COMPOUNDING INEQUITIES THROUGH DRUG IP AND UNFAIR COMPETITION

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ABSTRACT

In 2024, the United States experienced its worst drug shortage in over a decade—more than 300 drugs are in shortage, leaving patients without access to lifesaving medicines. Luckily, drug manufacturers are not the only source of drugs. Through drug compounding, licensed pharmacists can create medications that are not commercially available due to discontinuations, shortages, or other supply chain issues. The recent slew of severe drug shortages has forced patients and physicians to rely on compounding pharmacies to make critical drugs for patients—particularly vulnerable patient populations, including pediatric, disabled, and transgender patients—such as mixed amphetamine salts (sold as Adderall), semaglutide (sold as Ozempic and Wegovy) and tirzepatide (sold as Mounjaro and Zepbound), and injectable estrogen (sold as Depo-Estradiol). However, a corresponding uptick in litigation brought by innovator drug companies against compounding pharmacies alleging intellectual property (IP) infringement and unfair competition threatens the ability of compounding pharmacies to meet critical patient needs during such shortages. Compounding pharmacies serve smaller, local groups of patients and physicians and are less capable of withstanding the threats and costs of litigation. Without legal clarity about these risks, patients face real harms.

Drugs that are in shortage must be compounded, or else patients risk forgoing essential healthcare. While the U.S. Food and Drug Administration (FDA) permits such compounding during shortages, the Patent Act and Lanham Act do not exempt patent and trademark infringement by compounders. This conflict between FDA and IP law creates an incentive for drug manufacturers to deter compounding through the threat of IP litigation. This Article deconstructs the undertheorized IP and unfair competition risks of drug compounding in three ways. It documents the FDA's authority to regulate compounding and highlights

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vulnerabilities created by recent and proposed regulations. It also analyzes ongoing litigation against compounding pharmacies for patent and trademark infringement, as well as allegations of unfair competition. Finally, it proposes two practical mechanisms to curtail these liabilities: a patent use exception that creates statutory immunity for pharmacies compounding patented drugs during active shortages, and widespread adoption of name suffixes that indicate the origin of compounded drugs—similar to nonproprietary name suffixes that are used to distinguish biosimilar products from a reference biologic. Both mechanisms would address the conflict between the FDA and IP regimes that affect compounding while protecting patients' access to life-saving healthcare by promoting the availability of safe, effective, and high-quality drugs during shortages.

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INTRODUCTION

In 2018, nine-year-old Abby Bray in Tampa, Florida was running a low-grade fever and complaining about pain that seemed to move around her body.[1] "It feels like there's knives inside my bones trying to get out," she said.[2] Eventually, Abby was diagnosed with acute lymphoblastic leukemia (ALL), the most common form of childhood cancer and the second most common cause of death in children younger than fifteen.[3] Luckily, her prognosis was very good: her relatively early diagnosis and lack of special risk factors provided her with a better chance of being cured. Up to 90% of patients like Abby can be cured, so long as they adhere to a precise regimen of chemotherapy drugs administered at specific intervals over two to three

1. Brenda Goodman, *How One Mom Headed Off a Drug Shortage*, CNN (Dec. 29, 2022, 7:48 AM), https://www.cnn.com/2022/12/29/health/drug-shortage-mom-angels-for-change/index.html [https://perma.cc/W93L-J97G].
2. *Id.*
3. *Id.* (citing Ashkan Emadi & Jennie York Law, *Acute Lymphoblastic Leukemia (ALL)*, MERCK MANUAL: PRO. VERSION (Oct. 2023), https://www.merckmanuals.com/professional/hematology-and-oncology/leukemias/acute-lymphoblastic-leukemia-all [https://perma.cc/FA5K-VGS8]).

years.[4] But four months into her treatment, Abby and her mom went to begin her treatment with a chemotherapy drug called Erwinaze (asparaginase Erwinia chrysanthemi), only to be told to go home. She wasn't going to get the drug that day, because it was in shortage. "'What happens now?' she asked her mom. 'Don't I need this to live?'"[5]

Fortunately for Abby, her mother was Laura Bray, a community college adjunct business instructor who had the business acumen to locate the drugs she needed. Laura and her family meticulously charted out all of the children's hospitals across the United States and made phone calls to all of them. Eventually, they identified one hospital that had Erwinaze on its pharmacy shelves and no child in need of it.[6] Thanks to Laura's efforts, today, Abby is free of cancer and has been since 2021. In October 2019, Laura founded Angels for Change, a nonprofit that helps other patients locate critical drugs in shortage the same way Laura had helped Abby.[7] And in 2022, Laura helped develop an additional safety net for patients who require access to essential drugs that are vulnerable to shortages—she partnered with a "compounding pharmacy" called STAQ Pharma. Compounding pharmacies are facilities licensed to produce small batches of drugs in a quality-controlled environment to produce essential medicines in shortage for hospitals.[8]

Drug shortages, like the one Abby experienced, are becoming more common. In 2024, the United States experienced its worst drug shortage in over a decade—more than 300 drugs have been in shortage since 2023.[9] Drug shortages cause a world of pain for patients who rely on these drugs, and for healthcare providers who are forced to ration these drugs and make hard decisions about which of their patients to prioritize. As patients, physicians, and hospitals scramble to locate life-saving drugs before it's too late for many patients, stories like Abby's will become increasingly inevitable. Just as many hospitals rely on STAQ Pharma to make small batches of essential drugs in shortage, hospitals across the United States are

4. Up to 90% of "standard risk" patients diagnosed with ALL can achieve complete remission. *Id.* (citing *Acute Lymphoblastic Leukemia*, UCSF HEALTH, https://www.ucsfhealth.org/conditions/acute-lymphoblastic-leukemia [https://perma.cc/N2FA-ZTJ4]).

5. *Id.*

6. *Id.*

7. *Id.*; *see* ANGELS FOR CHANGE, https://www.angelsforchange.org [https://perma.cc/37ZT-QU69].

8. Goodman, *supra* note 1.

9. *See* Tina Reed, *Six Straight Quarters of Drug Shortages*, AXIOS (July 22, 2024), https://www.axios.com/2024/07/22/six-straight-quarters-of-drug-shortages [https://perma.cc/94ML-XD6L]; Mary Kekatos, *Drug Shortages Hit Record High, Pharmacists Warn*, ABC NEWS (Apr. 12, 2024, 12:08 PM), https://abcnews.go.com/Health/drug-shortages-hit-record-high-hundreds-short-supply/story?id=109160863 [https://perma.cc/2YPM-6NRQ]; AM. SOC'Y OF HEALTH-SYS. PHARMACISTS, NATIONAL DRUG SHORTAGES: JANUARY 2001–JUNE 2024, at 2 (2024), https://www.ashp.org/-/media/assets/drug-shortages/docs/2024/2024-Drug-Shortages-Survey.pdf [https://perma.cc/QJ25-XK43].

increasingly relying on drug compounding during this severe drug shortage.[10]

Drug shortages are also complicated. Shortages may be driven by manufacturing disruptions, quality issues, or ingredient supply problems, making it challenging to address the problem solely by increasing production at existing facilities.[11] Shortages are further complicated by challenges in predicting, reporting, tracking, and preventing them. While anyone—including health care professionals, professional organizations, patients, and other individuals—may submit drug shortage reports to the FDA, only drug manufacturers are required to report shortages.[12] From there, the FDA is "constrained by statutory requirements and agreements with companies on what information they are able to share with federal partners," limiting its ability to collect data from drug manufacturers, who have the most detailed and up-to-date information about impending disruptions in their respective supply chains.[13] A lack of centralized coordination among agencies and industry also impedes the ability of the FDA to extract useful information from the data it receives from manufacturers, preventing it from effectively evaluating and predicting shortages.[14]

In addition, certain types of drugs are more prone to shortages than others. A 2019 FDA report found that generic prescription drugs and sterile injectables are the most prone to shortages, including critical medicines such as antibiotics, flu therapeutics, saline, morphine, and cancer drugs.[15] Cancer drugs for children, specifically, are 90% more likely to go into shortage than other classes of medications.[16] The FDA report also concluded

10. Ed Silverman, *More Hospital Pharmacists Are Rationing Drugs Due to Increasing Shortages*, STAT (Aug. 11, 2023), https://www.statnews.com/pharmalot/2023/08/11/hospitals-pharmacist-shortages-fda-intas-cancer/ [https://perma.cc/3VGR-K8ZP].

11. *See* FDA, DRUG SHORTAGES: ROOT CAUSES AND POTENTIAL SOLUTIONS 4–10 (2020) [hereinafter FDA DRUG SHORTAGES], https://www.fda.gov/media/131130/download [https://perma.cc/6BTK-BJRD].

12. *Frequently Asked Questions About Drug Shortages*, FDA, https://www.fda.gov/drugs/drug-shortages/frequently-asked-questions-about-drug-shortages (Oct. 11, 2023) [https://perma.cc/FP7V-3EHN].

13. S. COMM. ON HOMELAND SEC. & GOVERNMENTAL AFFS., SHORT SUPPLY: THE HEALTH AND NATIONAL SECURITY RISKS OF DRUG SHORTAGES 39 (2023), https://www.hsgac.senate.gov/wp-content/uploads/2023-06-06-HSGAC-Majority-Draft-Drug-Shortages-Report.-FINAL-CORRECTED.pdf [https://perma.cc/S8DU-D2NE].

14. *See id.* at 37–38.

15. FDA DRUG SHORTAGES, *supra* note 11, at 12–15.

16. U.S. PHARMACOPEIA, VIZIENT & ANGELS FOR CHANGE, QUANTIFYING DRIVERS OF SUPPLY CHAIN RESILIENCE IN PEDIATRIC ONCOLOGY MEDICATIONS 1 (2021), https://www.usp.org/sites/default/files/usp/document/supply-chain/pediatric-oncology-drugs-and-supply-chain.pdf [https://perma.cc/649N-7WBE]. The report found that "structural factors inherent to essential pediatric oncology cause these drugs to have a 90% higher likelihood of shortage events than the average drug product, largely driven by the class's association with lower-priced sterile injectables." *Id.* at 6.

that economic factors are a root cause of drug shortages: there is less economic incentive to ensure a consistent supply of older, off-patent, generic prescription drugs that have slender or no profit margins.[17] The factories that produce these critical drugs are also concentrated overseas, resulting in a lengthened and fragmented drug supply chain.[18] Shortages may also be caused by quality-control issues, increases in demand, natural disasters, or product discontinuations.[19]

But some specialty pharmacies can counter the harmful effects of drug shortages with drug compounding. Drug compounding is the process of combining or altering pharmaceutical ingredients to create medication tailored to the needs of individual patients, particularly where those needs cannot be met by a drug approved by the FDA. In other words, it is the creation of a medication that is not commercially available. For example, a patient who is allergic to a certain dye used in a commercially available drug, or a young child who can only ingest a drug in liquid form when that drug is only sold as a tablet, may rely on a compounding pharmacy to make suitable versions of those respective drugs. Importantly, the FDA considers drugs in shortage[20] to not be "commercially available," and therefore pharmacies can compound copies of those drugs so long as they are not doing it "regularly or in inordinate amounts."[21]

Two types of drug compounding are recognized by the FDA: traditional compounding and bulk compounding. Traditional compounding is small-scale compounding that is largely exempt from FDA regulation if the practice meets certain exemptions under the federal Food, Drug, and Cosmetics Act (FDCA) section 503A, and is instead primarily regulated by state boards of pharmacy. To qualify for exemptions from FDA premarket review and approval under section 503A, among other requirements,[22] "a drug product must be compounded by a licensed pharmacist or physician who does not compound regularly or in inordinate amounts any drug

17. FDA DRUG SHORTAGES, *supra* note 11, at 6.

18. FDA DRUG SHORTAGES, *supra* note 11, at 6, 28.

19. *See id.* at 33. For instance, in December 2022, Intas Pharmaceuticals, a key supplier of essential cancer drugs based in India, temporarily suspended manufacturing after FDA found severe quality-control issues. Daniel Gilbert, *How Troubles at a Factory in India Led to a U.S. Cancer-Drug Shortage*, WASH. POST (June 27, 2023, 6:00 AM), https://www.washingtonpost.com/business/2023/06/27/cancer-drug-shortage-generics/ [https://perma.cc/422Z-B7W9]; *see also* S. COMM. ON HOMELAND SEC. & GOVERNMENTAL AFFS., *supra* note 13, at 30–31.

20. Drugs that are in shortage are listed on the regularly updated FDA Drug Shortage List. *See FDA Drug Shortages*: *Current and Resolved Drug Shortages and Discontinuations Reported to FDA*, FDA, https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm [https://perma.cc/8WKQ-RUAQ].

21. *Drug Compounding and Drug Shortages*, FDA (Mar. 24, 2023), https://www.fda.gov/drugs/human-drug-compounding/drug-compounding-and-drug-shortages [https://perma.cc/2QG6-NCB4].

22. The section 503A requirements are codified at 21 U.S.C. § 353a.

products that are essentially copies of a commercially available drug product."[23] Bulk compounding is large-scale compounding done by so-called "outsourcing facilities" through FDCA section 503B and the Drug Quality & Security Act (DQSA) of 2013.[24] According to the FDA, these restrictions are designed to protect patients from unsafe, ineffective, or poor-quality drugs by protecting incentives for sponsors to seek drug approval through the comprehensive new drug (NDA) and abbreviated new drug (ANDA) approval processes.[25] But these restrictions are relatively thin compared to the lengthy and burdensome process that innovator companies and generic drug manufacturers must go through when seeking FDA approval of a novel or generic drug. Compounded drugs do not undergo traditional FDA premarket review and approval for safety, efficacy, or quality.

However, compounding may not be a viable long-term solution to address all the complex causes of drug shortages. For instance, where bulk substances used to make an active pharmaceutical ingredient (API) are manufactured overseas and remain in shortage due to climate change, political instability, or a global pandemic, compounding pharmacies cannot do much to help, as they face the same hurdles with obtaining those starting ingredients as a traditional drug manufacturer would.[26] However, while global supply chains remain insecure (whether the disruptions in question are unforeseeable or not), the practice of compounding plays an important gap-filling role. Drug compounding allows pharmacists and physicians to create access to drugs that are not commercially available due to product discontinuation, drug shortages, and other supply chain issues, which can disproportionately affect vulnerable patient populations.

Many current drug shortages affect children, and not all patients are as lucky as Abby. In 2012, seven infants in the United States—five of which were born premature—were hospitalized to treat extreme choleostasis, a condition which impairs bile secretion from the liver.[27] As a result, these infants could not be fed by mouth or tube and required intravenous administration of parenteral nutrition (PN) formulations. At the time, the

23. FDA, COMPOUNDED DRUG PRODUCTS THAT ARE ESSENTIALLY COPIES OF A COMMERCIALLY AVAILABLE DRUG PRODUCT UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT: GUIDANCE FOR INDUSTRY 1 (2018) [hereinafter FDA GUIDANCE], https://www.fda.gov/media/98973/download [https://perma.cc/JWS9-9RDG].

24. The section 503B requirements are codified at 21 U.S.C. § 353b.

25. FDA GUIDANCE, *supra* note 23, at 4.

26. *See* Anna Levchuk & Molly Bowman, *What Is Contributing to the API Shortage?*, OUTSOURCED PHARMA (Feb. 8, 2023), https://www.outsourcedpharma.com/doc/what-is-contributing-to-the-api-shortage-0001 [https://perma.cc/QM8N-N22A].

27. Duke Ruktanonchai et al., Ctrs. for Disease Control & Prevention, *Zinc Deficiency–Associated Dermatitis in Infants During a Nationwide Shortage of Injectable Zinc — Washington, DC, and Houston, Texas, 2012–2013*, 63 MORBIDITY & MORTALITY WKLY. REP. 35, 35–36 (2014).

United States was experiencing a nationwide shortage of injectable zinc, a vital component of PN formulations. The hospital pharmacies, which had run out of injectable zinc, were only able to provide zinc-deficient PN to administer to each infant. Six out of seven infants subsequently experienced painful dermatitis and blisters, symptoms consistent with zinc deficiency. The seventh infant, who had experienced recurrent sepsis and liver failure before receiving zinc-deficient PN, died.[28] After the hospitals involved received emergency shipments of zinc, the remaining six infants received PN with zinc and improved clinically.[29]

Drug shortages also affect other vulnerable patient populations, including trans patients. Estradiol cypionate, a type of injectable estrogen that has been chronically in shortage since 2022, is rarely used outside of trans healthcare, leaving manufacturers with little incentive to produce it.[30] Pfizer, the only supplier of the drug, issued a statement explaining that the disruption was caused by a change in its manufacturing process.[31] According to gender-affirming care providers, injectable estrogen is one of the most commonly prescribed hormone products among trans women.[32] Injectable estrogen is occasionally used for hormone replacement therapy (HRT) during menopause, but the doses required for HRT are much smaller, so patients often use tablets, patches, sprays, and gels instead of injectable estrogen.[33] Shortages of injectable estrogen have prevented transgender, non-binary, and queer patients from obtaining hormone therapy, resulting in increased risk of mental health symptoms, osteoporosis, early onset menopause, and/or reversal of certain physical changes from transitioning.[34] As discussed further in Section II.C., compounded bioidentical hormone therapy, a type of HRT involving the administration of hormone substances with the exact same chemical and molecule structure as human hormones, has recently been embroiled in controversy: some experts have suggested that the risks of manufacturing hormones in a compounding pharmacy whose manufacturing practices are subject to sparse safety and quality oversight may outweigh benefits of the therapy for hormone replacement.[35]

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28. The CDC report of the incident indicates that it was not determined whether zinc deficiency disorder had a role in the seventh infant's death, as an autopsy was not performed. *Id.* at 36.

29. *Id.*

30. Oriana González, *Drug Shortages Squeeze Trans Patients' Access to Hormone Therapy*, AXIOS (July 21, 2023), https://www.axios.com/2023/07/21/drug-shortage-hormone-estrogen-transgender [https://perma.cc/BRV4-HV5D].

31. *Id.*

32. *Id.*

33. *Id.*

34. *Id.*

35. *Compounded Bioidentical Hormone Therapy*, ENDOCRINE SOC'Y (Oct. 2, 2019), https://www.endocrine.org/advocacy/position-statements/compounded-bioidentical-hormone-therapy [https://perma.cc/Y9ND-L69Q].

However, while injectable estrogen is in shortage, trans and non-binary patients may have no choice but to rely on compounded estrogen.[36]

Similarly, Adderall has been in shortage since October 12, 2022,[37] leaving disabled patients to suffer severe withdrawal effects. Adderall is a combination medication comprising mixed salts of amphetamine and dextroamphetamine that is used to treat attention deficit hyperactivity disorder (ADHD). Patients who suddenly stop taking Adderall may experience mood swings, irritability, headaches, intense fatigue, and, in severe cases, suicidal thoughts.[38] The likelihood of experiencing withdrawal symptoms can increase as a function of how long patients have been taking Adderall, how high the dosage is, and how suddenly patients stop taking the medication—which, in the case of an unexpected shortage, is likely beyond a patient's control.[39] While the cause of the Adderall shortage is not clear, Teva Pharmaceuticals, a major supplier of Adderall, reports that it had trouble hiring workers in 2021, which caused manufacturing delays and a corresponding surge in demand followed by a backlog of orders.[40] While Adderall can be compounded, the U.S. Drug Enforcement Administration (DEA) considers amphetamines to be a Schedule II controlled substance, with a high potential for misuse and dependence, and therefore strictly controls the supply and distribution of amphetamines through quotas.[41] Section II.B.v. explores this and other ways it may be more difficult for compounding pharmacies to obtain the starting ingredients to compound Adderall.

The most contentious drugs in shortage are the glucagon-like peptide-1 (GLP-1) agonists. GLP-1 agonists are a class of drugs used in the treatment of Type II diabetes and/or obesity, such as semaglutide (sold by Novo Nordisk as Ozempic and Wegovy) and tirzepatide (sold by Eli Lilly as Mounjaro and Zepbound). Although GLP-1 agonists have been used to treat Type II diabetes in the U.S. since 2005,[42] it is hard to overstate their recent, meteoric rise in popularity—due in part to the fact that Ozempic and Mounjaro are more effective at inducing weight loss than previous

36. González, *supra* note 30.

37. *FDA Announces Shortage of Adderall*, FDA (Aug. 1, 2023), https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-shortage-adderall [https://perma.cc/S5YK-CHSK].

38. Dani Blum, *Amid the Adderall Shortage, People with A.D.H.D. Face Withdrawal and Despair*, N.Y. TIMES (Nov. 16, 2022), https://www.nytimes.com/2022/11/16/well/mind/adderall-shortage-withdrawal-symptoms-adhd.html [https://perma.cc/GWK7-3MSZ].

39. *Id.*

40. *Id.*

41. Letter from Anne Milgram, Adm'r, Drug Enf't Admin. (Nov. 1, 2023), https://www.dea.gov/sites/default/files/2023-11/Quota-Shortages%20Letter.pdf [https://perma.cc/N4TS-YNYT].

42. Byetta (exenatide), manufactured by Amylin Pharmaceuticals, was the first GLP-1 agonist approved by the FDA in 2005. *Drug Approval Package: Byetta (Exenatide) Injection*, FDA (Aug. 4, 2005), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021773_byettatoc.cfm [https://perma.cc/CCH2-MFJA].

generations of GLP-1 agonists.[43] Some healthcare professionals have expressed concerns about this unprecedented explosion in prescriptions for GLP-1 agonists,[44] noting that patients who stop taking the drugs regain much of the weight lost and experience reversion of cardiometabolic improvements.[45] Nevertheless, J.P. Morgan forecasts that the market for GLP-1 drugs, coming in at $1.5 billion in FY2022, will exceed $100 billion by 2030, driven by prescriptions to treat both diabetes and obesity.[46] Even more promising, the FDA recently approved a new indication for Wegovy to reduce the risk of cardiovascular death, heart attack, and stroke in adults with cardiovascular disease and obesity or overweight.[47] A recent trial of patients with obesity and heart disease showed that Wegovy reduced cardiovascular risk by 20%, providing hope that eventually GLP-1 agonist indications could be used to treat heart disease.[48] More recently, early data and anecdotes hold promise that Ozempic and Wegovy could be used to treat a number of mental health illnesses, including depression and bipolar disorder.[49] As potential therapeutic uses of the GLP-1 agonists expand, market demand and the possible duration of the shortage increases in kind.

Unlike Ozempic and Wegovy, there has been little to no recent litigation related to the compounding of estradiol cypionate or Adderall, likely because both drugs are no longer patented. For generic drug companies, the remaining profit margins are slim pickings, not providing enough incentive to thwart compounding efforts. But where profit margins are available for the taking, even during an unprecedented drug shortage, pharmaceutical companies have challenged the increased activity of compounding

43. *The Increase in Appetite for Obesity Drugs*, J.P. MORGAN (Nov. 29, 2023), https://www.jpmorgan.com/insights/global-research/current-events/obesity-drugs [https://perma.cc/9M9R-XNRR].

44. *See, e.g.*, Magda Wojtara, Ashmita Mazumder, Yusra Syeda & Nikodem Mozgała, *Glucagon-Like Peptide-1Receptor Agonists for Chronic Weight Management*, ADVANCES MED., Sept. 20, 2023, at 1.

45. John P. H. Wilding et al., *Weight Regain and Cardiometabolic Effects After Withdrawal of Semaglutide: The STEP 1 Trial Extension*, 24 DIABETES, OBESITY & METABOLISM 1553 (2022).

46. J.P. MORGAN, *supra* note 43.

47. News Release, FDA, FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight (Mar. 8, 2024), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-reduce-risk-serious-heart-problems-specifically-adults-obesity-or [https://perma.cc/DP2B-35DM]; *see also* Rachel Cohrs Zhang, *Medicare Couldn't Cover Wegovy for Weight Loss. But now that It's Also a Heart Drug, the Door Is Open*, STAT (Mar. 14, 2024), https://www.statnews.com/2024/03/14/medicare-wegovy-fda-label-ruling-heart-health-benefits/ [https://perma.cc/Y6WN-VTSV] (noting that the label expansion could create paths to Medicare coverage for the drug).

48. Elaine Chen & Andrew Joseph, *Novo's Obesity Drug Wegovy Lowers Cardiovascular Risk by 20%, Landmark Trial Finds*, STAT (Aug. 8, 2023), https://www.statnews.com/2023/08/08/novo-nordisk-wegovy-cardiovascular-risk/ [https://perma.cc/XF42-MWY4].

49. Elaine Chen, *Can Wegovy Treat Depression as Well as Obesity? New Research Looks to GLP-1 Drugs for Mental Illnesses*, STAT (Jan. 30, 2024), https://www.statnews.com/2024/01/30/wegovy-ozempic-depression-bipolar [https://perma.cc/8DQX-RE5P].

pharmacies with a corresponding uptick in litigation.[50] In particular, Novo Nordisk and Eli Lilly have filed a string of lawsuits against a number of compounding pharmacies in the U.S. that are making these drugs, alleging trademark violations, false advertising, and unfair competition, and seeking damages and injunctions enjoining the named pharmacies from compounding these drugs in shortage.[51] Notably, none of the recent or pending lawsuits challenging compounding make out claims for patent infringement—as is the case with most drug IP litigation—but rather allege trademark infringement and unfair competition.[52] So far, most of these lawsuits have been dismissed as thinly veiled attempts to create a private cause of action to enforce the FDCA, but an adverse court decision would disrupt the stability of marginalized patients' access to essential medicines.

The risk of patent litigation also lurks in the background. The Alliance for Pharmacy Compounding (APC), a trade association for compounding pharmacies, takes the view that claims of patent infringement against pharmacies compounding drugs in shortage will not prevail, at least in part because FDA guidance on compounding makes no distinction for a patented drug.[53] On the other hand, Novo Nordisk, which claims to have sent cease-and-desist letters to several compounding pharmacies, claims that its patents prohibit compounding of semaglutide (sold as Ozempic or Wegovy).[54] Many of these lawsuits also allege that compounding pharmacies violate state unfair trade practices by selling compounded versions of Ozempic and Wegovy that are not FDA approved—all while Novo Nordisk and Eli Lilly themselves enjoy the ability to sell these drugs for off-label, unapproved uses, such as to treat overweight or obesity. The threat of litigation risks imposing a chilling effect on compounding, hurting patients who need it the

50. *See* Martha M. Rumore, *Legal Battles Intensify: Pharmaceutical Manufacturers' Lawsuits Targeting Compounding Pharmacies*, PHARMACY TIMES (July 12, 2023), https://www.pharmacytimes.com/view/legal-battles-intensify-pharmaceutical-manufacturers-lawsuits-targeting-compounding-pharmacies [https://perma.cc/YHV5-6QRZ].

51. *E.g.*, First Amended Complaint, Eli Lilly & Co. v. Wells Pharmacy Network, LLC, No. 23-cv-00576 (M.D. Fla. Dec. 18, 2023); First Amended Complaint, Novo Nordisk Inc. v. Brooksville Pharms. Inc., No. 23-cv-01503 (M.D. Fla. filed Nov. 29, 2023); Press Release, Novo Nordisk, Novo Nordisk Takes Actions to Help Protect US Patients from Unlawful Sales of Non-FDA Approved Medicines Claiming to Contain Semaglutide (June 20, 2023, 10:00 AM), https://www.novonordisk-us.com/media/news-archive/news-details.html?id=166121 [https://perma.cc/348M-LD5Y].

52. *See supra* note 51.

53. *Statement on Rules Governing Compounding, What FDA Guidance Says About Permissibility of Compounding "Essentially a Copy" of an FDA-Approved Drug - and What Those Have to Do with Semaglutide*, ALL. FOR PHARMACY COMPOUNDING (July 25, 2023), https://a4pc.org/files/APC-Compounding-Semaglutide-Media-Brief-REVISED-22May2023-REVISED-July-25.pdf [https://perma.cc/LM7J-6Q42].

54. Christine Blank, *Pharmacy Compounders Defend Semaglutide Compounding amid Continued Shortages*, DRUG TOPICS (June 15, 2023), https://www.drugtopics.com/view/pharmacy-compounders-defend-semaglutide-compounding-amid-continued-shortages [https://perma.cc/M2DK-K9TK].

most. Most compounding pharmacies serve smaller, local groups of patients and physicians and are less capable of withstanding the threats and costs of litigation. Without legal clarity about these risks, patients face real harms.

These risks, which had not risen to a level of urgency until now due to the severity of the current drug shortage, arise from conflicts between FDA and IP law. Compounding pharmacies have long looked to the FDA to provide clear guidelines as to when compounding is legally permissible. While private parties, such as drug manufacturers, have never had a right to encroach on FDA's authority to enforce its own laws, the recent spate of litigation against compounding pharmacies illuminates attempts by manufacturers to bypass this problem by undercutting FDA's authority with IP law. This conflict between FDA and IP law creates an incentive for drug manufacturers to deter compounding through the threat of IP litigation and unfair competition, putting patients at risk. Drug manufacturers and compounding pharmacies are both players operating in a large ecosystem regulated by complex FDA law intertwined with IP doctrine and must work together to ensure a consistent supply of essential drugs for patients, particularly during severe shortages.

Drawing on recent litigation, this Article highlights the IP and unfair competition risks of drug compounding and proposes two legal reforms that could mitigate these risks. Part II documents the creation and subsequent regulation of compounding pharmacies and highlights gaps created by recent and proposed regulation, including proposals to increase restrictions on compounding hormone therapies. In Part III, this Article illustrates the legal risks of compounding. Recent litigation related to drug compounding, including litigation against compounding pharmacies selling GLP-1 agonists, create real risks of patent infringement, trademark infringement and unfair competition allegations against compounding pharmacies. As patients and physicians are forced to rely on compounding pharmacies to provide essential drugs during times of shortage, there is a critical need for increased clarity on the IP infringement and unfair competition risks of compounding, which this Part seeks to provide. But in courtrooms, clarity may come too late. Part IV illuminates two actionable interventions that address the IP risks of compounding: (1) allowing a patent use exception, which would create limited statutory immunity for pharmacies compounding patented drugs during an active shortage, and (2) adopting name suffixes for compounded drugs that permit easy identification and origin tracking for drugs associated with adverse events, which helps catalogue quality concerns. By examining current authority to regulate compounding pharmacies and exploring undertheorized IP and unfair competition risks, this Article exposes a powerful path forward for drug compounding.

I. DEVELOPING DRUG COMPOUNDING

A. Pioneering the Practice

1. Historical Compounding

Traditional drug compounding is the process of combining or altering ingredients to create medicine for an individual patient, pursuant to a prescription, and to be dispensed directly to that patient.[55] Today, pharmacies that provide such services are known as "503A pharmacies."[56] Throughout most of pre-industrial history, most medicines were compounded by independent pharmacists or physicians to meet the unique needs of individual patients.[57] While it is difficult to pinpoint the precise origin of drug compounding, the practice of processing and combining different medicinal ingredients to create therapeutic treatments for individual patients can be traced to the origins of pharmacy itself, long before the term "drug compounding" even existed.[58]

By the 1800s, the Industrial Revolution had led to the rise of mass-produced pharmaceuticals, many of which were made from proprietary, synthetic materials that could no longer be easily obtained and prepared by independent pharmacists.[59] In 1796, Samuel Lee Jr. of Connecticut received the first American patent for a pill—for his composition of "bilious pills" made of juices from trees and plants, soap, and saltpeter (sodium nitrate and potassium nitrate) that claimed to provide relief from kidney stones, "dropsy" (fluid retention) and yellow fever.[60] The nineteenth century also coincided with the founding days of many of today's pharmaceutical giants, driven in part by the demand for large quantities of medicine for soldiers

55. *Frequently Asked Questions About Pharmaceutical Compounding*, AM. PHARMACISTS ASS'N, https://www.pharmacist.com/Practice/Patient-Care-Services/Compounding/Compounding-FAQs [https://perma.cc/4E3Z-BHVX].

56. So called because they are regulated by the FDA under FDCA section 503A. *See supra* notes 22–23 and accompanying text.

57. Benjamin Y. Urick & Emily V. Meggs, *Towards a Greater Professional Standing: Evolution of Pharmacy Practice and Education, 1920–2020*, 7 PHARMACY no. 98, 2019, at 1, 1; C. James Watson, James D. Whitledge, Alicia M. Siani & Michele M. Burns, *Pharmaceutical Compounding: A History, Regulatory Overview, and Systematic Review of Compounding Errors*, 17 J. MED. TOXICOLOGY 197, 199 (2021).

58. *See* Matt Poteet, *The History of Pharmaceutical Compounding*, COMPOUNDING PHARMACY AM. (Feb. 19, 2024), https://compoundingrxusa.com/blog/history-pharmaceutical-compounding/ [https://perma.cc/3ZSK-DCRK]. Some sources say the earliest known record of drug compounding is found in the *Sushrata Samhita*, a classical Sanskrit text on surgery and Indian traditional medicine dating back to the 6th century BC. *E.g.*, *The History of Pharmacy*, TEX. TECH UNIV. HEALTH SCIS. CTR., https://www.ttuhsc.edu/pharmacy/museum/pharmacy.history.aspx [https://perma.cc/9CWG-QQAC].

59. Urick & Meggs, *supra* note 57, at 1; Watson et al., *supra* note 57, at 199.

60. *First American Medicine Patent – Today in History: April 30*, CONNECTICUTHISTORY.ORG (Apr. 30, 2020), https://connecticuthistory.org/first-american-medicine-patent-today-in-history-april-30/ [https://perma.cc/695Q-GFJ6].

during the American Civil War. In 1849, two German immigrants, cousins Charles Pfizer and Charles Erhart, founded Pfizer Inc. as a chemicals business that in short course expanded rapidly to manufacture large quantities of painkillers and antiseptics during the American Civil War.[61] Meanwhile, Edward Robinson Squibb, who had served as a naval doctor during the Mexican-American War of 1846–1848, set up his own laboratory in 1858 to supply Union armies in the Civil War—the laboratory later developed into what we know today as Bristol Myers Squibb.[62] And in the same timeframe, a young cavalry commander and trained pharmaceutical scientist named Colonel Eli Lilly was serving in the Union Army. After his military career, in 1876, Lilly set up a successful pharmaceutical business that we know today as Eli Lilly & Co.[63]

As the traditional role of pharmacists as compounders was upended by the Industrial Revolution, along with the accompanying shift in how patients obtained medicine, by the early 1900s community pharmacists had turned their attention away from compounding and turned instead to general retail.[64] Although dispensing prescription medicine was still important to the identity of the pharmacy, it was not nearly as profitable as selling other retail goods and was therefore de-emphasized as part of the pharmacy business model.[65] By the 1930s, less than 1% of pharmacies in the United States made a majority of their income from pharmaceutical sales.[66] As the pharmaceutical industry continued to expand, and research and development of manufacturing methods enabled the industry to manufacture complex drugs directly in the factory, the practice of compounding itself became less necessary as medicines gradually required less processing by a pharmacist in the pipeline from factory to patient. In the 1930s, 75% of prescription medicines required some degree of in-pharmacy compounding. By the 1950s, that number fell to 25%, to less than 5% by 1960, and to 1% by 1970.[67]

Notably, while compounding by 503A pharmacies was declining, compounding in inpatient hospital settings was on the rise, particularly for complex treatment regimens, such as those required for chemotherapy, parenteral nutrition (PN), cardiac surgery, and hormone replacement

61. *A History of the Pharmaceutical Industry*, PHARMAPHORUM (Sept. 1, 2020), https://pharmaphorum.com/r-d/a_history_of_the_pharmaceutical_industry [https://perma.cc/Z29E-489C]; *Company Timeline: A Legacy of Innovation*, PFIZER, https://www.pfizer.com/about/history [https://perma.cc/H6PC-MLWS].

62. *Id.*

63. *Id.*

64. Watson et al., *supra* note 57, at 199.

65. Urick & Meggs, *supra* note 57, at 3.

66. *Id.*

67. Gregory J. Higby, *The Continuing Evolution of American Pharmacy Practice, 1952–2002*, 42 J. AM. PHARMACISTS ASS'N 12 (2002).

therapy.[68] From the 1980s to the early 2000s, the need for these advanced therapeutics began to spill into the home treatment and infusion setting,[69] emerging as "503B pharmacies."[70] 503B pharmacies, such as STAQ Pharma,[71] engage in large-scale or bulk compounding, manufacturing large quantities of medications that are unavailable commercially and distributing them widely to healthcare facilities and individual patients.[72] As discussed further below in Section II.B.iv, 503B facilities occupy a strange regulatory space created by the patchwork regulations that govern drug compounding—traditional compounding is largely regulated by state boards of pharmacy due to their small scale and local effect, but the FDA has long regulated mass-manufactured pharmaceuticals.[73] 503B facilities operate on a scale between the two, and the FDA has responded by attempting to increase its regulatory authority over 503B facilities.[74]

2. Contemporary Compounding

Today in the United States, compounded pharmaceuticals are estimated to comprise only between 1–3% of all prescriptions.[75] The majority of pharmaceuticals are produced in commercial facilities, subject to strict regulation and oversight by the FDA. The FDA oversees the manufacturing and marketing of two broad categories of drugs: small-molecule drugs and biologic products. Most pharmaceuticals on the market are small-molecule drugs: drugs with a low molecular weight, a known structure or formula, and often produced by chemical synthesis. Examples of common small-molecule drugs include aspirin, antihistamines, and beta blockers. Biologics, on the other hand, are made up of large molecules, such as sugars, proteins, and/or nucleic acids, whose structures are complex and not easily

68. Watson et al., *supra* note 57, at 199; Susan A. Cantrell, *Improving the Quality of Compounded Sterile Drug Products: A Historical Perspective*, 50 THERAPEUTIC INNOVATION & REGUL. SCI. 266, 266–67 (2016).

69. Cantrell, *supra* note 68, at 267 (describing an emergence in the 1970s and 1980s of the practice of administering intravenous therapy to patients in their homes, for those who required infusion over a sustained period of time, such as for cancer chemotherapy or pain management).

70. So called because they are regulated by the FDA under FDCA section 503B. *See supra* note 24 and accompanying text.

71. As discussed in Part I, Laura Bray (Abby's mother) partnered with STAQ Pharma, a 503B facility to produce essential medicines in shortage for hospitals. Goodman, *supra* note 1.

72. Watson et al., *supra* note 57, at 200–01.

73. Cantrell, *supra* note 68, at 268; Ethan D. Grober et al., *Accuracy of Testosterone Concentrations in Compounded Testosterone Products*, 12 J. SEXUAL MED. 1381, 1382 (2015); JoAnn V. Pinkerton & James H. Pickar, *Update on Medical and Regulatory Issues Pertaining to Compounded and FDA-Approved Drugs, Including Hormone Therapy*, 23 MENOPAUSE 215 (2016).

74. *See infra* Section II.b.iv.

75. Watson et al., *supra* note 57, at 199 (collecting sources).

identified or characterized.[76] Biologics encompass a wide range of products such as vaccines, blood, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins, and they may be manufactured from a variety of natural biological sources, including human, animal, or microorganism.[77] Biologics tend to be less stable. They are more heat-sensitive, so constituent proteins may denature when exposed to heat, and they are more susceptible to microbial contamination than small-molecule drugs.[78] As discussed in further detail below, this distinction is important—as of 2020, the FDA no longer considers most biologics to qualify for compounding exemptions.

Small-molecule drugs and biologics, as well as their follow-on products ("generics" for small-molecule drugs and "biosimilars" for biologics), each have their own regulatory pathway. The FDA approval process for both small-molecule drugs and biologics aims to ensure that pharmaceuticals are safe and effective for their intended use before they are made available to the public.[79] An innovator company seeking to obtain FDA approval of a novel small molecule drug must typically conduct preclinical testing, consisting of extensive laboratory and animal studies to assess a drug's pharmacological properties, as well as information on dosing and toxicity levels.[80] The company must also submit an Investigational New Drug (IND) Application to the FDA outlining a proposed plan for human clinical trials and conduct human clinical trials, typically occurring in at least three phases.[81] Finally, it must submit a New Drug Application (NDA) under

76. *See* 42 U.S.C. § 262(i)(1) (defining "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."); *What Are "Biologics" Questions and Answers*, FDA (Feb. 6, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers [https://perma.cc/8BVR-45WM].

77. *What Are "Biologics" Questions and Answers*, *supra* note 76.

78. *Id.*

79. *See The Drug Development Process*, FDA (Jan. 4, 2018), https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process [https://perma.cc/QB9C-DSGM]; *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA (Nov. 24, 2017), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective [https://perma.cc/6X3D-MUM8].

80. *Step 2: Preclinical Research*, FDA (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research [https://perma.cc/6ZA4-UBUJ].

81. *Step 3: Clinical Research*, FDA (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-3-clinical-research [https://perma.cc/NMY9-Q9VF]. Phase I human trials usually involve a small number of healthy volunteers (twenty to one hundred) to evaluate the drug's safety and dosage range over several months. *Id.* Phase II involves a larger group of patients (up to several hundred with the target disease or condition) to assess the drug's efficacy and further evaluate potential side effects. *Id.* Phase III involves a larger and more diverse patient population (300 to 3,000 patients) to confirm efficacy, monitor side effects, and compare the drug's benefits to existing treatments. *Id.*

FDCA section 505(b)(1) to the FDA with comprehensive data on the drug's safety and efficacy, manufacturing details, proposed labeling, and information on how the drug will be monitored and marketed.[82] Negative results at any stage of the process may result in failure to progress to the next phase or even a decision by the innovator company to halt drug development and testing. The FDA then conducts a thorough review of all the data submitted, occasionally with independent recommendations from a special advisory committee of external experts, and decides whether to approve the drug for marketing based on a determination that the drug's benefits outweigh its risks.[83] After approval, the FDA and innovator company continue to monitor the drug's safety and effectiveness through post-marketing surveillance, collecting data on adverse events and other relevant information.[84] The process for obtaining approval of a biologic drug is similar but involves submission of a Biologics License Application (BLA) under the Public Health Service Act (PHSA) section 351(a) (codified at 42 U.S.C. § 262(a)).[85]

The generic drug approval process is streamlined in order to allow a generic drug company and the FDA to rely on the existing safety and efficacy data of a Reference Listed Drug (RLD), a reference innovator drug that has already been approved by the FDA. The generic drug manufacturer must submit an Abbreviated New Drug Application (ANDA) under FDCA section 505(j) (codified at 21 U.S.C. § 355) demonstrating that the proposed generic drug is therapeutically equivalent to the RLD, such as by showing that the generic contains the same active ingredient, has the same dosage strength, uses the same dosage form (e.g., tablet, capsule, liquid), uses the same route of administration (e.g., oral, injectable, topical), and that the proposed generic is identical in quality, strength, purity, and stability to the RLD.[86] The FDA then reviews the ANDA, assessing the generic drug's safety, efficacy, and bioequivalence to the RLD, and if adequate, grants approval for the generic drug.[87] After approval, generic drugs, like innovator drugs, are subject to post-marketing surveillance to monitor for adverse

82. *Step 4: FDA Drug Review*, FDA (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review [https://perma.cc/Q7HV-LAPV].

83. *Id.*

84. *Step 5: FDA Post-Market Drug Safety Monitoring*, FDA (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring [https://perma.cc/RKZ5-T6LL].

85. *See Frequently Asked Questions About Therapeutic Biological Products*, FDA (May 16, 2024), https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products [https://perma.cc/RQ9L-CLB5].

86. *See Generic Drugs: Questions & Answers*, FDA (Mar. 16, 2021), https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/generic-drugs-questions-answers [https://perma.cc/J29M-KXQV].

87. *Id.*

events or any safety concerns.[88] Drug manufacturers seeking approval of a biologic follow-on product must submit similar information to the FDA in an abbreviated Biologics License Application (aBLA) under PHSA section 351(k) (codified at 42 U.S.C. § 262(k)), showing that the proposed biosimilar is highly similar to and has no clinically meaningful differences in terms of safety, purity, and potency from the existing FDA-approved reference biologic.[89]

Although traditional compounding is on the decline, the practice of compounding is still a core component of the training and education of all licensed pharmacists—many state pharmacy licensing bodies test the compounding knowledge and skills of aspiring pharmacists.[90] Additionally, most 503A pharmacies still offer some level of compounding services to meet the needs of patients who require a medication formulation that is not readily accessible on the commercial market.[91] According to the American Pharmacists Association, of about 56,000 community-based pharmacies in the United States, approximately 7,500 pharmacies specialize in compounding services.[92] These compounded preparations may be either sterile (typically "intended for the eye, or injection into body tissues or the blood") or non-sterile (topical "ointments, creams, liquids, or capsules for use in areas of the body where absolute sterility is not necessary").[93] Such pharmacies may be accredited by the Accreditation Council for Healthcare, which assesses both sterile and nonsterile compounding pharmacies by a set of standards defining the quality and consistency of formulations produced.[94]

More recently, the current drug shortage crisis has resulted in a resurgence of hospital pharmacies buying compounded drugs to meet

88. *Id.*

89. *Review and Approval*, FDA (Dec. 13, 2022), https://www.fda.gov/drugs/biosimilars/review-and-approval [https://perma.cc/2WWV-RBKJ].

90. AM. PHARMACISTS ASS'N, *supra* note 53.

91. *Id.* The American Pharmacists Association provides the following examples of indications for compounding:

- "[To c]ustomize strength or dosage."
- "[To f]lavor a medication (to make it more palatable for a child . . .)."
- "Reformulate the drug to exclude an unwanted, nonessential ingredient [. . .] to which a patient is allergic."
- "Change the form of the medication for patients who, for example, have difficulty swallowing or experience stomach upset when taking oral medication."

Id.

92. *Id.* Pharmacies that specialize in compounding services have pharmacists that spend most or all of their time compounding drugs for patients. *Id.*

93. *Id.*

94. *Id.*

patient needs for critical drugs.[95] A survey of more than 1,100 hospital pharmacists conducted in the summer of 2023 stated that 99% of hospital pharmacists reported shortages at their institutions, with 59% reporting buying more from compounding pharmacies as a result of those shortages.[96] As patients increasingly rely on compounding pharmacies to produce these essential drugs, it is more critical than ever that compounding pharmacies and their stakeholders have clarity about the legal risks of compounding.

B. Regulating the Practice

Although the FDA has historically had limited authority to regulate drug compounding, over the past century, the development of mandatory premarket review for new drugs, developments in FDA case law, and public health crises resulting from poorly compounded drugs have gradually built political will to bolster the FDA's authority to regulate compounding. This Section will discuss the evolution of key statutes and other sources of authority that empower the FDA to regulate the practice of drug compounding.

1. The Federal Food, Drug, and Cosmetic Act of 1938

In 1938, Congress passed the federal Food, Drug, and Cosmetic Act (FDCA) to grant the FDA authorization to oversee pharmaceutical manufacturing.[97] Under the FDCA of 1938, the FDA can conduct investigations and inspections and take enforcement action against entities that sell drugs that have not undergone pre-market review (section 505),[98]

95. Silverman, *supra* note 10; *see also* John Wilkerson, *Pharmacists Can Make Shortage Drugs, but at What Cost?*, STAT (Oct. 20, 2023), https://www.statnews.com/2023/10/20/pharmacists-drug-shortages/ [https://perma.cc/M3MY-M24B] (further reporting that Premier, a purchaser for over 4,000 hospitals across the United States, reported purchasing 41% more from compounding facilities in 2022 than in 2021).

96. Silverman, *supra* note 10.

97. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended in scattered sections of 21 U.S.C.).

98. *See* 21 U.S.C. § 355 (defining premarket review for new drugs).

are adulterated (section 501(a)(2)(B)),[99] or are misbranded (section 502(f)(1)).[100] However, the 1938 Act did not mention drug compounding.

2. The Kefauver-Harris Drug Amendments of 1962

In the late 1950s and early 1960s, the thalidomide crisis[101] spurred the enactment of the Kefauver-Harris Drug Amendments of 1962 ("Drug Amendments"), the first instance in which drug compounding was noted in federal law.[102] The Drug Amendments required drug manufacturers to register with the FDA and strengthened the ability of the FDA to conduct on-site inspections, but exempted pharmacies that did not compound "other than in the regular course of their business of dispensing or selling drugs at retail."[103] However, in *Wedgewood Village Pharmacy, Inc. v. United States*, the Third Circuit affirmed that the Drug Amendments granted federal authorities the right to enter establishments involved in the production of drugs to inspect equipment, materials, containers, and labeling used in the

99. *See* 21 U.S.C. § 351 (defining adulteration); *see also Glossary of Terms Related to FDA's Regulation of Animal Products*, FDA. (July 19, 2022) [hereinafter *FDA Glossary*], https://www.fda.gov/animal-veterinary/resources-you/glossary-terms-related-fdas-regulation-animal-products [https://perma.cc/CCL8-3PWJ] (defining adulteration as a "violation of the [FDCA] which includes products that are defective, unsafe, not shown to be safe, filthy, or produced under insanitary conditions. It also includes products which are manufactured under procedures and controls which do not comply with Current Good Manufacturing Practice regulations").

100. *See* FDCA § 502(f)(1), 21 U.S.C. § 352 (defining misbranding); *see also FDA Glossary* (defining a drug as misbranded (a) if its labeling is false or misleading; (b) if in package form without a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count; or (c) if any other information required by or under authority of the FDCA to appear on the label is not prominently placed on it and it likely to be read and understood by an ordinary individual under customary conditions of purchase and use).

101. In the 1950s and early 1960s, the drug thalidomide was prescribed liberally in Europe, Canada, and Australia as a non-habit-forming sedative. James H. Kim & Anthony R. Scialli, *Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease*, 122 TOXICOLOGICAL SCIS. 1, 1 (2011). Doctors also began prescribing it as a sedative and antiemetic, leading to severe birth defects in infants whose mothers had taken the medication during pregnancy. *Id.* The drug was never approved in the United States, thanks primarily to the insight of Dr. Frances Kelsey, an FDA officer assigned to review the drug application, who denied the approval based on a lack of safety data and emerging data linking thalidomide to neurologic toxicities. *Id.* The thalidomide crisis underscored the need for comprehensive pre-market testing, spurring the FDA to enact stricter regulations to prevent similar incidents. For more information on the thalidomide crisis, see generally Robert D. McFadden, *Frances Oldham Kelsey, Who Saved U.S. Babies from Thalidomide, Dies at 101*, N.Y. TIMES (Aug. 7, 2015), https://www.nytimes.com/2015/08/08/science/frances-oldham-kelsey-fda-doctor-who-exposed-danger-of-thalidomide-dies-at-101.html [https://perma.cc/P6NX-T2BP].

102. ANDREW NOLAN, CONG. RSCH. SERV., R43038, FEDERAL AUTHORITY TO REGULATE THE COMPOUNDING OF HUMAN DRUGS 5 (2013) (citing Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 U.S.C.)).

103. *Id.* (citing 21 U.S.C. § 360(g)(1)).

production process, and held that compounding pharmacies were not exempt from these requirements.[104]

3. The Food and Drug Administration Modernization Act of 1997

In the late 1990s, the FDA became concerned that entities that were compounding drugs in bulk were self-classifying as "pharmacies" rather than drug manufacturers to avoid the burdensome drug approval requirements under the FDCA.[105] Thus, in 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA),[106] which added Section 503A to the FDCA. Section 503A exempts traditional compounding pharmacies from complying with FDA's requirements concerning new drug approval, misbranding, and adulteration.[107] 503A pharmacies engage in drug compounding in response to specific prescriptions for individual patients and on a much smaller scale than conventional drug manufacturing.[108] Thus, compounded drugs do not undergo premarket review for safety, efficacy, or quality.

To qualify for these exemptions from premarket review under section 503A, among other requirements, a drug product must be compounded by a licensed pharmacist or physician who "does not compound regularly or in inordinate amounts . . . any drug products that are essentially copies of a commercially available drug product," among other conditions.[109] According to the FDA, these restrictions are designed to protect patients from unsafe, ineffective, or poor-quality drugs by protecting incentives for sponsors to seek drug approval through the comprehensive abbreviated new drug (ANDA) approval processes.[110]

Today, the FDA generally considers a compounded drug to be "essentially a copy of a commercially available drug product" if (1) the compounded drug product has the same active pharmaceutical ingredient(s) (API) as the commercially available product; (2) the API(s) have the same, similar, or an easily substitutable dosage strength (generally within ten percent of the dosage strength of the commercially available drug product); (3) the commercially available drug product can be used by the same route of administration as prescribed for the compounded drug; and (4) the compounded drug has the same characteristics (API, dosage strength, and

104. 421 F.3d 263, 269–71 (3d Cir. 2005) (holding that a compounder was not exempt from non-record inspections under 21 U.S.C. § 374(a)).

105. NOLAN, *supra* note 100, at 5.

106. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

107. 21 U.S.C. § 353a.

108. *Id.* § 353a(a); NOLAN, *supra* note 101, at 5–6.

109. 21 U.S.C. § 353a(b)(1)(D).

110. FDA GUIDANCE, *supra* note 23, at 4.

route of administration) as two or more commercially available drug products.[111] The FDA considers drugs in shortage to not be "commercially available," and therefore pharmacies can compound those drugs so long as they are not doing it "regularly or in inordinate amounts."[112]

According to recent FDA guidance, the following nonexhaustive list of factors may be considered in determining whether a drug is compounded regularly or in inordinate amounts:

> "[1] the compounded drug product amounts to more than a small number of prescriptions or a small percentage of the compounded drug products that a compounder prepares[;] [2] the compounder routinely substitutes compounded drugs that are essentially copies of commercially available drugs upon receiving prescriptions for patients[;] [3] the compounder offers pre-printed prescription pads that a prescriber can use to write a prescription for the drug product that is essentially a copy without making a determination that there is a change that will produce a significant difference for a patient[;] [4] the compounded drug product is not compounded on an as-needed basis, but on a routine or pre-set schedule."[113]

Instead of being subject to FDA oversight, traditional 503A compounding pharmacies are instead primarily regulated by state boards of pharmacy.[114] The majority of state boards reference and require 503A compounding facilities to adhere to quality standards established by the private, nonprofit organization, the United States Pharmacopeia (USP) Convention.[115] The USP establishes two important standards for the identity, quality, strength, and purity of drugs and other ingredients used in compounding preparations: USP General Chapters 795 and 797.[116]

USP General Chapter 795 is a standard providing compounders with guidance on preparing nonsterile preparations in health care settings.[117] It describes three general categories of nonsterile compounding (simple, moderate, and complex), and the different levels of experience, training, and physical facilities recommended for each.[118] This standard discusses general

111. *Id.* at 5–8.

112. *See* FDA, *supra* note 20.

113. FDA GUIDANCE, *supra* note 23, at 10.

114. AM. PHARMACISTS ASS'N, *supra* note 55.

115. PEW CHARITABLE TRS. & NAT'L ASS'N OF BDS. OF PHARMACY, STATE OVERSIGHT OF DRUG COMPOUNDING 5–6 (2018), https://www.pewtrusts.org/-/media/assets/2018/02/drug_safety_assesment_web.pdf [https://perma.cc/57PS-4P9E].

116. AM. PHARMACISTS ASS'N, *supra* note 55.

117. *General Chapters <795>, Pharmaceutical Compounding – Nonsterile Preparations*, U.S. PHARMACOPEIA (May 1, 2020), https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/gc-795-rb-notice-20200424.pdf [https://perma.cc/9A93-PN2F].

118. *Id.*

principles of compounding, compounding facilities and equipment, component selection, handling, and storage, stability criteria and beyond-use dating (i.e., expiration), packaging and drug preparation containers, quality control, and appropriate compounding documentation.[119] USP General Chapter 797 is a standard for the process, testing, and verification of compounded sterile preparations.[120] Sterile preparations require a higher level of care to prevent contamination than non-sterile preparations.[121] USP 797 discusses similar sub-topics as USP 795, but also offers additional guidance on preventing microbial contamination, excessive bacterial endotoxins, chemical and physical contaminants, and other unintended variances in compounded sterile preparations.[122] The chapter discusses aseptic techniques, procedures to minimize contact with nonsterile surfaces, and methods of preventing the introduction of particulate matter or biological fluids when formulating compounded sterile preparations.[123]

According to a 2018 report on state oversight of compounding practices, thirty-two state boards of pharmacy required 503A pharmacies that compound sterile drugs to be in full compliance with USP 797, eleven states had "strong" requirements on sterile compounding practice (which most characterized as "equivalent to or stricter than" USP 797), and an additional four states had pending policy changes that would require full compliance with 797 or other strong quality standards.[124] The report also noted that, as of 2018, thirty-nine states and the District of Columbia prohibited 503A pharmacies from compounding for "sterile office stock for human use"—in other words, from compounding large batches of non-patient-specific compounded drugs for hospitals, doctors' offices, and other health care facilities.[125] However, fewer than half of all states reported annual inspections of 503A pharmacies in 2018.[126] So while state boards of pharmacy may have strong standards of practice regulating compounding by 503A pharmacies, these regulations are accompanied by lackluster monitoring and enforcement.

The FDAMA of 1997 also required compounding pharmacies to adhere to certain criteria concerning advertising, including that the prescription be "unsolicited,"[127] and that the providers "not advertise or promote the

119. *Id.*

120. *General Chapter <797>, Pharmaceutical Compounding—Sterile Preparations*, U.S. PHARMACOPEIA (Dec. 1, 2019), https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/gc-797-postponement-rb-notice-20191122.pdf [https://perma.cc/HEJ2-EJGR].

121. *Id.*

122. *Id.*

123. *Id.*

124. PEW CHARITABLE TRS. & NAT'L ASS'N OF BDS. OF PHARMACY, *supra* note 115, at 2.

125. *Id.*

126. *Id.*

127. 21 U.S.C. § 353a(a) (2012) (amended 2013).

compounding of any particular drug, class of drug, or type of drug."[128] Pharmacists could only inform the public that they offered general compounding services.[129] In 2002, a group of licensed pharmacies specializing in drug compounding brought suit against the FDA and HHS, arguing that the FDAMA advertising and solicitation provisions violated the Free Speech Clause of the First Amendment and seeking to enjoin enforcement of them.[130] The district court agreed, holding that the provisions constituted unconstitutional restrictions on commercial speech.[131] The Ninth Circuit affirmed in part, reasoning that the Government had not shown that the advertising restrictions would directly advance its interests or that alternatives less restrictive of speech were unavailable.[132]

On appeal to the Supreme Court, in *Thompson v. Western States Medical Center*, the Court ruled in a 5-4 opinion that the FDAMA advertising prohibitions were unconstitutional restrictions on commercial speech that violated the First Amendment.[133] The Government asserted that the FDAMA provisions served the substantial interest of achieving the proper balance between two competing interests: preserving the effectiveness and integrity of the FDA drug approval process, and preserving the availability of compounded drugs for patients who cannot use commercially available products approved by the FDA.[134] The Court agreed, but observed that compounded drugs should not be forced to undergo premarket review, noting that, because "[p]harmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible," "it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process."[135]

While the Court agreed with the Government that the FDAMA provisions advanced the two asserted interests, it held that the provisions were more extensive than necessary. The Government needed "to be able to draw a line between small-scale compounding and large-scale drug manufacturing."[136] The Government argued that the challenged FDAMA provisions drew such a line by allowing pharmacists to sell compounded drugs without undergoing FDA approval so long as they did not advertise

128. *Id.* § 353a(c).
129. *Id.*
130. W. States Med. Ctr. v. Shalala, 69 F. Supp. 2d 1288 (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).
131. *Id.* at 1309.
132. *W. States Med. Ctr.*, 238 F.3d at 1096.
133. *Thompson*, 535 U.S. at 368–77.
134. *Id.* at 368.
135. *Id.* at 369–70.
136. *Id.* at 370.

particular compounded drugs.[137] However, the Court concluded that there were several alternative non-speech-related means of drawing such a line.[138] "For example, the Government could ban the use of 'commercial scale manufacturing or testing equipment for compounding drug products,'" "prohibit pharmacists from compounding more drugs in anticipation of receiving prescriptions than in response to prescriptions already received," or prohibit them from "[o]ffering compounded drug products at wholesale to other state licensed persons or commercial entities for resale."[139] The Court reasoned that "[f]orbidding the advertisement of compounded drugs" would "prevent pharmacists with no interest in mass-producing medications, but who serve clienteles with special medical needs, from telling the doctors treating those clients about the alternative drugs available through compounding."[140]

Oddly, many of these suggested alternatives to restricting unregulated large-scale compounding would seemingly prohibit the operation of most 503B bulk compounding pharmacies by barring them from practicing drug compounding outside of what 503A pharmacies may do. Perhaps recognizing this dilemma, and spurred by unsafe compounding that was affecting patients across the country as well as the ill-advised nature of prohibiting outsourcing facilities altogether, the FDA created a distinct regulatory pathway for 503B bulk compounding pharmacies in 2013. The Compounding Quality Act of 2013, discussed below, explicitly recognizes outsourcing facilities and creates a separate regulatory pathway that permits greater FDA oversight of them, and removes the offending advertising prohibitions that were struck down in *Western States*.[141]

4. The Drug Quality & Security Act of 2013

In September 2012, an unprecedented outbreak of fungal meningitis at the New England Compounding Center (NECC) in Framingham, MA prompted Congress to grant the FDA greater authority to regulate and monitor compounded drugs at outsourcing facilities. The outbreak was linked to injectable steroid products used for pain management, including methylprednisolone acetate epidural injections for back pain, that NECC

137. *Id.*
138. *Id.* at 370–77.
139. *Id.* at 372 (quoting Petition for a Writ of Certiorari at 76a, *Thompson*, 535 U.S. 357 (No. 01-344)).
140. *Id.* at 376–77.
141. FDA, FDA'S HUMAN DRUG COMPOUNDING PROGRESS REPORT: THREE YEARS AFTER ENACTMENT OF THE DRUG QUALITY AND SECURITY ACT 7–8 (2017), https://www.fda.gov/media/102493/download [https://perma.cc/N8VE-5HT6].

compounded and distributed nationally.[142] The preparations were later found to be contaminated with microbes, predominantly a fungus called *Exserohilum rostratum*.[143] The contaminated steroids led to an outbreak of fungal meningitis that infected hundreds of people across twenty states with fungal meningitis, resulting in sixty-four deaths and 753 cases of infection.[144]

The outbreak prompted a widespread investigation by health authorities, and NECC was found to have knowingly engaged in unsanitary and unsafe practices, such as producing large quantities of drugs without proper quality control measures.[145] Several individuals associated with NECC faced legal consequences, including criminal charges, and NECC ultimately shut down its operations.[146] Despite distributing its products nationally, NECC was only subject to state oversight given to 503A compounding pharmacies. The FDA had actually investigated NECC three times in the years preceding the outbreak and found multiple sterility violations, but was unable to take any enforcement action or issue any penalties due to the FDA's limited authority to regulate compounding pharmacies.[147] The incident raised concerns about the lack of regulatory oversight in the compounding pharmacy industry and also led to increased scrutiny of compounding pharmacies and efforts to prevent such incidents in the future. As a result, Congress enacted the Drug Quality & Security Act (DQSA) with bipartisan support in 2013.[148]

Title I of the DQSA, the Compounding Quality Act (CQA), delineates outsourcing facilities (503B pharmacies) as a second type of compounding pharmacy subject to federal oversight.[149] Whereas 503A pharmacies can avoid the more burdensome regulations required of drug manufacturers under the FDCA if they qualify for the exemptions outlined in the FDCA,

142. *See Multistate Outbreak of Fungal Meningitis and Other Infections*, CTRS. FOR DISEASE CONTROL & PREVENTION (Oct. 30, 2015), https://www.cdc.gov/hai/outbreaks/meningitis.html [https://perma.cc/6VUV-PJ95].

143. *Id.*

144. *Id.*; *see also* Rachel M. Smith et al., *Fungal Infections Associated with Contaminated Methylprednisolone Injections*, 369 NEW ENG. J. MED. 1598 (2013); Marion Kainer et al., Ctrs. for Disease Control & Prevention, *Multistate Outbreak of Fungal Infection Associated with Injection of Methylprednisolone Acetate Solution from a Single Compounding Pharmacy — United States, 2012*, 61 MORBIDITY & MORTALITY WKLY. REP. 839 (2012).

145. Watson et al., *supra* note 57, at 199 (citing, inter alia, Ted Alcorn, *Meningitis Outbreak Reveals Gaps in US Drug Regulation*, 380 LANCET 1543 (2012)).

146. Press Release, U.S. Dep't of Just., 14 Indicted in Connection with New England Compounding Center and Nationwide Fungal Meningitis Outbreak (Dec. 17, 2014), https://www.justice.gov/opa/pr/14-indicted-connection-new-england-compounding-center-and-nationwide-fungal-meningitis [https://perma.cc/CHX3-HPCK].

147. Watson et al., *supra* note 57, at 199 (citing Besu F. Teshome, Kelly R. Reveles, Grace C. Lee, Laurajo Ryan & Christopher R. Frei, *How Gaps in Regulation of Compounding Pharmacy Set the Stage for a Multistate Fungal Meningitis Outbreak*, 54 J. AM. PHARMACISTS ASS'N. 441 (2014)).

148. Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013) (codified as amended in scattered sections of 21 U.S.C.).

149. *Id.* tit. 1, 127 Stat. 587, 587–98 (codified at 21 U.S.C. § 353b).

503B pharmacies can qualify for such exemptions if they opt into classification as an outsourcing facility by registering with the FDA,[150] reporting certain information about the drug products it compounds, paying an annual user fee,[151] and complying with Current Good Manufacturing Practice (CGMP) standards and reporting requirements.[152] Drugs compounded by an outsourcing facility that meets the requirements of Section 503B can qualify for exemptions from relevant sections of the FDCA; specifically, the requirements codified at 21 U.S.C. § 352(f)(1) (drug labeling), § 355 (approval of novel small-molecule drugs under NDAs or generic small-molecule drugs under ANDAs), and § 360eee-1 (concerning drug supply chain security requirements).[153] Outsourcing facilities may compound in bulk in advance of receiving a prescription, and may even distribute their products across state lines.[154]

Yet, since the CQA was enacted, few pharmacies have registered as 503B outsourcing facilities. As of 2014, the FDA anticipated fifty pharmacies to register per year,[155] but only eighty-three total had submitted registration information as of August 2024.[156] Some of these compounding pharmacies cited the cost of compliance with CGMP standards as a prohibitively expensive barrier to registering as an outsourcing facility.[157] In response, the FDA described its intent to incentivize more compounding pharmacies to register as 503B outsourcing facilities by applying CGMP requirements

150. FDA, REGISTRATION OF HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FD&C ACT: GUIDANCE FOR INDUSTRY (2014), https://www.fda.gov/media/87570/download [https://perma.cc/46TW-W56L].

151. *See* FDA, OMB Control No. 0910-0776, FEES FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTIONS 503B AND 744K OF THE FD&C ACT: GUIDANCE FOR INDUSTRY 2–5 (2020), https://www.fda.gov/industry/fda-user-fee-programs/human-drug-compounding-outsourcing-facility-fees [https://perma.cc/R9M7-MDVP].

152. *See* 21 U.S.C. § 353b (defining outsourcing facilities); 21 U.S.C. § 351(a)(2)(B) (requiring current good manufacturing practice for drugs); FDA, CURRENT GOOD MANUFACTURING PRACTICE—GUIDANCE FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FD&C ACT: GUIDANCE FOR INDUSTRY (2020), https://www.fda.gov/media/88905/download [https://perma.cc/PPA2-CPWW] (draft guidance).

153. 21 U.S.C. § 353b(a).

154. *See* 21 U.S.C. §§ 353b(d)(4)(C); FDA, CENTER FOR DRUG EVALUATION AND RESEARCH: OUTSOURCING FACILITY INFORMATION 2 (2017), https://www.fda.gov/media/107569/download [https://perma.cc/T849-293V]; Pinkerton & Pickar, *supra* note 73, at 218–20.

155. Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Guidance for Industry on Fees for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug, and Cosmetic Act, 79 Fed. Reg. 52014 (Sept. 2, 2014), https://www.govinfo.gov/content/pkg/FR-2014-09-02/pdf/2014-20719.pdf [https://perma.cc/HGY3-PHVF].

156. FDA, *Registered Outsourcing Facilities* (Aug. 30, 2024), https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities [https://perma.cc/5RWA-U8V7] (listing the facilities currently registered under Section 503B).

157. *Examining Implementation of the Compounding Quality Act: Hearing before the Subcomm. on Health of the H. Comm. on Energy and Com.*, 115th Cong. 23–24 (2018) (testimony of Scott Gottlieb, Comm'r, FDA) [hereinafter Gottlieb Hearing].

flexibly to facilitate small-batch compounding and avoid undue regulatory burdens.[158] As acknowledged by the FDA, this approach could assist the agency in more efficiently targeting its limited resources, but it could also increase the likelihood of compounders engaging in unsafe practices that elude regulators.[159] Although the FDA published draft guidance in 2018 describing a proposed approach to altering CGMP requirements, the FDA has yet to issue final guidance on this matter.[160]

The CQA also creates additional regulations for 503A pharmacies to prevent another national outbreak like the NECC outbreak by reducing the likelihood that contaminated drugs cross state lines. It permits a 503A pharmacy to distribute no more than 5% of its total prescriptions out of state unless the pharmacy's home state enters into a Memorandum of Understanding (MOU) with the FDA.[161] If a state enters into a MOU with the FDA, 503A pharmacies in that state may distribute a higher percentage of prescriptions (up to 50%) across state lines if the state's board of pharmacy agrees to identify, investigate, and report associated adverse events.[162] The MOU standardizes procedures for state boards of pharmacy to monitor and report adverse events or general concerns to the FDA and other states, but grants participating states significant discretion in conducting investigations, allowing participating states to retain primary responsibility for regulating 503A pharmacies in their state.[163] While the FDA has primary regulatory authority over 503B outsourcing facilities, states may also impose additional requirements.[164]

5. Other Authority to Regulate Compounding

The FDA also has authority to oversee the safety and quality of Active Pharmaceutical Ingredients (APIs) used as starting ingredients in compounded preparations.[165] Sections 503A and 503B set out additional requirements specifying when bulk drug substances may be used in compounding medicines. Under 503A, bulk drug substances used in

158. *Id.*

159. *Id.* at 25–26.

160. Scott Gottlieb, *2018 Compounding Policies Priorities Plan*, FDA (June 21, 2018), https://www.fda.gov/drugs/human-drug-compounding/2018-compounding-policy-priorities-plan [https://perma.cc/9PUV-GXC3]; FDA, *supra* note 152 (draft guidance).

161. 21 U.S.C. § 353a(b)(3)(B)(i)–(ii).

162. Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State Board of Pharmacy or Other Appropriate State Agency and the Food and Drug Administration; Availability, 85 Fed. Reg. 68076 (Oct. 27, 2020).

163. Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State Board of Pharmacy or Other Appropriate State Agency and the Food and Drug Administration, 85 Fed. Reg. 68074 (Oct. 27, 2020).

164. Watson, *supra* note 57, at 200.

165. AM. PHARMACISTS ASS'N, *supra* note 55.

compounding must (1) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, and the USP chapter on pharmacy compounding; (2) if a monograph does not exist, be components of drugs approved by the FDA; or (3) if a monograph does not exist and the bulk drug substances are not components of an approved drug, appear on a pre-determined list developed by the FDA (the 503A Bulks List).[166] Similarly, bulk drug substances used in 503B facilities must (1) appear on a list established by FDA identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (2) the drug compounded from such bulk drug substances appears on FDA's drug shortage list at the time of compounding, distribution and dispensing.[167]

Additionally, the Drug Enforcement Administration (DEA) restricts and tracks the distribution of any controlled substances used in the preparation of compounded medications, such as narcotics, amphetamines, and benzodiazepines. Amphetamine, which is the active ingredient of Adderall, is regulated as a Schedule II controlled substance by the DEA.[168] Thus, the DEA along with the FDA regulates the production of Adderall and caps the amount of amphetamine available to Adderall manufacturers in a given year.[169] "Authorized manufacturers apply to receive a portion of the total supply and can request more if necessary . . . ."[170] In a November 2023 letter to the American public, the DEA explained that the Adderall shortage was not likely caused by these restrictions: "[I]n 2022, manufacturers did not produce the full amount that these limits permitted them to make—resulting in a shortfall of 1 billion doses that could have been produced but were not made or shipped . . . ."[171] As a result, the DEA did not increase the quota for 2023, but maintains the authority to do so if necessary.[172] The letter also outlined several possible changes to promote transparency from drug manufacturers and to allow the DEA to receive better data on drug production and impending shortages, including requiring drug manufacturers to submit anticipated production timelines to the DEA in advance of receiving quota allotments, prioritizing manufacturers who have demonstrated that they are actually using restricted substances to make and

166. 21 U.S.C. § 353a(b)(1)(A). For the 503A Bulks List, see 21 C.F.R. § 216.23 (2024).

167. 21 U.S.C. § 353b(a)(2). For the 503B Bulks List, see *503B Bulk Drug Substances List*, FDA (May 16, 2024), https://www.fda.gov/drugs/human-drug-compounding/503b-bulk-drug-substances-list [https://perma.cc/BY67-SNJN].

168. 21 C.F.R. § 1308.12(d) (2023).

169. Jamie Ducharme, *Why the Adderall Shortage Has Lasted So Long*, TIME (Apr. 18, 2023, 11:39 AM), https://time.com/6272668/adderall-shortage-update/ [https://perma.cc/EH3S-NLKL].

170. *Id.*

171. Letter from Anne Milgram, *supra* note 41.

172. *Id.*

sell medications, and specifying whether a manufacturer's quota allotment is for domestic or export production to better manage domestic supply.[173]

Because compounded drugs are exempt from FDA labeling laws, there are few federal laws regulating the labeling of compounded drugs. The American Pharmacists Association advises patients to "ask the person administering a medication or the pharmacist dispensing a prescription whether it was prepared in a compounding pharmacy or manufactured by a drug company," and notes that a "widely accepted standard of practice is to label all compounded preparations with information stating the medication has been 'compounded.'"[174] "If a prescription calls for a compounded drug, patients can ask whether the compounding pharmacy is accredited"—and "[l]ists of accredited compounding pharmacies are organized by state on the Pharmacy Compounding Accreditation Board's (PCAB) website."[175] Thus, the little guidance on the advertising and labeling of compounded drugs that exists is either voluntary or places the burden of information gathering squarely on patients.

C. Redefining the Practice

Compounding biologics is more challenging than compounding small-molecule drugs. Biologics are highly sensitive to changes in the manufacturing process and can break down or aggregate if exposed to heat, light, or improper storage and handling conditions.[176] They are also susceptible to microbial contamination in a short period of time, and manufacturing processes must therefore be highly sterile and tightly controlled to produce safe and effective batches of these large, complex proteins.[177] However, in practice, biologics can and must be altered from their approved forms and uses to meet the specific needs of patients—for example, some biological products (such as dialysis units) may be prescribed off-label for children, and must be diluted or repackaged into smaller doses for them.[178]

Nevertheless, as of March 23, 2020, the FDA no longer considers biological products eligible for exemptions for compounded drugs under 503A and 503B.[179] The Biologics Price Competition and Innovation Act

173. *Id.*
174. AM. PHARMACISTS ASS'N, *supra* note 55.
175. *Id.*
176. FDA, MIXING, DILUTING, OR REPACKAGING BIOLOGICAL PRODUCTS OUTSIDE THE SCOPE OF AN APPROVED BIOLOGICS LICENSE APPLICATION: GUIDANCE FOR INDUSTRY 3–4 (2018).
177. *Id.*
178. *Id.* at 4.
179. *Notice to Compounders: Changes that Affect Compounding as of March 23, 2020*, FDA (Mar. 5, 2020), https://www.fda.gov/drugs/human-drug-compounding/notice-compounders-changes-affect-compounding-march-23-2020 [https://perma.cc/HH38-ZCGA].

(BPCIA) of 2009—which created separate approval pathways and regulatory schemes for biologic drugs—required that ten years after its enactment (on March 23, 2020), biologic products previously approved under the FDCA would be deemed approved under the PHSA instead.[180] Unlike the FDCA, the PHSA contains no provisions similar to Sections 503A or 503B. After this change in the law, a pharmacy compounding and distributing products deemed biologics in interstate commerce would be in violation of the PHSA[181] and subject to the enforcement actions outlined in the Act.[182]

In further guidance on the topic, the FDA detailed specific conditions under which the agency does not intend to take action against pharmacies that are using FDA-approved products as starting ingredients, with minor changes such as mixing, diluting, or repackaging in ways that deviate from the approved label of the original product; but the FDA will not permit compounding pharmacies to synthesize biologics from scratch with bulk drug ingredients not approved by the FDA.[183]

Specifically, in addition to several other conditions, the FDA will not take enforcement action where a biologic is (1) mixed, diluted, or repackaged in a state-licensed pharmacy, federal facility, or outsourcing facility; (2) by or under the direct supervision of a licensed pharmacist; (3) in compliance with USP 797 and CGMP standards; (4) not sold or transferred by an entity other than the one that mixed, diluted, or repackaged the product (no intermediaries); and (5) meets all applicable state requirements, and (if not done by an outsourcing facility) distributed only after receipt of a valid prescription for an individual patient, or, if done by an outsourcing facility, complies with additional stringent requirements.[184]

In February 2020, the FDA also updated its definition of a biologic to specify that "proteins" are greater than forty amino acids in size.[185] This includes insulin, a drug made up of fifty-one amino acids that has been used

180. *Id.*; *see also* Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, sec. 7002(e), 124 Stat. 804, 817 (2010).

181. 42 U.S.C. § 262(a).

182. 42 U.S.C. § 262(f).

183. FDA, *supra* note 176, at 1 nn.2–3 (defining "mixing" as "combining an FDA-licensed biological product with one or more ingredients," and defining "repackaging" as "taking a licensed biological product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulating the product").

184. *Id.* at 7–13. For the full list of conditions, see *id.* at 7–13. For release testing requirements for biological products mixed, diluted, or repackaged by an outsourcing facility, see *id.* at 23–24.

185. *Definition of the Term "Biological Product" Final Regulatory Impact Analysis*, FDA (Feb. 20, 2020), https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/definition-term-biological-product-final-regulatory-impact-analysis [https://perma.cc/PG99-8YZU] ("Under this final rule, the term protein means any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size."); *see also Definition of the Term "Biological Product"*, 85 Fed. Reg. 10057 (Feb. 21, 2020) (codified at 21 C.F.R. § 600.3(h)).

to treat diabetes since the 1920s—even before the 1938 FDCA was passed—and approved by the FDA since 1941.[186] "Peptides," on the other hand, are molecules of forty amino acids or less in size,[187] such as Ozempic, Wegovy, and Mounjaro. However, pharmacies seeking to compound peptides must comply with the other requirements of Sections 503A or 503B.

Since hormones are fairly large proteins that exceed forty amino acids, they are considered biologics. However, compounded hormones largely fall under the exceptions outlined in the FDA Guidance on Mixing, Diluting, and Repackaging; in other words, the FDA does not intend to take enforcement action against those pharmacies that are not compounding hormones from unapproved bulk drug substances. Nevertheless, the FDA is currently considering placing several hormones used in Compounded Bioidentical Hormone Therapy (cBHT) on a "difficult to compound list," including estradiol, estradiol cypionate, estrone, estriol, progesterone, testosterone, testosterone cypionate, and testosterone propionate.[188]

One source of concern about the safety of creating compounded versions of the GLP-1 agonists is the inconsistent use of pharmaceutical-grade, rather than research-grade ingredients.[189] Research-grade ingredients are not subject to the same strict manufacturing practices as pharmaceutical-grade APIs.[190] Recently, some compounding pharmacies have been using semaglutide sodium and semaglutide acetate, research-grade salt forms of semaglutide.[191] While semaglutide is the active ingredient used in Ozempic and Wegovy, semaglutide salts are not used in any FDA-approved drug and

186. *See* FDA, *supra* note 185; *100 Years of Insulin*, FDA (June 8, 2022), https://www.fda.gov/about-fda/fda-history-exhibits/100-years-insulin [https://perma.cc/C6ZY-W7K9].

187. 21 C.F.R. 600.3(h)(6) (2023).

188. Martha M. Rumore, *Updates on 503A Compounding: The Impact of Drug Shortages*, PHARMACY TIMES (Apr. 12, 2023), https://www.pharmacytimes.com/view/updates-on-503a-compounding-the-impact-of-drug-shortages [https://perma.cc/4VH7-XMLR]. Sections 503A(b)(3)(A) and 503B(a)(6) state that exempted compounded drugs must not be difficult to compound and require the FDA to develop a list of difficult to compound drugs through notice and comment rulemaking. Jane A. Axelrad, Principal, Axelrad Sols. LLC, Understanding the List of Difficult to Compound Drug Products Presentation to the National Academy of Sciences, Engineering, and Medicine Committee re Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (June 27, 2019). FDA developed six criteria it proposes to use to develop this list: (1) complexity of the formulation; (2) complexity of the drug delivery mechanism; (3) complexity of the dosage form; (4) complexity of achieving bioavailability; (5) complexity of the compounding process; and (6) complexity of the physicochemical or analytical testing. *Id.* As a result, FDA nominated several of the above-mentioned hormonal products for this list, and it is actively working on a proposed rule to crystallize the evaluation criteria and the drugs to be added to the list. *Id.*

189. *Compounding Peptides: What Prescribers Should Know*, VLS PHARMACY & NEW DRUG LOFT (Mar. 24, 2023), https://newdrugloft.com/compounding-peptides-what-prescribers-should-know/ [https://perma.cc/NMT8-UFP5].

190. *Id.*

191. *Id.*

have not been shown to be safe and effective.[192] After receiving adverse event reports from patients who used compounded semaglutide, in April and October of 2023, the FDA sent letters to the National Association of Boards of Pharmacy and the Federation of State Medical Boards expressing the agency's concerns with the use of salt forms in compounded products.[193]

The FDA remains active and involved in providing training for compounding facilities, such as by publishing annual reports on the state of the outsourcing facility industry and via the Compounding Quality Center of Excellence, which provides training on compounding regulation and CGMP for healthcare professionals.[194] The FDA also actively monitors and enforces safety concerns against compounding pharmacies. Between 2013 and 2018, the FDA issued more than 180 warning letters to compounding pharmacies, resulting in approximately 140 recalls.[195] For example, in 2013, twenty-six patients experienced skin abscesses and other adverse events after receiving injections of compounded methylprednisolone acetate distributed to healthcare facilities in seventeen states.[196] The FDA subsequently identified insanitary conditions at the facility and confirmed bacterial contamination in the drug products.[197] Also in 2013, "a compounder recalled all [of its] purportedly sterile drugs" and "ceased sterile operations after [fifteen] patients developed bacterial bloodstream infections, and two patients died" after receiving an infusion of compounded calcium gluconate.[198] The FDA similarly identified insanitary conditions at the facility and confirmed bacterial contamination in the compounded injection drug product.[199] "In 2016, FDA alerted health care

192. *Medication Containing Semaglutide Marketed for Type 2 Diabetes or Weight Loss*, FDA (Jan. 10, 2024), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss [https://perma.cc/7M6R-7SCV].

193. Letter from F. Gail Bormel, Dir., CDER Off. of Compounding Quality and Compliance, to Lemrey (Al) Carter, Exec. Dir., Nat'l Ass'n Bds. of Pharmacy (Apr. 27, 2023), https://www.fda.gov/media/168390/download [https://perma.cc/2NLP-C2MD]; Letter from F. Gail Bormel, Dir., CDER Off. of Compounding Quality and Compliance, to Lemrey "Al" Carter, Exec. Dir., Nat'l Ass'n of Bds. of Pharmacy (Oct. 10, 2023), https://www.fda.gov/media/173456/download [https://perma.cc/M6NJ-WFMD]; Letter from F. Gail Bormel, Dir., CDER Off. of Compounding Quality and Compliance, to Humayun J. Chaudhry, President & Chief Exec. Off., Fed'n of State Med. Bds. (Oct. 10, 2023), https://www.fda.gov/media/173486/download [https://perma.cc/Q9QB-9FCE].

194. *Compounding Quality Center of Excellence*, FDA (June 13, 2024), https://www.fda.gov/drugs/human-drug-compounding/compounding-quality-center-excellence [https://perma.cc/6NFC-ZEML]. For a list of the annual reports published by the FDA Compounding Quality Center of Excellence, see *Compounding Outsourcing Facilities Annual Study*, FDA (Mar. 6, 2024), https://www.fda.gov/drugs/human-drug-compounding/compounding-outsourcing-facilities-annual-study [https://perma.cc/8RDB-D83Q].

195. Watson et al., *supra* note 57, at 201.

196. FDA, *supra* note 141, at 13.

197. *Id.*

198. *Id.*

199. *Id.*

professionals of a voluntary recall of a compounded morphine sulfate injectable drug product after laboratory results showed the product was super-potent by 2,460 percent" and reported awareness of "serious adverse events in three infants associated with the use of the recalled [product.]"[200]

As a result of these adverse events, healthcare professionals have understandably expressed skepticism about the quality and safety of drugs sold by compounding pharmacies.[201] Compounded bioidentical hormone therapy (cBHT), for instance, has recently been highly controversial with some experts drawing increased attention to its risks.[202] Bioidentical hormone therapy (BHT) is a type of hormone replacement therapy that involves the administration of lab-made hormones that are chemically identical to endogenous human hormones.[203] FDA-approved BHT products on the market include Estrace (oral estradiol), Climara (estradiol patch), Depot-estradiol (estradiol cypionate injection), and Prometrium (oral progesterone).[204] Compounded bioidentical hormone therapy (cBHT) is BHT made by compounding pharmacies to meet the needs of an individual patient for the same reasons patients generally rely on compounded drugs—patients may be allergic to one or more ingredients present in the FDA-approved BHT products, or may need a specific combination of hormones in non-standard doses or routes of administration.[205]

In July 2020, the National Academies of Sciences, Engineering, and Medicine (NASEM), a highly respected national organization of scientists and medical professionals, published a report criticizing the proliferation of compounded bioidentical hormone therapy and questioning its safety and efficacy.[206] In particular, NASEM noted that these therapies are often

200. *Id.* at 12–13.

201. *See, e.g.*, Jennifer Gudeman, Michael Jozwiakowski, John Chollet & Michael Randell, *Potential Risks of Pharmacy Compounding*, 13 DRUGS R&D 1 (2013); Pinkerton & Pickar, *supra* note 73.

202. *See, e.g.*, Louise Newson & Janice Rymer, *The Dangers of Compounded Bioidentical Hormone Replacement Therapy*, 69 BRIT. J. GEN. PRAC. 540 (2019); Bryce Harvey & Mikayla Spangler, *Compounded Bioidentical Hormone Therapy*, U.S. PHARMACISTS, Sept. 2020, at 27.

203. Kim Krieger, *Neither Natural nor Safe: Compounded Bioidentical Hormones Need Better Evidence*, UCONN TODAY (July 8, 2020), https://today.uconn.edu/2020/07/neither-natural-safe-compounded-bioidentical-hormones-need-better-evidence/[https://perma.cc/M677-N6EQ].

204. Alyssa Billingsley, *Bioidentical Hormone Replacement Therapy for Menopause: Safety, Uses, and Cost*, GOODRX HEALTH (May 27, 2022), https://www.goodrx.com/conditions/menopause/bioidentical-hormone-therapy [https://perma.cc/6XZU-MUTK]; JoAnn V. Pinkerton, *The Truth about Bioidentical Hormone Therapy*, 37 FEMALE PATIENT 16, 17 (2012), https://www.menopause.org/docs/professional/tfpbio_0812.pdf [https://perma.cc/82K9-S3DW].

205. Pinkerton, *supra* note 204, at 16.

206. NAT'L ACADS. OF SCIS., ENG'G & MED., THE CLINICAL UTILITY OF COMPOUNDED BIOIDENTICAL HORMONE THERAPY: A REVIEW OF SAFETY, EFFECTIVENESS, AND USE (Donald R. Mattison, Ruth M. Parker & Leigh Miles Jackson eds., 2020) [hereinafter NASEM REPORT]. The report was commissioned by the FDA in September 2018. *National Academies of Science, Engineering, and Medicine (NASEM) Study on the Clinical Utility of Treating Patients with Compounded "Bioidentical"*

marketed and promoted as "natural" and as being more safe and effective than FDA-approved drugs from synthetic sources.[207] While the report did not conclude that cBHTs are inherently unsafe, NASEM determined there was a lack of rigorous evidence from properly designed and controlled clinical studies to support claims that cBHT was superior to FDA-approved BHTs, with most information coming from anecdotal claims, patient reports, prescriber testimonies, and other low-quality data.[208] Given the lack of high-quality clinical evidence and minimal oversight of cBHT, NASEM concluded that their widespread use poses a public health concern.[209]

The NASEM report acknowledges that compounding can fill gaps in cases of shortages and discontinuations of FDA-approved drugs, but notes:

> FDA has reviewed and approved the sale of dozens of different BHT products, offering a selection of different doses and forms to address the diverse therapeutic needs of patient populations. Given the availability of FDA-approved bioidentical hormone products, *the question remains, why do certain patients and providers use cBHT in lieu of available FDA-approved drug products?*[210]

Yet, patients in the United States and across the globe have faced a surge of chronic shortages of injectable estrogen since 2022.[211] FDA approval of a drug is not sufficient to assure a constant supply of the drug and it does not immunize a drug from vulnerability to shortages. As discussed above in Part I, economic factors undermine incentives for generic drug manufacturers to make sufficient quantities of critical drugs that are off-patent. Additionally, as discussed in Section II.C., the injectable estrogen shortage leaves trans and non-binary patients seeking gender-affirming care with no choice but to rely on compounding pharmacies to provide them with estrogen.

The NASEM report acknowledges an important socioeconomic inequity that specifically affects transgender and non-binary patients—lack of

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Hormone Therapy, FDA, (July 2, 2019), https://www.fda.gov/drugs/human-drug-compounding/national-academies-science-engineering-and-medicine-nasem-study-clinical-utility-treating-patients [https://perma.cc/YF7P-RCHV].

207. NASEM REPORT, *supra* note 206, at 8.

208. *Id.* at 4–6.

209. *Id.* at 17–18.

210. *Id.* at 176 (citation omitted); *see also id.* at 30.

211. *See* Sarah Prager, *Ongoing Shortages of Injectable Estrogen and Testosterone Are Harming Trans People*, EVERYDAY HEALTH (Apr. 24, 2023), https://www.everydayhealth.com/public-health/shortages-of-injectable-estrogen-and-testosterone-are-harming-trans-people/ [https://perma.cc/G8UL-UUBD] (noting that Pfizer, the sole manufacturer of injectable estrogen in the United States, "has reported chronic shortages due to manufacturing delays since early 2022"). As of July 2024, the FDA has since removed injectable estrogen from its shortage list. *See FDA Drug Shortages*: *Current and Resolved Drug Shortages and Discontinuations Reported to FDA*, FDA, https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm [https://perma.cc/J2BP-6W7Q].

insurance coverage for drugs prescribed off-label.[212] Off-label use is the use of an FDA-approved drug to treat a condition other than the condition(s) for which it has been approved, for administration by a different route than the one approved (e.g., taking an FDA-approved tablet as an oral solution), or by a dosage other than the approved one(s).[213] Many insurance companies refuse to provide coverage for drugs prescribed off-label, on the grounds that such use is "experimental" or "investigational."[214] The report notes that, because there are currently no treatments with FDA-approved indications for gender-affirming care or gender dysphoria, it is not uncommon for patients diagnosed with gender dysphoria to be denied coverage for hormone therapy and other treatments for gender-affirming care, so healthcare providers often prescribe cBHT to this patient population.[215] José Manautou, a UConn Professor of Pharmacology who serves on the NASEM Committee that authored the report, noted that "[gender-affirming care] was not what the FDA asked [NASEM] to concentrate on, but [NASEM] thought it was important to touch on. . . . Compounded cBHT medications are marketed as a lower cost alternative to conventional FDA-approved therapy. However, the committee was not able to make definite a conclusion on cost, since no studies have specifically examined the cost of cBHT therapy for transitioning genders."[216]

As the FDA considers whether and how to update its regulations on cBHT in light of the NASEM Report (particularly its recommendations to restrict the use and availability of cBHT[217]), it is critical that the FDA consider the importance of the availability of cBHT to transgender and non-binary patients, the primary patient population that will be adversely affected by restrictions on cBHT. The report sets forth several other recommendations that would not necessarily restrict access to cBHT for gender-affirming care, including additional federal and state-level oversight of cBHT, and strengthening and expanding data on the safety, effectiveness, and use of cBHT.[218] Because the NASEM report did not conclude that cBHT is inherently unsafe, the FDA may also choose to focus on compounders

212. NASEM REPORT, *supra* note 206, at 195.

213. *Understanding Unapproved Use of Approved Drugs "Off Label,"* FDA (Feb. 5, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label [https://perma.cc/LKP8-LRK5].

214. *Off-Label Drug Use*, AM. CANCER SOC'Y, https://www.cancer.org/cancer/managing-cancer/treatment-types/off-label-drug-use.html (Mar. 17, 2015) [https://perma.cc/CWQ5-CM2M].

215. NASEM REPORT, *supra* note 206, at 195; *see also* Ivette Gomez et al., *Update on Medicaid Coverage of Gender-Affirming Health Services*, KFF (Oct. 11, 2022), https://www.kff.org/womens-health-policy/issue-brief/update-on-medicaid-coverage-of-gender-affirming-health-services/ [https://perma.cc/7DR8-C7MB].

216. Krieger, *supra* note 203.

217. NASEM REPORT, *supra* note 206, at 222–23.

218. *Id.* at 224–28.

that are misbranding (i.e., making false or misleading claims about) cBHT with statements that it is superior to FDA-approved BHT.[219]

D. Risking the Practice

The pharmaceutical industry has occasionally voiced its desire for greater FDA oversight of drug compounding and enforcement pursuant to the DQSA. As the FDA was implementing the DQSA, drug manufacturers brought lawsuits against the FDA challenging the guidance that the agency issued on bulk compounding for 503B outsourcing facilities.[220] The Pharmaceutical Research and Manufacturers of America (PhRMA), a trade organization that represents the interests of the pharmaceutical industry in the United States, is well-known for aggressively lobbying against healthcare reform efforts that cut into the pharmaceutical industry's profits,[221] and its views on drug compounding—though hardly controversial relative to its other lobbying efforts—are not surprising. A 2014 PhRMA blog post announces a joint letter between PhRMA and other healthcare organizations urging the FDA's robust enforcement of the then-newly enacted DQSA.[222] Similarly, in 2017, PhRMA and other organizations sent letters to Congress urging support for FDA oversight of drug compounding and enforcement of the DQSA.[223] While these letters rightly emphasize the need for the FDA to inspect compounding facilities and the importance of protecting patients from nonsterile manufacturing practices, it is not hard to guess why PhRMA and others in the pharmaceutical industry would oppose large-scale compounding of prescription drugs that would cut into the profits of the traditional pharmaceutical industry.

For the most part, though, the mainstream pharmaceutical industry has remained relatively quiet on the subject of drug compounding, likely due to

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219. *Id.* at 54–55; *see also* 21 U.S.C. § 352 (governing misbranded drugs).

220. *See, e.g.*, Complaint, Par Sterile Prods., LLC v. Hargan, No. 17-cv-02221 (D.D.C. dismissed Sept. 27, 2019); Athenex Inc. v. Azar, 397 F. Supp. 3d 56 (D.D.C. 2019).

221. *See, e.g.*, Joyce Frieden, *PhRMA Warns of Dire Consequences if Medicare Allowed to Negotiate Drug Prices*, MEDPAGE TODAY (Sept. 8, 2021), https://www.medpagetoday.com/publichealthpolicy/generalprofessionalissues/94411 [https://perma.cc/2RGH-N8LT]; Jay Hancock, *The Stealth Campaign to Kill Off Obamacare*, N.Y. TIMES (July 27, 2018), https://www.nytimes.com/2018/07/27/business/the-stealth-campaign-to-kill-off-obamacare.html [https://perma.cc/6X39-YQA5]; Jay Hancock, *In Election Year, Drug Industry Spent Big to Temper Talk About High Drug Prices*, NPR (Dec. 18, 2017, 7:00 AM), https://www.npr.org/sections/health-shots/2017/12/18/571206699/in-election-year-drug-industry-spent-big-to-temper-talk-about-high-drug-prices [https://perma.cc/Q7MZ-L4FH].

222. Mark Grayson, *Patient Safety Demands that Drug Compounders Comply with Law*, PHRMA (Dec. 11, 2014), https://phrma.org/blog/patient-safety-demands-that-drug-compounders-comply-with-law [https://perma.cc/YE9C-RH4P].

223. Zachary Brennan, *BIO, PhRMA and Others Urge Further FDA Clarity on Drug Compounding*, REGUL. AFFS. PROS. SOC'Y: REGUL. FOCUS (June 14, 2017), https://www.raps.org/News-and-Articles/News-Articles/2017/6/BIO-PhRMA-and-Others-Urge-Further-FDA-Clarity-on [https://perma.cc/89RN-4XBC].

the fact that most compounded medicines are generic and therefore no longer subject to the exclusionary intellectual property tools that protect large profit margins on drugs—in other words, most drugs that are compounded are no longer protected by patents or sold under registered trademark names.

But the explosive popularity of the new GLP-1 agonists has challenged this status quo. Although Ozempic and Wegovy are still protected by patents,[224] both drugs are currently in shortage—a shortage that compounding pharmacies are attempting to fill. In an effort to combat these compounding practices, Novo Nordisk, the manufacturer of both drugs, not only filed multiple suits alleging trademark infringement and unfair competition, but also asserted that such compounded drugs were "adulterated" and "misbranded."[225] Although adulteration and misbranding are regulated by the FDA,[226] and there has never been a right to a private cause of action to enforce the FDCA,[227] the recent wave of litigation against compounding pharmacies relies on novel arguments that misbranding and adulteration of brand-name drugs amounts to unfair competition and trademark infringement. Many of these lawsuits also allege that compounding pharmacies violate state unfair trade practices by selling compounded versions of Ozempic and Wegovy that are not FDA approved—all while Novo Nordisk and Eli Lilly themselves enjoy the ability to sell these drugs for off-label, unapproved uses, such as to treat overweight or obesity. Part III explores recent litigation and threats of litigation (via cease-and-desist letters) for patent infringement against compounding pharmacies.

II. LITIGATING DRUG COMPOUNDING

Drugs are primarily protected by three forms of intellectual property: patents, trademarks, and trade secrets. These forms of IP protection collectively help pharmaceutical companies protect their monopolies on novel drugs, and as a matter of public policy, are intended to help them

224. FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at ADA 375–77 (44th ed. 2024) (listing patents on Ozempic); *id.* at ADA 377 (listing patents on Wegovy); *see also id.* at ADA410 (listing patents on Mounjaro); *id.* at ADA 411 (listing patents on Zepbound).

225. Press Release, Novo Nordisk, Novo Nordisk Takes Additional Legal Actions to Help Protect US Patients from Potentially Unsafe and Ineffective Compounded Drugs Claiming to Contain Semaglutide that Are Not FDA Approved (Nov. 29, 2023, 5:29 PM), https://www.novonordisk-us.com/media/news-archive/news-details.html?id=166352 [https://perma.cc/X8BM-AWX9].

226. *See* 21 U.S.C. § 351 (defining when a drug shall be deemed adulterated); 21 U.S.C. § 352 (defining when a drug shall be deemed misbranded).

227. 21 U.S.C. § 337 (requiring that all proceedings for the enforcement of the FDCA shall be by and in the name of the United States, with a narrow exception that permits states to enforce certain FDCA provisions related to standards for food and misbranded food that is located within the state).

recoup the costs involved in the research, development, and regulatory approval of novel drugs. Pharmaceutical companies may also protect drugs as trade secrets. Trade secret law, though a critical method for pharmaceutical companies to protect certain aspects of their drug manufacturing practices and processes, is beyond the scope of this article.[228] Trade secrets, unlike patents and trademarks, are not generally known outside of the company that holds them.[229] Thus, compounding pharmacies cannot be liable for trade secret misappropriation in the absence of a specific act of misappropriation by improper means.[230] This section will thus review basic doctrines of patent and trademark law as they relate to the pharmaceutical industry and discuss the liability of compounding pharmacies for patent and trademark infringement.

A. Patent Liability for Compounders

Patents offer the holder the exclusive right to make, use, and sell the subject of an invention, usually for a period of twenty years from the filing date[231]—although the actual term of the patent may be shorter due to delay while the Patent Office reviews the patent application or while the FDA reviews and approves the drug application, or longer due to time added by Patent Term Adjustment[232] (which seeks to rectify Patent Office delay) or Patent Term Extension[233] (which seeks to compensate for FDA delay). Patents on drugs may be filed on a novel or improved composition of matter (directed to the chemical composition of a new drug or a new form of an

228. This includes proprietary manufacturing processes, specific formulations, and other confidential information that provides a competitive advantage to manufacturers. Actions for trade secret misappropriation may be brought under state law or federal law. The elements of a federal claim for trade secret misappropriation are outlined in the Defend Trade Secrets Act of 2016, 18 U.S.C. § 1836(b). For a detailed discussion of the use of trade secrets in manufacturing biologics, see Robin Feldman, *Trade Secrets in Biologic Medicine: The Boundary with Patents*, 24 COLUM. SCI. & TECH. L. REV. 1 (2022), and W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023 (2016).

229. 18 U.S.C. § 1839(3) (defining "trade secret," and stating that a valid trade secret exists if "(A) the owner has taken reasonable measures to keep such information secret; and (B) the information derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable through proper means by, another person who can obtain economic value from the disclosure or use of the information").

230. 18 U.S.C. § 1839(6) (defining "improper means" as including "theft, bribery, misrepresentation, breach or inducement of a breach of a duty to maintain secrecy, or espionage through electronic or other means," and excluding "reverse engineering, independent derivation, or other lawful means of acquisition"). These improper means would thus need to result in the unconsented disclosure of a trade secret, such as a former employee of a drug manufacturer informing a compounding pharmacy of trade secret knowledge in violation of a nondisclosure or noncompete agreement.

231. 35 U.S.C. § 271(a) (describing the exclusive rights of patent owners); 35 U.S.C. § 154(a)(2) (defining the term of a patent as twenty years from filing).

232. 35 U.S.C. § 154(b).

233. 35 U.S.C. § 156.

existing drug), method-of-use (directed to specific methods or processes of using a drug for treating a particular condition), formulation (directed to a specific formulation or delivery system of a drug), or method of manufacturing (directed to a process of manufacturing a drug). Patents are intended to operate as a quid pro quo—in exchange for the right to exclude others from making, using, or selling an invention for a limited period of time, patentees must fully disclose the invention so that the public may benefit from and improve the invention upon expiration of the patent.[234]

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, helps facilitate the entry of generic drugs into the market while protecting the patent rights of innovator drug manufacturers.[235] The Act established the Abbreviated New Drug Application (ANDA) process, which, as discussed above in Section II.A.ii, allows generic drug manufacturers to expedite the approval of their products by demonstrating bioequivalence to a reference drug that is already FDA-approved.[236] Although FDA law and patent law typically occupy separate spheres, Hatch-Waxman litigation creates an instance where FDA and patent doctrine overlap.

As part of the generic approval process, generic drug manufacturers must submit a notice known as a "Paragraph IV certification." During the New Drug Application (NDA) process, an innovator company submits a comprehensive list of patents to the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book")[237]—the patents that cover the drug that is the subject of the NDA.[238] In a Paragraph IV certification, the generic company notifies the FDA and the innovator company of its intent to introduce a generic drug into the market along with its opinion that, to the best of its knowledge, any patents listed in the Orange Book entry for the reference drug are expired, invalid, or will not be

234. *See, e.g.*, Universal Oil Prods. Co. v. Globe Oil & Refin. Co., 322 U.S. 471, 484 (1944) ("[T]he *quid pro quo* is disclosure of a process or device in sufficient detail to enable one skilled in the art to practice the invention once the period of the monopoly has expired. . . ."); Amgen Inc. v. Sanofi, 598 U.S. 594, 604 (2023) (noting the "*quid-pro-quo* premise of patent law"); Brenner v. Manson, 383 U.S. 519, 534 (1966) ("The basic *quid pro quo* . . . for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility."); J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc., 534 U.S. 124, 142 (2001) ("The disclosure required by the Patent Act is 'the *quid pro quo* of the right to exclude.'" (quoting Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 484 (1974))).

235. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of the U.S. Code) (Hatch-Waxman Amendments).

236. *Id.* sec. 101, 98 Stat. 1585, 1585–92 (codified as amended at 21 U.S.C. § 355). As discussed above in Section II.a.ii., generic drugs must be identical to the branded drug in terms of efficacy, safety, usage, route of drug administration, pharmacokinetics, and pharmacodynamics.

237. FDA, *supra* note 224.

238. 21 U.S.C. § 355 (b)(1)(A)(viii).

infringed by the generic product.[239] This certification constitutes an artificial[240] act of infringement that triggers a forty-five-day deadline for the innovator company to initiate suit for patent infringement against the generic company, which in turn triggers a thirty-month stay of regulatory approval during which time the FDA cannot approve the generic drug or any other proposed generic (unless the patent suit resolves before the thirty-month period).[241]

The Hatch-Waxman Act aims to strike a balance between incentivizing new drug development and encouraging rapid generic market entry by offering additional market exclusivities to both innovator and generic companies.[242] The first generic applicant to submit a substantially complete ANDA and file a Paragraph IV certification challenging one or more listed patents is eligible to win a 180-day period of exclusivity upon entering the market, during which time the FDA cannot approve any other generic drug.[243] The Hatch-Waxman Act also incentivizes innovator companies by granting them data exclusivities, which prevent generic competitors from relying on an innovator company's clinical trial data for a certain period of time,[244] and market exclusivities that prevent FDA from approving generic versions of a drug for a period of time, such as exclusivities for new chemical entities and new clinical investigations.[245]

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239. 21 U.S.C. § 355(b)(2)(A) (stating that an ANDA applicant must certify, with respect to each of the patents listed in the Orange Book entry for the RLD, "(i) that such patent information has not been filed, (ii) that such patent has expired, (iii) of the date on which such patent will expire, or (iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted").

240. A Paragraph IV certification is considered an artificial act of infringement, because no actual infringing use, sale, or offer for sale has occurred yet. 35 U.S.C. § 271(e)(2); *see* Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 678 (1990) (describing § 271(e)(2) as creating a "highly artificial" act of infringement). Typically, patent owners and their licensees only have standing to sue for patent infringement after an act of infringement has occurred. 35 U.S.C. §§ 271, 281.

241. 21 U.S.C. § 355(c)(3)(C), (j)(5)(B)(iii).

242. *Small Business Assistance | 180-Day Generic Drug Exclusivity*, FDA (Oct. 26, 2023), https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-180-day-generic-drug-exclusivity [https://perma.cc/DJG7-TDMR].

243. 21 U.S.C. § 355(j)(5)(B)(iv). For more information about the 180-day exclusivity period for generic companies, see *Guidance for Industry: 180-Day Exclusivity: Questions and Answers*, FDA (Jan. 2017), https://www.fda.gov/media/102650/download [https://perma.cc/3R3T-39KW].

244. *See generally Frequently Asked Questions on Patents and Exclusivity*, FDA (Feb. 5, 2020), https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity [https://perma.cc/V7RF-KGVX].

245. *See* 21 C.F.R. § 314.108 (2023) (discussing new chemical entity exclusivity, which grants four to five years of exclusivity to drugs comprised of a new active moiety, and new clinical investigation exclusivity, which grants three years of exclusivity to sponsors of certain new clinical investigations); *see also* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa–360ff-1); 21 C.F.R. §§ 316.20, .31, .34 (2023) (discussing orphan drug exclusivities, generally seven years from FDA approval, granted to drugs approved to treat conditions affecting patient populations of fewer than 200,000 in the United States); 21 U.S.C. § 355a (discussing pediatric exclusivities, which add six months to existing patent term and regulatory exclusivities).

But where do compounded drugs fit into the regulatory framework? There is no equivalent process for compounders to challenge Orange Book patents, and no section of the FDCA, Hatch-Waxman Act, or any other FDA statute discusses whether or how drug compounders are liable for patent infringement. Nor do any FDA regulations or guidance documents discuss whether compounding that is permissible under FDA regulations is similarly permissible under patent law. Similarly, there is no provision in the Patent Act that creates exceptions for drug compounding. This is not necessarily surprising, as generic, off-patent drugs are most prone to shortages.[246] The section below discusses when compounding pharmacies might be liable for patent infringement.

There are no examples of patent infringement lawsuits brought by drug manufacturers against compounding pharmacies that reached trial or substantive judgments by courts. There are one or more potential reasons for this. First, if most prescriptions for compounded drugs are for drugs that are generic and off-patent, it is unlikely for 503A or 503B pharmacies to compound drugs that are covered by unexpired patents. Second, because compounding pharmacies know they are less capable of withstanding the costs and threat of litigation,[247] they may be careful not to offer to compound patented drugs. Third, since 503A compounding pharmacies serve small, local groups of patients and 503B facilities can directly serve hospitals, it may also be the case that drug companies cannot easily identify compounding pharmacies that are infringing patents in the absence of pharmacies advertising their compounding services—particularly with online advertising. Fourth, pharmacies that receive cease-and-desist letters from drug manufacturers may choose not to persist. As compounding is far less profitable than other products and services offered by pharmacies, a pharmacy that offers compounding services but does not "specialize" in compounding has no incentive to continue compounding in the face of a cease-and-desist letter from a large pharmaceutical company threatening litigation. Finally, any pharmacies that choose to continue compounding in spite of receiving cease-and-desist letters may choose to settle rather than proceed with litigation. Further research, such as a survey asking compounding pharmacies across the country whether they have received cease-and-desist letters from pharmaceutical companies on the basis of alleged patent infringement may be instrumental in identifying the scope and prevalence of the issue.

246. *See supra* Part I.

247. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 369–70 (2002) ("Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible . . . .").

The few cases where drug manufacturers sued compounding pharmacies ended up settling or resulting in default judgment. In 2004 and 2005, DUSA Pharmaceuticals of Massachusetts sued The Cosmetic Pharmacy of Tucson, AZ, and the New England Compounding Center (NECC) in Framingham, MA, alleging infringement of its patents on aminolevulinic acid, which DUSA sold as Levulan.[248] The Cosmetic Pharmacy presented no defense, so a default judgment was entered in the court in DUSA's favor.[249] The lawsuit against NECC settled a little over a year after it was filed.[250] The terms of the settlement agreement between DUSA and NECC were not publicly disclosed, and—due to the ubiquity of confidentiality clauses in settlement agreements—it is unlikely that any settlement resulting from litigation between drug manufacturers and compounding pharmacies would be available to the public.

Another rare example involved a veterinary medication for horses. In 2009, Bayer Healthcare sued New Jersey-based compounding pharmacy Wedgewood Village Pharmacy for patent infringement, accusing Wedgewood of infringing on a patent protecting the Bayer product Marquis (ponazuril), an oral paste-style medication approved by the FDA to treat equine protozoal myeloencephalitis (EPM), a parasitic disease affecting horses.[251] Wedgewood had been selling compounded preparations of toltrazuril, which is closely related, but not identical to ponazuril.[252] Ponazuril is a derivative of toltrazuril that is sometimes referred to as toltrazuril-sulfone.[253] Not surprisingly, this case also settled within the year it was filed.[254]

Because no court has ever been tasked with deciding whether compounding drugs during a recognized shortage constitutes patent infringement, there is some uncertainty about liability for compounding a patented drug in shortage. Alliance for Compounding Pharmacies (APC)

248. Complaint, DUSA Pharms. v. New Eng. Compounding Pharmacy, 232 F.R.D. 153 (D. Mass. 2005) (No. 04-cv-12703), 2004 WL 3114445; Complaint, DUSA Pharms. v. Cosmetic Pharmacy, No. 05-cv-00060 (D. Ariz. July 25, 2005), 2005 WL 3661789.

249. Order Granting Motion for Default Judgment, DUSA Pharms. v. Cosmetic Pharmacy, No. 4:05-cv-00060 (D. Ariz. July 25, 2005).

250. *DUSA Pharmaceuticals and New England Compounding Center Announce Favorable Settlement in Compounding Pharmacy Suit*, BIOSPACE (Apr. 10, 2006), https://www.biospace.com/article/releases/dusa-pharmaceuticals-and-b-new-england-compounding-center-b-announce-favorable-settlement-in-compounding-pharmacy-suit-/ [https://perma.cc/GP9R-HLFS].

251. Complaint, Bayer HealthCare v. Wedgewood Vill. Pharmacy, Inc., No. 09-cv-053450 (D.N.J. July 6, 2009).

252. Edie Lau, *Drug Maker Sues Compounding Pharmacy: Bayer Says Wedgewood Infringing on Patent*, VIN NEWS SERV. (Dec. 17, 2009), https://news.vin.com/default.aspx?pid=210&catId=-1&id=4350785 [https://perma.cc/59R6-V7XS].

253. *Id.*

254. Consent Judgment, Bayer HealthCare v. Wedgewood Vill. Pharmacy, Inc., No. 09-cv-053450 (D.N.J. July 6, 2010).

has argued that compounding pharmacies may compound drugs so long as the drug appears on the FDA Drug Shortage List, reasoning that the FDA guidance on compounding makes no distinction for a patented drug:

> However, FDA guidance on the compounding of copies of FDA-approved drugs when they are in shortage makes no distinction for a patented drug. Rather, the guidance indicates that if an FDA-approved drug is listed as "currently in shortage" on the FDA shortage list . . . FDA will not view compounded versions of it as "essentially a copy" of the FDA-approved drug. Some argue that if Congress or FDA had intended there to be an exception for patented drug, the guidance would have stated that. . . . [W]e do note that such an exception for patented drugs would contradict the very reason the law allows compounding of FDA-approved drugs in shortage in the first place – to assure patients can continue to access needed and often essential medications, even when the manufacturer cannot maintain its supply chain.[255]

It would indeed be counterintuitive for the FDA to prohibit the compounding of drugs in shortage only if they are patented when no statutes, regulations, or guidance say otherwise. Unfortunately, the FDA has no jurisdiction over patent law and no power to immunize compounding pharmacies from liability for patent infringement—the Patent Act grants patentees a private right to enforce their patents and a remedy for infringement.[256] In other words, the mere fact that the FDA states that it will not take enforcement action against a pharmacy compounding drugs that are "essentially copies" of a commercial drug that is in shortage does not mean that a compounder is immune from suit by the patent owner.

This conflict that arises from separate spheres of patent and FDA law is mirrored in the recently litigated issue of skinny labeling. In *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA*, Teva filed a Paragraph IV certification on patents listed for GlaxoSmithKline's (GSK's) Coreg (carvedilol), a beta-blocker approved by FDA to treat three indications: hypertension, congestive heart failure (CHF), and to reduce cardiovascular mortality in patients suffering from left ventricular dysfunction after a

255. *Statement on Rules Governing Compounding, What FDA Guidance Says About Permissibility of Compounding "Essentially a Copy" of an FDA-Approved Drug—and What Those Have to Do with Semaglutide*, ALL. FOR PHARMACY COMPOUNDING (July 25, 2023), https://a4pc.org/files/APC-Compounding-Semaglutide-Media-Brief-REVISED-22May2023-REVISED-July-25.pdf [https://perma.cc/F4UL-JZ7U]; *see also* Christine Blank, *Pharmacy Compounders Defend Semaglutide Compounding amid Continued Shortages*, DRUG TOPICS (June 15, 2023), https://www.drugtopics.com/view/pharmacy-compounders-defend-semaglutide-compounding-amid-continued-shortages [https://perma.cc/CCX4-43V6].

256. 35 U.S.C. § 281.

myocardial infarction.[257] In its ANDA, Teva submitted what is known as a "skinny label," a label that intentionally carved out the indication for CHF, on which GSK still held valid patents, a tactic that would permit Teva to begin marketing a generic version of carvedilol without being liable for patent infringement (but would not stop doctors from prescribing generic carvedilol off-label for patients with CHF).[258] FDA eventually approved Teva's skinny label and ANDA package, and Teva's generic carvedilol product entered the market. GSK brought suit against Teva, alleging that its skinny label had induced physicians to prescribe the generic drug to treat CHF.[259] Despite the fact that skinny labeling was permissible under the relevant FDCA provisions, and the FDA approved Teva's skinny label, the Federal Circuit found that GSK had established induced patent infringement.[260] *GlaxoSmithKline* stands for the proposition that the FDA and FDA statutes often cannot protect alleged infringers from patent infringement liability.

So too it is the case that Section 503A and related FDA guidance cannot protect compounding pharmacies from liability for patent infringement. Thus, drug compounders are not immune from liability for patent infringement for compounding drugs in shortage. An innovator company's failure to meet the demand for a drug could, however, impact the availability of lost profit damages it seeks to recover in a suit for patent infringement against a compounding pharmacy.[261]

However, this leaves patients vulnerable during shortages of essential drugs—if an innovator company cannot produce sufficient quantities of a drug, and will not permit compounding pharmacies to fill the gap in the market (or perhaps, the mere threat of litigation is sufficient to chill compounding), what are patients to do? Section IV.A. proposes a solution by creating a specific exception for compounding drugs in shortage in the Patent Act.

Other factors, such as differences in financial and legal power, difficulty in identifying small-scale infringement, and ability to withstand the risk of litigation, likely contribute to the dearth of patent litigation against compounding pharmacies. Patents are also usually far more expensive to

257. GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1323–24 (Fed. Cir. 2021).
258. *Id.* at 1323–25.
259. *Id.* at 1325.
260. *Id.* at 1332–40.
261. Under the *Panduit* test, a patentee is entitled to lost profit damages if it can establish: (1) demand for the patented product; (2) absence of acceptable non-infringing alternatives; (3) *manufacturing and marketing capability to exploit the demand*; and (4) the amount of profit it would have made. Panduit Corp. v. Stahlin Bros. Fibre Works, 575 F.2d 1152, 1156 (6th Cir. 1978).

litigate and enforce than trademarks[262]—which may be why Novo Nordisk and Eli Lilly are focusing heavily on those compounding pharmacies that are advertising compounded semaglutide, as discussed in Section III.B. below. Thus, most litigation against pharmacies compounding semaglutide during the shortage has focused on trademark law and unfair competition.

B. Trademark and Unfair Competition Liability for Compounders

Trademarks can also be used to protect the brand name and logo associated with a drug. Trademarks include words, names, symbols, devices, and combinations thereof that are used with a bona fide intent to use the mark in commerce in order to identify and distinguish certain goods from those manufactured or sold by others and to indicate the source of the goods.[263] This helps protect against counterfeiting and fraud, as well as preventing other companies from using similar names that could lead to consumer confusion. Thus, trademarks exist to protect consumers and prevent unfair competition between companies that may capitalize on consumer confusion.

Most drugs have both a proprietary (brand) name and an established name that describes the composition of the drug (often, the active ingredient). The FDA must approve a proposed proprietary name as part of the overall drug approval process,[264] and may reject a proposed proprietary name for any number of reasons, including if the proposed name (1) has obvious similarities in spelling and pronunciation to other proprietary names in a way likely to confuse consumers, (2) references inert or inactive ingredients, or (3) merely combines the names of its active ingredients.[265] FDA regulations and guidance on drug product names, labels, and advertising require that proprietary and established names should almost

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262. *Compare How Much Does Patent Litigation Cost?*, COPPERPOD INTELL. PROP. (May 11, 2022), https://www.copperpodip.com/post/how-much-does-patent-litigation-cost [https://perma.cc/J3BL-JKAQ] (noting that patent lawsuits cost between $2.3 million and $4 million on average, lawsuits take one to three years on average to teach trial, and 95–97% of patent infringement lawsuits are settled); *Trademark Litigation 101*, THOMSON REUTERS: LEGAL (Nov. 14, 2022), https://legal.thomsonreuters.com/blog/trademark-litigation-101/ [https://perma.cc/7AB5-SPMY] (noting that trademark infringement lawsuits that advance to trial run between $375,000 and $2 million).

263. 15 U.S.C. § 1127; *see What Is a Trademark?*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/trademarks/basics/what-trademark [https://perma.cc/8SKN-W6VC].

264. FDA, CONTENTS OF A COMPLETE SUBMISSION FOR THE EVALUATION OF PROPRIETARY NAMES: GUIDANCE FOR INDUSTRY (2016), https://www.fda.gov/media/72144/download [https://perma.cc/U6B6-XBBJ].

265. FDA, BEST PRACTICES IN DEVELOPING PROPRIETARY NAMES FOR HUMAN PRESCRIPTION DRUG PRODUCTS: GUIDANCE FOR INDUSTRY 4–5 (2020), https://www.fda.gov/media/88496/download [https://perma.cc/X5UX-D7HH].

always appear juxtaposed together.[266] For instance: Advil® (ibuprofen), Rogaine® (minoxidil), and Humira® (adalimumab).

In recent years, drug manufacturers have attempted to curb competition from compounding pharmacies by suing them for unfair competition, including claims for deceptive business practices under state law and for false advertising under the Lanham Act (15 U.S.C. § 1125(a)). So far, these lawsuits have largely been dismissed, with courts holding that there is no private right of action to enforce the FDCA.

In 2019, Allergan brought suit against Imprimis Pharmaceuticals, which owned 503A and 503B compounding pharmacies based in New Jersey and California that sold ophthalmic drugs, alleging unfair competition and false advertising in violation of the Lanham Act and unlawful and/or unfair business practices in violation of California law.[267] Allergan alleged that Imprimis violated California's laws regulating business practices by compounding in violation of Sections 503A, 503B, and the DQSA. Allergan also argued that Imprimis made false statements regarding the legality of its business under Sections 503A and 503B and the efficacy of its formulations.[268] The court dismissed the false advertising claims under the Lanham Act, noting that "[t]he Court does not wish to set a policy that limits the ability of the FDA to determine whether there is a clinical need for particular drugs while simultaneously allowing the compounding of certain drugs to meet health needs."[269] Importantly, the court concluded that Allergan's lawsuit was an impermissible attempt to create a private cause of action to enforce the FDCA and related regulations, requiring the court "to invade the FDA's exclusive authority to enforce and restrain violations of the FDCA and related regulations—something that the court has previously, and correctly, declined to do."[270]

Similarly, in 2022, the Ninth Circuit dismissed three cases brought by Nexus Pharmaceuticals, which sold the trademarked and FDA-approved drug Emerphed (ready-to-use ephedrine syringes) against various compounding pharmacies that were also selling ready-to-use ephedrine

266. 21 C.F.R. §§ 201.10(g)(1), 202.1(b)(1) (2024); FDA, OMB NO. 0910-0686, PRODUCT NAME, PLACEMENT, SIZE, AND PROMINENCE IN PROMOTIONAL LABELING AND ADVERTISEMENTS: GUIDANCE FOR INDUSTRY 2–3 (2017), https://www.fda.gov/media/87202/download [https://perma.cc/N4BF-GYDL].

267. Allergan USA, Inc. v. Imprimis Pharms., Inc., No. 8:17-cv-01551, 2019 WL 4545960 (C.D. Cal. Mar. 27, 2019).

268. *Id.* at *4.

269. *Id.* at *8 (citing Allergan USA, Inc. v. Prescribers Choice, Inc., 364 F. Supp. 3d 1089, 1106 (C.D. Cal. 2019)).

270. *Id.*

syringes.[271] Nexus alleged violations of various state laws that prohibit the sale of drugs not approved by the FDA, but the Ninth Circuit held that the lawsuits would impermissibly extend into the FDA's authority to enforce the DQSA, and that the FDCA's prohibition on private enforcement barred such actions.[272] Also in 2022, the First Circuit dismissed a similar suit brought by Azurity Pharmaceuticals against Edge Pharma, a compounding pharmacy based in Vermont, alleging violations of the Lanham Act and a Massachusetts consumer protection law based on Edge Pharma's Compliance and Registration statements on its website, which stated that it was not in violation of Section 503B.[273] Azurity sold the trademarked and FDA-approved product FIRVANQ (vancomycin hydrochloride), while Edge also produced and marketed an oral vancomycin solution.[274] The First Circuit upheld the lower court's dismissal of Azurity's Lanham Act claim, with the lower court reasoning that "[b]ecause the FDCA forbids private rights of action . . . [a] Lanham Act [claim] may not be pursued when, as here, the claim would require litigation of the alleged underlying FDCA violation where the FDA has not itself concluded that there was such a violation."[275]

Both Novo Nordisk and Eli Lilly have filed multiple lawsuits against several compounding pharmacies around the U.S. for selling compounded versions of their respective GLP-1 agonists alleging trademark violation, false advertising, and unfair competition.[276] Unlike previous litigation against compounding pharmacies, most of these lawsuits also allege strong claims of trademark infringement. The first group of lawsuits was filed by Novo Nordisk against five compounding pharmacies in different states on June 20, 2023, alleging various claims for trademark infringement, false advertising, and unfair competition.[277] All of the allegations of trademark

271. *See* Nexus Pharms., Inc. v. Cent. Admixture Pharmacy Servs., Inc., 48 F.4th 1040 (9th Cir. 2022); Nexus Pharms. v. Quva Pharma, Inc., No. 20-56160, 2022 WL 4181714 (9th Cir. Sept. 13, 2022); Nexus Pharms. v. Leiters Inc., No. 20-56158, 2022 WL 4181716 (9th Cir. Sept. 13, 2022) (cases consolidated before the Ninth Circuit).

272. *Cent. Admixture Pharmacy Servs.*, 48 F.4th at 1040.

273. Azurity Pharms., Inc. v. Edge Pharma, LLC, 45 F.4th 479 (1st Cir. 2022).

274. *Id.* at 492 n.6.

275. *Id.* at 489 (alteration in original) (citing Azurity Pharms., Inc v. Edge Pharma, LLC, 540 F. Supp. 3d 141, 144 (D. Mass. 2021)).

276. *See, e.g.*, Complaint, Eli Lilly & Co. v. Wells Pharmacy Network, LLC, No. 23-cv-00576 (M.D. Fla. Dec. 18, 2023) [hereinafter *Eli Lilly v. Wells Pharmacy*]; Complaint, Novo Nordisk Inc. v. Brooksville Pharms. Inc., No. 23-cv-1503 (M.D. Fla. Nov. 8, 2023) [hereinafter *Brooksville Pharms.*]; Complaint, Novo Nordisk Inc. v. Wells Pharmacy Network, LLC, No. 23-cv-00689 (M.D. Fla. filed Nov. 29, 2023) [hereinafter *Novo Nordisk v. Wells Pharmacy*].

277. Complaint, Novo Nordisk A/S v. Pro Health Invs., No. 23-cv-02369 (W.D. Tenn. Mar. 15, 2024) [hereinafter *Pro Health*]; Complaint, Novo Nordisk A/S v. Champion Health and Wellness Clinics LLC, No. 23-cv-02246 (S.D. Tex. May 3, 2024) [hereinafter *Champion Health*]; Complaint, Novo Nordisk A/S v. Ekzotika Corp., 23-cv-22256 (S.D. Fla. Feb. 5, 2024) [hereinafter *Ekzotika*]; Complaint,

infringement are supported by screenshots of the defendants' websites wherein semaglutide is advertised and referred to by its proprietary names (either Ozempic or Wegovy), creating viable claims for trademark infringement, false advertising, and unfair competition under the Lanham Act.[278] Screenshots in two of the complaints say that Wegovy is "FDA approved" and offer "personalized plans with FDA approvals," which deceptively suggests that the products offered *are* Wegovy or are approved by the FDA.[279] While Novo Nordisk reached confidential settlements with two Florida compounding pharmacies,[280] most of the other lawsuits remain pending in their respective courts. The takeaway is that while compounders may be tempted to use proprietary names to boost their marketing and aid consumer recognition of drug products, pharmacies compounding drugs in shortage should be careful to use the established names of drug products (e.g., "semaglutide") rather than proprietary names, to avoid trademark infringement.

In July 2023, Novo Nordisk also filed suit against Brooksville Pharmaceuticals, a compounding pharmacy in Florida that was selling semaglutide.[281] Unlike its first batch of lawsuits, this time, Novo Nordisk didn't have any concrete evidence of trademark infringement to point to, instead alleging that Brooksville violated Florida's Deceptive and Unfair Trade Practices Act[282] by selling and distributing a new drug in Florida that is not approved under FDCA section 505 "or otherwise permitted by the Secretary of the United States Department of Health and Human Services for shipment in interstate commerce" in violation of Florida law.[283] The complaint does not refer to Section 503A or explain why compounding semaglutide, which was—at the time the complaint was filed—and still is in shortage, does not comply with Section 503A. Because Section 503A permits the compounding of copies of drugs that are not commercially available, and drugs that are in shortage are not commercially available, Section 503A of the FDCA arguably constitutes "permission" by the Secretary of HHS within the meaning of Florida law. Not surprisingly, Novo

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Novo Nordisk A/S v. Effinger Health, P.A., No. 23-cv-265 (N.D. Fla. Feb. 3, 2024) [hereinafter *Effinger Health*]; Complaint, Novo Nordisk A/S v. Flawless Image Med. Aesthetics, LLC, No. 23-cv-00739, 2023 WL 5200435 (N.D.N.Y. Feb. 27, 2024) [hereinafter *Flawless Image*].

278. *Pro Health*, *supra* note 277, at 8–9; *Champion Health*, *supra* note 277, at 8–9; *Ekzotika*, *supra* note 277, at 8; *Effinger Health*, *supra* note 277, at 10–11; *Flawless Image*, *supra* note 277, at 9–10.

279. *Pro Health*, *supra* note 277, at 8; *Champion Health*, *supra* note 277, at 8.

280. Kevin Dunleavy, *Novo Nordisk Settles with 2 Florida Sellers of Compounded Ozempic*, FIERCE PHARMA (Feb. 9, 2024, 12:52 PM), https://www.fiercepharma.com/pharma/novo-nordisk-settles-2-florida-sellers-compounded-ozempic [https://perma.cc/R2M5-8TYA].

281. *Brooksville Pharms.*, *supra* note 276.

282. FLA. STAT. §§ 501.201–.213 (2024).

283. *Brooksville Pharms.*, *supra* note 276, at 3–4, 8–9 (quoting FLA. STAT. § 499.023 (2023)).

Nordisk's lawsuit against Brooksville was orally dismissed without prejudice on October 5, 2023.[284] The lawsuit was re-filed by Novo Nordisk on November 29, 2023, along with another suit alleging similar claims against Wells Pharmacy Network.[285]

The next batch of lawsuits was filed on September 19, 2023 by Eli Lilly, manufacturer of Mounjaro (tirzepatide), against ten clinics and compounding pharmacies selling compounded tirzepatide.[286] In April 2024, a motion to dismiss one of these suits was granted, with the court finding that Lilly's use of state law claims to enforce the FDCA were an attempt to preempt federal law.[287] Another of these complaints, filed against Wells Pharmacy, largely mirrors Novo Nordisk's initial complaint against Brooksville, with Lilly seeking "to stop [Wells] from unlawfully manufacturing and selling unapproved new drugs" in violation of Florida state laws against unlawful and unfair business and trade practices.[288] The complaint alleges that Wells is engaged in "unfair methods of competition, unconscionable acts or practices, and unfair or deceptive acts or practices."[289] Although the complaint was filed in the District Court for the Middle District of Florida, the same court where Novo Nordisk's initial complaint against Brooksville was filed and dismissed, Lilly's suit remains pending. Lilly and Novo Nordisk filed multiple similar lawsuits against compounding pharmacies in May and June of 2024.[290]

While many of the claims in these suits involve actionable acts of trademark infringement and false advertising on compounding pharmacies' websites, there are also multiple complaints that don't point to such specific acts. It is apparent that certain pharmaceutical companies are using these

284. Clerk's Minutes, Novo Nordisk Inc. v. Brooksville Pharms. Inc., No. 23-cv-1503 (M.D. Fla. Nov. 8, 2023); *see also* Ed Silverman, *Judge Dismisses Novo Nordisk Lawsuit over Compounded Versions of Ozempic and Wegovy*, STAT (Oct. 6, 2023), https://www.statnews.com/pharmalot/2023/10/06/novo-lilly-wegovy-ozempic-obesity-weight-fda-lawsuit-compounding-pharmacy/ [https://perma.cc/NH7R-W9MT].

285. First Amended Complaint, Novo Nordisk Inc. v. Brooksville Pharms. Inc., No. 23-cv-1503 (M.D. Fla. Nov. 8, 2023); *Novo Nordisk v. Wells Pharmacy*, *supra* note 276.

286. Annika Kim Constantino, *Eli Lilly Sues Clinics Allegedly Selling Knockoff Versions of Mounjaro Diabetes Drug*, CNBC (Sept. 19, 2023, 5:14 PM), https://www.cnbc.com/2023/09/19/eli-lilly-sues-clinics-allegedly-selling-knockoff-versions-of-mounjaro.html#/ [https://perma.cc/VH97-G5XE].

287. Order Granting Motion to Dismiss at 6–11, Eli Lilly & Co. v. RxCompoundStore.com, LLC, 2024 WL 1554339 (S.D. Fla. Apr. 10, 2024) (No. 23-cv-23586).

288. *Eli Lilly v. Wells Pharmacy*, *supra* note 276, at 1–2.

289. *Id.* at 10.

290. *See* Company Statement, Novo Nordisk, Novo Nordisk Escalates Legal Actions to Safeguard Patients from Potentially Harmful Compounded "Semaglutide" Drugs (May 30, 2024, 9:00 AM), https://www.novonordisk-us.com/media/news-archive/news-details.html?id=168519 [https://perma.cc/M2DT-V4P8]; News Release, Eli Lilly & Co., Lilly Warns Patients About Counterfeit and Compounded Medicines Releases Open Letter and Takes Further Legal Action Against Counterfeit, Fake, Unsafe, and Untested Products (June 20, 2024), https://investor.lilly.com/news-releases/news-release-details/lilly-warns-patients-about-counterfeit-and-compounded-medicines [https://perma.cc/PK8V-G3RT].

lawsuits as an attempt to weaponize FDA's authority to oversee and regulate drug compounding. By capitalizing upon the fact that compounded drugs are exempted from FDA approval under Sections 503A and 503B and concerns about the safety and quality of compounded drugs, pharmaceutical companies seek to preserve their exclusive market for their drugs, even during shortages when patients are left with no other options. Although courts have generally been protective of the FDA's exclusive authority to enforce the FDCA, courts should be wary of this invitation to step into the FDA's jurisdiction by regulating compounded drugs as unapproved drugs.

On the other hand, concerns of consumer confusion and deception about compounded drugs may be valid, particularly when compounding pharmacies use proprietary drug names and tout "FDA approval" on their advertising and promotional materials. How can the FDA and state boards of pharmacy regulate the advertising and labeling of compounded drugs to avoid consumer confusion, assist consumers in recognizing and identifying drug products, and help the FDA and consumers identify the origin of compounded drugs and facilitate adverse event reporting? Section IV.B. proposes a solution that draws upon existing nomenclature used to create unique identifiers for biosimilar products.

III. IMPROVING DRUG COMPOUNDING

The causes of drug shortages are complicated. Given the FDA's current limited authority to regulate and oversee drug compounding, compounding may not be a long-term solution to address drug shortages. But compounding is indeed an essential short-term resolution for patients trying to access critical drugs that are part of their treatment plans—which are often time-sensitive, as with nine-year-old Abby Bray. When examining the stakeholders and parties interested in compounding and its regulation, it is clear that there is an urgent need for legal clarity on the risks of compounding drugs in shortage, particularly for drugs protected by patents and trademarks. It is also clear that the current regulatory framework and patent doctrine are insufficient to provide adequate clarity on the IP risks of drug compounding. This section proposes two key reforms to address these issues: one related to patents, and one related to drug nomenclature.

A. Allowing a Patent Use Exception

The conundrum is this: drugs that are in shortage, and drugs for which commercial versions do not meet the needs of specific patients, must be compounded. While FDA permits this compounding, the Patent Act does not. Why not create a simple exception in the Patent Act that provides

immunity from patent infringement liability for pharmacies that are compounding drugs for individual patients and during shortages? According to a 2013 World Intellectual Property Organization (WIPO) report, thirty-nine UN member states indicated that their respective laws already provided exceptions or limitations related to patent liability for compounded drugs for much the same reasons that the FDA and FDCA have created exemptions from regulatory review for compounded drugs[291]:

> [T]he response from Cyprus stated that the exception was "based on principles of the public benefit and the well being of mankind". Similarly, the response from France stated that the "exception is in the interest of public health". The answer from Poland was "not making impossible individual treatment". . . . The responses from Japan and the Republic of Korea indicated that taking into account that an act of preparing medicine by a physician or a dentist has a social mission with a particular purpose of helping patients in recovering their health, it is considered inappropriate for the effect of a patent right to extend to an act of preparing medicine". . . . The response from Serbia stated that the general ethical and health interest required that the patent for the drug would not be an obstacle that the drug in individual cases was produced and put on the market. The policy objectives for providing the exception in the Eurasian Patent Convention were "protection of the human health, assurance of the access to medicines".[292]

Many of these responses justify a patent use exception with the end goal of preserving public health and access to medicine, as well as recognizing the importance of not permitting patent rights to obstruct the treatment of individual patients. Some scholars have noted that the U.S. patent law is generally hostile toward broad exemptions to patent rights,[293] such as the narrowly tailored experimental use doctrine that can operate as a defense against infringement.[294] However, the UN member responses on patent exemptions—although coming from a legal perspective outside of the

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291. World Intell. Prop. Org. [WIPO], Standing Committee on the Law of Patents, *Exceptions and Limitations to Patent Rights: Extemporaneous Preparation of Medicines*, at 2, WIPO Doc. SCP/20/5 (Oct. 9, 2013), https://www.wipo.int/edocs/mdocs/patent_policy/en/scp_20/scp_20_5.pdf [https://perma.cc/ULF2-BF2A].

292. *Id.* at 2–3.

293. Adam N. Froehlich, *The Viability of a Compounding Pharmacy Patent Exception in the United States*, ABA HEALTH ESOURCE (Aug. 24, 2022), https://www.americanbar.org/groups/health_law/publications/aba_health_esource/2021-2022/august-2022/viability-of-a-compounding-pharmacy-patent-exception/ [https://perma.cc/9XDQ-PFEU].

294. *See* Madey v. Duke Univ., 307 F.3d 1351 (Fed. Cir. 2002) (narrowing experimental use exception and holding academic research institution liable for infringement for using patented technology in experimental research).

United States—reflected many existing doctrines and policies in U.S. patent and FDA law. For instance, Portugal's answer regarding the rationale for the patent use exception was "not to limit access to treatment and not to interfere with the relationship doctor/patient."[295] Similarly, the FDA has repeatedly insisted that it does not regulate the practice of medicine (hence, why FDA does not interfere when healthcare providers prescribe drugs off-label).[296] The responses from Germany and Italy also stated that the provision "is intended to facilitate the exercise of medical activities, since patents should not restrict the freedom of the doctor (physician) to prescribe medicines in the interest of health promotion."[297]

Similarly, in U.S. patent law, a medical practitioner who performs a patented medical or surgical procedure on a patient that would normally constitute patent infringement is not liable for patent infringement.[298] As discussed in Part III.a. above, 35 U.S.C. § 271(e)(2) of the Patent Act holds that submitting a Paragraph IV certification as part of an ANDA application constitutes an artificial act of patent infringement. Adding an additional provision to U.S.C. § 271(e) holding that compounding activities that qualify for exemptions under Sections 503A or 503B and related FDA guidance do not constitute an act of infringement would close the gap on a vulnerability created by a mismatch in FDA and IP law.

Furthermore, such patent immunity would be exceptionally limited in scope. First, the FDA regulatory framework already limits the breadth of permissible compounding. Under Sections 503A and 503B, FDA only permits licensed pharmacies to compound customized drugs for patients that are not commercially available, or to compound copies of commercially available drugs during active shortages of the commercial drug in question. Second, FDA regulations also limit the quantity and frequency of compounding by holding that drugs in shortage must not be compounded "regularly or in inordinate amounts."[299] A patent use exception would only apply to compounding activities that are permitted by the FDA in the first instance. In other words, only a pharmacy whose compounding activities are permitted under FDA guidance would be entitled to immunity from patent infringement.

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295. WIPO, *supra* note 291, at 2.

296. *See, e.g.*, FDA, ABOUT FDA: PATIENT Q&A, https://www.fda.gov/media/151975/download [https://perma.cc/GAD3-ELMS]. For a historical analysis of FDA's insistence that it does not regulate the practice of medicine, and the legislative intent behind the FDCA, see Carol R. Berry, The Dividing Line Between the Role of the FDA and the Practice of Medicine: A Historical Review and Current Analysis (1997) (unpublished paper), http://nrs.harvard.edu/urn-3:HUL.InstRepos:8846812 [https://perma.cc/B5A2-RC8A].

297. WIPO, *supra* note 291, at 2.

298. 35 U.S.C. § 287(c)(1).

299. FDA GUIDANCE, *supra* note 23, at 1.

Additionally, a patent use exception is not akin to a free, perpetual license for a compounding pharmacy to make copies of a drug without permission from the patentee. An innovator company whose patented drug is in shortage may resolve the issues that led to the shortage and resume manufacturing sufficient quantities of the drug such that the drug is removed from the FDA Shortage List. In that case, both the FDA regulations that permit compounding and the patent use exception (which is contingent on the challenged compounding being permissible under FDA law) would cease to be applicable. As a result, an innovator company that fails to produce sufficient quantities of drugs to meet patient needs would not lose profit as a result of pharmacies compounding drugs during active shortages. As soon as the company resolves the relevant shortage, it can continue to enjoy its monopoly profits on the patented drug. Ultimately, drug companies that benefit from patent protections have an obligation to produce enough drugs to meet patient needs. If drug manufacturers cannot meet the demand for essential drugs, policymakers must allow compounding pharmacies to step in to fill that need.

B. Adopting Nonproprietary Suffixes

The nonproprietary names of biosimilars may seem odd to some. For instance, "filgrastim-sndz" denotes the biosimilar version of filgrastim (sold under brand names such as Granix, Neupogen, Nivestym, Releuko, or Zarxio), a drug used to treat low white blood cell count caused by cancer medicines. Bevacizumab-bvzr is the biosimilar version of bevacizumab (sold as Avastin, Mvasi, or Zirabev), a type of targeted cancer treatment. Unlike generic drugs, biosimilar products are not necessarily interchangeable with their reference biologic drug. As discussed above in Section II.C., because biologics and biosimilars are large, complex proteins that are highly sensitive to changes in manufacturing, storage, and handling, a biosimilar can have a very different pharmacologic and therapeutic effect than its reference biologic on a particular patient.

The four letters affixed at the end of each drug name are used to distinguish a biosimilar from the original biologic product in order to help patients and healthcare providers avoid medication selection errors and help FDA track the adverse events associated with biologics and biosimilars during post-market surveillance.[300] FDA guidance on the topic states that a proposed suffix should be a unique, non-proprietary, four-letter identifier that is devoid of meaning and attached to the core non-proprietary name

300. Nancy J. Globus, *Alphabet Soup: The Story Behind Biosimilar Nonproprietary Name Suffixes*, CTR. FOR BIOSIMILARS (Aug. 8, 2020), https://www.centerforbiosimilars.com/view/alphabet-soup-the-story-behind-biosimilar-nonproprietary-name-suffixes [https://perma.cc/R3TM-8YJV].

with a hyphen.[301] Additionally, the suffix should not be false or misleading, such as by making representations concerning safety or efficacy, or look similar to a currently marketed product or FDA-designated nonproprietary suffix.[302]

A similar system to denote the origin of compounded drugs would fulfill primarily the same functions, enhancing patient safety by assisting the FDA and state boards of pharmacy to track adverse events to a specific compounding pharmacy, as well as assessing the need for additional inspections, warning letters, and possible interventions by the state board of pharmacy. The system may be implemented simply through an additional requirement for compounding pharmacies to qualify for the exemptions under 503A and 503B—compounding pharmacies must use unique non-proprietary suffixes to distinguish all drugs compounded at their facility. For instance, a pharmacy compounding semaglutide while it is in shortage may be required to label and advertise the product as "semaglutide-zfkl." The change would also require pharmacies to label and advertise all of their compounded products with the suffix "-zfkl"—a minor restriction on commercial speech unlikely to face the same First Amendment challenges as FDAMA's blanket advertising prohibition, which was struck down by the Supreme Court in *Western States*.[303]

The nomenclature change would also serve the policy goals of trademark law while simultaneously protecting compounding pharmacies from liability for trademark infringement by providing clarity on how compounded drugs should be labeled. This would allow pharmacies to advertise the availability of drugs in shortage for consumers, while protecting against counterfeiting, fraud, and consumer confusion, as well as deterring compounding pharmacies that distribute poor-quality drugs. The widespread adoption of nonproprietary suffixes would be a small price to pay for preserving patient safety and preventing consumer confusion while ensuring the continued availability of essential compounding services.

CONCLUSION

Compounding pharmacies play a critical role in ensuring that patients have access to vital medications during drug shortages and for patients who require customized drugs. Though the FDA has traditionally had limited authority to regulate and oversee compounding, recent legislation such as the DQSA and BPCIA have added restrictions to the operation of 503B

301. FDA, NONPROPRIETARY NAMING OF BIOLOGICAL PRODUCTS: GUIDANCE FOR INDUSTRY 10 (2017), https://www.fda.gov/media/93218/download [https://perma.cc/GMY4-RNA5].

302. *Id.*

303. Thompson v. W. States Med. Ctr., 535 U.S. 357, 368–78 (2002).

outsourcing facilities. As the FDA considers how to regulate the compounding of biologics, it must center the needs of vulnerable patient populations, such as transgender and non-binary patients that rely on compounded bioidentical hormone therapy for gender-affirming care.

As hospitals, physicians, and patients increasingly rely on compounding pharmacies to address severe drug shortages, it is critical for compounding pharmacies and their stakeholders to understand how to avoid liability for patent infringement, trademark infringement, and allegations of unfair competition and unfair business and trade practices. This Article underscores the need for clarity in navigating the legal landscape surrounding drug compounding and underscores the need for a patent use exception in the United States that creates immunity from patent infringement liability for pharmacies that compound drugs during shortages. This Article also proposes the adoption of non-proprietary name suffixes to indicate the origin of compounded drugs, which would address many of the concerns that are voiced by experts and healthcare professionals and reflected in the recent wave of litigation against compounding pharmacies, by helping the FDA trace adverse events to their pharmacy of origin and facilitating adverse event reporting. These proposed mechanisms seek to establish a legal framework that supports the continued viability of compounding pharmacies by striking a balance between safeguarding patients' access to essential healthcare and promoting the availability of safe, effective, and high-quality drugs during times of scarcity.