Drug Administration) ("Traditional compounding would remain the purview of the States. The higher risk posed by nontraditional compounding would be addressed by Federal standards, including standards for quality control.").

[107] *Id.* at 34 (statement of John Dingell, Member, Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Com.). Commissioner Hamburg replies, "[t]he problem is that the current legal regulatory framework says either you are a compounder or you are a manufacturer . . . ." *Id.* (statement of Margaret A. Hamburg, Comm'r, U.S. Food & Drug Administration).

[108] *See id.* at 35 (statement of Joe Barton, Member, Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Com.) ("If there really is a regulatory gap - based on the record that I have reviewed, I don't believe there is. But if there is, I suggest there is a bipartisan coalition on this subcommittee and full committee that will move legislation to correct it. If, however, there is no regulatory gap, I also think there is a bipartisan coalition on this subcommittee and full committee to work to make sure that the State and the Federal agencies with jurisdiction work together to solve this problem and to prevent it from happening in the future.").

[109] *See id.* at 42 (statement of Michael C. Burgess, Member, Subcomm. on Oversight & Investigations of H. Comm. on Energy & Com.). "How many companies are out there labeled as compounding pharmacies that ship 17,000 doses of sterile, preservative-free steroids every year?" Commissioner Hamburg replies, "We don't know how many compounding pharmacies are, in fact, engaging in those kinds of practices. What we do know is that the industry, though, has evolved and that there are an increasing number of nontraditional compounders who are acting, for example, with hospitals and clinics." *Id.* (statement of Margaret A. Hamburg, Comm'r, U.S. Food & Drug Administration).

response to the tragedy was palpable at the hearing. Georgia's Eleventh District Congressman Phil Gingrey said,

> Tragic in so many ways, of the lives lost and the number of cases of meningitis as a result of this bad actor. . . . Because if we are going to change the law, if we are going to rewrite the Federal Food, Drug, and Cosmetic Act, particularly in regard to section 503(a) [sic] and the vagueness of that section and the conflicting court decisions, then we have to get this right. And I have some great concerns that we might not get it right, in regard to overreacting in regulating compounding pharmacies.[110]

Compared to other landmark pieces of federal legislation, the legislative history for the CQA is sparse. Neither the House nor the Senate produced a committee report, but it is clear the legislation was prompted by the NECC tragedy.[111] This context is helpful in examining the text of the Act and its effects and controversies. For starters, CQA reanimates section 503A of the FDCA by removing the commercial speech prohibition.[112] The CQA creates and inserts into the FDCA a new section, 503B, establishing a new type of compounding entity called an outsourcing facility.[113] The law exempts these facilities from two of the same requirements of the FDCA as 503A compounding pharmacies: the labeling requirement and the NDA process.[114] Notably, outsourcing facilities are not exempt from compliance with cGMP, meaning their standards for production are elevated compared to 503A compounding pharmacies. Because of this higher production standard, 503B outsourcing facilities are not required to obtain a patient-specific prescription prior to sale of the compound.[115] The effect of this provision is to allow other licensed entities, like hospitals, to buy compounds from a 503B outsourcing facility in bulk. This allowance of bulk sales to hospitals and doctors' offices is commonly referred to as "office use compounding."[116]

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[110] *Id.* at 49 (statement of Phil Gingrey, Member, Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Com.). In response to a question following these statements about how to properly regulate "these little compounding pharmacies" from Mr. Gingrey, see *id.* at 50 (statement of Phil Gingrey, Member, Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Com.), Commissioner Hamburg responds, "we need a tiered approach," *id.* (statement of Margaret A. Hamburg, Comm'r, U.S. Food & Drug Administration).

[111] "Neither chamber produced a committee report. Yet, no one disputes that the event that motivated Congress to enact the DQSA was the deadly meningitis outbreak caused by the contaminated injections produced by . . . NECC." Athenex Inc. v. Azar, 397 F. Supp. 3d 56, 72 (D.D.C. 2019).

[112] Compounds meeting the requirements of section 503A are excluded from the FDCA requirements in sections 351(a)(2)(B), 352(f)(1), and 355, that is, GMP, labeling, and the NDA process, respectively. Compounding Quality Act, Pub. L. No. 113-54, 127 Stat. 587 (2013).

[113] *See id.* § 503B.

[114] *FD&C Act Provisions that Apply to Human Drug Compounding*, U.S. FOOD & DRUG ADMIN. (Aug. 13, 2021), https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding. *See also* 21 U.S.C. §§ 352(f)(1), 355, 503B (explaining that outsourcing facilities are also exempt from Section 582).

[115] 21 U.S.C. § 503B(d)(4)(C).

[116] U.S. FOOD & DRUG ADMIN., PRESCRIPTION REQUIREMENT UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT—GUIDANCE FOR INDUSTRY (Dec. 2016), https://www.fda.gov/files/drugs/published/Prescription-Requirement-Under-Section-503A-of-the-Federal-Food--Drug--and-Cosmetic-Act-Guidance-for-Industry.pdf.

Section 503A places limits on the interstate distribution of compounded drugs to no more than 5% of total prescriptions unless the pharmacy's home state has entered into a memorandum of understanding (MOU) with FDA.[117] There are no interstate distribution limits placed on 503B outsourcing facilities. The MOU would standardize state regulatory responsibilities and establish reporting from the state to FDA by its own terms which were supplied by FDA. In exchange for the obligation of complaint investigation and enhanced reporting by the state, a 503A pharmacy located in a state that entered into the MOU with FDA would be allowed to introduce compounds up to 50% of total prescriptions into interstate commerce.[118]

Section 503A does not address wholesaling of compounded products because the individual patient prescription requirement obviates the need for any prohibition on wholesaling. There is no mechanism for a sale of a 503A compounded product other than dispensing by the pharmacy pursuant to a valid prescription. Section 503B contains a "prohibition on wholesaling,"[119] which prevents the compounded drug from being "sold or transferred" other than by the 503B outsourcing facility, but further specifies that "This paragraph does not prohibit administration of a drug in a health care setting or dispensing a drug pursuant to a prescription executed in accordance with section 503(b)(1)."[120] The meaning and effect of this language will be more fully explored in Part III.

The only relevant licensing requirements in section 503A for a compounding pharmacy refer to a "state licensed facility,"[121] making it clear that states control the licensing requirements for a 503A-regulated compounding pharmacy. Outsourcing facilities, however, have specific federal registration requirements,[122] though states may require additional licensure beyond the federal requirements. This overlap, depending on the content of the relevant state laws and regulations, raises questions about the possibility of federal preemption beyond the scope of this Article.[123]

For example, there is no federal requirement for 503A-regulated compounding pharmacies to report adverse events; however, outsourcing facilities are obligated to report adverse events to FDA.[124] States typically do not have adverse event reporting for compounding pharmacies. States may require outsourcing facilities to report adverse events to a state agency.

The variations between 503A and 503B can also give rise to confusion. For example, though there is some overlap, the requirements for compounding from API differ between 503A and 503B. Both compounding pharmacies and outsourcing facilities using API must use bulk drug substances manufactured in a facility

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[117] *Id.* § 503A(b)(3)(B).

[118] U.S. FOOD & DRUG ADMIN., MEMORANDUM OF UNDERSTANDING ADDRESSING CERTAIN DISTRIBUTIONS OF COMPOUNDED HUMAN DRUG PRODUCTS BETWEEN THE [INSERT STATE BOARD OF PHARMACY OR OTHER APPROPRIATE STATE AGENCY] AND THE U.S. FOOD AND DRUG ADMINISTRATION (last visited Sept. 14, 2023), https://www.fda.gov/media/143283/download [hereinafter FDA, MOU].

[119] 21 U.S.C. § 503B(a)(8).

[120] *Id.*

[121] *Id.* § 503A(a)(1)(A).

[122] *Id.* § 503B(b).

[123] Nathan A. Brown & Eli Tomar, *Could State Regulations be the Next Frontier for Preemption Jurisprudence? Drug Compounding as a Case Study*, 71 FOOD & DRUG L.J. 271 (2016).

[124] 21 U.S.C. § 503B(b)(5).

registered with FDA, and the API must be accompanied by a valid certificate of analysis.[125] Section 503A requires a compounding pharmacy to use API that conforms to a USP monograph or API that is a component of an FDA-approved drug.[126] Section 503B requires an outsourcing facility to only use API that have been placed on a list of clinical need by the Secretary or to make versions of FDA-approved drugs that appear on a shortage list.[127] Considering the assumed intent of creating a safer market of compounded drugs from outsourcing facilities, the CQA makes it easier for a 503A compounding pharmacy to use API compared to a 503B outsourcing facility, thereby limiting the available compounds from an outsourcing facility. This paradox will be explored more fully in Part III.

In closing the general discussion of the CQA, one can see that aside from clarifying section 503A as valid federal law, its other main function was to create an entirely new regulatory entity, the 503B outsourcing facilities. In essence, in exchange for federal registration, following cGMPs, and adverse event reporting, an outsourcing facility is not limited by an individual, patient-specific prescription requirement to sell its product.

III. GAPS AND CONTROVERSIES FROM THE COMPOUNDING QUALITY ACT

On January 30, 2018, a hearing titled, "Examining the Implementation of the Compounding Quality Act," was held before the subcommittee on Health of the House Committee on Energy and Commerce.[128] Comments from that hearing are reviewed here as a starting point to explore unintended effects or gaps left by the CQA.

In opening remarks highlighting the federalism tensions, the subcommittee's Chair, Representative Michael Burgess (R-TX 26th), mentioned his home state of Texas' statutory framework for the regulation of compounding pharmacies and noted criticism of the prescription requirement in 503A and the inability in 503A to compound for office use.[129] Another Texas congressman, Gene Green, went on to name several related controversies, including an insufficient development of the 503B outsourcing facility sector.[130] Other comments acknowledged that the CQA,

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[125] *Id.* § 503A(b)(1)(A). *See also id.* § 503.

[126] *Id.* § 503A(b)(1)(A).

[127] *Id.* § 503B(a)(2)(A).

[128] *Examining Implementation of the Compounding Quality Act: Hearing Before the H. Subcomm. on Health of the Comm. on Energy and Com.*, 115th Cong. 96 (2018), https://www.govinfo.gov/content/pkg/CHRG-115hhrg29991/html/CHRG-115hhrg29991.htm.

[129] "In my home State of Texas, there already exists in statute the framework and manner in which a compounding pharmacy should conduct its practice. Other stakeholders have also expressed concern around office-use compounding and the prescription requirement. I hope these and other issues in the drug compounding space will be discussed today." *Id.* (statement of Hon. Michael C. Burgess).

[130] "I understand questions remain about the office stock, bulk list, the MOU, the interstate distribution, and copies of FDA-approved products, and other issues. More needs to be done to foster a robust 503B sector." *Id.* (statement of Hon. Gene Green).

while imperfect, was intended to balance the needs of patients, providers, pharmacists, and manufacturers.[131]

There is in the hearing an ever-present concern for balance between access and protecting the innovation and safety encouraged by FDA's approval process.[132] FDA Commissioner Gottlieb made a lengthy statement summarizing the agency's work in implementing the CQA, acknowledging delays as well as tensions regarding the cooperative federalism approach embodied in the legislation.[133] The commissioner expressed a preference for compounded drugs intended for wide distribution to come from outsourcing facilities rather than 503A compounding pharmacies because of the cGMP standards.[134] Asked directly, "are you confident . . . FDA now has the clear authority it needs to ensure that we don't see a repeat of [NECC]?" Dr. Gottlieb responded that he believes the authority and tools are robust; however, he also seemed to express doubt about the current regulatory framework and acknowledged the federalism-related tensions.[135]

One way, discussed in the hearing, to promote the development of the 503B outsourcing facility industry was to encourage 503A facilities to change their registration status to 503B. This could make the compounded supply chain safer because these flipped facilities would then be required to follow cGMPs. Whether

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131 "DQSA was not perfect, and like all compromises, not every problem was solved to everyone's satisfaction and not everyone got exactly what they wanted. During bipartisan, bicameral negotiations, we tried to address as many discrepancies as we could and satisfy the needs of patients, providers, pharmacists, and manufacturers. What was ultimately important is . . . fix the problems that led to the deadly fungal meningitis outbreak . . . ." *Id.*

132 "While outsourcing facilities are intended to meet healthcare providers' needs for office-stock compounded products, it is also critical that implementation of the law does not undermine our nation's drug approval framework. The regulatory system for both innovative therapies and generic drug products, reflects an intricate balance, keeping us on the cutting edge of medicine while making more affordable medications available to millions of Americans. It now falls on FDA to uphold the integrity of that system, by making sure that outsourcing facilities do not evade the requirements of the Hatch-Waxman Amendments, and do not undermine the protections in place that drive pharmaceutical research and development." *Id.* (statement of Hon. Greg Walden). "FDA must also guarantee that bulk drug substances are not used in compounding by outsourcing facilities, until there has been a final determination that there exists a clear clinical need to do so." *Id.*

133 "But I know there is still a lot left to be done, and I know that there are some who say we haven't implemented certain aspects of DQSA with the speed you had hoped. We have had our own challenges addressing certain aspects of this complex framework, including our constant challenge to make sure we are striking the right balance between safety and access, and addressing the oftentimes very divergent views on these issues." *Id.* (statement of Scott Gottlieb, Comm'r).

134 "I think this underscores the need to make sure that, when drugs are being compounded on a wide basis and distributed on a wide basis, it is done in facilities where we can apply GMP standards to them. And this is, in part, why I think Congress contemplated the whole creation of the 503B structure, where drugs that would be used on a wider scale would be compounded under that kind of supervision." *Id.*

135 "I think I felt what Congress contemplated was a framework that gave the FDA the proper tools to provide oversight over this industry. But I think we need to keep in mind that we are now implementing a framework on an industry that is vast, that grew up, that was allowed to grow up largely outside regulatory purview for a long period of time, and retrofitting a regulatory framework back onto an already existing industry is always a difficult task. Do I believe the authorities and the tools that we are able to exercise are robust? I do. I think that it is going to take time to get them fully implemented and get the kinds of tools and practices we want applied over that industry. And it is superimposed on an environment where, admittedly—and people have good arguments on both sides of this debate—there has been some discussion around how FDA is using those authorities and whether they are using them in an appropriate fashion. I believe we are and I believe we need to continue to move forward." *Id.*

the business could support the additional costs associated with compliance is of course an open question.[136] To manage the expense of the increased regulatory burden, the scrutiny of the requirements could be adjusted based on the risk of a facility's activities.[137]

As is evident from this hearing, disagreement persists about the path forward to continue to implement the CQA. In the following section, I have provided commentary regarding some of the ideas discussed in this particular hearing. I have also laid out several novel ideas, unmentioned at the hearing, that may offer opportunities to improve the CQA.

A. Eliminate the Interstate Shipment Enforcement Limitations Within the FDCA's "New Drug" Language Pressing Federal Regulations to the Limits of Modern Commerce Clause Jurisprudence and Clarify Meaning of Dispense and Distribute in the MOU

The U.S. Constitution grants Congress the power "To regulate commerce . . . among the several States."[138] In 1938, when the FDCA was passed, the Commerce Clause was construed relatively narrowly.[139] Around this same time, President Franklin D. Roosevelt's threats to pack the Supreme Court with justices supportive of New Deal legislation caused a shift in Supreme Court jurisprudence.[140] In 1942, the Court handed down a decision in *Wickard v. Filburn* that construed the Commerce Clause to allow federal power to reach intrastate activities that in aggregate would exert a substantial economic effect on interstate commerce.[141] In 1946 the Ninth Circuit Court of Appeals held that the language in the FDCA's adulteration provisions did not authorize the government to seize adulterated product "after" it had traveled in interstate commerce as the statutory prohibition was, "when introduced into or while in interstate commerce."[142] To claim this power, in 1948, Congress amended prohibited acts to include acts that caused the adulteration or

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[136] "We estimated that it would cost a large manufacturer about a million dollars to become a 503B facility, a large pharmacy, and a medium sized pharmacy, about $600,000." *Id.*

[137] "In particular, I am pleased to see that FDA is taking steps to encourage registration of 503B outsourcing facilities. In your 2018 Compounding Policy Priorities Plan you suggested the FDA will be taking a more risk-based approach to the development and implementation of current good manufacturing practices, or CGMPs. I understand FDA is working on revising the 2014 draft guidance to apply CGMP requirements in a way that is tailored to the nature of the specific operations conducted by an outsourcing facility and move away from one-size-fits-all. I appreciate the agency's goal of improving patient safety by making the regulatory framework more flexible by recognizing volume as a factor in its risk-based evaluation. Can you elaborate more about the agency's thinking around what has been referred to as '503B-light'?" *Id.*

[138] U.S. CONST. art. I, § 8, cl. 3.

[139] Hammer v. Dagenhart, 247 U.S. 251 (1918). *See also* A.L.A. Schechter Poultry Corp. v. United States, 295 U.S. 495 (1935); Anna B. Laakmann, *Customized Medicine and the Limits of Federal Regulatory Power*, 19 VAND. J. ENT. & TECH. L. 285 (2016).

[140] NIKOLAS BOWIE, FEDERAL CONSTITUTIONAL LAW 134 (2022).

[141] Wickard v. Filburn, 317 U.S. 111 (1942).

[142] United States v. Phelps Dodge Mercantile Co., 157 F.2d 453, 454 (9th Cir. 1946).

misbranding of products while those products were "held for sale (whether or not the first sale) after shipment in interstate commerce."[143]

Since the Court's seismic shift in *Wickard v. Filburn*, most jurisprudence has continued to broadly interpret Congress' power under the Commerce Clause. Even a more modern case applying the first limits to the Commerce Clause in decades reiterated that federal regulation of solely intrastate economic activity that substantially affects interstate commerce will be sustained.[144] In 2005, the Supreme Court held that the reach of federal power under the Commerce Clause extends to marijuana grown legally for personal use exclusively within the State of California having never entered interstate commerce.[145]

Based on these precedents, a strong argument can be made that the activities of a compounding pharmacy are economic and that the dispensing of a compounded drug even merely intrastate is part of a more general regulation of interstate commerce. It is therefore likely that expanding the reach of the FDCA to capture wholly intrastate activities of compounding pharmacies would be interpreted as a constitutional exercise of federal Commerce Clause power. For those in favor of expansive federal power, Congress could alter the interstate shipment language of the FDCA and press federal regulation of compounded drugs to the full extent of Commerce Clause authority. Considering the tensions displayed in the legislative history of the CQA in statements related to respecting states' rights as the government addressed the NECC tragedy, it is unlikely the political will for this solution exists.

While there are fears that giving FDA unfettered authority in this manner over the now state-regulation of the practice of pharmacy would cause access problems for patients, FDA has some history of exercising restraint in enforcement action against small compounding pharmacies engaged in low-risk activities. As for riskier sterile 503A operations, FDA is already actively inspecting at least some of them, though the agency's criteria for selecting these pharmacies for inspection are unknown.[146] Further, large sterile operations, such as those that are the size of NECC, can still exist as a 503A compounding pharmacy limited only by the prescription requirement.[147] While the prescription requirement is, in theory, a rate limiting factor, it does nothing to mitigate patient risk from improper operations. The prescription requirement allows the lower USP 797 regulatory standard to apply over the more stringent cGMP and applies a more lenient standard than 503B with regard to the use of bulk API. The prescription requirement, therefore, may not be the appropriate mechanism to lower the reach of these risks. Some of this uncertainty in the continued long reach of the risks of compounds dispensed pursuant to a prescription was meant to be reduced by the MOU.

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[143] 21 U.S.C. § 331(k); *see also* Laakmann, *supra* note 139, at 289.

[144] United States v. Lopez, 514 U.S. 549 (1995).

[145] Gonzales v. Raich, 545 U.S. 1 (2005).

[146] *See generally*, *Compounding: Inspections, Recalls, and other Actions*, U.S. FOOD & DRUG ADMIN. (last visited Sept. 18, 2023), https://www.fda.gov/drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions.

[147] U.S. FOOD & DRUG ADMIN., PRESCRIPTION REQUIREMENT UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT GUIDANCE FOR INDUSTRY (Dec. 2016), https://www.fda.gov/files/drugs/published/Prescription-Requirement-Under-Section-503A-of-the-Federal-Food--Drug--and-Cosmetic-Act-Guidance-for-Industry.pdf.

As mentioned, the MOU's goal was to enhance the cooperative federalism approach to managing 503A compounds by requiring states to perform certain complaint follow up and reporting.[148] States that refused to enter into the MOU would find their 503A compounding pharmacies restricted to interstate distribution limits of no more than 5% of total prescriptions.[149] States who entered into the MOU with FDA would find their 503A compounding pharmacies facing less restrictive interstate distribution limits, up to 50%.[150] The risk from the less stringent USP 797 production standards used by 503A compounding pharmacies because of the prescription requirement would, therefore, be somewhat offset by the MOU's reporting requirements and distribution limits.[151]

In response to FDA's notice of the Final Standard MOU, seven compounding pharmacies filed a complaint alleging violations of rulemaking procedure, failing to conduct an analysis of the Final Standard MOU's impact on small entities (as required by the Regulatory Flexibility Act), and that FDA exceeded its statutory authority by conflating the definitions of the terms "distribute" and "dispense."[152] In 2021, the U.S. District Court for the District of Columbia held that the MOU is subject to the Regulatory Flexibility Act (Count II) and remanded the rule to FDA for further consideration consistent with the opinion without deciding the remaining counts.[153]

The gravamen of the argument is that the plain text of 503A uses the term "distribute" in giving the MOU authority.[154] Plaintiffs contend that dispensing and distribution are mutually exclusive activities. Dispensing is done pursuant to a prescription, while distribution is the changing hands of a drug without a prescription (e.g., a wholesale transaction). So the argument goes, the now-existing prescription requirement guidance already forbids a 503A compounding pharmacy from "distributing" because the only way to avail itself to the 503A exemptions requires a prescription—thereby requiring that they engage in dispensing, as opposed to distributing.

The notion of the MOU has been pending since FDAMA first created the 5% distribution limit in 1997.[155] Assuming FDA finds a way to satisfy the constraints of the Regulatory Flexibility Act, one can imagine a future where FDA, unyielding in its conflation of dispensing and distribution, lands in court yet again for judicial interpretation of the statute. Considering the language was drafted in 1997, at a time when FDA was concerned pharmacies were using compounding as a pretext to circumvent rules, it is plausible the statutory language did only intend to restrict distribution, not dispensing. Statutory words must be given the meaning they had at the time of enactment.[156] An MOU controlling dispensing and distribution will likely

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[148] *See* FDA, MOU, *supra* note 118.

[149] 21 U.S.C. § 353a(b)(3)(B)(ii).

[150] FDA, MOU, *supra* note 118, at 12.

[151] *Id.*

[152] Wellness Pharmacy, Inc. v. Becerra, No. 20-cv-3082 (CRC), 2021 WL 4284567, at *6 (D.D.C. Sept. 21, 2021).

[153] *Id.* at *14.

[154] 21 U.S.C. § 353a(b)(3)(b).

[155] Pub. L. No. 105-115, 111 Stat. 2328 (1997).

[156] People ex rel. Fyfe v. Barnett, 319 Ill. 403, 408, 150 N.E. 290, 292 (1925).

go to the Supreme Court where, if not settled purely by judicial interpretation, it is possible the relatively new Major Questions Doctrine is one of many ways the Court could limit the agency's interpretation of its authority.[157] In the alternative, Congress could clear the path by explicitly defining distribution for the purposes of section 503A.

B. Regulatory Uncertainty and Regulatory Safeguards are Causing Fewer 503B Outsourcing Facilities to Exist than Congress had Envisioned

FDA's list of Registered Outsourcing Facilities shows seventy-two facilities as of September 2023.[158] Although the total number of players in the 503B space has stabilized around seventy since 2018, those players are not static. Over the two-year period of 2018 and 2019, twenty-eight facilities became registered as 503B outsourcing facilities while twenty-four exited the market.[159] In listing the advantages of registering as a 503B outsourcing facility, a 2017 FDA publication enumerated just two: distribution of drugs for office use without a prescription and the general reputation of higher quality assurance due to federal oversight.[160] As described above, the lack of the prescription requirement features prominently as a 503B benefit, but in exchange for this supposed benefit, the outsourcing facility must follow cGMP and is restricted from using the same swath of API available to 503A facilities. The lack of prescription requirement does create access to a health system/hospital market allowing bulk purchases from a 503B outsourcing facility, but this access may not create a large enough incentive alone to foster a robust 503B sector. The revenue potential for the outsourcing facility market is estimated at between $2.3 to $4.6 billion, where the total U.S. pharmaceutical market is $507 billion.[161]

In a survey of the 503B industry, regulatory uncertainty and financial demands were cited as preventing market entry and limiting sector growth. Compliance issues were noted as broad and consistent.[162] Achieving an overall culture of quality in a cGMP framework requires staffing and knowledge not normally associated with a compounding pharmacy, but rather more commonly found in a pharmaceutical manufacturer. With a smaller market for 503B products, but a level of skill and expertise normally found in the larger manufacturing market, outsourcing facilities may struggle to source and afford talent. Some states require outsourcing facilities to

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[157] "EPA claimed to discover an unheralded power representing a transformative expansion of its regulatory authority in the vague language of a long-extant, but rarely used, statute designed as a gap filler. That discovery allowed it to adopt a regulatory program that Congress had conspicuously declined to enact itself." West Virginia v. EPA, 142 S. Ct. 2587, 2595 (2022).

[158] *Registered Outsourcing Facilities*, U.S. FOOD & DRUG ADMIN. (last updated Sept. 12, 2023), https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities.

[159] MEGHAN MURPHY, U.S. FOOD & DRUG ADMIN., STATE OF OUTSOURCING FACILITY SECTOR AND POSSIBILITIES FOR THE FUTURE (Sept. 15, 2021), https://www.fda.gov/media/156346/download.

[160] U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., OUTSOURCING FACILITY INFORMATION (Sept. 2017), https://www.fda.gov/files/drugs/published/Outsourcing-Facility-Information-September-2017.pdf.

[161] U.S. FOOD & DRUG ADMIN., COMPOUNDING OUTSOURCING FACILITIES ANNUAL STUDY EXECUTIVE SUMMARY (Aug. 18, 2020), https://www.fda.gov/media/163704/download.

[162] *Id.*

staff pharmacists.[163] Pharmacy school curriculum focuses more on clinical patient management education and less on production, meaning an expensive staff position required by regulation at an outsourcing facility may not be the best equipped to ensure compliance with cGMP.

Further, 503B outsourcing facilities are registered with FDA, but are also regulated differently by each state. The variability in state-by-state regulation creates an unnecessary expense and barrier to entry, suppressing the 503B market.[164] For an outsourcing facility located in one state to send product to another, registration in the receiving state is typically also required.[165] Difficulty navigating state regulation has been cited as a common reason for market participants to exit the 503B sector.[166] Congress could help foster the developing 503B sector by expressly preempting state regulation of 503B outsourcing facilities.[167] This would leave 503A compounding pharmacies to the states while leaving 503B outsourcing facilities exclusively subject to federal oversight.

The role of outsourcing facilities within the existing regulatory structure is also unclear. Outsourcing facilities may help alleviate drug shortages from manufacturers, but existing regulatory safeguards limit this opportunity. The statutory grant enabling API usage by a 503B facility when an FDA-approved product is in shortage and allowing a 503B facility to sell a copy may be an insufficient market to allow the industry to flourish. A 503B facility must complete certain pre-product launch testing to validate its product under cGMP. This includes production process validation, personal validation, product-specific stability studies, and more. The financial burden for this testing is significant. A 503B outsourcing facility cannot develop a business plan for a product line and prepare for product launch because this market only exists when a current FDA-approved product hits the shortage list. If the 503B sector is intended to serve as a backup for America's drug supply when a manufacturer falters, there is no way for the industry to plan for such preparedness. Further, as will be discussed more, even assuming a 503B did take the financial risk to validate a product once it is in shortage, when an FDA-approved product manufacturer resolves the shortage and the product is removed from short supply, the 503B outsourcing facility can only sell the product for sixty days following shortage resolution. This means that any investment made in qualifying a product and process for the market may not be recouped by the time the market closes.[168]

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[163] *See* N.Y. EDUC. LAW § 6808(5)(f) (McKinney 2014).

[164] Lee H. Rosebush & Marc N. Wagner, *State-by-State Patchwork Creates Onerous Burdens for 503B Outsourcing Facilities*, FOOD & DRUG L. INST., UPDATE MAG. (Fall 2022).

[165] *See, e.g.*, COLO. REV. STAT. ANN. § 12-280-133.5 (West 2021).

[166] U.S. FOOD & DRUG ADMIN., COMPOUNDING OUTSOURCING FACILITIES ANNUAL STUDY EXECUTIVE SUMMARY (Sept. 21, 2021), https://www.fda.gov/media/163703/download [hereinafter FDA, 2021 EXECUTIVE SUMMARY].

[167] Brown & Tomar, *supra* note 123.

[168] "Relative stability in the number of outsourcing facilities and value of the market might also be evidence that the market incentivizes certain types of behavior, including the production of large-batch standardized products, and creates perceived business risk among stakeholders that might deter certain types of production. Moving forward, the role that outsourcing facilities can, and should, play remains a question. For example, outsourcing facilities are perceived to play a role in responding to drug shortages even though few are reportedly equipped to respond because of costs and regulatory safeguards. Thus, the expectation for outsourcing facilities to serve this purpose might be at odds with the market realities that

C. Eliminate Clinical Need from the Statutory Language for API to be Placed on the Bulks List; Alternatively, FDA Can Change its Interpretation of Clinical Need, as Defined in the Statute, to Include Healthcare Provider Convenience

For an outsourcing facility to qualify for the exemptions under the FDCA, one of the conditions is that it must not compound using API unless that API appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need.[169] Paradoxically, use of API for 503A compounding pharmacies is less restrictive, requiring no showing of clinical need, but merely that a USP monograph exists or the bulk substance is a component of an FDA-approved drug.[170] Understanding that it would take time to develop the bulks list, FDA adopted a more lenient interim policy, placing several bulk substances on a Category 1 list composed of "substances nominated for the bulks list currently under evaluation," allowing them to be used in production at an outsourcing facility while under consideration for inclusion on the final bulks list.[171] On March 1, 2019, FDA announced that vasopressin, a drug used in emergency, operating, and intensive care units to increase blood pressure, would be removed from the Category 1 list and excluded from the bulks list.[172] The agency reasoned that there is no clinical need for use of vasopressin API; rather, a 503B facility that wished to compound using vasopressin could only use the FDA-approved finished product.[173] At that time, vasopressin was available approved by FDA in 1mL vials containing 20 units per mL[174] along with a handful of other injectable concentrations.[175]

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drive most outsourcing facility business decisions." FDA, 2021 EXECUTIVE SUMMARY, *supra* note 166, at 1.

[169] 21 U.S.C. § 503B(a)(2)(A).

[170] 21 U.S.C. § 503A(b)(1)(A).

[171] U.S. FOOD & DRUG ADMIN., INTERIM POLICY ON COMPOUNDING USING BULK DRUG SUBSTANCES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT—GUIDANCE FOR INDUSTRY 8 (Jan. 2017), https://www.fda.gov/media/94402/download.

[172] *FDA In Brief: FDA Finalizes Guidance on Evaluating the Clinical Need for Outsourcing Facilities to Compound Drugs with Bulk Drug Substances; Provides Final Decision on Two Substances*, U.S. FOOD & DRUG ADMIN. (Mar. 1, 2019), https://www.fda.gov/news-events/fda-brief/fda-brief-fda-finalizes-guidance-evaluating-clinical-need-outsourcing-facilities-compound-drugs-bulk.

[173] *Id.*; U.S. FOOD & DRUG ADMIN., EVALUATION OF BULK DRUG SUBSTANCES NOMINATED FOR USE IN COMPOUNDING UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT—GUIDANCE FOR INDUSTRY (Mar. 2019), https://www.fda.gov/media/121315/download ("If the bulk drug substance is a component of an FDA-approved drug, FDA intends to consider the following questions: (a) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (i) an attribute of FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (ii) the drug product proposed to be compounded is intended to address that attribute? (b) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product? If FDA answers 'no' to either threshold question, the Agency does not intend to include the nominated bulk drug substance on the 503B Bulks List.").

[174] HIGHLIGHTS OF PRESCRIBING INFORMATION: VASOSTRICT, U.S. FOOD & DRUG ADMIN. (2014), https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204485Orig1s000lbl.pdf.

[175] *Product Summary: Vasostrict*, PAR PHARM., https://www.parpharm.com/products/sterile/vasostrict/ (last visited Sept. 15, 2023).

Prior to the agency's March 1, 2019 decision, a 503B outsourcing facility, Athenex, Inc., developed a product using vasopressin API.[176] The Athenex product supplied vasopressin in ready-to-use IV bags (e.g., 20 units per 100mL bag, 50 units per 250mL bag), eliminating any requirement for a healthcare provider to measure or prepare a dose prior to use.[177] With no ability to continue to produce its vasopressin compound using API, Athenex filed suit against FDA under the Administrative Procedure Act challenging FDA's decision to exclude vasopressin from the bulks list.[178]

Athenex argued that FDA-approved versions of vasopressin are not available in ready-to-use form and must be diluted prior to use, thereby creating a clinical need for their product and a clinical need to make it from API.[179] The court agreed with FDA's reasoning that the lack of a ready-to-use dosage form by a healthcare practitioner did not mean that the FDA-approved product was medically unsuitable for certain patients and restated FDA's test for clinical need as asking "whether the bulk drug product fills a gap of medical unsuitability left by an approved drug and, if so, whether that gap cannot be filled by compounding with the approved drug."[180]

Stepping back from the specifics, this example provides an excellent illustration of the ongoing tensions of access, safety, efficacy, and protection of innovation. Par Pharmaceutical followed the NDA process, and its drug, Vasostrict (vasopressin), was approved in vials requiring dilution before administering to the patient. When it was the only available product, healthcare professionals had no choice but to dilute the product themselves prior to use. As simple as this sounds, it requires opening a sterile syringe, placing a needle on the syringe, swabbing the top of the Vasostrict vial with alcohol, swabbing the port on the IV bag intended to dilute the Vasostrict, drawing up and measuring the required dose, and completing the manipulation to dilute the Vasostrict. This process adds time and room for error in what may be a clinical situation requiring quick action. The Athenex products eliminated this work on the part of the healthcare provider.

Competition from a 503B outsourcing facility may lead to improvement in Par's formulation. For Par to change the FDA-approved form of its product from a vial to a ready-to-use form would require collection of data and submission of an application to FDA, an expensive and lengthy process. The 503B exemptions from the NDA process allow an outsourcing facility to produce the drug without following that process.

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[176] Athenex Inc. v. Azar, 397 F. Supp. 3d 56, 60 (D.D.C. 2019).

[177] Douglas W. House, *Athenex Launches Vasopressin Ready-to-Use Premix IV Bags in U.S.*, SEEKING ALPHA (Aug. 13, 2018), https://seekingalpha.com/news/3382027-athenex-launches-vasopressin-ready-to-use-premix-iv-bags-in-u-s; ATHENEX, VASOPRESSIN INJECTION, https://www.athenexpharma.com/wp-content/uploads/materials/Catalog/Vasopressin_Catalog.pdf.

[178] *Athenex*, 397 F. Supp. 3d at 62.

[179] *Id.*; Aislinn Antrim, *Litigation Against FDA Over Vasopressin is Resolved*, PHARMACY TIMES (Oct. 2, 2019), https://www.pharmacytimes.com/view/two-lawsuits-against-fda-resolved-favoring-endo-international (at the time of Athenex's production of ready-to-use vasopressin, the drug in its FDA-approved form branded as Vasostrict was produced by Par Pharmaceutical, also known as Par Sterile Products, LLC, a subsidiary of Endo International, and brought in more than $450 million of revenue for the company in 2018).

[180] *Athenex*, 397 F. Supp. 3d at 71–72.

The focus on the statutory requirement of an FDA determination of clinical need may benefit from a legislative rewrite. Both Athenex and Par produced their versions of the product under cGMP. Both began with API. The safety playing field is pretty near level between these organizations, though Par is safer due to the premarket review and approval by FDA. While there is value in protecting the integrity of the drug approval process, there is also value in supplying healthcare providers with a dosage form they need. If Athenex were allowed to produce vasopressin in a ready-to-use form from API, its market share would create pressure on Par to pursue the FDA approval process for a new formulation of its drug. Once FDA approval were secured, the "essentially a copy" provision of section 503B would foreclose on Athenex production of its compound. This proposed system of innovation, followed by competition from 503B if allowed to use API, followed by reactionary competition from the manufacturer at least presses formulation enhancements for healthcare providers rather than merely stopping competition and denying providers a more easily usable product. This end could be achieved by removing the clinical need requirement from the statute or by FDA changing its interpretation of the statute to incorporate ease of use into the existing clinical need determination.

On February 7, 2022, Par launched a ready-to-use formulation of Vasostrict.[181] The removal of vasopressin from the bulks list created an almost-three-year gap in the availability of a formulation sought after by healthcare providers.

D. Add Express Preemption Language to the 503B Prohibition on Wholesaling, Thereby Preventing States From Imposing Additional Requirements on the Sale of a 503B Product to a 503A Compounding Pharmacy; Create a Pathway to Payment for 503B Product Sold Through a 503A Compounding Pharmacy

Section 503B(a)(8) states:

> Prohibition on wholesaling.--The drug will not be sold or transferred by an entity other than the outsourcing facility that compounded such drug. This paragraph does not prohibit administration of a drug in a health care setting or dispensing a drug pursuant to a prescription executed in accordance with section 503(b)(1).

In 2017, FDA stated its intent to issue a policy document on this provision.[182] The language of the provision is confusing and had been initially interpreted at least once by a state board of pharmacy to mean that an outsourcing facility could not sell a product to a doctor's office for the doctor to subsequently dispense to a patient.[183]

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[181] *Endo Announces Launch of Ready-to-Use VASOSTRICT (vasopressin injection, USP) in Pre-Mix Bottles*, PR NEWSWIRE (Feb. 7, 2022), https://www.prnewswire.com/news-releases/endo-announces-launch-of-ready-to-use-vasostrict-vasopressin-injection-usp-in-pre-mix-bottles-301476236.html.

[182] U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., *supra* note 160.

[183] *January 2021 Meeting Handouts*, NEV. BD. OF PHARMACY, https://bop.nv.gov/uploadedFiles/bopnvgov/content/board/ALL/2021_Meetings/January%202021%20Meeting%20Handouts.pdf (last visited Sept. 18, 2023).

There has been no federal judicial explication of the provision.[184] The anticipated FDA guidance was published in draft form in June 2023.[185]

The prohibition on wholesaling prevents an outsourcing facility from selling its product to a traditional drug wholesaler—an intermediary in the distribution chain—who would in turn sell the product more broadly to hospitals, doctors' offices, and pharmacies. One sale by the outsourcing facility directly to a hospital, doctor's office, or pharmacy wherein that entity subsequently administers or dispenses the product is allowed. The draft guidance provides explicitly clear examples of allowed behavior, including a 503B outsourcing facility selling to a doctor's office that administers or dispenses and a 503B outsourcing facility selling to a 503A compounding pharmacy that in turn dispenses pursuant to a prescription.[186]

This allowance of administration or dispensing by a subsequent healthcare provider offers possibilities to make the drug supply of compounded medications in the United States safer. A 503A compounding pharmacy can, rather than compounding their own formulations, purchase compounds from a 503B facility and dispense them to patients pursuant to a prescription. Because of USP 797 rules related to beyond use dating,[187] when a 503A compounding pharmacy compounds a product, it can have a limited shelf life.[188] The cGMP requirements under which the same compound would be produced by a 503B outsourcing facility allow for a longer shelf life. This longer shelf life, along with the increased confidence in the safety of the product, creates an attractive opportunity to increase the quality of compounded products dispensed by 503A compounding pharmacies wherein the 503A obtained the compound from a 503B facility.

State laws may place further restrictions on how a 503B outsourcing facility sells its products or how a 503A compounding pharmacy would dispense a 503B compound. Some pharmacies appear to manage this process through central fill agreements.[189] Far simpler would be for 503B(a)(8) to preempt state laws

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[184] Westlaw returns just two hits for 503B(a)(8) or its analog, 21 U.S.C. § 353b(a)(8). One is a case that offers merely an enumeration of the text, the other offers the following, "That rule creates a clear market advantage for approved drugs. Congress also required outsourcing facilities to sell their drug products directly to hospitals and physicians for use as 'office stock,' and expressly prohibited them from using wholesalers to make sales." *Athenex*, 397 F. Supp. 3d at 71.

[185] U.S. FOOD & DRUG ADMIN., PROHIBITION ON WHOLESALING UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT—DRAFT GUIDANCE FOR INDUSTRY (June 2023), https://www.fda.gov/media/169838/download.

[186] *Id.*

[187] "Beyond Use Date" is a compounding term of art largely analogous for our purposes here to the more commonly understood expiration date.

[188] U.S. PHARMACOPEIA, USP COMPOUNDING STANDARDS AND BEYOND-USE DATES (BUDS) (2019), https://www.usp.org/sites/default/files/usp/document/our-work/compounding/usp-bud-factsheet.pdf.

[189] *Central Filing Centers*, OLYMPIA PHARMS., https://www.olympiapharmacy.com/providers/central-filling-centers/ (last visited Sept. 18, 2023); *Central Fill Pharmacy Agreement*, OLYMPIA PHARMS., https://olympiapharmacy.com/wp-content/uploads/2018/05/Olympia-Central-Fill-Contract.pdf (last visited Sept. 18, 2023); *Central Fill Agreement with Other Pharmacies*, TOWN & COUNTRY COMPOUNDING PHARMACY, https://tccompound.com/central-fill-agreement-with-other-pharmacies/ (last visited Sept. 18, 2023) (Town and Country is a 503A compounding pharmacy but appears to be using central fill to expand the reach of its dispensing activities); Linda Witzal, *Long-Term Care Facilities and Central Fill Agreements*, N.J. STATE BD. OF PHARMACY NEWS (July 2017), https://nabp.pharmacy/wp-content/uploads/2020/12/New-Jersey-Newsletter-July-2017.pdf ("When a service such as infusion or compounding is needed to fill a prescription or medication order for these entities and the retail pharmacy

complicating the dispensing of a 503B product from a 503A compounding pharmacy pursuant to a prescription. The overall safety of compounds will increase if states make it easier for 503A compounding pharmacies to purchase products from a 503B outsourcing facility and dispense per the grant in FDCA 503B(a)(8). State laws hindering a 503A compounding pharmacy from dispensing a product purchased from a 503B outsourcing facility conflict with 503B(a)(8) by creating an obstacle to achievement of the federal goal of a safer compounded drug supply.

Further, billing for compounded medications is complex and often disallowed by payors. It is possible that when a 503A compounding pharmacy compounds a product itself, a pathway to payment exists with an insurer. But if that 503A pharmacy—rather than compounding itself—procures a safer compounded product from a 503B outsourcing facility, pathway to payment from an insurer may not exist. The labyrinthine contractual payment relationships between healthcare providers and insurers are beyond the scope of this Article, but as seen here, the U.S. pharmaceutical supply of compounded medications would be safer if there were a clear mechanism for a 503A compounding pharmacy to bill for its dispense of a compound obtained from a 503B outsourcing facility.

E. Harmonize "Essentially a Copy" Standards for 503A and 503B Operations; Allowing Greater Use of API by Changing the Definition of or Eliminating Clinical Need Still Allows FDA to Protect the Integrity of the New Drug Approval Process Using "Essentially a Copy" Prohibitions

Both 503A compounding pharmacies and 503B outsourcing facilities are statutorily prohibited from producing compounds that are "essentially a copy" of an approved drug.[190] FDA guidance documents are available to provide the agency's current thinking on interpretation of the copy language from the statute, and the thoughts on copies from 503A and 503B facilities differ.[191] As the focus of this Article is on the implementation of the Compounding Quality Act specific to its creation of 503B outsourcing facilities, the "essentially a copy" analysis focuses on 503B outsourcing facilities.

503B products can be deemed copies of commercially available FDA-approved products by FDA if they are identical or nearly identical to an FDA-approved product (drugs in shortage are exempted from the copy prohibition and will be discussed later). The analysis offered by FDA states that a compounded product will be deemed identical or nearly identical if, when compared to the FDA-approved product, it has the same active ingredient, route of administration, dosage form, dosage strength, and excipients.[192]

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is not equipped to supply infusion medications, a contract with an infusion or compounding pharmacy is established by a central fill agreement.").

[190] 21 U.S.C. §§ 353a(b)(1)(D), 353b(a)(5).

[191] U.S. FOOD & DRUG ADMIN., 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 9 n.16 (2018), https://www.fda.gov/media/98964/download [hereinafter FDA, COMPOUNDED DRUG PRODUCTS].

[192] *Id.* at 6.

Recall the vasopressin discussion from Section III.C, above. While 503B outsourcing facility Athenex's product produced in ready-to-use form was foreclosed from sale by removal of vasopressin from the bulks list, consider it through the lens of the "essentially a copy." The active ingredient in both Par's formulation and Athenex's was vasopressin. The route of administration for both was intravenous. The dosage form for both was injection.[193] The dosage strength for Par was typically more concentrated than Athenex's products, but some strengths were identical. Excipients were likely different, though without access to Athenex's compounding records, we cannot be certain. Although Athenex's product is a 503B product, it is worth mentioning that on the facts above, it would very likely be deemed a copy if the product were produced in a 503A compounding pharmacy.[194] FDA's post-inspection observations of the Athenex facility do not list "essentially a copy" violations.[195] While it is impossible to know for sure, the absence of the violation could mean FDA did not consider Athenex's vasopressin to be a copy of Par's vasopressin due to strength or excipients, that FDA missed the observation, or that Athenex's vasopressin may have been a copy but FDA used enforcement discretion to avoid issuing the violation.[196]

Similar developments occurred with ephedrine. Prior to 2020, the only FDA-approved version of ephedrine was a 50mg/mL vial requiring dilution prior to use.[197] Ephedrine was in Category 1 of FDA's interim bulks list until August 21, 2023,[198] meaning it was allowed to be used in compounding at a 503B outsourcing facility pending the agency's final determination.[199] Nexus Pharmaceuticals, a manufacturer, developed and secured FDA approval for a 5mg/mL vial branded as Emerphed.[200] This new dosage strength eliminates the need for dilution in an emergency situation in a hospital. Of note, the Nexus product would still require opening the vial, swabbing the stopper with alcohol, opening a sterile needle and syringe, and drawing up the 5mg prior to administration. Meanwhile, a 503B outsourcing facility, Central Admixture Pharmacy Services (CAPS), began producing ephedrine in ready-to-use syringes, eliminating the vial and therefore the need to draw up the product prior to administration.[201] As with vasopressin, this is a packaging enhancement for

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[193] *Dosage Forms*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/structured-product-labeling-resources/dosage-forms (last updated Feb 3, 2022).

[194] FDA, COMPOUNDED DRUG PRODUCTS, *supra* note 191 (explaining that relevant 503A copy standards are: same API; same, similar, or easily substitutable strength; and same route of administration).

[195] *Compounding: Inspections, Recalls, and other Actions*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions#C (last visited Sept. 18, 2023); INSPECTIONAL OBSERVATIONS FORM 483 TO ATHENEX PHARMA SOLUTIONS, LLC DATED 12/5/2017–12/31/2017, U.S. FOOD & DRUG ADMIN. https://www.fda.gov/media/110078/download.

[196] *See, e.g.*, Nexus Pharms., Inc. v. Cent. Admixture Pharmacy Servs., Inc., 48 F.4th 1040, 1048 (9th Cir. 2022) (referencing the court's discussion of FDA's enforcement discretion in a related case).

[197] *Id.* at 1042.

[198] List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 88 Fed. Reg. 56,837, 56,837–43 (Aug. 21, 2023).

[199] BULK DRUG SUBSTANCES NOMINATED FOR USE IN COMPOUNDING UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, U.S. FOOD & DRUG ADMIN. (updated Sept. 29, 2023), https://www.fda.gov/media/94164/download.

[200] *Nexus Pharms.* 48 F.4th at 1042.

[201] *Id.*

healthcare providers. Of note, although CAPS' 503B outsourcing facilities have been inspected by FDA, no "essentially a copy" violation has been reported in the inspection observations.[202] Unlike Athenex's vasopressin, however, CAPS is not using API to produce its product. CAPS begins with FDA-approved finished dosage forms, dilutes them, then places the product in a ready-to-use syringe.[203]

In the absence of a determination from FDA, Nexus brought a lawsuit, which it later appealed to the Ninth Circuit Court of Appeals. The company pointed to state laws that prohibit the sale of drugs not approved by FDA to restrict sales of CAPS' product.[204] The court held the FDCA did not create a private right of action and that the determination of "essentially a copy" is therefore for FDA alone to make. The court went on to decide that any related state law claim is barred by implied preemption.[205] Ideally, competitive market pressure from CAPS' product on Nexus' Emerphed would induce Nexus to seek FDA approval for its product in a prefilled syringe. And arguably, it has; on March 3, 2023, FDA approved Nexus' Emerphed in prefilled syringes.[206]

In Part III.C above, it was proposed that FDA change its interpretation to incorporate ease of use into the existing clinical need determination for a bulks list determination. Congress could amend section 503B to eliminate the clinical need provision entirely, thereby authorizing liberal use of API. FDA would still be able to use its enforcement discretion under "essentially a copy" to protect the integrity of the new drug approval process. Said another way, considering the vasostrict example, even if FDA allowed vasopressin API to be used by a 503B outsourcing facility, it could still curb Athenex' production using "essentially a copy" by clarifying its definitions. Considering the ephedrine example, even if FDA allowed ephedrine API to be used, it could still curb CAPS production under "essentially a copy." The rules appear to be two paths leading to the same regulatory end. Allowing the use of APIs would ease existing regulatory uncertainty facing the 503B

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[202] U.S. FOOD & DRUG ADMIN., INSPECTIONAL OBSERVATIONS FORM 483 TO CENTRAL ADMIXTURE PHARMACY SERVICES DATED 2/14/2022–2/25/2022, https://www.fda.gov/media/159221/download; U.S. FOOD & DRUG ADMIN., INSPECTIONAL OBSERVATIONS FORM 483 TO CENTRAL ADMIXTURE PHARMACY SERVICES DATED 8/27/2018–9/11/2018, https://www.fda.gov/media/123194/download; U.S. FOOD & DRUG ADMIN., INSPECTIONAL OBSERVATIONS FORM 483 TO CENTRAL ADMIXTURE PHARMACY SERVICES DATED 08/04/2014–08/08/2014, https://web.archive.org/web/20170111213823/; U.S. FOOD & DRUG ADMIN., INSPECTIONAL OBSERVATIONS FORM 483 TO CENTRAL ADMIXTURE PHARMACY SERVICES DATED 08/04/2014–08/08/2014, https://web.archive.org/web/20170111213823/; U.S. FOOD & DRUG ADMIN., INSPECTIONAL OBSERVATIONS FORM 483 TO CENTRAL ADMIXTURE PHARMACY SERVICES DATED 7/30/2018–8/22/2018, https://www.fda.gov/media/123195/download; U.S. FOOD & DRUG ADMIN., INSPECTIONAL OBSERVATIONS FORM 483 TO CENTRAL ADMIXTURE PHARMACY SERVICES DATED 8/29/2016–9/19/2016, https://www.fda.gov/media/100652/download.

[203] Answering Brief at 2, *Nexus Pharms*., 48 F.4th.

[204] 21 U.S.C. § 337(a); *Nexus Pharms*., 48 F.4th at 1044 ("Nexus does not base its claim on Central Admixture's alleged violation of section 353b, no doubt because the statute is part of the [FDCA]. This Act includes a prohibition on private enforcement: all proceedings to enforce or restrain violations of the FDCA must be 'by and in the name of the United States,' except for certain proceedings by state governments.").

[205] *Nexus Pharms*., 48 F.4th at 1051.

[206] *FDA Approves Nexus' Emerphed Pre-Filled Syringes*, FDA NEWS (Mar. 3, 2023), https://www.fdanews.com/articles/211352-fda-approves-nexus-emerphed-pre-filled-syringes#:~:text=The% 20FDA%20has%20approved%20Nexus,be%20approved%20by%20the%20agency.

industry. Allowing API use would also increase demand for APIs, help secure competition in the API market, and encourage additional chemical manufacturer participation in the production of APIs. Lack of API supply, and single source suppliers of APIs, are currently vulnerabilities of the global supply chain.[207]

F. Create Compounded Product Exclusivity to Incentivize the Creation of 503B Outsourcing Facilities

Exclusivity in relation to pharmaceutical manufacturers was briefly mentioned in Part I.A. A period of exclusivity prevents FDA from approving another manufacturer's product for a period time. There are currently five type of exclusivity for pharmaceutical manufacturers.[208] One possible mechanism to incentivize the creation of 503B outsourcing facilities by minimizing financial risk from 503B product development would be to create criteria for statutory compounded product exclusivity.

While there is currently no premarket review or approval by FDA for 503B products, which would be the inflection point for such compounded exclusivity provisions, 503B facilities are required twice annually to report all products produced to FDA.[209] Adding criteria for premarket review for certain 503B products for the purpose of creating exclusivity may be an additional incentive encouraging entry into the 503B market. This suggestion is not to create premarket review for all 503B products. Further, 503B premarket review should be a standard less rigorous than the new drug application process. Congress could delegate to FDA the authority to create premarket review for the purpose of exclusivity for certain therapeutic areas, products for which there is a critically low supply of drugs, or products for which there are a low number of pharmaceutical manufacturers. Exclusivity could also be broadened from its traditional manufacturing sense of only one approved product while under exclusivity, to allow limited exclusivity for two to three 503B facilities. Some form of limited compounded product exclusivity would also allow 503B outsourcing facilities to invest in product development to prepare for shortages of FDA-approved manufactured pharmaceuticals.

G. Extend the Period for 503B Outsourcing Facilities to Sell a Copy and Use API After Shortage to Greater than Sixty Days

One purpose of 503B outsourcing facilities is to allow production of compounded versions of otherwise commercially available FDA-approved products when those products are in shortage.[210] FDA is statutorily required to maintain an up-to-date

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[207] Mariana P. Socal, Kiefer Ahn, Jeremy A. Greene & Gerard F. Anderson, *Competition and Vulnerabilities in the Global Supply Chain For US Generic Active Pharmaceutical Ingredients*, 42 HEALTH AFFS. 407 (Feb. 15, 2023), https://www.healthaffairs.org/doi/epdf/10.1377/hlthaff.2022.01120; S. COMM. ON HOMELAND SEC. & GOVERNMENTAL AFFS., SHORT SUPPLY: THE HEATH AND NATIONAL SECURITY RISKS OF DRUG SHORTAGES (Mar. 2023), https://www.hsdl.org/c/abstract/?docid=876660.

[208] Lal, *supra* note 59.

[209] 21 U.S.C. § 353b(b)(2)(A).

[210] FDA, 2021 EXECUTIVE SUMMARY, *supra* note 166 ("For example, outsourcing facilities are perceived to play a role in responding to drug shortages even though few are reportedly equipped to respond because of costs and regulatory safeguards. Thus, the expectation for outsourcing facilities to serve this purpose might be at odds with the market realities that drive most outsourcing facility business decisions.").

shortage list.[211] When an FDA-approved drug is on the shortage list, a 503B outsourcing facility's restrictions on compounding from API and the "essentially a copy" prohibition do not apply.[212] This allows a 503B facility to fill the gap created by the manufacturer shortage, although the compounded product may not be immediately available due to the inability to predict a shortage and the product validation and business preparation processes required for a 503B outsourcing facility to release a new product.

Incentives for a 503B outsourcing facility to produce a product in shortage may be misaligned. A comparison of drugs on the FDA shortage list to those drugs produced by 503B outsourcing facilities showed little overlap.[213] Once an FDA-approved product is removed from the shortage list, the statutory prohibitions resume. Because a 503B outsourcing facility may have begun production of product or have product sequestered awaiting the release of testing results, FDA allows the outsourcing facility to sell its compounded product for sixty days from the time of the removal of the FDA-approved product from the shortage list.[214] This regulatory flexibility from FDA is an incentive for shortage production by outsourcing facilities but also clearly focuses on the integrity of the drug approval process by reenforcing the preference for FDA-approved product.

The U.S. drug supply could benefit from extending the duration for which a 503B outsourcing facility can use API and sell a copy of an FDA-approved product after a shortage. The increased duration would be an additional incentive for 503B outsourcing facilities to prepare for a product's shortage or to enter the market once a shortage occurs. Further, an FDA-regulated manufacturer would be incentivized to take additional measures to protect its supply chain and otherwise adhere to regulatory requirements knowing that a shortage of their product could lead to further loss of revenue while an outsourcing facility is permitted to sell compounded version for an extended period after the shortage concludes.

IV. CONCLUSION

FDA continues to implement the CQA. By eliminating the confusion stemming from the circuit split related to section 503A, the CQA has clarified the role of FDA in the state-regulated practice of pharmacy. Through section 503B, it has created a new industry of outsourcing facilities regulated by both FDA and the states. Outsourcing facilities have the potential to make the U.S. supply of compounded medications safer while providing a critical back up for patients and healthcare providers when a pharmaceutical manufacturer's FDA-approved product is in short supply.

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[211] 21 U.S.C. § 356e. The FDA shortage list can be found here: *FDA Drug Shortages*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

[212] 21 U.S.C. §§ 353b(a)(2)(A)(ii), (d)(2).

[213] Ashlee N. Mattingly, *The Role of Outsourcing Facilities in Overcoming Drug Shortages*, 61 J. AM. PHARM. ASSOC. 110 (2021), https://www.japha.org/article/S1544-3191(20)30438-6/fulltext.

[214] *See* U.S. FOOD & DRUG ADMIN., INTERIM POLICY ON COMPOUNDING USING BULK DRUG SUBSTANCES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT GUIDANCE FOR INDUSTRY § III.A (Jan. 2017), https://www.fda.gov/media/94402/download; FDA, COMPOUNDED DRUG PRODUCTS, *supra* note 191, at § III.A.1.a.ii.

Many obstacles remain for the outsourcing facility industry and compounding pharmacies. The restrictions on outsourcing facilities' use of API create prohibitive costs for these facilities while FDA continues to move slowly to develop the bulks list, which in turn creates uncertainty about the proper ingredients for production at these facilities. Meanwhile, compounding pharmacies regulated under section 503A are paradoxically allowed more freedom to use API in production than outsourcing facilities. More liberal allowances with regard to the use of API would likely create a more stable operating situation for the 503B industry overall.

Although FDA has issued guidance on the compounding of "essentially a copy," it is unclear why the policies for 503A compounding pharmacies differ from 503B outsourcing facilities. Federal supremacy on allowing a 503A compounding pharmacy to dispense a 503B product through implied preemption enforced by federal courts or written into an amended statute would make the U.S. compounded drug supply safer. Legislative clarity regarding FDA's authority to regulate interstate volume of dispensing from a 503A compounding pharmacy using the MOU would save years of uncertainty and inevitable legal action. A federal model for a path to payment for compounded products when produced by an outsourcing facility and dispensed by a 503A compounding pharmacy would incentivize this practice, thereby increasing the safety of the U.S. compounded drug supply. Additionally, a path to payment would spur entry into the 503B outsourcing facility space by creating additional product demand. In conclusion, additional incentives exist, as explored above, to allow the nascent outsourcing facility industry to flourish while also improving access to safe drugs.