Customized Medicine and the Limits of Federal Regulatory Power

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ABSTRACT

The Food and Drug Administration (FDA) plays a dominant role in setting national policy and standards for the biomedical industry. Yet there are significant statutory constraints on the agency’s power. The FDA’s main implementing statute, the Federal Food, Drug, and Cosmetic Act (FDCA), bounds the scope of the FDA’s regulatory authority. The FDCA cabins FDA power in two important ways: (1) with a few notable exceptions, the FDA lacks power to regulate local activities that are not directly connected to interstate commerce, and (2) the agency may regulate product manufacturers, but not service providers. The FDA has long grappled with the limits of its authority to regulate conduct that encompasses the practice of medicine or the practice of pharmacy, such as physician off-label prescribing and drug compounding. These tensions will intensify as the life science industry evolves from a mass-market distribution scheme to a more customized, service-oriented business model. Autologous stem cell therapies and 3D-printed drugs and devices are two prominent examples of medical innovation that may evade the FDA’s purview. Sophisticated, organized patient advocacy groups that develop and share individualized treatments further expose the limits of the FDA’s statutory authority. These technological and social changes in medical product development and dissemination raise profound questions about the FDA’s future place within our contemporary healthcare regulatory system.

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I. INTRODUCTION

Pharmaceutical and medical device manufacturers have long been subject to comprehensive federal regulation. The Federal Food, Drug, and Cosmetic Act (FDCA or “the Act”), enacted in 1938 and strengthened by numerous subsequent amendments, dictates national policy and standards for the biomedical industry. The FDCA gives the US Food and Drug Administration (FDA) enormous power to determine which products are brought to market and how those products are manufactured, promoted, and distributed to hospitals, physicians, and patients. However, the FDA’s jurisdiction is


3. Id. at 2 (summarizing the FDA’s activities, which include, inter alia, reviewing applications to market new products or make changes to existing products, assessing reports and data on the safety of marketed products, inspecting factories and goods offered for importation,
statutorily confined to the regulation of manufacturers and distributors that introduce products into interstate commerce. The agency generally lacks authority to regulate purely intrastate or noncommercial activities. Further, it may not interfere with the practice of medicine or the practice of pharmacy in ways that unduly conflict with the states’ historical enforcement of their plenary police powers.

The dividing line between FDA-regulated product manufacturers, on the one hand, and healthcare service providers outside the scope of the FDA’s purview, on the other, has always been important and contested. This legal distinction will become increasingly significant as the life science industry evolves from a mass-market distribution scheme toward a more customized, service-oriented business model. Emerging technologies, such as autologous stem cell therapies and 3D-printed drugs and devices, coupled with unprecedented patient participation in product development and dissemination, blur the lines between medical technology creators and users. As the boundaries between product manufacturers, service providers, and consumers become increasingly uncertain, so too does the scope of federal regulatory power. These technological and social developments raise profound questions about the FDA’s role in our contemporary healthcare regulatory system.

II. REQUISITE NEXUS TO INTERSTATE COMMERCE

The US Constitution grants Congress power “[t]o regulate commerce with foreign nations, and among the several States, and with the Indian tribes.” Since the 1940s, the Supreme Court has construed the Commerce Clause broadly. In addition to regulating the channels of interstate commerce, and persons and things therein, Congress has authority to regulate activities that “substantially affect” interstate commerce. The Court has upheld federal restrictions on conduct that takes place wholly within a state, such as

5. See infra p. 288.
6. See infra p. 293.
7. See infra pp. 293–312.
8. U.S. Const. art. I, § 8, cl. 3.
the intrastate sale of milk, the cultivation of wheat for personal consumption, and racial discrimination by restaurants frequented only by local customers. Most recently, the Court decided that the federal Department of Justice has commerce power to ban the intrastate cultivation and possession of marijuana authorized by state law for personal medical purposes. The Supreme Court’s constitutional interpretation thus provides Congress wide berth to regulate local, noncommercial activities that have only a nominal or indirect connection to interstate commerce.

Yet Congress often refrains from extending its legislative reach to the constitutionally permissible bounds of its authority, and federal agencies’ regulatory jurisdiction extends only to the statutory parameters defined by Congress. Indeed, the FDCA falls significantly short of the outer limits of the federal commerce power. Statutory constraints on FDA authority reflect longstanding concerns about federal interference with the states’ regulation of the practice of medicine and the practice of pharmacy.

A. Local Distribution

In 1942, the Supreme Court, in Wickard v. Filburn, expansively construed the Commerce Clause to uphold federal regulation of homegrown, home-consumed wheat. The Court affirmed this sweeping view of the Commerce Clause in 2005, holding in Gonzales v. Raich that the federal government could enforce the Controlled Substances Act against parties who cultivated or possessed locally grown marijuana for personal use. But Congress enacted the FDCA in 1938, four years before Wickard, at a time when then-prevailing Supreme Court jurisprudence imposed meaningful limits on the commerce power. Taking account of presumed constitutional constraints, the 1938 Congress restricted the scope of the FDCA to products that moved in interstate commerce. The statutory limits on

14. Gonzales v. Raich, 545 U.S. 1, 22 (2005).
17. Raich, 545 U.S. at 22.
19. Peter Barton Hutt, Richard A. Merrill, & Lewis A. Grossman, Food and Drug Law: Cases and Materials 271–72 (4th ed. 2014) (“The scope of the [FDCA] is largely limited to products that have moved, are moving, or will be moving in interstate commerce. This is hardly surprising, for when the Act was enacted in 1938, the Supreme Court had only just begun to
the FDA’s regulatory authority are, therefore, more significant than the constitutional limits under modern Commerce Clause jurisprudence. In the years since Wickard, Congress has expanded the FDA’s statutory jurisdiction to cover some intrastate activities. Congress revised the FDCA in 1948 to clarify that its prohibitions against adulteration and misbranding apply to articles that are held for sale within a state after being shipped in interstate commerce. Amendments to the FDCA promulgated in 1976 permit the FDA to seize misbranded or adulterated medical devices without proof that they have traveled in interstate commerce. The FDA also has authority under the Public Health Service Act (PHSA) to prohibit false labeling of biological products whether or not they move in interstate commerce, and section 361 of the PHSA authorizes FDA regulation to prevent the spread of communicable disease without any interstate commerce limitations. However, despite these extensions of FDA jurisdiction, the agency lacks statutory authority to regulate a large swath of wholly intrastate conduct.

While the FDCA’s adulteration and misbranding prohibitions apply to actions that are taken after an article has traveled in interstate commerce, the Act’s “new drug” provisions apply only to the introduction of products into interstate commerce.

20. As enacted in 1938, section 304(a) of the FDCA authorized the seizure of articles that were adulterated or misbranded “when introduced into or when in interstate commerce.” 52 Stat. 1040, 1044. In 1946, the Ninth Circuit Court of Appeals held that this provision did not empower the government to seize adulterated pasta that was sitting in a warehouse after traveling in interstate commerce. United States v. Phelps Dodge Mercantile Co., 157 F.2d 453 (9th Cir. 1946). In response, Congress amended section 304(a) in 1948 to also permit the seizure of an article that is adulterated or misbranded “while held for sale (whether or not the first sale) after shipment in interstate commerce.” See Hutt, Merrill & Grossman, supra note 19, at 277; see also FDCA § 301(k), 21 U.S.C. § 331(k) (2012) (prohibiting any act that results in an article being adulterated or misbranded “if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce”).


22. PHSA § 351(b), 42 U.S.C. § 262(b) (2012); see also United States v. Calise, 217 F. Supp. 705, 708 (S.D.N.Y. 1962) (concluding that the mislabeling ban of 42 U.S.C. § 262(b) extends further in scope than the labeling requirements of 42 U.S.C. § 262(a)).

23. 42 U.S.C. § 264(a) (2012) (“The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.”). The FDA assumed responsibility for implementing the PHSA provisions pertaining to biological products in 1972. Hutt, Merrill & Grossman, supra note 19, at 272.

defines a “new drug” as “[a]ny drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.”

A manufacturer cannot market a new drug without first obtaining FDA approval of a new drug application (NDA). Since the FDCA prohibits the interstate shipment of any unapproved new drug, manufacturers must obtain an exemption from this prohibition in order to supply drugs to researchers who conduct the clinical trials required to gain FDA approval.

Physicians do not violate the new drug provisions when they prescribe drugs for unapproved, “off-label” purposes. This is dictated by the statutory interstate commerce limitation. When a physician prescribes a drug for an unapproved use, the drug usually meets the statutory definition of a “new drug,” since it is not generally recognized by experts as safe and effective for that indication. However, as the FDA has noted, “[u]nlike the adulteration and misbranding provisions of the Act, the new drug provisions apply only at the moment of shipment in interstate commerce.” Hence, the

licensing requirement for new biological products similarly applies only to articles “introduce[d] or deliver[ed] for introduction into interstate commerce.”

27. Section 505(i) of the FDCA permits the FDA to allow manufacturers to ship unapproved new drugs in interstate commerce for investigational purposes only. FDCA § 505(i), 21 U.S.C. § 355(i) (2012). The procedure the FDA has created to implement this exemption is the investigational new drug application (IND), governed by 21 C.F.R. Pt. 312. Investigational biologics are subject to the FDCA’s IND requirements. 21 C.F.R. § 312.2(a) (2016). Medical device investigations are subject to a separate process called the Investigational Device Exemption (IDE). FDCA § 520(g), 21 U.S.C. § 360j(g) (2012).
28. FDA regulations exempt from the IND requirements the use in the practice of medicine of an approved drug for an unlabeled indication. 21 C.F.R. § 312.2(d) (2016). The only drug for which Congress has specifically prohibited off-label prescribing is human growth hormone (HGH). See 21 U.S.C. § 333(e)(1) (2012) (making it a criminal offense for a physician to distribute HGH for any use other than an FDA-approved use). Congress enacted this provision in 1990 out of concerns about unsafe use of HGH to enhance athletic performance. See infra p. 293.
29. See Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 632 (1973) (concluding “that a drug can be ‘generally recognized’ by experts as effective for intended use within the meaning of the [FDCA] only when that expert consensus is founded upon ‘substantial evidence’ as defined in §505(d)”). Section 505(d) of the FDCA establishes the standard for approval of a NDA and requires “evidence consisting of adequate and well-controlled investigations.” FDCA § 505(d), 21 U.S.C. § 355(d) (2012); see also 21 C.F.R. § 314.126(e) (2016) (“Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness.”).
FDCA’s new drug provisions are no longer applicable once an approved drug lawfully travels in interstate commerce and lands on the shelf of a local pharmacy or physician’s office.\textsuperscript{31} A physician who acts outside the doctor-patient relationship to sell a drug for an unapproved purpose may violate the new drug requirements because, in that case, the physician is considered a person in the chain of distribution.\textsuperscript{32} The FDCA also prohibits the intrastate manufacture and administration of an unapproved drug or device made from components that have traveled in interstate commerce.\textsuperscript{33} And anyone who distributes a drug that has traveled in interstate commerce is subject to the FDCA’s adulteration and misbranding prohibitions.\textsuperscript{34} But a physician who merely prescribes a drug for an off-label use as part of the practice of medicine commits no violation of the FDCA because a prescriber who acts in the context of a doctor-patient relationship is not considered a person in the chain of distribution.\textsuperscript{35}

Statutory limitations similarly constrain the FDA’s authority to regulate the local distribution of medical devices. Like the new drug provision, the requirement for premarket device approval applies to devices that are introduced into interstate commerce.\textsuperscript{36} Although the Medical Device Amendments of 1976 gave the FDA the power to

\begin{footnotesize}
\begin{enumerate}
\item Id.
\item See id. (explaining that, while a physician is permitted to prescribe off-label, “where a manufacturer or his representative, or any person in the chain of distribution, does anything that directly or indirectly suggests to the [treating] physician or to the patient that an approved drug may be properly used for unapproved uses for which it is neither labeled nor advertised, that action constitutes a direct violation of the Act and is punishable accordingly”) (emphasis added).
\item See Baker v. United States, 932 F.2d 813, 814 (9th Cir. 1991) (noting that the FDCA’s “drug” definition includes “articles intended for use as a component of” a recognized drug, therefore “the ‘shipment in interstate commerce’ requirement is satisfied even when only an ingredient is transported interstate”); Retkwa v. Orentreich, 579 N.Y.S.2d 577 (Sup. Ct. 1991) (holding that physicians who received an interstate shipment of nonmedical grade silicone and compounded the silicone for use in cosmetic procedures violated the FDCA’s prohibition against selling an unapproved medical device); United States v. Dianovin Pharm., Inc., 475 F.2d 100 (1st Cir. 1973), cert. denied, 414 U.S. 830 (1973) (upholding the district court’s determination that a drug manufacturer’s use of the raw material vitamin K, which had been shipped in interstate commerce, to make an injectable drug solely for local consumption was governed by the FDCA because articles intended for use as components of a drug are also defined as drugs).
\item Hutt, Merrill & Grossman, supra note 19, at 820 (“Although a physician does not violate section 505 of the [FDCA] by prescribing an approved new drug for an unapproved use, a physician who distributes either unapproved drugs or approved drugs for unapproved uses is fully subject to the requirements of section 505.”); see also infra pp. 292–96.
\item See 21 U.S.C. § 360(e)(b) (2012) (authorizing the Secretary to require premarket approval of class III devices that were introduced into interstate commerce before May 28, 1976, and devices that are substantially equivalent to such devices).
\end{enumerate}
\end{footnotesize}
seize adulterated or misbranded devices without regard to interstate commerce, the agency cannot impose criminal penalties or obtain an injunction absent an interstate commerce connection.\(^{37}\) Congress included a provision in the Device Amendments that relieves the government of the burden of establishing an interstate commerce connection in criminal and injunction proceedings.\(^{38}\) But the provision only creates a rebuttable presumption,\(^{39}\) so a defendant who can show that neither the allegedly nonconforming product nor any of its components traveled in interstate commerce avoids penalty (other than product seizure) under the FDCA.

\textbf{B. Noncommercial Activities}

In addition to crossing state lines at some point in its distribution, a drug or device must be “held for sale” in order for the FDA to have statutory authority over those who distribute it.\(^{40}\) This statutory limit prevents the FDA from banning noncommercial distribution of drugs and devices, even if the agency can show that the products (or their components) have moved in interstate commerce.\(^{41}\) As explained above, the FDA does have authority to seize adulterated or misbranded devices, regardless of their connection to interstate commerce.\(^{42}\) And the FDA has unlimited statutory authority under the PHSA to regulate in order to prevent the spread of communicable diseases.\(^{43}\) But the FDA cannot enjoin or punish individuals who

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37. Hutt, Merrill & Grossman, supra note 19, at 285 (noting that the Medical Device Amendments do not authorize criminal penalties or injunctive relief absent proof that a device traveled in interstate commerce).

38. \textit{Id.} at 286 (“[T]he Device Amendments added a new section 709 to the Act, which provided: In any action to enforce the requirements of this Act respecting a device the connection to interstate commerce required for jurisdiction in such action shall be presumed to exist.”) Further, in 1997, Congress extended this provision to cover food, drugs, and cosmetics, as well. \textit{Id.}

39. \textit{Id.}

40. See 21 U.S.C. §331(k) (2012) (prohibiting any act that causes a regulated product to become adulterated or misbranded, “if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce”) (emphasis added).

41. See \textit{id.}

42. See supra pp. 287–89; see also United States v. Olsen, 161 F.2d 669, 671 (9th Cir. 1947) (reversing the district court’s dismissal of the government’s seizure of a device in the appellee’s private home, because the device allegedly had been misbranded prior to its shipment in interstate commerce and “[i]t is immaterial . . . that appellee did not intend to use it commercially or to permit its use by persons other than himself and his mother and brothers”).

43. See 42 U.S.C. §264 (a) (2012) (“The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.”).
engage in the noncommercial exchange of drugs and devices that allegedly violate the FDCA’s new drug, misbranding, or adulteration provisions.

This statutory limit on the FDA’s authority hovered at the margins of a contentious political battle between the agency and nonprofit organizations that facilitated access to unapproved drugs at the height of the AIDS epidemic in the 1980s and 1990s. The FDA elicited public backlash when it acted to stop two companies from selling a substance made from eggs and soybeans that, although marketed as a food, was promoted as an AIDS treatment by activists who had formed a network of buyers’ clubs. The agency ceased regulatory action in response to the protests. FDA Commissioner Frank Young later declared in a conciliatory speech: “FDA’s new policy regarding self-help, nonprofit clinics is similar to our policy regarding the use of unproven substances in self-treatment—that is, not to interfere as long as patients are not being harmed, clinics do not promote unproven products outside the clinic, and the clinic does not serve as a subterfuge for a commercial enterprise.”

While not ceding its regulatory authority, the FDA sought to draw a clear policy line between nonprofit and for-profit distribution of unapproved drugs. However, the agency was later forced to squarely confront the “held for sale” statutory limitation in an unusual case involving gratuitous drug distribution. In United States v. Geborde, the FDA levied a misbranding charge against an individual who had manufactured and freely given to several teenagers a homemade designer drug called gamma hydroxy butyrate, commonly known as GHB. Geborde did not dispute that his conduct had a sufficient interstate nexus to support an FDCA violation. Though the GHB never traveled in interstate commerce, the ingredients that Geborde


45. Id. (“[T]he agency called off the embargo and informed Nutricology that if it would comply with agency regulations and stop implying that the substance is useful against AIDS, it could resume selling the product.”).

46. HUTT, MERRILL & GROSSMAN, supra note 19, at 770.

47. In contrast to its forbearance toward nonprofit AIDS organizations, during the same period the FDA aggressively pursued for-profit clinics distributing unapproved cancer drugs. See, e.g., United States v. Burzynski Cancer Research Inst., 819 F.2d 1301 (5th Cir. 1987).

48. United States v. Geborde, 278 F.3d 926, 927–28 (9th Cir. 2002) (explaining that the government sought a conviction under the FDCA because, at the time that Geborde distributed the drug, GHB was not listed as a controlled substance and thus the government could not bring a conventional drug case).

49. Id. at 930.
used to make it presumably did. But the Ninth Circuit overturned Geborde’s misbranding conviction, concluding that the government had failed to prove the “held for sale” statutory element of the offense. The court rejected the government’s position that the FDCA covered all articles not intended solely for personal consumption, observing that it knew of “no case . . . in which the ‘held for sale’ language of the FDCA ha[d] been applied to an individual who gave away a homespun drug or product in a wholly noncommercial setting.”

While Geborde’s facts involved criminally dangerous activity prohibited under state law, the Ninth Circuit’s interpretation of the FDCA’s “held for sale” provision applies to the distribution of any unapproved drug. The decision thus highlights a key statutory limitation on the FDA’s regulatory power. This statutory limit will become increasingly important as patient advocacy groups gain the technological tools to create and share homespun individualized therapies.

III. PRODUCT/SERVICE DISTINCTION

A. Practice of Medicine

Congress made it clear when it enacted the FDCA that it did not intend for federal regulation to interfere with the practice of medicine. While subsequent amendments to the Act have expanded the agency’s regulatory jurisdiction, this fundamental restriction on federal regulatory power remains intact. The agency does have statutory authority to restrict distribution of a medical device if “the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness.” Additionally, amendments to the FDCA enacted in 2007 gave the FDA express authority to

50. See id. at 928 (explaining that Geborde made a batch of GHB by mixing, in a bucket, sodium hydroxide and a common industrial solvent).
51. Id. at 932.
52. Id. at 931–32.
53. Id. at 927 (noting that Geborde was convicted of manslaughter in state court and sentenced to prison).
54. See infra pp. 311–14.
55. Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16503 (proposed Aug. 15, 1972) (rule not adopted) (“Congress . . . declined to provide any legislative restrictions upon the medical profession.”).
restrict distribution of licensed drugs. However, the agency directly imposes these controls on product sponsors, not medical practitioners. Since the statute’s enactment in 1938, the FDA has consistently conceded that it cannot prevent physicians from prescribing approved products for unapproved, off-label uses. Once a medical product has been approved or cleared by the FDA and lawfully shipped in interstate commerce, its use in the practice of medicine is regulated by the states pursuant to their plenary police powers. Hence, the FDA’s regulatory jurisdiction extends to the manufacture, promotion, and dissemination of medical products themselves, but not to practitioners’ delivery of health care services that utilize those products.

57. Under section 505-1 of the FDCA, added by the Food and Drug Administration Amendments Act of 2007, a new drug applicant must submit, as part of its application, a proposed risk evaluation and mitigation strategy (REMS) if the FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. The Act lists several possible elements of a REMS, which may require a drug sponsor to create a communication guide for patients; educate and train health care providers on proper use of the drug; implement a patient monitoring system; establish a scheme for certifying pharmacies to dispense the drug; or ensure that the drug is administered only in certain settings, such as hospitals. See 21 U.S.C. § 355-1(a), (e), (f) (2012).

58. See 21 U.S.C. § 333(f)(4)(A) (2012) (providing that any “responsible person” who violates § 355-1 shall be subject to civil monetary penalties); § 355-1(b)(7) (“The term ‘responsible person’ means the person submitting a covered application or the holder of the approved such application.”).

59. Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16503 (“Once a new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.”); see also 21 U.S.C. § 396 (2012) (“Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”).

60. Lars Noah, Ambivalent Commitments to Federalism in Controlling the Practice of Medicine, 53 U. KAN. L. REV. 149, 159 (“The Supreme Court long ago recognized that the police powers of the states justified their regulation of the practice of medicine.”).

61. The lone exception to the general rule that the FDA does not regulate off-label prescribing is the federal prohibition against knowingly prescribing, dispensing, or administering human growth hormone (HGH) for anything other than FDA-approved uses. 21 U.S.C. § 333(e) (2012). Congress made this amendment to the FDCA via the Anabolic Steroids Control Act, enacted as Title XIX of the Crime Control Act of 1990, Pub. L. No. 101-647, § 1904, 104 Stat. 4851, 4853 (1990). Congress passed this statute to prevent the use of HGH to enhance athletic performance, and reiterated when it passed separate legislation in 1997: “In general, the FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice.” H.R. REP. No. 105-310, at 60 (1997).
1. Off-Label Prescribing

The Fifth Circuit’s decision in United States v. Evers\(^{62}\) sharply illuminates this essential product/service distinction. Dr. H. Ray Evers owned and operated the Ra-Mar clinic, an inpatient facility that specialized in the use of “chemo-endarterectomy therapy” for the treatment of circulatory disorders caused by atherosclerosis.\(^ {63}\) The cornerstone of Evers’s therapy was the use of chelating drugs, compounds that bond with heavy metals and cause them to be excreted through the kidneys.\(^ {64}\) The FDA had approved chelating drugs for the treatment of lead and other heavy metal poisoning, but it had not approved any chelating drug for the treatment of circulatory disorders.\(^ {65}\) Seeking to enjoin Evers’s vigorous promotion and advertising of his off-label use of these drugs, the agency charged him with violating section 301(k) of the FDCA, 21 U.S.C. § 331(k).\(^ {66}\) This provision prohibits any act with respect to a drug that “is done while such [drug] is held for sale (whether or not the first sale) after shipment in interstate commerce and [which] results in such article being . . . misbranded.”\(^ {67}\) Specifically, the government alleged that Dr. Evers misbranded the chelating agent Calcium EDTA under section 502(f)(1) of the FDCA, 21 U.S.C. § 352(f)(1), by failing to provide “adequate directions for use” of Calcium EDTA in the treatment of circulatory disorders.\(^ {68}\)

The government stipulated that the FDCA’s misbranding provisions do not prohibit a licensed physician from prescribing a licensed drug for any purpose, whether or not that purpose has been FDA approved.\(^ {69}\) In fact, the FDA had expressly informed Dr. Evers that he was permitted to prescribe Calcium EDTA for the treatment of circulatory disorders.\(^ {70}\) The basis for the government’s prosecution was Dr. Evers’s aggressive promotion and advertising of his off-label use of chelating drugs.\(^ {71}\) The government asserted that Evers’s promotional efforts took his actions outside the bounds of the routine

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63. Id. at 1044–45 (noting that the lay term for atherosclerosis is “hardening of the arteries”).
64. Id. at 1045.
65. Id.
66. Id. at 1045–47.
67. Id. at 1045.
68. Id. at 1047–48 (explaining that § 502(f)(1) of the FDCA, 21 U.S.C. § 352(f)(1), deems a drug to be misbranded “unless its labeling bears . . . adequate directions for use”).
69. Id. at 1048.
70. Id.
71. Id.
practice of medicine and into the scope of FDA regulation. The Fifth Circuit, however, scrutinized sections 301(k) and 502(f)(1) of the FDCA and concluded that the provisions did not apply to Dr. Evers. Although the court held the chelating drugs were for sale within the meaning of section 301(k) when Dr. Evers administered them to his patients, Dr. Evers’s actions did not cause the drugs to be misbranded under section 502(f)(1).

The court grounded its decision in a careful reading of the FDCA’s labeling provisions and the context of the overall federal regulatory scheme. Since Calcium EDTA was a prescription drug, it was not possible for Dr. Evers to provide “adequate directions for [lay] use.” Thus, if the labeling requirements applied to Dr. Evers, the only way for him to avoid a misbranding charge would have been to meet the criteria for a statutory or regulatory exemption from section 502(f)(1). A statutory exemption from the “adequate directions for use” requirement applies at the time that a prescription drug is prescribed and dispensed if certain basic information is provided on the label. Additionally, a broader regulatory exemption applies if a prescription drug’s label includes “adequate information for its use . . . under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended.” The court reasoned that the purpose of this scheme is to ensure that essential information about a drug’s safety and efficacy reaches the person who will ultimately decide whether and how to administer it. In the case of over-the-counter drugs, the decision maker is a lay user and, therefore, the drug’s label must include adequate directions for lay use. In the case of prescription drugs, on the other hand, a physician makes the ultimate judgment and, therefore, the drug is not misbranded so long as its label contains adequate information for licensed practitioners.

72. Id.
73. Id. at 1049–53.
74. Id. at 1050.
75. Id. at 1053.
76. Id. at 1050–51 (citing 21 C.F.R. § 201.5 (1980), which interprets “adequate directions for use” to mean “directions under which the layman can use a drug safely and for the purposes for which it is intended”).
77. 21 U.S.C. § 353(b) (2012) (listing the information that must be contained on a prescription drug’s label in order to qualify for this exemption, including “directions for use and cautionary statements, if any, contained in such prescription”).
78. 21 C.F.R. § 201.100(1) (2016) (emphasis added).
79. Evers, 643 F.2d at 1052.
80. Id.
81. Id.
Herein lies the fatal flaw in the government’s case. The FDA argued that Dr. Evers violated section 301(k) of the FDCA by holding his chelating drugs for sale to patients without providing adequate directions for use by prescribing physicians. Yet, the government conceded that Dr. Evers was the only physician who used the allegedly misbranded Calcium EDTA. Its argument thus turned on the “nonsensical” proposition that Dr. Evers did not provide adequate directions to himself. The court reasoned: “Section 301(k) cannot reasonably be read to require a physician who is holding a drug for sale only to patients to provide adequate information to physicians to whom he is not distributing the drug.” Since Dr. Evers did not distribute Calcium EDTA to other licensed physicians, the court concluded that he did not violate the FDCA’s misbranding provisions. Notably, the court expressly declined to assess the safety and efficacy of Dr. Evers’s practices, the reasonableness of which undoubtedly was governed by state law.

2. Controlled Substances

The FDCA’s statutory constraints are evident when compared to the federal government’s more expansive regulatory jurisdiction under the Controlled Substances Act (CSA). Enacted in 1970, the CSA criminalizes the unauthorized manufacture, distribution, dispensing, and possession of substances classified in any of the CSA’s five schedules. Substances are placed in one of the five schedules based on their potential for abuse or dependence, their accepted medical use, and their accepted safety when used under medical supervision. Congress scheduled several drugs when it passed the CSA and authorized the US Attorney General to add, remove, or reschedule substances based on scientific and medical findings by the Secretary of Health and Human Services. A 1971 regulation implementing the CSA requires that every prescription for a controlled substance “be issued for a legitimate medical purpose by an

82. Id. at 1053.
83. Id.
84. Id.
85. Id.
86. Id. at 1053–54.
87. Id. at 1053 (“We have not been called upon in this case to consider the safety and effectiveness of Dr. Evers’s use of chelation therapy; accordingly, we neither approve nor criticize his medical practices.”).
89. Raich, 545 U.S. at 13–14.
individual practitioner acting in the usual course of his professional practice.”91 Physicians must be registered with the Drug Enforcement Agency (DEA) to issue lawful prescriptions for controlled drugs, and the Attorney General may deny, suspend, or revoke a physician’s registration if the prescriber’s registration would be “inconsistent with the public interest.”92

In Gonzales v. Raich, the Supreme Court upheld the federal government’s enforcement of the CSA against individuals who used marijuana for personal, physician-recommended medical purposes.93 Citing Wickard v. Filburn, the Court ruled that Congress’s Commerce Clause authority includes the power to prohibit the intrastate, noncommercial cultivation and possession of cannabis as recommended by a patient’s physician in compliance with state law.94 Importantly, once the Court resolved the contested constitutional question, it indisputably followed that the federal government had statutory authority to outlaw medical marijuana use.95 The CSA gives the DEA authority to ban the manufacture and use of cannabis, supplanting contrary state law, because marijuana has no federally recognized legitimate medical purpose and is consequently classified as a Schedule I drug.96 This scheduling designation also leaves no role for the FDA, other than to oversee marijuana’s interstate shipment for


92. 21 U.S.C. § 822(a)(2) (2012); 21 U.S.C. § 824(a)(4) (2012). When deciding whether a practitioner’s registration is in the public interest, the Attorney General shall consider:

“(1) The recommendation of the appropriate State licensing board or professional disciplinary authority.

“(2) The applicant’s experience in dispensing, or conducting research with respect to controlled substances.

“(3) The applicant’s conviction record under Federal or State laws relating to the manufacture, distribution, or dispensing of controlled substances.

“(4) Compliance with applicable State, Federal, or local laws relating to controlled substances.

“(5) Such other conduct which may threaten the public health and safety.”


93. Raich, 545 U.S. at 5–9.

94. Id. at 18–19 (“Wickard thus establishes that Congress can regulate purely intrastate activity that is not itself ‘commercial,’ in that it is not produced for sale, if it concludes that failure to regulate that class of activity would undercut the regulation of the interstate market in that commodity.”); id. at 29 (“The Supremacy Clause unambiguously provides that if there is any conflict between federal and state law, federal law shall prevail.”).

95. Id. at 32–33.

96. Id. at 14.
investigational use in clinical trials designed to test marijuana’s therapeutic effects.97

Gonzales v. Oregon,98 decided only seven months after Gonzales v. Raich, highlights the significance of a Schedule I classification for the federal drug regulatory scheme. Gonzales v. Oregon considered whether the federal government has authority under the CSA to prohibit doctors from prescribing lethal drugs for use in physician-assisted suicide, notwithstanding state law permitting the practice.99 Specifically, the US Attorney General sought to revoke the DEA registration of physicians who issued prescriptions in compliance with the Oregon Death With Dignity Act, on the ground that dispensing or prescribing controlled substances for this use violates the CSA because physician-assisted suicide is not a legitimate medical purpose.100 The Supreme Court ruled that the Attorney General had exceeded the bounds of his statutory authority, as he lacked the power to declare unlawful clinical procedures specifically authorized under state law.101 The Court explained that the CSA did not give the Attorney General unbridled discretion to define the legitimate practice of medicine.102 Rather, Congress’s delegation of authority to the federal executive branch was limited to scheduling controlled substances and setting medical standards of care for the treatment of narcotic addiction.103

The key factual distinction driving the divergent outcomes in Gonzales v. Raich and Gonzales v. Oregon is the different scheduling of the relevant controlled substances in each case. Marijuana, the substance at issue in Raich, has no legitimate medical use under

97. Id. (“By classifying marijuana as a Schedule 1 drug, as opposed to listing it on a lesser schedule, the manufacture, distribution, or possession of marijuana became a criminal offense, with the sole exception being use of the drug as part of a Food and Drug Administration preapproved research study.”).


99. Id. at 248–49.

100. Id. at 253–54 (explaining that the Attorney General issued an Interpretive Rule announcing his view that prescribing controlled substances for the purpose of physician-assisted suicide violates the CSA, regardless of whether state law authorizes the practice).

101. Id. at 258–63 (“It would be anomalous for Congress to have so painstakingly described the Attorney General’s limited authority to deregister a single physician or schedule a single drug, but to have given him, just by implication, authority to declare an entire class of activity outside ‘the course of professional practice,’ and therefore a criminal violation of the CSA.”).

102. Id. at 263.

103. Id. at 265–69 (explaining that the Attorney General shares decision-making power with the Secretary of the Department of Health and Human Services, whose authority to make medical judgments is limited to the narrow statutory objectives of scheduling controlled substances and determining appropriate methods of treatment for narcotic addiction).
federal law and is therefore listed as a Schedule I drug.\(^{104}\) Hence, the federal government has constitutional power under the Commerce Clause and statutory power under the CSA to prohibit its possession and use, regardless of conflicting state law. In contrast, the drugs at issue in Gonzales v. Oregon are classified as Schedule II drugs and are FDA approved for therapeutic uses other than physician-assisted suicide.\(^{105}\) The CSA prohibits physicians from trafficking these controlled substances under the guise of providing medical treatment.\(^{106}\) Otherwise, the states retain exclusive authority to determine whether a physician’s off-label use of an FDA-approved, non-Schedule I drug is for a legitimate medical purpose. The Supreme Court explained that this resolution is both consistent with the statutory language of the CSA and accords with federalism principles:

The statute and our case law amply support the conclusion that Congress regulates medical practice insofar as it bars doctors from using their prescription-writing powers as a means to engage in illicit drug dealing and trafficking as conventionally understood. Beyond this, however, the statute manifests no intent to regulate the practice of medicine generally. The silence is understandable given the structure and limitations of federalism, which allows the States “great latitude under their police powers to legislate as to the protection of the lives, limbs, health, comfort, and quiet of all persons.”\(^{107}\)

**B. Practice of Pharmacy**

1. 1997 FDAMA Safe Harbor

As with the practice of medicine, statutory constraints limit the FDA’s authority to regulate the practice of pharmacy. Drug compounding is the process by which a pharmacist combines or alters drug ingredients pursuant to a physician’s prescription to create a medication that meets the unique needs of an individual patient.\(^ {108}\) Compounding is typically used to develop a therapy that is not commercially available, such as a drug for a patient who is allergic to an ingredient in a mass-produced product or who requires a different dosage or route of administration.\(^ {109}\) It is a traditional aspect of the practice of pharmacy and is regulated by the states through their

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104. Gonzales v. Raich, 545 U.S. 1, 14 (2005).
106. Id. at 250–51.
licensing authorities.\textsuperscript{110} The FDCA, as amended, permits compounding pharmacies to avoid the new drug approval process under certain statutorily defined circumstances.\textsuperscript{111} Pharmacy compounding thus straddles a boundary between product manufacturing within the scope of the FDA’s jurisdiction and service delivery outside the FDA’s regulatory domain.

In the early 1990s, the FDA became concerned that some pharmacies were taking advantage of the agency’s historically lenient stance toward compounding.\textsuperscript{112} The agency asserted that pharmacies were endangering public health by engaging in large-scale drug production while evading the FDCA’s new drug approval, adulteration, and misbranding provisions.\textsuperscript{113} To prevent circumvention of FDA regulation, in 1992, the agency promulgated a Compliance Policy Guide (CPG) declaring that it had expansive regulatory authority over all compounding activities and would initiate enforcement actions against pharmacies that performed practices “normally associated with a manufacturer.”\textsuperscript{114} The 1992 CPG listed nine non-exhaustive factors the FDA would consider in exercising its enforcement discretion.\textsuperscript{115} These factors included whether a pharmacy advertised specific compounded drug products, regularly produced essentially generic copies of commercially available products, used commercial scale equipment, compounded large amounts of drugs in anticipation of receiving prescriptions, offered compounded drugs at wholesale to other entities, or distributed inordinate amounts of compounded products out of state.\textsuperscript{116}

Congress partially codified the FDA’s 1992 compounding policy when it enacted the Food and Drug Modernization Act of 1997 (FDAMA).\textsuperscript{117} The FDAMA added section 503A to the FDCA, establishing a statutory safe harbor from the Act’s new drug approval

\textsuperscript{110} See id. (noting that some states require all licensed pharmacies to offer compounding services).

\textsuperscript{111} Med. Ctr. Pharmacy v. Mukasey, 536 F.3d 383, 387 (5th Cir. 2008) (holding that new human drugs that result from compounding are exempt from the adulteration, misbranding, and new drug approval provisions of 21 U.S.C. §§ 351(a)(2)(B), 352(f)(1), and 355 if they comply with the conditions in § 353a).

\textsuperscript{112} Id. at 389.

\textsuperscript{113} Id. at 389–90.


\textsuperscript{115} See Petition for a Writ of Certiorari at 76a–77a, W. States, 535 U.S. 357 (No. 01-344).

\textsuperscript{116} See W. States, 535 U.S. at 363.

\textsuperscript{117} Id. at 364.
and other requirements. Like the 1992 CPG, section 503A conditioned the exemption on compliance with several restrictions on compounding pharmacies’ practices and advertising. Congress thereby aimed to limit the safe harbor to traditional compounding as opposed to disguised manufacturing.

In 2002, the Supreme Court in Thompson v. Western States Medical Center invalidated the advertising-related provisions of section 503A as unconstitutional restrictions on commercial speech. The Court affirmed the Ninth Circuit’s holding that the advertising provisions violated the First Amendment but declined to address whether the stricken provisions were severable from section 503A’s non-speech-related provisions. Western States thus created uncertainty as to whether the FDAMA statutory safe harbor for traditional compounding had been invalidated in its entirety.

The FDA issued a revised CPG in response to the Western States decision in which it took the position that all of section 503A had been invalidated. The agency asserted that compounded drugs were not exempt from the FDA’s new drug, adulteration, and misbranding provisions, but assured pharmacists that it would continue to exercise enforcement discretion with respect to traditional compounding activities. The 2002 CPG on compounding human drugs again listed factors that the FDA would use in determining whether to bring enforcement actions. These factors were similar, but not identical, to those listed in the 1992 CPG. The agency eliminated the factors relating to advertising and out-of-state distribution, and it added two new factors that would support enforcement action: compounding drugs that were withdrawn from the

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119. See id.; Petition for a Writ of Certiorari at 76a–77a, W. States, 535 U.S. 357 (No. 01-344).
121. See id. at 360.
122. Id. (noting that the parties had not appealed the Ninth Circuit’s holding that § 503A was invalid in its entirety because the FDAMA was non-severable).
123. See id.
125. See id. at 3.
126. See id. at 3–4.
market for safety reasons and compounding drugs from bulk ingredients that are not components of FDA-approved drugs.  

The FDA’s reassertion of its authority over pharmacy compounding sparked new legal challenges. In 2006, a federal district court held that the invalidated advertising provisions of section 503A were severable from the remainder of the statute and that the rest of section 503A remained in full effect. The court further found that the statutory safe harbor demonstrated “that Congress intended to declare that compounding is an approved and legal practice.” It interpreted section 503A to create a blanket “implicit exemption” from the FDCA’s new drug approval process for pharmacy compounders. On appeal, the Fifth Circuit split with the Ninth Circuit and affirmed the district court’s holding that the unconstitutional advertising restrictions were severable from the rest of section 503A. However, the Fifth Circuit overturned the district court’s determination that compounding pharmacies were wholly exempt from the FDCA’s new drug requirements. Rather, the court interpreted the FDCA to create a narrow, conditional exemption only for drug compounders who complied with section 503A’s extant requirements.

The FDA triggered an additional challenge to its statutory authority in 2010 when it sought to enjoin Franck’s Lab, a Florida compounding facility, from distributing veterinarian-prescribed compounded animal drugs. The agency’s action was prompted by a 2009 incident in which twenty-one polo horses died after receiving an overly potent medication that Franck’s Lab had incorrectly

128. Compliance Policy Guide No. 460.200, Pharmacy Compounding, supra note 114, at 3–4. The FDA also issued a CPG on compounding animal drugs. U.S. Food & Drug Admin., Compliance Policy Guide No. 608.400, Compounding of Drugs for Use in Animals (July 14, 2003). The thirteen factors applicable to animal drugs were similar, but not identical, to those applicable to human drugs. See id. at 4–5; Compliance Policy Guide No. 460.200, Pharmacy Compounding, supra note 114, at 3–4.


130. See id. at 862–63.

131. Id. at 863.

132. Id. (“Because pharmacies are permitted to compound, this Court finds that any drugs created by the compounding process are therefore implicitly exempt from the new drug approval process.”).


134. Id. at 395, 405–06 (“The ‘new drug’ definition contains no general exception for drugs created by compounding.”).

135. Id. at 405 (“[C]ompounded drugs are in fact ‘new drugs’ as defined by [21 U.S.C.] § 321(p) but are exempt from the requirements of §§ 351(a)(2)(B), 352(f)(1), and 355 if and only if they comply with the conditions set forth in § 353a.”).

compounded due to a mathematical error.\textsuperscript{137} Although the Florida Board of Pharmacy thoroughly investigated the matter and decided to allow Franck’s to continue its compounding practice without restriction, the FDA charged Franck’s with violating the FDCA by compounding animal drugs from bulk substances.\textsuperscript{138} In response, Franck’s submitted numerous declarations from veterinarians, pharmacists, and other experts asserting that, \textit{inter alia}, compounding from bulk was a ubiquitous, life-saving technique and was “widely preferred” over compounding from finished products.\textsuperscript{139} Franck’s further noted that Florida, like many other states, expressly recognized compounding from bulk substances as a well accepted part of the practice of pharmacy.\textsuperscript{140}

Citing the Fifth Circuit’s decision in \textit{Medical Center Pharmacy v. Mukasey}, the district court agreed that the FDCA’s “new drug” definition contains no general exception for compounding pharmacies.\textsuperscript{141} But the court observed that the FDA’s “maximalist” interpretation of the FDCA was a marked departure from its prior position on drug compounding.\textsuperscript{142} The agency had previously acknowledged the utility of bulk compounding and had delineated circumstances in which it would not subject pharmacists to regulatory action for compounding drugs from bulk for non food-producing animals.\textsuperscript{143} Moreover, the FDA’s 2002 CPG strongly suggested that it would allow bulk compounding of human drugs so long as the bulk

\textsuperscript{137} Id. at 1213.

\textsuperscript{138} Id. at 1213–14 (“FDA has taken the bright-line position that \textit{any} compounding of animal medications from bulk substances violates its enabling statute, the [FDCA], even when conducted by a state-licensed pharmacist for an individual animal patient pursuant to a valid veterinary prescription.”); see 21 C.F.R. § 207.3(a)(4) (2016) (defining “bulk drug substance” as “any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug”).

\textsuperscript{139} \textit{Franck’s Lab}, 816 F. Supp. 2d at 1215, 1217–18 (“Pharmacists also favor compounding from bulk because use of bulk ingredients ensures that the compounded medicine is of the expected purity, potency, and quality; further, it is often not practical or possible to compound a medically necessary drug product from an FDA-approved finished drug product.”).

\textsuperscript{140} Id. at 1218–19.

\textsuperscript{141} Id. at 1236 (“As the Fifth Circuit noted in \textit{Medical Center}, . . . [b]elying the Pharmacies’ argument that compounded drugs are not “new drugs” by virtue of their creation by licensed pharmacists, the definition of “new drug” focuses on the drug’s composition and use rather than on the process by which it was created.”).

\textsuperscript{142} Id. at 1239 (“[T]he Fifth Circuit’s faith that the FDA would not seek to enforce a ‘maximalist’ interpretation of its authority turned out to be misplaced.”).

\textsuperscript{143} Id. at 1227–28 (noting that the FDA adopted a “decidedly more hostile tone” toward compounding in its 2003 CPG on animal drug compounding than it did in its 2002 human drug counterpart and in its earlier 1996 CPG on animal drug compounding).
substances were components of FDA-approved drugs. The district court concluded that the agency’s new hostile stance contravened the policy objectives of the FDCA: “Because Congress appeared to be focused on the fact that manufacturing—unlike the practice of pharmacy—was conducted by unlicensed, unregulated nonprofessionals, it seems unlikely that it would have intended to subject professionally dispensed drugs to the same regulatory scheme.” The court, therefore, held that the FDA lacked statutory authority to enjoin a pharmacy from practicing traditional compounding to meet the unique needs of individual patients in compliance with state law.

The government appealed the district court’s decision to the Eleventh Circuit. But before the appellate court heard oral arguments, the parties jointly filed a motion to vacate and dismiss the decision as moot, citing the sale of Franck’s Lab and the company’s decision to permanently discontinue its compounding operations. The Eleventh Circuit granted the motion in 2012, leaving unresolved questions about the scope of the FDA’s statutory authority to regulate compounding pharmacies.

2. Compounding Quality Act of 2013

At the same time that the Franck’s Lab litigation was winding down, a deadly fungal meningitis outbreak linked to a large-scale compounding facility placed a national spotlight on the FDA’s hazy regulatory authority over drug compounding. In response, Congress enacted the Compounding Quality Act as part of the Drug Quality and

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144. Id. at 1227 (noting that the 2002 CPG listed a compounder’s use of bulk ingredients that were not components of FDA approved drugs as a factor that the FDA would consider in deciding whether to bring an enforcement action).

145. Id. at 1245–46.

146. Id. at 1250.


148. See Joint Motion to Vacate and Dismiss as Moot at 3–4, Franck’s Lab, 2012 WL 10234948.

149. Id.

150. See Kurt Eichenwald, Killer Pharmacy: Inside a Medical Mass Murder Case, NEWSWEEK (Apr. 16, 2015), http://www.newsweek.com/2015/04/24/inside-one-most-murderous-corporate-crimes-us-history-322665.html [https://perma.cc/292T-T9J4] (reporting that, in 2012, eight hundred patients were infected by a contaminated injectable steroid solution manufactured and shipped throughout the country by a Massachusetts compounding facility, leading to sixty-four deaths and numerous federal indictments against individuals who worked for or were connected to the facility, including charges of murder, racketeering, and fraud).
Security Act of 2013. The Compounding Quality Act amended section 503A of the FDCA to remove the restrictions on the promotion of specific compounded products and the solicitation of prescriptions for compounded drugs. Traditional pharmacy compounders that meet section 503A’s revised criteria are exempt from the FDCA’s current Good Manufacturing Practices (cGMP), labeling, and new drug approval requirements. The Act also added a new section 503B that created a new category of compounding pharmacy known as an “outsourcing facility.” Registered outsourcing facilities that meet section 503B’s criteria are exempt from the new drug approval process but still must comply with cGMPs and certain other FDCA requirements.

After the passage of the Compounding Quality Act, the FDA withdrew its 2002 CPG and issued policy statements on implementation of the new law. In October 2015, the FDA published a new guidance on traditional pharmacy compounding of human drugs under amended section 503A. The agency stressed that the section 503A exemption applies only to products that are compounded for an identified individual patient in the context of an established relationship between the patient and healthcare professionals licensed under state law to prescribe and compound


153. Id. Traditional compounders that fall within the section 503A exemption remain subject to other FDCA requirements, including prohibitions against unsanitary manufacturing conditions; misrepresentations about the quality, strength, or purity of compounded drugs; and false or misleading labeling, advertising, or promotion. Id. at 6–7.

154. Id. at 1 n.2. Section 503B(b)(4) of the FDCA defines an “outsourcing facility” as “a facility at one geographic location or address that—(i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section.” Drug Quality and Security Act § 102 (amendments codified at 21 U.S.C. § 353b). Requirements under section 503B include, inter alia, compliance with restrictions on the use of bulk drug substances, compliance with US Pharmacopeia standards, a prohibition against compounding drugs that are essentially copies of approved drugs, a requirement to prominently label products as compounded drugs, and compliance with registration and reporting requirements.


157. Id.
drugs. The guidance permits bulk compounding if the drug product is compounded in compliance with a US Pharmacopoeia or National Formulary monograph or the bulk ingredients are either components of an FDA-approved drug or on a list of acceptable bulk substances designated by the FDA through regulation. The FDA further requires traditional compounding pharmacies either to operate in a state that has entered into a memorandum of understanding (MOU) with the FDA to investigate inordinate interstate distribution of compounded products or to cap interstate distribution at no more than 5 percent of the pharmacy’s total prescription orders.

In August 2015, the FDA issued guidances for entities considering whether to register with the FDA as outsourcing facilities under section 503B. The agency clarified that section 503B only applies to facilities that compound sterile human drugs. It does not cover the manufacture of biological products subject to licensure under the PHSA. The guidance noted that an outsourcing facility differs from a traditional compounding pharmacy in that it need not be licensed by the state. An outsourcing facility also may compound and distribute drugs to healthcare providers without first obtaining prescriptions for individual patients. Outsourcing facilities must satisfy several conditions in order to qualify for exemptions from the new drug approval process and from the FDCA’s “adequate directions for use” labeling requirement and track and trace requirements. These conditions include registering with the FDA, submitting reports to the agency, complying with restrictions on bulk compounding, not producing copies of commercially available products, not compounding drugs that the FDA designates as presenting “demonstrable difficulties” for compounding, and not acting as a wholesale supplier of compounded drugs.

IV. EMERGING TRENDS INCREASINGLY STRAIN THE LIMITS OF FEDERAL
POWER

A. New Technologies

1. Autologous Stem Cell Therapy

Until the 1980s, the procurement of cadaver tissue for surgical use was considered an aspect of the practice of medicine outside the scope of FDA regulation.\textsuperscript{168} However, as technological advances expanded the range of human-source materials that could be used as alternatives to man-made replacement parts, hospitals began to out-source procurement operations to independent tissue banks.\textsuperscript{169} In 1993, the FDA published an interim rule mandating screening of tissue donors, testing of donated tissues, and the maintenance of records for inspection by FDA regulators.\textsuperscript{170} These requirements did not apply to tissues that were already regulated as drugs, devices, or biological products or to whole organs and bone marrow (which are overseen by other administrative agencies).\textsuperscript{171}

This initial assertion of control over tissue banks culminated in the creation of a comprehensive federal regulatory scheme for suppliers of human cellular and tissue-based products. The FDA published a final rule on Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) in 2001.\textsuperscript{172} The crux of the rule was the delineation of criteria for determining when a cellular or tissue-based product would be classified as a new drug or Class III medical device.\textsuperscript{173} The FDA cited two main factors: (1) whether the donated tissue is expected to perform the same function in the recipient that it performed in the donor ("homologous use") \textsuperscript{174} and (2) whether the

\textsuperscript{168} HUTT, MERRILL & GROSSMAN, supra note 19, at 1168.
\textsuperscript{169} Id.
\textsuperscript{172} 66 Fed. Reg. 5447 (Jan. 19, 2001) (codified at 21 C.F.R. § 1271 (2016)). These regulations define HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d).
\textsuperscript{173} Merrill, supra note 171, at 48.
\textsuperscript{174} Id. The agency defines "homologous use" as "the replacement . . . or supplementation of a recipient's cells or tissues with a HCT/P that performs the same basic function or functions in the recipient as in the donor." 21 C.F.R. § 1271.3(c).
tissue has been more than "minimally manipulated." The HCT/P rule thus categorically distinguished between products regulated solely under section 361 of the PHS Act and products regulated more extensively under either or both the drug and device provisions the FDCA and section 351 of the PHS Act. The FDA also entirely exempted certain medical procedures from the federal regulatory scheme. "You are not required to comply with the requirements of [Part 1271 promulgated under section 361 of the PHS Act] if you are an establishment that removes HCT/P's [sic] from an individual and implants such HCT/P's [sic] into the same individual during the same surgical procedure" or "if you are an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor."

In 2004, the FDA issued current Good Tissue Practice (cGTP) regulations pursuant to its authority under section 361 of the PHS Act. The agency clarified that HCT/Ps categorized as drugs, devices, or biological products must be manufactured in accordance with cGTP regulations, in addition to applicable Current Good Manufacturing Practice (cGMP) and quality system regulations. The FDA treats umbilical cord blood as transplantable tissue subject to its general human tissue regulations rather than as whole blood subject to the requirements for donated blood and blood products. The agency regulates autologous administration—the return of cord blood to its original donor—solely under section 361 of the PHS Act. However, the FDA has cautioned that more rigorous regulation may

175. Merrill, supra note 17, at 48.
176. 21 C.F.R. § 1271.15.
177. 21 C.F.R. § 1271.15(b) (emphasis added).
178. 21 C.F.R. § 1271.10(a).
180. cGMPs for drugs are codified at 21 C.F.R. pts. 210 & 211. cGMPs for devices are codified at 21 C.F.R. pt. 820. In the 1990s, the FDA substantially revised 21 C.F.R. pt. 820 and renamed it the "Quality System" regulation to reflect the expansion of the device cGMPs to cover a comprehensive system of quality control. HUTT, MERRILL & GROSSMAN, supra note 19, at 1261–63.
be required if cord blood is significantly manipulated to enhance its therapeutic properties.\textsuperscript{184}

Stem cells are a widely touted class of HCT/Ps that have particularly captured the FDA’s attention. Stem cell therapies may be created using either embryonic stem cells or adult stem cells.\textsuperscript{185} By the somatic cell nuclear transfer (SCNT) technique, scientists create embryonic stem cells from a recipient’s own cells and turn the stem cells into various tissues for transplantation, thereby avoiding immunological rejection of genetically non-identical tissue.\textsuperscript{186} Alternatively, adult stem cells may be harvested from patients, cultured in a laboratory, and then returned to patients for repair or replacement of damaged and diseased tissue.\textsuperscript{187} Embryonic stem cell therapy is referred to as therapeutic cloning, as it involves the creation of an embryo that is a genetic copy of the intended recipient of the transplanted tissue.\textsuperscript{188} Since the production of adult stem cells does not require the creation of an embryo and thereby evades attendant moral controversy, autologous adult stem cell therapies hold great clinical and commercial promise.

A recent dispute between the FDA and a pair of Colorado physicians who promoted and administered adult stem cell therapy highlights the limits of the agency’s power to regulate this emerging technology. Dr. Christopher Centon and Dr. John Schultz developed the Regenexx\textsuperscript{™} Procedure, a cellular therapy for orthopedic patients that involves harvesting stem cells from a patient’s bone marrow or synovial fluid, culturing those cells for several weeks in a laboratory with growth factors from the patient’s blood, placing the cultured cells

\begin{itemize}
  \item \textsuperscript{184} HUTT, MERRILL & Grossman, \textit{supra} note 19, at 1173–74.
  \item \textsuperscript{187} See \textit{Adult Stem Cells 101}, BOS. CHILD. HOSP., (Oct. 31, 2016), http://stemcell.childrenshospital.org/about-stem-cells/adult-stem-cells-101/ [https://perma.cc/37R8-ADK5].
  \item \textsuperscript{188} See \textit{What Are Stem Cells? How Are They Regulated?}, \textit{supra} note 185. Therapeutic cloning differs from reproductive cloning in that the cloned embryo is used to produce cellular therapies rather than being implanted into a uterus to produce a human being. DAVID ORENTLICHER, MARY ANNE BOBINSKI & MARK A. HALL, \textit{Bioethics and Public Health Law} 557 (2d ed. 2008). In 1998, the FDA asserted regulatory authority over reproductive cloning and prohibited clinical research to create a somatic cell clone intended to produce a cloned human being without an effective investigational new drug application (IND). HUTT, MERRILL & Grossman, \textit{supra} note 19, at 1187–89.
  \item \textsuperscript{189} The FDA defines autologous use as “the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.” 21 C.F.R. § 1271.3 (2016).
\end{itemize}
into a syringe along with the antibiotic doxycycline and other additives, and injecting the contents of the syringe into the patient’s injured area.\textsuperscript{190} The doctors formed Regenerative Sciences LLC (“Regenerative”) to commercialize this practice.\textsuperscript{191} FDA officials inspected Regenerative’s facilities in 2009 and 2010 and found that its laboratory operations did not conform to cGMP regulations.\textsuperscript{192} When the FDA charged Regenerative with manufacturing and distributing adulterated and misbranded biological drug products in violation of section 301(k) of the FDCA and section 262(k) of the PHSA,\textsuperscript{193} the defendant physicians responded that they were lawfully practicing medicine within the state of Colorado and that the Regenexx\textsuperscript{TM} Procedure fell outside the FDA’s regulatory purview.\textsuperscript{194}

The district court quickly disposed of the defendants’ argument that the FDA lacks constitutional authority to regulate any aspect of the practice of medicine.\textsuperscript{195} It reasoned that since the FDCA provisions at issue require a direct nexus to interstate commerce, agency action pursuant to its statutory authority necessarily falls within the bounds of its Commerce Clause power.\textsuperscript{196} The case thus presented a matter of statutory interpretation. The threshold question was whether the defendants’ cellular therapy was a “drug” as defined by the FDCA or a “biological product” as defined by the PHSA.\textsuperscript{197} The court held that the stem cell therapy satisfied both the statutory definition of a “drug” under the FDCA and the statutory definition of a “biological product” under the PHSA\textsuperscript{198} and that the

\begin{itemize}
\item \textsuperscript{190} United States v. Regenerative Scis., LLC, 878 F. Supp. 2d 248, 251–52 (D.D.C. 2012). Doxycycline is added to prevent bacterial contamination of the stem cells. United States v. Regenerative Scis., LLC, 741 F.3d 1314, 1318 (D.C. Cir. 2014).
\item \textsuperscript{191} \textit{Regenerative Scis.}, 878 F. Supp. 2d at 251.
\item \textsuperscript{192} \textit{Id.} at 252; see also 21 C.F.R. pts. 210 & 211 (cGMP regulations promulgated under 21 U.S.C. § 351(a)(2)(B) (2012)).
\item \textsuperscript{193} Most of the FDCA’s provisions, including its manufacturing and labeling requirements, are incorporated by reference into the PHSA. See \textit{Regenerative Scis.}, 741 F.3d at 1319 n.1 (“Because the PHSA simply incorporates the FDCA’s substantive provisions by reference, the scope of the FDCA’s provisions is determinative of the reach of the PHSA’s provisions as well.”).
\item \textsuperscript{194} \textit{Regenerative Scis.}, 878 F. Supp. 2d at 254.
\item \textsuperscript{195} \textit{Id.}
\item \textsuperscript{196} \textit{Id.} (noting the prohibition against adulteration and misbranding stated in 21 U.S.C. § 331(k) applies only if a drug is held for sale “after shipment in interstate commerce”).
\item \textsuperscript{197} \textit{Id.} (“The question presented here is whether the Regenexx\textsuperscript{TM} Procedure constitutes a drug (or biologic product) subject to FDA regulation or whether it is merely an intrastate method of medical practice subject only to the laws of the State of Colorado.”).
\item \textsuperscript{198} \textit{Id.} at 255–57 (citing 21 U.S.C. § 321(g)(1)(B) & (C) (2012), which define “drug” to mean “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” or “articles (other than food) intended to affect the structure or any function of the body of man,” and 42 U.S.C. § 262(i)(1) (2012), which defines a “biological product” as, \textit{inter alia}, any
Regenexx™ Procedure did not qualify for regulatory exemption from the FDCA’s drug provisions because the cultured stem cells were more than minimally manipulated.\(^\text{199}\) It further found that the defendants were subject to the FDCA because they held their cellular therapy out for sale after shipment in interstate commerce.\(^\text{200}\) Consequently, the district court ruled that the defendants violated the FDCA’s adulteration prohibition by failing to comply with cGMP regulations and violated the FDCA’s misbranding prohibition by not labeling their cellular therapy “Rx only” and for failing to provide adequate directions for use.\(^\text{201}\)

The crux of the district court’s decision was its determination that the defendants’ actions were directly connected to interstate commerce. Section 331(k) of Title 21 of the United States Code prohibits any act “with respect to, a . . . drug . . . if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.”\(^\text{202}\) Citing Evers, the court determined that the Regenexx™ Procedure was “held for sale” within the meaning of section 331(k).\(^\text{203}\) The defendants did not contest that they held the procedure out for sale to their patients.\(^\text{204}\) They argued, however, that since the entire process of harvesting, culturing, and re-implanting patients’ stem cells took place within the state of Colorado, the procedure did not meet section 331(k)’s “interstate commerce” requirement.\(^\text{205}\) The court rejected this argument by noting that the FDCA’s expansive “drug” definition includes “articles intended for use as a component of any article . . .”\(^\text{206}\) The defendants added the antibiotic doxycycline to the stem cell mixture prior to administering it to patients, which rendered doxycycline a “component” of the cellular therapy.\(^\text{207}\) Since the doxycycline indisputably was shipped

\(^{199}\) Id. at 257–78. During the culturing process, the defendants added substances to the stem cells that affected their growth and differentiation. The FDA concluded that this process altered the cells’ “relevant biological characteristics,” and therefore the cells did not meet the criteria for the regulatory exemption for HCT/Ps that are no more than “minimally manipulated.” See United States v. Regenerative Scis., LLC, 741 F.3d 1314, 1321–22 (D.C. Cir. 2014) (concluding that the defendants failed to carry their burden of establishing that the § 1271.10 regulatory exemption applies to the Regenexx™ Procedure).

\(^{200}\) Id.

\(^{201}\) Id. at 259–60.

\(^{202}\) Id. at 258.

\(^{203}\) Id.

\(^{204}\) Id. at 259.

\(^{205}\) Id.

\(^{206}\) Id. (citing 21 U.S.C. § 321(g)(1)(D) (2012)).

\(^{207}\) Id.
from out of state to the defendants’ Colorado facilities, the court concluded that the Regenexx™ Procedure met the “interstate commerce” requirement.208 The district court rejected the defendants’ contention that its statutory interpretation contradicted legislative intent because Congress did not intend the FDCA to regulate the practice of medicine.209 The court drew a key distinction between clinical activities that fall outside the scope of the FDA’s authority and activities that fall within the FDA’s regulatory jurisdiction:

There is a difference between a licensed physician’s use of an FDA-approved drug such as doxycycline in an off-label way, which is permissible within the “practice of medicine,” and adding doxycycline to a cell product to be administered to patients, which renders the latter a “drug” that has connections to interstate commerce. The question of interstate commerce is not relevant to the first issue but controls the second.210

Finding a “cognizable danger of a recurrent violation,” the district court entered a permanent injunction prohibiting the defendants from committing further violations of the FDCA’s adulteration and misbranding provisions.211

On appeal, the D.C. Circuit affirmed the district court’s summary judgment for the government and the permanent injunction against the defendants.212 It found the defendants’ assertion that the FDA exceeded its statutory authority “wide of the mark” because the focus of the agency’s enforcement action was the stem cell mixture itself, not the procedures used to administer the mixture.213 The court reasoned that the FDCA’s comprehensive regulatory scheme generally applies to licensed healthcare practitioners, which is why physicians and pharmacists who compound drugs in the course of their professional practice must rely on specific statutory exemptions to avoid FDA regulation.214 The appellate court further explained that the defendants could not rely on the drug compounding exemption because the exemption only covers drugs compounded using certain

208. Id. ("Courts have held that the ‘interstate commerce’ element is met if any component of that drug moved in interstate commerce.").
209. Id. at 260–61.
210. Id. at 261.
211. Id. at 262–63.
213. Id. at 1319 (“That is, the FDA does not claim that the procedures used to administer the Mixture are unsafe; it claims that the Mixture itself is unsafe.”).
214. Id. at 1319–20 (finding the defendants’ construction of the FDCA untenable because it “would allow states to gut the FDCA’s regulation of doctors, and thereby create an enormous gap in the FDCA’s coverage, by classifying the distribution of drugs by doctors as the practice of medicine”).
types of bulk drug substances.\textsuperscript{215} The stem cells at issue did not qualify as bulk drug substances that were components of an FDA-approved drug.\textsuperscript{216} Finally, it rejected the defendants’ argument that they should not be subject to the FDCA’s misbranding provisions because they produced the stem cell therapy for their own use.\textsuperscript{217} The court distinguished this case from \textit{Evers} by noting that the drug at issue in \textit{Evers} was FDA approved and thus Dr. Evers unquestionably had the right to prescribe it for off-label use.\textsuperscript{218} In contrast, the defendants’ stem cell therapy had not been approved for any therapeutic use.\textsuperscript{219} The D.C. Circuit therefore justified its finding of FDA jurisdiction by the absence of a recognized drug compounding exception coupled with the distinction from \textit{Evers} regarding the existence of FDA approval.

The D.C. Circuit’s determination that the FDA has authority to regulate the Regenexx\textsuperscript{™} Procedure as a drug stands on a remarkably thin reed. The court accepted the government’s finding that the stem cells were more than minimally manipulated because substances were added to the cell culture that affected cell differentiation. But the court left open the possibility that future defendants could challenge this point with additional evidence.\textsuperscript{220} If providers can show that the culturing process does not alter cells’ relevant biological characteristics, then, like autologous cord blood administration,\textsuperscript{221} autologous stem cell therapy should be exempt from drug regulation and subject only to section 361 of the PHSA.

Furthermore, the defendants’ conduct satisfied the statutory interstate commerce requirement only because the doxycycline was shipped into Colorado from out of state and added to the stem cells prior to the mixture’s administration to patients.\textsuperscript{222} Had the doxycycline been manufactured in Colorado and shipped intrastate, the FDA would have lacked a jurisdictional hook.\textsuperscript{223} Alternatively, suppose the defendants had administered the doxycycline separately

\begin{footnotesize}
\begin{enumerate}
\item \textit{Id.} at 1323.
\item \textit{Id.} (citing 21 C.F.R. § 207.3(a)(4) (2016), which states that, to qualify as a “bulk drug substance,” an item must be “represented for use in a drug,” and noting that there is no evidence that the stem cells in the defendants’ mixture are held out for use in any drug).
\item \textit{Id.}
\item \textit{Id.} at 1324.
\item \textit{Id.} at 1323–25 (“We will not broaden \textit{Evers} to vitiate the FDCA's labeling requirements in these circumstances.”).
\item \textit{Id.} at 1321–22 (“Because appellants concede that culturing [mesenchymal stem cells] affects their characteristics and offer no evidence that those effects constitute only minimal manipulation, they fail to carry [their burden of proof] as a matter of law.”).
\item See Suski, \textit{supra} note 182.
\item \textit{Regenerative Scis.}, 741 F.3d at 1320.
\item \textit{Id.}
\end{enumerate}
\end{footnotesize}
rather than mixing it with the stem cells in a single syringe. If the Regenexx™ Procedure were modified to comprise two separate injections—a first syringe of stem cells and a second syringe of doxycycline—the FDA presumably would lose its regulatory authority under the FDCA, even if the doxycycline were shipped from out of state.\textsuperscript{224} In this case, the defendants would be prescribing doxycycline for off-label use, an activity that the FDA lacks power to regulate regardless of its connection to interstate commerce.\textsuperscript{225}

The D.C. Circuit’s interpretation of the misbranding prohibition also elides the Fifth Circuit’s reasoning in \textit{Evers}. In holding that a physician who administers a prescription drug for an off-label use is not required to provide adequate directions for such use, the \textit{Evers} court stressed that it was nonsensical to require a physician to provide directions to himself.\textsuperscript{226} The logic behind this argument does not turn on the drug’s regulatory approval status. While the FDA has a compelling public health reason to hold the defendants liable for violating the FDCA’s adulteration provisions in failing to comply with cGMPs, its misbranding charge against Regenerative was just as absurd as the one in \textit{Evers}. Like Dr. Evers, the defendants were not selling their stem cell therapy to patients for self-medication or to other practitioners for administration to their own patients.\textsuperscript{227} The policy rationale for enforcing the FDCA’s labeling requirements is simply absent where a licensed healthcare professional both manufactures and administers a therapeutic substance to his own patients, regardless of whether that substance has been FDA approved.

Given this shaky basis for the FDA’s misbranding charge, what exactly would the defendants need to put on the mixture’s label in order to meet the agency’s requirements? As noted by the D.C. Circuit, since the mixture is a prescription drug, by definition it cannot contain “adequate directions for [lay] use.”\textsuperscript{228} The regulatory exemption for prescription drugs requires the label to contain “adequate information for use . . . under which practitioners . . . can use the drug safely and for the purposes for which it was intended.”\textsuperscript{229} Presumably, therefore, the Regenexx™ label must include its indications, dosages, routes of administration, side effects, and other necessary information to ensure that \textit{other} physicians can provide it

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\item \textsuperscript{224} \textit{Id.} at 1319.
\item \textsuperscript{225} \textit{Id.} at 1324.
\item \textsuperscript{226} \textit{United States v. Evers}, 643 F.2d 1043, 1053 (5th Cir. 1981).
\item \textsuperscript{227} \textit{Regenerative Sci.}, 741 F.3d at 1323.
\item \textsuperscript{228} \textit{Id.} at 1324.
\item \textsuperscript{229} 21 C.F.R. § 201.100(c)(1) (2016).
\end{itemize}
safely to patients. But if Regenerative were to add this information to the mixture’s label, the FDA could then assert a new misbranding charge under 21 U.S.C. § 352(a) on the theory that the label’s claims are “false and misleading in any particular.” This raises thorny questions about the type and amount of safety and efficacy data the FDA would require providers to produce in order to establish that a stem cell therapy’s labeling is not false and misleading. If the agency were to pursue this path, it would more directly confront the longstanding prohibition against federal interference with the practice of medicine. It would also put itself on a collision course with the First Amendment.

2. 3D-Printed Drugs and Devices

Additive manufacturing, better known as 3D printing, is another technological innovation that is poised to strain the bounds of the FDA’s regulatory authority. Although 3D printing has existed since the 1980s, the field has exploded in recent years as rapid technological advances and substantially reduced prices for 3D printers have created opportunities in a wide range of areas. To accelerate progress in this emerging industry, in 2012 President Obama launched the National Additive Manufacturing Innovation Institute, an effort to provide infrastructure for 3D printing projects and to foster collaboration among commercial entities, academia, and the federal government.

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230. The government has invoked this provision to prohibit manufacturers’ off-label promotion in labeling. HUTT, MERRILL & GROSSMAN, supra note 19, at 926–27 (“[T]he government may allege a misbranding violation under section 301(a) or 301(k) [of the FDCA] because the labeling is ‘false or misleading in any particular’ (502(a)), or fails to include ‘adequate directions for use’ (502(b)(1), or both.”).

231. See supra Part IV.


While the technical aspects vary with different types of additive manufacturing, the basic concept of 3D printing is that components are built up layer by layer on an extremely small scale. Additive manufacturing is essentially the inverse of traditional subtractive manufacturing, which involves whittling down a starting block of material to create the desired shape. A 3D printer produces shapes based on data contained in an electronic file—usually a computer aided design (CAD) file or an image file created by scanning an object. Because the printer only uses that material necessary to build objects that correspond to the electronic file, additive manufacturing is more efficient and cost-effective than traditional manufacturing. 3D printers use a variety of different materials to build fully integrated shapes that are not possible using conventional manufacturing processes. Thus, this technology has the potential to substantially disrupt conventional product supply chains, including those in the pharmaceutical and medical device industries.

The FDA has already cleared at least eighty-five medical devices that are produced using 3D printing technology. These include products such as Oxford Performance Materials, Inc.’s OsteoFab® Patient-Specific Facial Device, a maxillofacial implant that is created from an individual’s magnetic resonance imaging (MRI) or computerized tomography (CT) scan, and Zimmer Biomet Holdings’ Unite3D™ Bridge Fixation System, which uses 3D-printed biomaterials and eliminates the need for plates, screws, and staples in joint fusion surgery. Other examples of 3D-printed medical devices that have been cleared by the FDA include hearing aids, skull plates, hip cups, spinal cages, surgical instruments, and Invisalign® braces.

While medical applications of 3D printing have so far focused predominantly on devices, the technology promises to revolutionize the pharmaceutical sector, as well. In August 2015, the FDA made

237. Id. at 2.
238. Id. at 3.
239. Id.
240. Maya M. Eckstein & Kyle Sampson, How Will the FDA Regulate 3D Printing?, INSIDE COUNSEL (Mar. 9, 2016), http://www.insidecounsel.com/2016/03/09/how-will-the-fda-regulate-3d-printing [https://perma.cc/YB3T-PD67] (explaining that almost all of the legally marketed 3D-printed medical devices were cleared by the FDA via the 510(k) pathway and a small number were authorized for emergency use, compassionate use, or via the custom device exemption pathway).
241. Id.
headlines when it announced the approval of Spritam, an epilepsy treatment touted as the first 3D-printed drug ever approved by the FDA. Spritam’s sponsor, Aprecia Pharmaceuticals, uses 3D printing to produce a “fast-melt” pill that is easier to swallow than tablets or capsules. The additive manufacturing process enables physicians to administer precise doses of medication uniformly calibrated to each patient’s unique needs.

3D-printed drugs and devices that are distributed through traditional channels indisputably fall within the FDA’s purview. Changes in manufacturing processes alone do not affect the scope of the FDA’s regulatory jurisdiction. However, this technology gives every individual who can afford to buy a 3D printer the ability to become a manufacturer. Hospitals, physicians, and even patients who purchase 3D printers can create their own individualized products on-site, a dramatic departure from the traditional distribution scheme whereby healthcare providers obtain identical, mass-produced items in bulk from a conventional supplier. The FDA may lack the statutory authority to regulate such local production of customized medical products. Creators of 3D-printed drugs and devices have several possible bases to challenge the agency’s regulatory authority. For instance, their activities may lack a connection to interstate commerce or may constitute aspects of the practice of medicine or the practice of pharmacy outside the bounds of the FDA’s regulatory jurisdiction.

The FDA has taken steps to address 3D printing, but the full regulatory implications of this disruptive technology remain unexplored. A key unanswered question is if and when the agency will designate 3D-printed products as “custom” devices. As amended in 2012, section 520(b) of the FDCA provides that the requirements of section 314 (performance standards) and section 515 (premarket approval)
approval) do not apply to a device that, to comply with an order of an individual physician or dentist, necessarily deviates from an otherwise applicable performance standard or premarket approval (PMA) application.\(^{250}\) The custom device exemption applies only if the device is not generally available for commercial distribution in finished form, is designed to treat “a unique pathology or physiological condition,” and is manufactured “on a case-by-case basis to accommodate the unique needs” of either an individual patient or an individual healthcare provider.\(^{251}\)

3D-printed products may fit the criteria for the custom device exemption, but it is not yet clear whether this is a viable regulatory strategy for manufacturers seeking to avoid federal regulatory requirements.\(^{252}\) The FDCA caps production of a custom device at five per year “of a particular device type.”\(^{253}\) Hence, the extent to which additive manufacturers may rely on the custom device exception critically turns on whether the FDA deems a 3D-printed product to comprise its own distinct device type.

In October 2014, the FDA held a public workshop on 3D printing for medical device makers, but regulatory policy issues were expressly excluded from the discussion.\(^{254}\) The FDA made no further public pronouncements on 3D printing until May 2016 when it issued a draft guidance entitled “Technical Considerations for Additive Device Manufacturers.”\(^{255}\) While the draft guidance provides useful insight into agency expectations regarding design, manufacturing, and product testing, many questions remain unanswered. Notably, the draft guidance lacks any information about the criteria that the FDA will use to deem an entity a product manufacturer. The draft guidance states, “point-of-care device manufacturing may raise additional technical considerations,” which suggests that point-of-care


\(^{251}\) Id.

\(^{252}\) Eckstein & Sampson, supra note 240.


\(^{254}\) Public Workshop — Additive Manufacturing of Medical Devices: An Interactive Discussion on Medical Considerations of 3D Printing, U.S. FOOD & DRUG ADMIN. (Oct. 8, 2014), http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM425399.pdf [https://perma.cc/YBC7-HRHY] (“We are not going to be talking about regulatory policy at all, that’s going to be a whole separate discussion . . . . So if you guys ask us any hypothetical questions, we’re going to say either no or that will be for a different workshop. Today we just want to be focused on technical considerations.”) (opening remarks of Matthew Di Prima, PhD, materials scientist within the FDA’s Division of Applied Mechanics in the Office of Science and Engineering Laboratories).

manufacturing falls within the scope of the guidance. However, it is unclear whether hospitals that own 3D printers will be considered manufacturers subject to device requirements. As the agency works to develop a comprehensive framework for 3D-printed products and producers, it will be against a backdrop of lingering uncertainty about the limits of its regulatory authority.

**B. Unprecedented Patient Participation**

The FDA’s struggle to keep pace with substantial technological advances in medical product development and distribution is compounded by fundamental shifts in the dynamics between patients, industry, and the agency. Historically, some patient groups have sought to influence regulatory policy by submitting their views to the FDA. An important example of sustained, successful patient advocacy is the effort by activists in the 1980s and 1990s to accelerate access to drugs to combat HIV/AIDS. But patient involvement in healthcare decision making has intensified to an unprecedented degree in recent years. The success of companies such as 23andMe, which provides direct-to-consumer genomic testing, and PatientsLikeMe, an online community whose members self-organize to conduct research and exchange medical information, reflects the growing prominence and sophistication of contemporary participatory health initiatives.

The rise of an increasingly influential patient empowerment movement has forced the FDA to significantly revise its review and

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257. Id.


260. See *Straight Talk with... Jamie Heywood*, 20 NATURE MED. 457, 457 (2014), [https://perma.cc/3WPS-EKNX](https://perma.cc/3WPS-EKNX) (“What we get from the patients is essentially a clinical interview that asks about how the patient is doing, the symptomology of their disease, what drugs they’re taking, what novel therapies they’re trying, what supplements they’re using and even lab values.”).
approval processes.\footnote{261} Congress mandated that the FDA incorporate patient stakeholders into agency proceedings when it passed the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).\footnote{262} Section 1137 of FDASIA directs the FDA to “develop and implement strategies to solicit the views of patients during the medical development process and consider the perspectives of patients during regulatory discussions.”\footnote{263} The agency has developed several patient engagement programs and activities in response to this provision. For example, it has appointed over two hundred Patient Representatives to participate on FDA Advisory Committees and panels and in product review meetings.\footnote{264} The agency has also taken steps to systematically obtain and consider patient perspectives on disease states, the benefits of their treatments, and the risks patients are willing to accept for access to effective therapies.\footnote{265}

But some patient advocacy groups are not content to wait for the FDA to revamp its policies and procedures. Nightscout, a project developed by the parents of children with Type I Diabetes, offers a striking illustration of a patient-led organization baldly challenging the regulatory status quo.\footnote{266} The goal of the Nightscout project is to enable patients and caregivers to hack into FDA-cleared devices in order to extract data and transfer them to the Internet, thereby allowing remote monitoring of blood glucose levels.\footnote{267} The project’s Facebook group grew from forty members to over 15,000 members in eighteen months, prompting FDA scrutiny of Nightscout’s efforts to create do-it-yourself mobile technology for diabetes management.\footnote{268} In meetings with Nightscout leaders, the FDA has expressed concerns about the project’s lack of infrastructure to systematically monitor and


\footnote{263} 21 U.S.C. § 360bbb-8c(a) (2012).

\footnote{264} FDASIA, supra note 261, at 7.

\footnote{265} Id. at 8–10 (summarizing the FDA Patient Network, Patient Reported Outcomes, Patient Focused Drug Development initiative, Professional Affairs and Stakeholder Engagement Staff, Patient Perspectives in Benefit-Risk Determinations for Medical Devices, Device Patient Preference Initiative, and Patient Engagement Advisory Committee).

\footnote{266} See Nightscout, Welcome to Nightscout (2016), www.nightscout.info [https://perma.cc/7CB5-MKJL] (prominently displaying the organization’s Twitter hashtag, #WeAreNotWaiting, an explicit reference to members’ impatience with current FDA regulatory hurdles).

\footnote{267} Id.

measure the technology’s safety and effectiveness. However, since Nightscout gives away information and services for free, the agency has limited statutory authority to proscribe the organization’s conduct.

The FDA can seize adulterated or misbranded articles, whether or not they have traveled in interstate commerce. However, the government cannot penalize or prosecute individuals who obtain products that have traveled in interstate commerce, modify those products, and then either use them or gratuitously share them with others. Given these statutory constraints, the FDA lacks authority to demand that the Nightscout community cease or scale back its operations. Although Nightscout appears eager to maintain good relations with the FDA, other patient advocacy groups may opt to take a more aggressive stance. If that happens, the agency will be forced to confront the limits of its regulatory power to police noncommercial patient-driven product development and dissemination.

C. Policy Considerations

There are several potential responses to the increasingly conspicuous gaps in the FDA’s regulatory authority. Congress has constitutional power under the Commerce Clause to enact legislation that expands the reach of the FDA’s jurisdiction and gives the agency express authority to ban the distribution of unapproved customized products. However, this tactic would face significant, likely insurmountable, political obstacles. Moreover, such an expansion of

269. Id.
270. Id. (“[Q]uestions have arisen about whether the Nightscout project and projects like it should escape FDA regulation simply because they are given away for free rather than sold.”).
272. See supra text accompanying notes 30–31; see also HUTT, MERRILL & GROSSMAN, supra note 19, at 281 (discussing the case of United States v. Olsen, 161 F.2d 669 (9th Cir. 1947), which held that the government could seize a misbranded device from a consumer’s private home, but noting that the government could not have penalized the appellee under FDCA § 301(k), because he did not hold the device for sale).
273. Comstock, supra note 268 (reporting that Nightscout has engaged with the FDA on a regular basis with the hope of receiving regulatory approval of the project).
274. See supra text accompanying notes 8–15.
275. The wave of “right to try” laws enacted in states across the country in recent years reflects widespread dissatisfaction with federal regulatory restrictions on access to experimental therapies whose safety and efficacy have not yet been shown. See Julie Turkewitz, Patients Seek ‘Right to Try’ New Drugs, N.Y. TIMES (Jan. 10, 2015), http://www.nytimes.com/2015/01/11/us/patients- seek-right-to-try-new-drugs.html?_r=0 (reporting that a string of states have passed or are considering laws that allow patients to obtain drugs that have not yet been approved by the FDA).
federal regulatory power may be unwise as a matter of policy. The FDA is designed to regulate the production and sale of mass-market articles distributed by nonprofessional manufacturers, not bespoke medications delivered by licensed healthcare professionals to provide individualized care to specific patients.\textsuperscript{276}

A preferable approach is to adopt a flexible, multi-pronged regulatory scheme based on principles of cooperative federalism.\textsuperscript{277} For instance, the FDA could establish a voluntary certification system for healthcare facilities and organizations that produce customized medical therapies, analogous to its program for outsourcing compounding facilities.\textsuperscript{278} International standards for medical 3D printing are being developed\textsuperscript{279} and should be incorporated into FDA certification criteria. Alternatively, the FDA could craft a set of model codes for customized medicine that are adopted and enforced at the state level, patterned after the model Food Code that has been adopted in all fifty states.\textsuperscript{280}

The Centers for Medicare and Medicaid Services (CMS) should also play a part in setting evidentiary benchmarks for demonstrating the clinical utility of customized therapies. By identifying treatment protocols that satisfy the medically “reasonable and necessary” statutory standard for reimbursement under federal programs,\textsuperscript{281} CMS could buttress the FDA’s efforts to ensure the safety and efficacy of customized medicine. Such federal standards would complement and reinforce state rules for professional licensure and standards of care under tort law.

\textsuperscript{276} See United States v. Franck’s Lab, Inc., 816 F. Supp. 2d 1209, 1245–46 (M.D. Fla. 2011) (“Because Congress appeared to be focused on the fact that manufacturing—unlike the practice of pharmacy—was conducted by unlicensed, unregulated nonprofessionals, it seems unlikely that it would have intended to subject professionally dispensed drugs to the same regulatory scheme.”).

\textsuperscript{277} See, e.g., Erwin Chemerinsky, Jolene Forman, Allen Hopper & Sam Kamin, Cooperative Federalism and Marijuana Regulation, 62 UCLA L. REV. 74, 77 (2015) (proposing that states be permitted to opt out of the CSA’s marijuana provisions, if they can show that they have devised a regulatory scheme that addresses the federal government’s safety concerns).

\textsuperscript{278} See supra text accompanying notes 151–68.

\textsuperscript{279} IEEE Standards Ass’n, P3333.2.5 – Bio-CAD File Format for Medical Three-Dimensional (3D) Printing, IEEE.ORG (2016), http://standards.ieee.org/develop/project/3333.2.5.html [https://perma.cc/4T2X-EYZU].


V. CONCLUSION

Congress created the federal regulatory scheme for medical products in response to the industrialization of the biomedical industry in the late nineteenth and early twentieth centuries. It enacted the FDCA at a time when the artisanal model by which healthcare providers prepared and administered therapies for individual patients gave way to the mass production of off-the-shelf products distributed to large patient populations. Today we are experiencing a revival of the artisanal model as technological and social changes spur a new type of customized medicine. Comprehensive federal regulation remains essential to ensure high product quality and safety standards. But the regulatory framework must adapt to address scientific advances in areas such as stem cell therapy and 3D printing, as well as the increasingly prominent role that patients play in drug and device innovation. These fundamental shifts in medical product development and distribution prompt a fresh look at the FDA’s role within our present healthcare regulatory system.

282. See Hutt, Merrill & Grossman, supra note 19, at 793 (“Long before there were independent drug manufacturers, apothecaries, now known as pharmacists, compounded drugs both for their own patients and in response to prescriptions of physicians. Companies engaged in the manufacture and distribution of drugs did not emerge in the United States until the latter half of the 19th century.”).