

THE FDA'S MISGUIDED
REGULATION OF
STEM-CELL PROCEDURES:
How Administrative
Overreach Blocks
Medical Innovation

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The current biomedical revolution has its most tangible application to ordinary people in the new cutting-edge techniques devised by individual physicians for the cure and palliation of chronic and degenerative diseases. The rate of advance in this area is a testimony to the creative forces unleashed by the decentralized control over medical procedures. But that progress is now threatened by the federal Food and Drug Administration (FDA), which seeks to extend its statutory authority to subject these practices to the same oversight that is given to large drug manufacturers in the design and production of new products for the mass market. One area over which the FDA has asserted its power is private adult stem-cell treatment, which has developed treatment protocols that were not possible a generation, or even a decade, ago.

The FDA has taken the aggressive position that it has oversight authority over any stem-cell procedure that reinjects harvested stem cells into the same person from whom they were removed, so long as those cells were grown and cultured outside the human body. Indeed, one promising use of this technique for heart-attack patients was scuttled after the FDA stepped in to require extensive clinical trials over a hospital that could not afford the high costs of FDA compliance. It is unclear how many promising similar avenues have been shut off by physicians who were unwilling to run the FDA gauntlet of initial approval and constant oversight to bring their techniques to the market in the United States without risk of regulatory censure. But two physicians utilizing one such approach are now challenging in federal court the FDA's authority to regulate—and effectively prohibit—the use of adult stem cells to mitigate the effects of one widespread malady: degenerative joint conditions, including those caused by sports injuries.

Regenerative Sciences, LLC v. United States, now pending before the U.S. Court of Appeals for the D.C. Circuit, concerns a stem-cell procedure developed by Colorado doctors Christopher Centeno and John Schultz. The doctors' procedure involves the patient-specific extraction of blood and bone marrow stem cells, centrifuged, grown, and sterilized in their in-house laboratory, and then reinjected into the patient's own body. The FDA claims that the doctors' procedure involves the manufacturing of "drugs" for sale in "interstate commerce" that falls within its statutory purview to prevent the spread of "communicable diseases."

This paper analyzes the government's position on legal and policy grounds. Legally, the government incorrectly reads the "interstate commerce" clause of the Federal Food, Drug and Cosmetic Act of 1938 (FFDCA) as identical to the broad authority that contemporary cases attach to the Commerce Clause in the U.S. Constitution. A close reading of the statutory text and history suggests that it is anything but that. Properly read, the clause clearly places the doctors' procedure outside the FDA's purview. Similarly, the government's broad definition of the doctors' procedure as a "drug" rather than the "practice of medicine" strains the ordinary meaning of both terms. Read as a whole, the government's theory boils down to the proposition that its power to prevent the spread of "communicable diseases" applies to the doctors' procedure because the patient's own stem cells may become contaminated during the process, as could happen in all common forms of surgical procedures widely understood to fall outside FDA authority. This sweeping assertion of new statutory authority, if consistently applied, would grant the FDA broad powers to regulate common surgical practice, traditionally regulated by the states.

This paper reviews and rebuts specific arguments as they relate to these issues in more detail:

1. **Interstate Commerce.** The FFDCA gives the FDA authority to regulate an act involving a drug if the act occurs "after shipment in interstate commerce and results in such article being adulterated or misbranded." The government,

as well as the district court that ruled on the government's behalf below, has argued that the broad deference that the Supreme Court affords Congress's constitutional power to regulate interstate commerce gives the FDA ample authority to oversee any local business that receives supplies or customers from out of state. What the government position misses is that the *statutory* authority does not extend as far as the *constitutional* authority. The FFDCa was enacted four years before the Supreme Court's 1942 decision in *Wickard v. Filburn*, which expanded Congress's power over interstate commerce to reach purely intrastate activities that influenced interstate commerce. It was only as late as 1964 in *Katzenbach v. McClung* that the Supreme Court held that Congress's power over interstate commerce covered any business that received some of its supplies through the channels of interstate commerce. In context, the statutory definition of interstate commerce in the FFDCa—like the parallel language in the statute's predecessor, the 1906 Pure Food and Drug Act—makes conscious and explicit reference to the pre-*Wickard* account of interstate commerce. The stem-cell procedure developed by doctors Centeno and Schultz clearly is not interstate commerce as defined in the statute.

2. Drugs Versus the Practice of Medicine. The government and district court also misfire when they assume that the stem cells removed from and reinjected into patients are “drugs” subject to FDA regulation rather than the “practice of medicine,” the regulation of which Congress has traditionally left to the states. The traditional mass-production manufacturer that makes a drug that is sold downstream for physicians’ use has little in common with the physician who grows a patient’s own stem cells for reinjection into the same patient. Those differences all cut in favor of removing the FDA from a role of direct oversight over the physician’s practice. Although the government insists that the FDA should be afforded substantial deference in defining the meaning of the term “drug,” the Supreme Court has often cut back against FDA definitions that generate major extensions of the agency’s jurisdiction into areas already subject to alternative schemes of regulation, as in the Court’s 2000 decision in *FDA v. Brown & Williamson Tobacco*.

3. Communicable Diseases. The government claims that the FDA may also regulate the Colorado doctors’ stem-cell procedures under the 1944 Public Health Service Act, which gives the agency authority “to make and enforce such regulations as ... 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.” Whatever risks the stem-cell procedure developed by Centeno and Schultz might create for the doctors’ patients—and there are no documented cases of adverse side effects cited by the FDA—such risks would not involve “communicable diseases,” according to those words’ ordinary meaning, given that their procedure involves injecting not foreign stem cells but the patients’ own stem cells into their own bodies. The government’s fear that under the Colorado doctors’ procedure, “samples may be improperly labeled, mixed up with other cells, and contaminated or exposed to communicable disease agents,” is doubtless correct but only identifies risks routinely found in a clinical setting whenever a lab technician makes a similar error. These local issues should be, and typically are, regulated by local public health authorities. Such errors are far more likely to happen in routine hospital settings when blood, stool, or urine samples are taken from sick individuals who are known to carry various infectious agents than in the controlled process used in the Colorado doctors’ lab. Tellingly, the FDA’s own report asserting regulatory authority over stem-cell procedures of the sort developed by Centeno and Schultz impliedly claims the power to control any common form of surgery that requires drug use, which, in practice, is all surgeries.

The legal questions at play in *Regenerative Sciences* highlight broader policy questions, particularly the disconnect between the FDA’s review standards and the new style of personalized medicine. The FDA operates under a strong premarket clearance system, which places heavy burdens on the proponents of new therapies to prove them safe

and effective. The FDA model of large double-blind clinical trials imposes enormous costs, which today could run to hundreds of millions of dollars and years of delay in getting new molecular entities to market. The FDA then sets a high bar for the warnings and instructions under which these products must be sold. Although large trials and strict controls may work well for testing a new high-blood-pressure medicine on a large population, no small, customized medical operations can find funds to pay the compliance costs associated with FDA clinical trials. The FDA rules thus freeze out of the market the people in the best position to make decisive medical innovations.

The decision to receive the stem-cell treatments offered by the Colorado doctors resembles the practice of medicine far more than the large-scale development, marketing, and sale of single-formula pharmaceutical products and medical devices. Control over critical medical procedures should lie with patients themselves, in consultation with their own physicians subject to state regulatory authority, and not with the FDA. The record in *Regenerative Sciences* demonstrates that the FDA has neither the medical insight nor the legal expertise to justify the extraordinary new powers that it claims for itself over the practice of medicine.

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THE FDA'S MISGUIDED REGULATION OF STEM-CELL PROCEDURES: HOW ADMINISTRATIVE OVERREACH BLOCKS MEDICAL INNOVATION

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INTRODUCTION: A MATTER OF LIFE AND DEATH

In March 2003, *Wired* magazine reported that sixteen-year-old Dimitri Bonnville was shot in the heart with a three-inch fishing nail while working on some home repairs.¹ An open-heart surgery failed, so as a last measure of desperation, Bonnville was rushed to Beaumont Hospital in Royal Oak, Michigan, where Dr. William O'Neill headed a team of physicians that tried a novel procedure that saved Bonnville's life. The process started with the injection of a drug that stimulated the growth of stem cells in his body, which the doctors then harvested. Once harvested, these cells were transferred into the front wall of Bonnville's heart, which had ceased functioning before the procedure had started. The stem cells took: a week later, Bonnville was able to return home. Four months later, he was playing basketball. The recovery was unprecedented. The *Wired* story ended with this line: "Beaumont doctors said they hope soon to begin clinical trials of their stem-cell technique."

Those trials never took place.² Dr. O'Neill had planned to run a clinical trial on 400 patients with recent major heart attacks, half of whom would have the experimental infusions and half of whom would have dummy infusions. The federal Food and

Drug Administration (FDA), however, vetoed the procedure as too risky without prior animal testing. Dr. O'Neill disputed this decision for two reasons. First, he claimed that injecting a person's own cells into his or her body did not present the rejection risk that is common in other situations. Second, he insisted that the risk of not having the procedure was great for the patient as well: 35 percent of those eligible for the trials were likely to die within the year, which helps explain why at least a dozen people in the Detroit area tried to join the trial that never took place. Dr. O'Neill "predicted that human trials would push quickly ahead in Europe or South America, where 'regulatory bodies are less averse' to new procedures."³ He rightly anticipated that the barriers to clinical trials in the United States, which only tightened in the ensuing years, would block these extensive trials that could not be financed out of the revenues of some future patented pharmaceutical.

The Beaumont Hospital never sued to challenge the power of the FDA to regulate these stem-cell procedures. Indeed, it is unclear how many promising similar avenues have been shut off by physicians who were unwilling to run the FDA gauntlet. Many issues that arose in that case, however, are now before the U.S. Court of Appeals for the District of Columbia, in *Regenerative Sciences, LLC v. United States*,⁴ where doctors legally challenged an FDA enforcement action against the administration at their clinic of an orthopedic stem-cell therapy. One central question in this complex litigation is whether stem-cell treatments that are being developed should be regarded as the administration of a drug therapy that is under the thumb of the FDA or the practice of medicine, which is allowed to proceed independently of FDA authority.⁵ Where is the line between these two activities, one regulated and the other not? And, in disputed cases, who gets to draw it? After its success in the district court for the District of Columbia, the FDA now holds the trump card, and the smart money says that it is likely to prevail on appeal. But that conclusion should be resisted on both legal and policy grounds. On the

former, the legal interpretations used to prop up the FDA position have an all too familiar "Alice in Wonderland" quality. On policy grounds, the patient risk, as patients would judge it, does not justify the harm that is done to medical innovation.

I. BACKGROUND: THE REGENERATIVE SCIENCES CASE

Regenerative Sciences, LLC v. United States involves stem-cell procedures that apply to far less dramatic situations than the life-and-death crisis at Beaumont Hospital. *Regenerative Sciences* revolves around the proper classification of the "Cultured Regenexx Procedure" that was devised by two physicians, Christopher Centeno and John Schultz, for treating patients suffering from certain musculoskeletal damage, which can arise from a variety of causes, including athletic injuries. The defendant's website, www.regenexx.com, describes the doctors' RegenexxTM Procedure as "an alternative to [certain] types of" traditional knee-replacement surgeries⁶ that can treat "[f]ractures that have failed to heal, joint cartilage problems, partial tears of tendons, muscles, or ligaments, chronic bursitis, avascular necrosis of the bone, and lumbar disc bulges."⁷ Elsewhere the defendants' website claims: "The Regenexx Procedures are a family of non-surgical stem cell and blood platelet treatments for common injuries and degenerative joint conditions, such as osteoarthritis and avascular necrosis. These stem cell procedures utilize a patient's own stem cells or blood platelets to help heal damaged tissues, tendons, ligaments, cartilage, spinal disc, or bone."⁸

The Regenexx procedure operated as follows. After determining whether someone was a good candidate for the procedure, the physicians extracted marrow and blood samples from the patient. These samples were sent to a laboratory, where they were centrifuged, to isolate active cells from various contaminants, including surface proteins that could set up immunological side effects. Thereafter, the laboratory treated the patient's blood platelets with com-

monly used nutrients, infused them into the marrow sample, and incubated the material in a medical-grade plastic flask. After the resulting mesenchymal stem cells (MSCs) adhered to the plastic flask for several days, the cells were removed and placed in a new plastic flask, where the cycle was repeated with new platelets drawn from the patient's blood and a new round of basic nutrients. After two weeks—following several iterations necessary to grow sufficient quantities of the needed stem cells for injection into the patient's own joints—the resulting material was sent to the University of Colorado for quality testing. This procedure is commonly called an “autologous use,” in that it involves solely “the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.”⁹

The opening salvo in this dispute was a letter dated July 25, 2008, sent to Regenerative Sciences from Mary A. Malarkey, director of the Office of Compliance and Biologics Quality at the Center for Biologics Evaluation and Research at the FDA, which stated: “Please be advised that in order to introduce or deliver for introduction a drug that is also a biological product into interstate commerce, a valid biologics license must be in effect. Such licenses are issued only after a showing of safety and efficacy for the product's intended use. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug application in effect as specified by FDA regulations.”¹⁰

The letter was brief and did not identify, or even ask whether Regenerative Sciences knew of, any reported instances of adverse medical side effects associated with the procedure, let alone any that arose solely from its proper application. The letter was followed by two site visits to Regenerative Sciences' facilities in February and April of 2009, and again twice in June 2010, after which the FDA issued its order to shut down the Regenexx facilities on the ground that it did not comply with the agency's current good manufacturing practices (CGMP).¹¹ The

FDA's communications with Regenerative Sciences make it appear that the full weight of FDA premarket clearance procedures applies to stem-cell medical procedures of the type developed by physicians Centeno and Schultz when conducted anywhere in the United States.

II. ANALYSIS

The issue in *Regenerative Sciences* is whether the use of these stem cells, isolated under these procedures, should be subject to regulation by the FDA. Should the FDA be without such regulatory authority, the alternative legal regime need not be one of no regulation on matters of health and safety but rather of regulation through the standard devices by which the medical profession is regulated. The two regulatory systems are starkly different in their approach: regulation by the FDA involves a complicated, costly, years-long premarket-approval process that keeps products and procedures off the market until the FDA is satisfied that they are safe and effective.¹² In contrast, the *ex post* review of medical procedures only kicks in when an event, such as a physician review panel, lawsuit, or patient complaint, triggers a response from a public authority.¹³

The litigation dispute over the regulatory procedures that might apply to Regenerative Sciences is not cast in these functional terms, beyond the commonplace general assertion that the FDA's procedures are advanced “in the interest of public safety” for which the agency provides “an appropriate regulatory structure.”¹⁴ Rather, the litigation takes place within a network of complex statutory and regulatory provisions that worry more about the interaction of such key terms as “communicable diseases,” “interstate commerce,” and “held for sale” than they do about the relative efficacy of these alternative regulatory regimes.

Indeed, the best way in which to parse the *Regenerative Sciences* decision in the district court is to follow the complex interactions among the various

statutes, regulations, and reports before attempting to evaluate the merits of the district court's decision that the FDA may exercise legitimate legislative authority over the practices, which follows in Part A. After that breakdown of the textual pyrotechnics is completed, I turn in Part B to a functional analysis that advances the proposition that the shift from a decentralized, largely *ex post*, regulatory regime to an aggressively centralized *ex ante* system of regulation does a disservice to the public safety that our system of health-care regulation is designed to advance. In making this claim, I am not arguing in this context that pure contractual solutions should be accepted, no matter how attractive that solution may be. Instead, the discourse in this area starts with accepting the claim of potential risks in communication and disease that call for some government oversight, so that the only question is what form, at what time. But even within that constraint, the received wisdom embodied in the cases, statutes, regulations, and reports is sadly deficient and in need of fundamental reorientation.

A. Statutory Analysis

Our statutory analysis focuses on legislative provisions that together define the power of the FDA in this context, under two statutes: the Federal Food, Drug, and Cosmetic Act of 1938 (FFDCA);¹⁵ and the Public Health Service Act of 1944 (PHSA).¹⁶ The FFDCA deals with the definition of “interstate commerce” as it is found in sections 201 and 301 of the original statute, codified at 21 U.S.C. §§ 321 and 331¹⁷ and the definition of “drug” as also codified at 21 U.S.C. § 321. Section 361 of the PHSA, codified at 42 U.S.C. § 264, defines the power of the FDA to regulate “communicable diseases.”¹⁸

Before turning to the statutory provisions in detail, I note that these statutory provisions contain many gaps, which are generally filled in by regulations found at 21 CFR § 1271, initially issued in May 1998, and subsequently modified from time to time, most notably in 2005. The FDA's original 1998 regulations dealing with cellular and tissue-

based products (“Human Cells, Tissues, and Cellular and Tissue-Based Products,” or HCT/P's)¹⁹ covered only those transfers of human cells or tissues “into another human”—so-called allogeneic transfers, as opposed to the autologous transfers at issue in the Regenexx procedure. The newer 2005 definition—which was adopted without notice or hearing—vastly expands the scope of the regulation to cover all “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient,” so that the risks from autologous transfers are treated on a par with those from allogeneic transfers.²⁰

The FDA's regulations were not issued in a void but developed in part from a prior 1997 report by the agency, *Proposed Approach to Regulation of Cellular and Tissue-Based Products*, published on February 28, 1997 (henceforth referred to as the “1997 Report”).²¹ Although this report laid much of the groundwork for the comprehensive regulations eventually implemented in the regulations one year later, subject to the key 2005 amendment noted above, it strikingly contained no external references to the statutory language, to the applicable case law, or to any of the medical or legal literature on which its conclusions rested. Rather, the 1997 Report reads like a meditation on how the FDA should approach this problem. The most evident danger of this particular approach is that the want of any ballast or counterweight invites an aggressive expansion of the FDA's regulatory authority in ways that do not comport well with the relatively modest statutory framework that it seeks to apply, to which I now turn.

1. The FFDCA: Defining Interstate Commerce and Drugs

Under the FFDCA, the FDA has the power to prohibit “[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded,”²² as well as the “alteration,

mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, 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.”²³

The FFDCA further defines “interstate commerce” as follows: “The term ‘interstate commerce’ means (1) commerce between any State or Territory and any place outside therefore, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body.”²⁴ The statute also next defines “drugs” as:

- (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals.²⁵

This article will consider the application of the statutory definitions of “interstate commerce” and “drugs” as applied to the *Regenerative Sciences* case, in turn.

a. Interstate Commerce

In a startling omission, neither the FDA in its 1997 Report nor Judge Rosemary Collyer in her district court opinion cites the narrow statutory definition of commerce contained in the 1938 statute. The government contends, correctly, that the FDA’s power over interstate commerce necessarily preempts any contrary claim under Colorado’s law.²⁶

Yet the statutory question here is not one of preemption but of the scope of statutory authority, and on this question, the government’s claim is fatally overbroad when it states that “in conducting [their] business, defendants receive and use multiple drug components that have traveled in interstate commerce, and they attract patients from out-of-state to purchase their drug product.”²⁷

The statutory requirement set out above is not whether a reagent used in the process has moved in interstate commerce but whether the dangerous (“adulterated or misbranded”) article itself has moved in interstate commerce. The key government error is to rely on cases that discuss the scope of Congress’s power to regulate various activities under today’s expansive interpretation of the Constitution’s Interstate Commerce Clause. To be sure, under the modern law, there is ample authority to exercise federal power over any local business that receives supplies or customers from out of state. That was the test developed in dealing with the Civil Rights Act of 1964, which essentially brought all local restaurants, including Ollie’s Barbecue, under federal control.²⁸ If that test is applied here, the link to interstate commerce is always established, without looking to see whether the dangerous product itself has moved in interstate commerce, for there is always some gauze or solution that has moved in interstate commerce. What the government misses is that the reach of *statutory* authority need not extend as far as the scope of *constitutional* authority. Under the FFDCA, the government does not gain power over local activities whenever a safe (indeed, FDA-regulated) product is shipped in interstate commerce and reaches its final destination.

The historical evolution of these statutory provisions bears out this conclusion. In her brief treatment of the interstate commerce issue, Judge Collyer was content to quote from key passages in Chief Justice William Rehnquist’s decision in *United States v. Lopez*,²⁹ which delineated three heads of federal power under the Commerce Clause: “(1) ‘channels of interstate commerce’ (2) ‘instrumentalities of in-

terstate commerce, or persons or things in interstate commerce,’ (3) ‘those activities having a substantial relation to interstate commerce,’ or ‘those activities that substantially affect interstate commerce.’”³⁰ That last, all-inclusive category rests in part on the authority of the Supreme Court’s 1942 decision in *Wickard v. Filburn*,³¹ which held that the Constitution’s Interstate Commerce Clause reached feeding one’s own wheat to one’s own cattle because of its effects in aggregate on interstate commerce. Thereafter, Judge Collyer quotes the following passage from the Court’s 1947 decision *United States v. Walsh*,³² which specifically addresses the parallel provision under the FFDCA: “The Federal Food, Drug, and Cosmetic Act rests upon the constitutional power resident in Congress to regulate interstate commerce. Article 1, § 8, cl. 3. To the end that the public health and safety might be advanced, it seeks to keep interstate channels free from deleterious, adulterated and misbranded articles of the specified types. *United States v. Dotterweich*, 320 U.S. 277, 280 (1944). It is in that interstate setting that the various sections of the Act must be viewed.”³³

That was indeed the situation in *Dotterweich*, which involved “a jobber in drugs” who “purchased them from their manufacturers and shipped them, repacked under its own label, in interstate commerce.”³⁴ Neither *Walsh* nor *Dotterweich* rested on the modern constitutional interpretation of the Constitution’s Commerce Clause but solely on the statutory requirement “to keep interstate channels free from deleterious, adulterated and misbranded articles.”³⁵ In context, that language—enacted in 1938, four years before *Wickard* was decided—is a conscious reference to the pre-*Wickard* account of interstate commerce that has nothing to do with feeding one’s own grain to one’s own cows.

Thus, under the 1938 FFDCA, “interstate commerce” does not include those activities that take place within individual states, unlike similar activities that take place within the Territories.³⁶ The passage from *United States v. Walsh* cited by Judge Collyer,³⁷ in historical context, stands for a proposi-

tion that is the exact opposite proposition that she quotes it for.

Walsh was brought under section 21 U.S.C. § 331(h) of the 1938 FFDCA,³⁸ whose guaranty provision itself contains no reference to interstate commerce. The Supreme Court nonetheless held that the provision was constitutional, after all: “[W]here such a guaranty, as in this case, is given to a dealer regularly engaged in making interstate shipments and who may therefore have need of the guaranty, § 301(h) imposes liability on the guarantor if that guaranty turns out to be false. And that liability attaches even where the particular shipment which renders the guaranty false is not alleged to have been an interstate one.”³⁹

Walsh was barely defensible only because it was limited to “a dealer regularly engaged in making interstate shipments,”⁴⁰ a description that does not remotely describe the situation of Regenerative Sciences. Writing about the case in 1954, the *Harvard Law Review*, in its “Developments in the Law” issue, concluded that *Walsh* “rests on rather debatable statutory construction, and since the primary purpose of the Act is to prohibit the movement of certain articles in interstate commerce, it is hard to see why in this one situation liability should depend on the kind of business which the defendant’s vendee conducts.”⁴¹

It is worth recalling that the 1906 version of the Pure Food and Drug Act had a similarly restrictive scope when it provided that “it shall be unlawful for any person to manufacture within any Territory or the District of Columbia any article of food or drug which is adulterated or misbranded, within the meaning of this Act”⁴²—which, in turn, meant that it did not apply to the manufacture of drugs within the several states. The 1906 act did, however, provide in section 2 “[t]hat the introduction into any State or Territory or the District of Columbia from any other State or Territory or the District of Columbia, from any other State or Territory or the District of Columbia, or from any foreign country, or shipment to any

foreign country of any article of food or drugs which is adulterated or misbranded, within the meaning of this Act, is hereby prohibited.”⁴³ At no point, therefore, did the 1906 act apply to the manufacture of drugs within the several states.

Nor is this an accident. The careful wording of the 1906 statute was included to bring the statute within the constitutional limitations that were firmly established at the time. The Supreme Court’s 1895 decision in *United States v. E. C. Knight*⁴⁴ had kept the U.S. from regulating manufacture within a state. The authority of the U.S. to regulate interstate shipments of these drugs was, in 1906, only of recent origin insofar as it depended on the 1903 decision of the U.S. Supreme Court in *Champion v. Ames*,⁴⁵ which held that the U.S. could regulate the shipment of lottery tickets in interstate commerce even when they were legal in both the state where they were manufactured and the state in which, after shipment, they were sold. That decision was strictly necessary to ground the FDA because there was no evidence that the misbranded or adulterated drugs shipped in interstate commerce posed any threat to the modalities of transportation. The definition of interstate commerce used in the 1938 FFDCA faithfully tracked all these preexisting limitations, which are simply read out of the statute under the interpretation advanced by the government and accepted by Judge Collyer.

“Held for Sale” After Shipment in Interstate Commerce

The difficulties in the government’s interpretation of section 331(k) extend to other elements of the statutory provision, apart from the definition of “interstate commerce.” Section 331(k) applies only to an article “held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.”⁴⁶ As a simple linguistic matter, the notion of goods “held for sale” suggests that they count as inventory that can be sold to unidentified customers in their ordinary course of the business of a firm. The most ob-

vious examples are the various articles of commerce that are held for sale in an ordinary pharmacy. The term does not appear in any sensible way to apply to the provision of the autologous reinjection of stem cells, after growth and purification, as part of a general medical procedure.

That restrictive view of the “held for sale” language is confirmed by the Supreme Court decision in *United States v. Sullivan*,⁴⁷ which treats the provision as dealing with the ordinary flow of standard goods through channels of interstate commerce. *Sullivan* involved a criminal prosecution against a retail druggist for selling misbranded drugs—in this instance, “a number of bottles, each containing 1,000 sulfathiazole tablets.”⁴⁸ The bottles had been properly shipped in interstate commerce from Chicago to Atlanta, where they were received by a local wholesaler who resold these pills in their proper containers to the defendant in an intrastate transaction. On two occasions, the defendant sold to his customers—in the ordinary course of his business—bottles of 12 pills, labeled sulfathiazole, without the required statutory warnings. These transactions took place some nine months after the shipment of drugs arrived in Atlanta from Chicago.

The defense to the prosecution in *Sullivan* was that the defendant had engaged in a wholly intrastate transaction that should not be brought under a criminal statute. That argument had prevailed in the circuit court⁴⁹ but was rejected in the Supreme Court on the ground that the transaction fell unambiguously in section 331(k), even though at the time that section did not contain the parenthetical phrase “(whether or not the first sale),” which was introduced in a 1948 amendment to the statute.⁵⁰ The 1948 amendment was sparked by the antigovernment decision in the court of appeals,⁵¹ and its purpose was to reinforce Congress’s intention that the FDA’s authority was not limited by a gap in the chain of shipment after particular goods left interstate commerce, without regard to how long after the initial interstate shipment the misbranding occurred, how many intrastate transfers had inter-

vened, or who had received the articles at the end of the interstate shipment.⁵² The Supreme Court reached its conclusion notwithstanding the circuit court's thought that the government's broad "construction would raise grave doubts as to the act's constitutionality."⁵³

No one can read the full text of *Sullivan* and come away with the impression that, either before or after the 1948 amendment, the FFDCA reaches any article that had never been in interstate commerce. Yet the government's brief in *Regenerative Sciences* mangles *Sullivan* when it says: "The Supreme Court has previously rejected a constitutional challenge to the application of section 331(k) to intrastate sales that followed interstate shipment of the product," without noting that the stem cells at issue in *Regenerative Sciences* had never moved in interstate commerce.⁵⁴ The district court similarly mischaracterizes the statute by noting: "[A] doctor who ha[s] held drugs for use in his practice ha[s] held those drugs for sale within the meaning of [§ 331(k)]."⁵⁵

Both the government and the district court reach this conclusion through a misreading of the important 1981 decision of *United States v. Evers*.⁵⁶ The district court credits the government's contention that in *Evers*, "Dr. Evers 'held (Calcium EDTA) for sale' when he maintained a supply of the drug for use on his own patients at [his] Ra-Mar Clinic."⁵⁷ But that contention is strained, at best.

Evers involved a criminal prosecution in which the government challenged Evers's efforts to promote his Calcium EDTA, an unapproved chelating agent that uses heavy-metal ions to alter blood balances.⁵⁸ The government's theory was that Evers had "misbranded" the drug under the statutory definition that holds a drug misbranded when its labeling does not contain "adequate directions for use."⁵⁹ In this instance, the government lost because, although Evers had promoted the drug actively, he had not made any sales to physicians. He was the only person who had sold the product, and the Court quite

properly concluded that it was "nonsensical" to concoct a criminal charge that required Evers to provide an adequate warning to himself.⁶⁰

Having reached that conclusion, the earlier question of whether these drugs were held for patient use was not necessary for the Court's decision. To be sure, the Court mentioned the issue; but it did not endorse the government's position. Instead, the Court simply noted that "the government *argues* that Dr. Evers 'held (Calcium EDTA) for sale' within the meaning of section 301(k) [§ 331(k)] because he maintained a supply of the drug for use on his own patients," a point that it never decided.⁶¹

Evers, then, does not support the government's position on two key points about the FDA's authority. First, *Evers* observes that the district court had viewed FDA prosecutions for doctors' decisions to prescribe drugs for "off-label" uses⁶² because "as a licensed physician [Dr. Evers] has a right to prescribe any lawful drug for any purpose, whether or not that purpose has been approved by the FDA."⁶³ The district court agreed with Dr. Evers and held that no misbranding could result from a doctor's prescription of a lawful drug to his own patients. Second, the district court had relied on the statutory intent, "which seeks to avoid interference with 'the practice of medicine'; on supposed limitations on the powers of Congress; and on the patient's constitutional right to privacy in the context of medical care."⁶⁴

b. Drug Manufacture Versus the Practice of Medicine

This passage from *Evers* offers an instructive segue to a second critical question raised in *Regenerative Sciences*: Were Drs. Centeno and Schultz engaged in the practice of medicine, or in the manufacture of a drug when they engaged in their Regenexx procedures?

Once again, the inquiry starts, but does not end, with key statutory definitions. As previously noted, the FFDCA defines "drug" in 21 U.S.C. § 321:

- (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals.⁶⁵

This critical provision sets in motion any inquiry into the location of the line between the manufacture of a drug product, which is subject to extensive FDA oversight, and the practice of medicine, which is not. The section offers no special statutory guidelines, so finding the line reduces itself to understanding the ordinary meaning of both terms. This standard should be uncontroversial: in the context of the Controlled Substances Act, the federal government has embraced the position that “[t]he ordinary meaning of the term ‘medical’ is ‘pertaining or related to the healing art’ or ... to ‘medicine.’”⁶⁶ This ordinary meaning accords with Colorado’s statutory definition of medicine as “[h]olding out one’s self to the public within this state as being able to diagnose, treat, prescribe for, palliate, or prevent any human disease, ailment, pain, injury, deformity, or physical or mental condition,” or recommending or prescribing such treatments.⁶⁷

Moreover, as a matter of ordinary English, the two doctors are not “manufacturers” because that notion carries several key characteristics absent in *Regenerative Sciences*. We do not have a single firm that takes inputs from a variety of sources, from which it makes standardized products that it ships through a chain of distribution after which they are held for sale to customers in the ordinary course of business. The process in question would normally be regarded as a provision of services for which the growth of the cells under these highly specified procedures would

be regarded as, at most, an “incidental” element to the transaction, just as a dentist who prepares mixtures for fillings is regarded as having supplied services and not as having manufactured and sold a mixture of silver and bonding solutions.

An Analogy from Tort Law

The relevant inquiry here is not unique to the Regenxx procedure but is also found in tort law, where it is often necessary to distinguish between the sale of a product, including, of course, a drug, and the provision of a service, including medical services. The standard distinction in tort law squarely cut against the FDA’s broad oversight claims.

Start with the key product-liability provision found in section 402A of the Second Restatement of Torts,⁶⁸ which applies to a “seller” of a “product.” Both these terms have given rise to an extensive literature in the effort to deal with over- and under-inclusion in cases in which the sale of products and the provision of services are, in fact, mixed. Thus, in *Murphy v. E. R. Squibb & Sons, Inc.*,⁶⁹ the California Supreme Court held that a pharmacist who filled a prescription for DES was engaged in the provision of a service and not the sale of a product. The court’s reasoning was that the pharmacist was required to meet “stringent educational and professional requirements for obtaining and retaining a license.”⁷⁰

In dealing with this definitional issue, it should be noted that in the product-liability context, the shift from strict liability to negligence is huge. To be sure, in the original strict liability case of the exploding Coke bottle in *Escola v. Coca-Cola Bottling Company of Fresno*,⁷¹ the California Supreme Court upheld the jury verdict under a conventional negligence rule, aided by the presumption of *res ipsa loquitur*—the thing speaks for itself. Justice Roger Traynor wrote his famous concurrence in favor of a strict liability rule, which he narrowly defined “in terms of the safety of the product in normal and proper use,” which “should not extend to injuries that cannot be traced to the product as it reached

the market.”⁷² Given that limitation, the application of *res ipsa loquitur* under a negligence system means that few, if any, cases come out differently under the two theories, which is why the political debates over product liability did not heat up until after those limitations were successfully removed in the years after the adoption of section 402A.⁷³ But with pharmacy services, *res ipsa loquitur* can never be invoked to hold liable the pharmacist, who has no control over the research and marketing of the product in question.

In the end, the courts retreated from strict liability for pharmacists because they were hard-pressed to think that pharmacists as a class should be required to answer for the development or approval process for the thousands of products that they routinely dispense. Their function is only to fill prescriptions and properly label the drugs sold. If either of those functions is not done properly, *res ipsa loquitur* would aid the plaintiff. But section 402A, which was promulgated before these specialized issues of distribution came to the fore, is ill-suited to that purpose. The judicial decisions thus represent an effort to cut back the scope of that provision to manageable proportions, by holding the pharmacist responsible for his own actions and for nothing more. The same logic applies in those cases in which plaintiffs seek to use a product-liability theory against a doctor or hospital, on the ground that at least one of the health-care providers’ proper medical functions is to supply particular products, typically acquired from an upstream manufacturer, to particular patients. Thus, in *Cafazzo v. Central Medical Health Services, Inc.*,⁷⁴ the court refused to hold a hospital and physician strictly liable for the defects in a mandibular prosthesis that the physician supplied to the patient and then implanted in surgery. The product suit was brought against the physician when the manufacturer went bankrupt. The sale was treated as “ancillary” to the provision of medical services and thus outside the scope of section 402A of the Second Restatement:

While we do not slavishly adhere to the language of 402A, the rule enunciated there, as

with other non-statutory declarations, is a common law pronouncement by the court, which “always retains the right and the duty to test the reason behind a common law rule in determining the applicability of such a rule to the facts before it.”...

However, to ignore the ancillary nature of the association of product with activity is to posit surgery, or indeed any medical service requiring the use of a physical object, as a marketing device for the incorporated object. This is tantamount to deciding that the surgical skills necessary for the implantation of, e.g., mandibular prostheses, are an adjunct to the sale of the implants. Moreover, under such a theory, no product of which a patient in any medical setting is the ultimate consumer, from CT scanners to cotton balls, could escape the assignment of strict liability. Clearly, the relationship of hospital and/or doctor to patients is not dictated by the distribution of such products.⁷⁵

Once again, the best explanation for using the negligence standard is functional, not linguistic. No physician can be exempted from the law of medical malpractice because he or she is a product seller. Clearly, the implantation of devices and the injection of various kinds of drugs and fluids is an ordinary part of medical practice, all of whose aspects should be governed by a single liability standard. Neither efficient allocation of resources nor the provision of cutting-edge medical care would be achieved by asking the physician to defend the design or construction of a product that is made by distant manufacturers of whose activities the physician has no knowledge, especially when the device is already subject to FDA approval.

Drug Manufacturing in the FDA Context

There are, of course, major differences between a setting in which a traditional manufacturer makes a drug that is sold downstream for physicians’ use and the physician who grows stem cells for reinjection into the same patient. But those differences cut

more in favor of removing the FDA from a role of direct oversight over the physician's practice. The standard drug has a constant chemical composition that is invariant over time. That uniqueness makes it relatively easy (if not necessarily wise) to engage in the upstream regulation of these products. Drug standardization simplifies clinical trials, which now have to deal with only a single pharmacological constant. Therefore, once a drug is approved, it is approved for all individuals and diseases that fall into the same general category. That uniformity also makes it easy to run production and inspection to see that each tablet is the same as the others and to draft suitable warnings for use. Indeed, because that kind of identity is not available in the case of biosimilar (generic near-equivalent) drugs, the approval process is far more complicated than it is for standard small-molecule drugs.⁷⁶

Ordinary manufacturing cases, then, are not subject to a requirement that their manufacturer possess an M.D. But under the standard state law, including the Colorado statute under which Drs. Centeno and Schultz worked, no person without an M.D. could order or perform the Regenxx procedure in question. The reason is that the doctors' stem-cell procedure is very different from the processes that we normally classify as drug manufacture. These stem cells necessarily vary from person to person, and the process by which the cells are reproduced will necessarily vary from case to case. It is very hard to see why the standard techniques for double-blind drug-manufacturing studies conducted over large populations should be applied to these circumstances. Nor is it clear what the supposed advantage of the FDA's current preferred manufacturing standards would afford in cases of this sort, especially when past experience, which the FDA ignores systematically, indicates that there is no breakdown in the procedure to date. It is critical to note that in this case, the target population for each "production" run is one person, and that person is the same person from whom the stem cells are extracted. Also, the growth process is not going to prove a precise science, so variations in concentrations of stem cells are to be expected among cases.

In response to these arguments, the FDA answers that its interpretation of the meaning of the term "drug" is entitled to extensive deference by the court. The strongest support for its position is the key 1969 case of *United States v. Bacto-Unidisk*,⁷⁷ which considered a "definitional controversy" involving "a laboratory aid known as an antibiotic sensitivity disc, used as a screening test for help in determining the proper antibiotic drug to administer to patients."⁷⁸ Although the disk in question was used not for treatment but to determine the proper dosages of the relevant antibiotic, the Supreme Court reversed the decision below by pointing to evidence in the legislative history that Congress did not intend to use the "medical" definition of a drug but should defer to the agency. The Court placed particular weight on the fact that in the *Bacto-Unidisk* case, there had been "numerous complaints" by the medical profession, hospitals, and laboratory technicians—confirmed by exhaustive studies. Yet no such complaints were present in the *Regenerative Sciences* case. In effect, the Court treated the sensitivity disk as a complement to the drugs that it tested, and let the FDA have its way, opining: "[I]t is no part of the judicial function to examine the public need for, or medical wisdom of, the Secretary's regulations requiring premarket clearance of antibiotic sensitivity discs. It is enough for us that the expert agency charged with the enforcement of remedial legislation has determined that such regulation is desirable for the public health, for we are hardly qualified to second-guess the Secretary's medical judgment."⁷⁹ In its *Regenerative Sciences* brief, the government takes the view that this approach to deference resolves the case.⁸⁰

The case is far more complicated than this simple account suggests. Note that the only question in *Bacto-Unidisk* was whether this peculiar product (which cannot, by any stretch of the imagination, be thought of as a service) should be treated as a drug, as a device, or as nothing at all. The stakes of that decision are relatively low because they do not generate a major extension of FDA jurisdiction into areas that are already subject to alternative schemes of regulation.

When the stakes get higher, the level of deference is and should be reduced. Thus, in the much more recent case of *FDA v. Brown & Williamson Tobacco*,⁸² the Court pushed back on the FDA when it sought to include cigarettes and tobacco as drugs under the FFDCA, for no one has ever made a claim of therapeutic use for tobacco, which would be key to finding tobacco products to be drugs under the statute, and “a product is not a drug or device under the FDCA unless the manufacturer or vendor makes some express claim concerning the product’s therapeutic benefits.”⁸³ There is no particular administrative expertise in finding out what the term “drug” means, even if it takes great skill to figure out how to regulate drugs, and the government’s broad claims for *Chevron* deference⁸⁴ here should not override the ordinary meanings of “drugs” versus “medicine.”

As in *Brown & Williamson*, the FDA’s effort to expand the definition of “drug” in *Regenerative Sciences* is high-stakes, since it would result in major incursions on the domain of medical practice, given that the distinction between drug manufacturing and medical practice is a key structural feature of current law. To allow the FDA to expand its jurisdiction by a definitional ploy should be greeted with no more sympathy in this case than it was in *Brown & Williamson*. On this ground, *Bacto-Unidisk* comes out second-best in light of the broader institutional implications that turn on the line between the sale or transfer of a drug and the practice of medicine.

2. The Public Health Service Act: FDA Control over Communicable Diseases

Apart from the definitional limits imposed by the FFDCA, the government argues that the FDA’s statutory authority to regulate Regenexx is found in the PHSA, as codified at 42 U.S.C. § 264, which provides: “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.”⁸⁵ Although originally applied to the surgeon general, today the regulatory authority intended to prevent the spread of “communicable diseases” extends to the FDA.⁸⁶

The most obvious question to ask about this statute is how it gives the FDA power to regulate procedures like Regenexx at all. The relevant text does not offer a definition of what counts as a “communicable disease,” so that question, like all similar questions, has to be answered by finding out the ordinary meaning of the term in the English language. That sensible approach tracks the position that the government has taken on that interpretive question elsewhere—most notably, in connection with the Controlled Substances Act, where it has insisted that whenever the statute or the “implementing regulations do not specifically define those terms, they should be given their ‘ordinary meaning.’”⁸⁷

That approach casts serious doubt on the ability of the FDA to regulate the Regenexx procedure by the simple expedient of defining the phrase “communicable disease” as it pleases. Nor can the FDA take liberties with the second inquiry, by noting that the FDA commissioner may determine which regulations “in his judgment are necessary” to achieve the stated statutory end. That discretion goes in allowing him to pick the means toward the ends but does not allow him to define out of existence the jurisdictional limitations contained within this section, including the key term “communicable diseases.”

Unfortunately, the FDA offers no definition in its 1997 Report of what counts as a “communicable disease.” But notwithstanding its silence, the basic accounts of communicable diseases⁸⁸ all stress the presence of various types of pathogens that lead to infectious or contagious diseases that operate through viruses, bacteria, fungi, protozoa, parasites, and other biological agents. Immunological responses, however important, are not communicable diseases. The key trait of a communicable disease is that the pathogen in question can enter

a host, where it survives and multiplies. The correct question with regard to Regenxx, therefore, is whether any risks are associated with these, and only with these, diseases. By way of contrast, the FDA's 2007 report is on relatively stronger ground when it claims that allogeneic reproduction of stem cells could "increase" this type of risk;⁸⁹ but even in this case, the agency offers little detailed explanation as to how pathogens could enter the production cycle of these stem cells, let alone enter into interstate commerce, if they are kept in isolated containers.

Rather than grapple with these problems, the FDA report veers into uncharted territory when it baldly asserts, without citation or explanation, that the risks in dealing with cellular and tissue-based products "depend[s] in substantial part on ... whether the cells or tissues are minimally, or more-than-minimally, manipulated."⁹⁰ The report thus assumes that more than minimal manipulation imposes an additional risk of communicable disease without explaining why it should be the case, for example, that centrifuging something once in a sterile environment is safe while doing the same procedure several times with growth factors and reagents is not.

The 1997 Report goes on to state that it matters "whether or not [cellular and tissue-based products] are used for their normal (homologous) function."⁹¹ Again, the point seems right, at least for allogeneic uses, because it is always known that the injection of a substance that is naturally found in the recipient is far less dangerous than the injection of some other product that could have side effects that are dangerous and deadly. It was for this reason that many people at the onset of the AIDS crisis withdrew their own blood for future use in some later surgery.

Finally, the report says that much depends on "whether or not they are combined with noncell/non-tissue components," without specifying what those other components might be.⁹² It is one thing to deal with the manufacture of products that take cell lines from multiple patients and put them all into a single stew. But it is quite another thing to

use a standard reagent for that purpose, especially one that is FDA-approved and known not to carry any organic matter that could lead to the risk of contamination. But the government refuses to acknowledge that difference; in its respondent's brief on appeal, it takes the position that there is more than minimal manipulation because "after the patients' cells are removed from cryopreservation, they are combined with doxycycline and other additives and placed in syringes."⁹³

What is needed to support this assertion is an explanation as to why adding an antibiotic to the mix increases the risk of a contagious disease. What is given in its place, however, is the observation that the FDA has defined "component" quite broadly, so that it reads: "Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product."⁹⁴ More generally, the choice of growth medium should also make a difference. If these are synthetic, they should present no risk of communicable diseases. If they are organic, the analysis should ask whether these have themselves been subject to production controls, including those ordered by the FDA and local health authorities, that have eliminated the risk of spreading communicable diseases. Even though the FDA proposal purports to use a "tiered" approach to risk taking, it does not appear to draw the distinctions necessary to implement that approach. Indeed, with its key 2005 modifications to the regulations, the current position is that the regulatory apparatus should be identical for autologous and allogeneic risks.

The many gaps in the 1997 Report and the subsequent regulations have not been closed by the FDA in its prosecution of the current case. In its appellate brief, the FDA notes that the defendants' procedures fall within the statutory definition "based on the scientific evidence before it—that the cells' biological characteristics were altered by defendants' processing and, therefore, that the cultured cell product was more than 'minimally manipulated.'"⁹⁵ But the FDA gives the right answer to

the wrong question. The detailed evidence that it offers on how these cellular changes may take place does not explain why or how any of them create an increased risk of communicable disease, which is what section 264 of the PHSA requires. Similarly, the government may be absolutely right in asserting that “when defendants culture the cells removed from the patient’s bone marrow or synovial fluid [found in the cavities between joints] they alter the original bone marrow or synovial cells, whether or not such changes are intended, because cells grow and respond to the conditions under which they are grown.”⁹⁶ But again, the government is giving the right answer to the wrong question, for these changes present no self-evident risk of spreading a communicable disease. The government gets closer to the mark, when, at last, it does address the risk of spreading communicable disease: “During all of these steps, regardless of whether the cells or tissues are for use in the same patient or a different one, samples may be improperly labeled, mixed up with other cells, and contaminated or exposed to communicable disease agents. See, e.g., 21 C.F.R. § 1271.190(c). As a government expert explained, ‘A single drip from an over filled syringe could deposit thousands of infectious agents within the work environment. These inadvertent drops of patients’ tissue or cells may become a source of contamination for the next cultured cell preparation for a different patient.’”⁹⁷

The risks of communicable disease set out here are surely important, but these risks are routinely found in a clinical setting every time a lab technician makes that same sort of error. They are local issues that should be, and typically are, regulated by local public health authorities. Indeed, errors are far more likely to happen in hospitals when blood, stool, or urine samples are taken from sick individuals who are known to carry infectious agents of all kinds. Yet the question remains as to whether the FDA thinks that it can regulate these widespread and commonplace risks, even in routine surgery, solely on the ground that some materials used to perform these tests come from out of state.

Sadly, the FDA does not shrink from this extreme conclusion. Thus in its 1997 Report: “The agency *would* not assert any regulatory control over cells or tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure. The communicable disease risks, as well as safety and effectiveness risks, would generally be no different from those typically associated with surgery.”⁹⁸ This statement raises two types of concerns. First, in own backhand way, the FDA implies that it does have the power to regulate the removal and transplantation of cells in ordinary procedures if it thought that the risks were great enough. It states: “The agency *would* not assert any regulatory control”—not “The agency *could* not assert any regulatory control.” At that point, it is hard to see how any surgery could escape the FDA’s assertion of control.

Second, at no point does it ask whether the risk of a controlled procedure in a sterile environment is greater or less than the risk associated with ordinary surgery, an open environment where it is much more difficult to maintain a sterile field. The FDA concedes that “autologous use of cells and tissues raises lesser communicable-disease concerns than does allogeneic use”;⁹⁹ but that claim does not establish that this “lesser” risk is greater than the baseline for nonregulated procedures. On that point, it would be helpful to ask whether there have been reported adverse reactions to this procedure when performed by the defendants, or their competitors, in the U.S. or in other countries. But, as noted, the FDA did not investigate the detailed data that Regenerative Sciences has collected on the results of its own procedures. By turning this case into a purely jurisdictional battle, the FDA, as is its wont, ignores all evidence about risk levels gleaned from past practice, in the particular case and elsewhere, that might shed light on the danger of the transmission of communicable diseases. In so doing, it shows the risks of intervention before the fact. It is one thing to respond to an incident that causes danger in order to prevent its repetition. It is quite another to respond in advance without having identified any danger worthy of regulation. The only point that

the FDA establishes is that contamination can kill, which hardly requires a comprehensive FDA approval of the underlying process for autologous stem-cell growth.

Indeed, the government's proposition here presumes that these infectious agents are found in the Regenxx samples—a rare event, at best, which, if it occurred, would be subject to direct regulation by the Colorado public health authorities under their state statutory powers.¹⁰⁰ Yet that approach operates under general principles that apply to cellular and tissue-based products but are not unique to them. Existing protocols seem to deal with these situations, at least in the absence of any explanation as to why these elementary precautionary strategies do not supply an adequate response. They can occur at any time in any type of medium that is exposed to any recognized pathogens. Those kinds of regulation, moreover, are easy to implement and easy to comply with.

The government's exploration of these issues offers little or no reason as to why the Regenxx protocol poses a risk of communicable disease. Indeed, the situation creates an odd dilemma. As noted, the extraction of stem cells carries the risk of immunological reaction from surface proteins, which is controlled by repeated cleansings. So if either doctor had reinjected the stem cells without the cleansing, they would have been guilty of medical malpractice by failing to follow established procedures in this case. So the same multiple treatments required by sound medical practice are what trigger the requirement of FDA oversight. It is odd that the case for greater regulation is triggered by taking steps to reduce the risk of medical maloccurrences. It would be disastrous if physicians took fewer precautions with their patients to avoid a regulatory risk by direct reinfusion. If that would happen, the FDA would likely again widen its regulatory net until it asserted FDA control over virtually all common forms of surgery, which always require a use of drugs, given the FDA's broad interpretation of the statutory definitions that circumscribe its authority.

B. Functional Analysis

One regrettable feature about this technical discussion of the statutory definitions at play in *Regenerative Sciences* is that such exegesis tends to obscure from public view the serious debate from first principles over the proper scope of FDA regulation. In this section, I will focus briefly on these issues.

The first point to make is simple. There are two axes on which the FDA's regulatory regime could be evaluated both generally and in this case. The first involves the distinction between autologous and allogeneic transfers. The second involves the distinction between physician practice and standard manufacturing. Many proposals for more extensive FDA regulation involve the fabrication of allogeneic products by standard manufacturers. I put those aside for these purposes and concentrate exclusively on autologous transfers that are done on a small-scale basis as part of ordinary medical practice.

It is important to stress again that the FDA operates under a strong premarket clearance system, which places heavy burdens on the proponents of new therapies to prove them safe and effective. Even in areas of unquestioned FDA jurisdiction, there is no reason today to think that the FDA has developed the optimal rules for dealing with clinical trials for those (indubitable) drugs and devices that are made by large firms that never engage in medical practice. I have criticized those rules elsewhere¹⁰¹ and do so on grounds that are likewise relevant in cases of medical innovation such as those present in *Regenerative Sciences*. The FDA model of large double-blind clinical trials imposes enormous costs, which amount today to hundreds of millions of dollars and years of delay in getting new molecular entities to market, and then sets the warnings and instructions under which these products must be sold.¹⁰² These trials may work well for testing a new high-blood-pressure medicine on a large population, but they are a lot harder to organize when there is only a limited class of cancer patients available for a large number of possible clinical trials. Faced with these

difficulties, the FDA's top-down system still refuses to take into account any other form of evidence that might be used to prove the worth of drugs, including past usage in the United States or its usage in other countries.

In addition to all these structural difficulties, the FDA cannot find ways to match its own review standards with the new style of personalized medicine that Regenexx's autologous use of cell lines exemplifies. There is simply no reason to subject stem-cell treatment to comprehensive federal regulation because investigators can and do mislabel test tubes in the labs. That same risk happens every day that a lab technician draws blood from a sick person. The systems of internal hospital regulation, backed up by state public health regulation and medical-malpractice legal actions, can deal adequately with these risks. The FDA lives in its private universe when it ignores its role in the overall system of patient safety.

There are, moreover, deep structural reasons as to why the FDA's aggressive preclearance system is likely to prove dangerous. All FDA judgments are subject to two kinds of errors. Regulators can commit a type I error by letting products onto the market that should be kept off or a type II error by keeping off the market products that should be let on. The correct balance depends not only on the likelihood of each type of error but also on its seriousness. Assuming for the sake of argument that the likelihood of both errors is equal, what should be done about the choice of legal regime? In facing this question, the standard private law approach was to hold off on any injunction until there was a sign of imminent harm. Under the FDA's current approach, conversely, the regulatory prohibition kicks in unless and until the agency is satisfied with the safety of the product released or the practice undertaken.

As a first approximation, the FDA approach is incorrect. If goods and services are kept off the market, there is no way that type II errors caused by poor government can be corrected by other downstream

actors. But if the goods and services are left on the market, downstream corrections can kick in to limit type I errors. The long list of potential players includes not only individual physicians and patients but also institutional players such as voluntary organizations that specialize in certain kinds of diseases and public health boards that can pick up the errors that crop up. These downstream bodies have two huge advantages. First, they can individuate cases so that a treatment that works for one need not be used for another. Second, they can take advantage of the information collected in the field after initial approval to shape individual decisions. Seizing these advantages has the potential to decrease type I as well as type II errors. Yet the FDA—in this case, as in so many others—turns a blind eye to existing practices and their strengths and weaknesses, in making its own regulatory decisions.

One way to see the power of this distinction is to note that for many diseases, including cancer, the vast bulk of drug use is for off-label treatments.¹⁰³ Those treatments are not randomly administered but depend upon an elaborate network of information paths that include voluntary organizations such as the National Comprehensive Cancer Network, which continuously gathers information on success rates in the field. This approach does not limit the use of data to whether a drug should be used. Instead, it permits constant revisions in indications, counter-indications, drug interactions, dosage, and timing, none of which works its way into the rigid FDA on-off approval system. It is not just for chance that the vast bulk of cancer therapies are for off-label uses, without, as best anyone can tell, a serious increase in patient risk levels.

The use of stem-cell treatments could well follow different paths so that it is difficult to generalize from one area to another. But everything depends on the generalization sought. The clinical trials that Dr. O'Neill sought for persons with dead heart tissue at risk for congestive heart failure were much more delicate than stem-cell treatments intended to fix athletic injuries. But which way do these differ-

ences cut, given the bad health prognosis, anyway? Clearly in favor of greater use of stem-cell treatments, where the risks seem less dangerous, and the potential returns a bit higher. Indeed, in this instance, professional athletes seeking this treatment will likely find it somewhere or somehow and will, on average, be better for the results. Why deny these treatments to others who would like to take advantage of the information gathered from the treatment of sophisticated patients at little or no additional cost? Stated more generally, the presumption should always be set against FDA intervention in ordinary drug cases. The situation with stem-cell treatments is an *fortiori* case.

Additional considerations cut the same way. As noted earlier, a central issue in this regulatory environment is whether Regenerative's stem-cell therapy should be treated like a drug treatment or like medical practice. In dealing with this issue, Halme and Kessler identify four generic risks: "Does the donor pose a risk of transmitting infectious or genetic diseases? Does cell or tissue processing pose a risk of contamination or damage? What are the types of cells, and what are the purity and potency of cells in the final product? Will the product be safe and effective in vivo?"¹⁰⁴

So how do they rate here? Since the transactions are autologous, we can cross the first risk factor off the list. Since the cell processing is done under locally controlled circumstances, it does not appear to be greater than or different from the risk associated with other standard laboratory procedures that now lie outside the FDA's jurisdiction. Likewise, issues of purity and potency are common in all medical procedures, as are those associated with possible adverse events in vivo. It was this insight that led Mary Ann Chirba and Stephanie M. Garfield to attack the FDA intervention in the Regenexx case and other forms of standard adult-stem-cell (or ASC treatments):

Practicing physicians and surgeons are increasingly taking the lead in treating patients with ASC therapies, particularly with the patient's

own autologous ASCs. In theory, this may seem like a brave new world, but in practice, extracting and re-injecting a patient's own cells is not that different from other reparative or surgical procedures. For instance, coronary artery bypass graft surgery typically removes the saphenous vein from the patient's leg with the purpose of using that vein to re-route coronary circulation to bypass an occluded artery. Spinal surgery often uses bone from a patient's pelvis or rib to fuse vertebrae. Further, withdrawing adult stem cells from adipose tissue is much less invasive than either of these or many other procedures relying on the patient's own tissue. The fact that such procedures have recently become a matter of routine is largely attributable to the innovations of physicians and surgeons involved in the practice of medicine.¹⁰⁵

This passage is especially relevant because it reminds us of the importance of decentralized control over medical research: innovation vitally depends on the constant interplay that requires large amounts of trial and error in any given area. It is that constant stream of low-level innovations that the FDA's bright-line *ex ante* prohibitions serves to destroy. The point is yet another application of the basic Hayekian insight that central planning creates powerful monopoly elements that destroy innovation by making it difficult, if not impossible, for different entrepreneurs (including physicians and surgeons) to take their best shot at a particular problem.¹⁰⁶ There is no way that small, customized operations can find funds to pay the compliance costs associated with FDA clinical trials. Yet these may be the people best positioned to make decisive advances. The FDA may have some of the finest scientists on the planet, but there is no human being who can master all the detailed knowledge of any given subspecialty of medicine. FDA regulators, by virtue of their broad regulatory responsibilities, cannot have direct working knowledge of such subspecialties, given the highly specialized nature of advanced research. FDA scientists are always playing catch-up with teams of scientists and inventors with years of

experience in any given field. Sight unseen, I trust Dr. O'Neill on choice of research protocols far more than an anonymous set of FDA officials, whose greatest contribution to medical research would be to back off now.

Nonetheless, dominant opinion runs the other way, given the constant calls for greater supervision of stem-cell treatments, chiefly by those who think that decentralized processes of oversight are inadequate. Munzer writes:

I immediately put one possible view to the side: that there ought not to be any administrative regulation of, or indeed any other form of governmental control over, stem cell products. Such a position would just rely on the market to sort out ways of responding to these products. I reject this view because there is, especially in such a new and unpredictable area as stem cell products, little justification for leaving all governance in this area to willing buyers and willing sellers. It is far too difficult for everyone to obtain and process all of the relevant information. Further, at this time, stem cell products do not satisfy the ideal market dynamic of perfect competition, for there are few producers or sellers that are willing and able to supply stem cell products and there are high barriers to entry.¹⁰⁷

This position is deeply flawed. First, no “robust market” consists solely of buyers and sellers. In those “new and unpredictable areas,” buyers and sellers both call for the assistance of third parties to help with these decisions. Patients always rely on the advice of their personal physicians before taking treatments of this sort and can quickly run to the Internet to find both favorable and unfavorable information about new treatments—information that can vary in real time, in stark contrast to the FDA’s static, one-time approval processes that are so difficult to update. Similarly, as Munzer acknowledges, my article “Against Permittitis”¹⁰⁸ showed how professional societies now address these multiple risks. One such organization is the International Cellular

Medicine Society (ICMS), which takes on an audit function with respect to stem-cell procedures.

That organization has been criticized by Barbara von Tigerstrom for its lack of independence from the key medical players in this market niche, including Regenerative Sciences, whose work it oversees. Fair point, but only to a limit. First, that want of independence is certainly something that cuts against the validity of its reports, given the obvious conflict of interest. By the same token, it is risky to conclude that the work that it does and the information that it supplies is of no worth, given that all the relevant parties put their reputations on the line. Indeed, that criticism would be far more effective if it identified an institutional breakdown in patient care. If such did occur, the adverse publicity would have an immediate effect: anyone can visit the website of Public Citizen Health and Safety,¹⁰⁹ and anyone can set up his own stem-cell website to critique ICMS performance. In other words, the cure for the supposed inside deal is not to stop the ICMS in its tracks or to ban these procedures; it is to develop new sources of information to improve patient choices.

Second, wholly apart from these voluntary organizations, the absence of an FDA presence does not signal the absence of all regulation. In this, as in other areas, reputable merchants often prefer to have government regulation. Thus, when the government certifies the purity of food, drugs, and yes, tobacco, shipped into the marketplace, it eases the reluctance of consumers to purchase what was hitherto a relatively unknown quality. So here, the fact that there is state public health oversight may well increase the willingness of people to use a stem-cell technique, and providers can advertise that they are regulated by the state or local board of health. The same cannot be said about FDA oversight, which blocks the technology from being used in the first place.

Third, it is odd to point to existing barriers to entry as a reason to support further FDA regulation, when the FDA sets up the greatest barrier, at least

within the United States. Remove the FDA from its gatekeeper role, and entry into this market will expand, increasing choice, lowering cost, and improving information at the same time. Critics like Munzer and von Tigerstrom do not push hard to reduce the barriers to entry at home; instead, they decry the decision of Regenerative to take its business offshore. Von Tigerstrom thus laments “the rise of concerns about ‘stem cell tourism,’ the phenomenon of patients travelling to other countries to seek novel, often unproven, therapies which are not available in the United States or other jurisdictions with strong regulatory oversight.”¹¹⁰ She quotes “Douglas Sipp, an expert commentator on experimental stem-cell treatments,” who decries market liberalization, saying, “Companies would likely feel empowered to ignore requirements for demonstrable safety and efficacy of autologous medicinal products, creating an ‘anything goes’ atmosphere,” which “would be, as they say, a bad thing.”¹¹¹ Munzer echoes this point: “The physicians have ceased doing so until the lawsuit is finally decided. However, von Tigerstrom reports that the company ‘has licensed its technology to clinics offering it in China and Argentina, and is opening a stem cell culture lab in the Cayman Islands.’ Stem-cell tourism, anyone?”¹¹²

But why assume that only the FDA stands between medical patients and incipient disaster? The reason that these technologies will sell in foreign places is that they have already been battle-tested in the United States. Informed individuals who would prefer to be treated in Colorado may well prefer to travel to the Cayman Islands than to forgo all treatment. People from other places may be willing to travel there because they believe that a reputable firm with a solid track record had to move there because its operations were banned in the United States. Using the pejorative epithet “stem cell tourism” makes it appear, falsely, that only gullible and superficial people are willing to take this step when, in all likelihood, only informed consumers on physician recommendation will be prepared to take the journey. The power of choice in general—and of exit rights in particular—offers great protection against arbi-

trary power. The exercise of these rights should be seen not as a sign of weakness of this program but as a sign of its strength. Only the die-hard pro-FDA paternalists think otherwise.

CONCLUSION: PROTECTION VERSUS PROGRESS

This exploration of the FDA regulation of autologous stem-cell transfers is part of a larger story about the role of the FDA in the regulation of pharmaceutical and medical research. Institutionally, the FDA sees its role as “Protecting and Promoting *Your Health*,”¹¹³ which makes it all seem rather personal to you. It is perhaps instructive that the FDA puts “protecting” before “promoting” because, in general, its background norm of operation is “better safe than sorry,” which lets it set the presumption against innovation rather than in its favor. Yet as a personal matter, most Americans do not set their personal presumptions in that way. When healthy, they do not think about the issue much; but when injury, illness, or disease strikes, they are far more willing to take what they regard as prudent risks than the FDA is willing to let them take. It is for that reason we see patient groups like Abigail Alliance¹¹⁴ (which cannot be tainted by the populist charges of greed that dog pharmaceutical and device companies) pushing to get new therapies on the market as quickly as possible. It is for that reason that we see sick individuals constantly petitioning the FDA for compassionate exemptions that allow them to receive experimental treatments. It is for that reason that we see the widespread use of off-label treatment. It is for that reason that we see people go outside the U.S. to avail themselves of treatments that the FDA bans in the U.S.

The message behind these persistent trends is that most people do not want the FDA to protect their own health in making these life-or-death choices. That attitude does not mean that they want to abolish the FDA, for they (like virtually all American businesses) are comfortable with the FDA’s role in protecting food and drugs from contamination and

impurities. But it does mean that they are uneasy with its aggressive intervention on medical issues, preferring their own judgment as informed by their own physicians and personal advisers.

Why, then, does the FDA take this institutional position? It is partly because it distrusts the competence of the people whom it wishes to protect. It is partly because it is staffed by individuals who share the populist sentiment that looks with deep suspicion on the activities of profit-making firms to act responsibly on matters of health and safety. But there is also a third reason: when the FDA keeps a drug or a practice off the market, the losses are relatively invisible to the public at large. The best of medicine and science have not been able to contend with the ravages of cancer, heart disease, diabetes, or a host of other human ailments. But let a product get on the market that is associated with adverse reactions—think Vioxx—and all hell breaks loose. The social losses from the denial of new therapies are, in principle, just as important as the social losses from the use of new therapies that should never have been used. But with respect to the institutional cost to the FDA, it is no contest. It gets flayed in the press in the one case and a free pass in the media in the other.

So the FDA's motivations are, in some measure, laudable; in some measure, misinformed; and, in some measure, self-protective. But what about the role of the courts in all this? As the district court decision in *Regenerative Sciences* indicates, the courts take a largely deferential role in the actions of administrative agencies. That attitude is based on two key premises. The first is deference to expertise. The second is the acceptance of the larger view that agencies act in the public interest in ways that profit-making firms do not. Where these two attitudes lead is the inexorable expansion of FDA authority, as statutory provisions, like those involved in this case, are given broad renderings that are inconsistent with their text and their legislative history.

The upshot is that ordinary people are denied medical options that they in good faith prefer to adopt. This style of uninformed paternalism should end. I am the last person to say whether anyone should undertake the stem-cell treatments that *Regenerative Sciences* offers to its customers. That choice should lie with patients themselves—not with the FDA, which, from a review of the record in *Regenerative Sciences*, has neither the medical insight nor the legal expertise to justify its assumption of extraordinary new powers over the practice of medicine.

ENDNOTES

- ¹ See Kristen Philipkoski, *Stem Cells Heal a Broken Heart*, WIREd, Mar. 7, 2003, <http://www.wired.com/medtech/health/news/2003/03/57944?currentPage=all>.
- ² Bill Laitner, *Beaumont Doctors Ordered to End Stem-Cell Procedure*, DET. FREE PRESS, June 13, 2003, at B3, available at <http://sci.rutgers.edu/forum/showthread.php?t=2389>
- ³ *Id.*
- ⁴ On appeal from *U.S. v. Regenerative Sciences, et al.*, 878 F. Supp. 2d 248, available at http://www.gpo.gov/fdsys/pkg/USCOURTS-dcd-1_10-cv-01327/pdf/USCOURTS-dcd-1_10-cv-01327-0.pdf.
- ⁵ Mary Ann Chirba & Stephanie M. Garfield, *FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?*, 7 J. Health & Biomedical L. 233, 257 (2011). The statutory basis for this distinction comes from 21 C.F.R. §§ 1271.1, 1271.3 (2006).
- ⁶ Regenexx, Knee Replacement Surgery, <http://www.regenexx.com/the-regenexx-procedures/knee-surgery-alternative/types-of-knee-surgeries> (last visited Sept. 3, 2013).
- ⁷ Regenexx, FAQ's, <http://www.regenexx.com/common-questions> (last visited Sept. 3, 2013).
- ⁸ Regenexx, <http://www.regenexx.com>.
- ⁹ 21 C.F.R. 1271(a). Where the product is transferred into a different individual, it is called an "allogeneic use."
- ¹⁰ Regenerative Sciences, Inc., FDA Priv. Ltr. Compliance Action (July 25, 2008), available at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/ucm091991.htm>. For a strong support of this position, see Dina Gould Halme & David A. Kessler, *FDA Regulations of Stem-Cell-Based Therapies*, 355 NEW ENG. J. MED. 1730, 1730-31 (2006) ("As a class of therapeutic agents, stem-cell-based products meet the definitions of several different kinds of regulated products: biologic products, drugs, devices, xenotransplantation products, and human cells, tissues, and cellular and tissue-based products.").
- ¹¹ *Regenerative Sciences*, 878 F. Supp. 2d, at 253.
- ¹² For a description of the various steps, see Stephen R. Munzer, *How to Integrate Administrative Law and Tort Law: The Regulation of Stem Cell Products*, 64 ADMIN. L. REV. 743, 752-754 (2012) (outlining the costs and complications of the FDA procedure).
- ¹³ For a discussion of the contrast and interplay between FDA and state regulation in the pharmaceutical arena, see generally Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 YALE J. HEALTH POL'Y, L. & ETHICS 587 (2005); James R. Copland & Paul Howard, *In the Wake of Wyeth v. Levine: Making the Case for FDA Preemption and Administrative Compensation*, Project FDA Report No. 1, (Manhattan Inst. for Pol'y Res., Mar. 2009), available at http://www.manhattan-institute.org/html/fda_01.htm.
- ¹⁴ Halme & Kessler, *supra* note 10, at 1730.
- ¹⁵ See 21 C.F.R. § 1271.3(d) (2006); Federal Food, Drug, and Cosmetic Act, Pub. L. 75-717, 52 Stat. 1040 (1938).
- ¹⁶ Public Health Service Act, Pub. L. 78-410, 58 Stat. 682 (1944).
- ¹⁷ See 21 C.F.R. § 1271.3(d).
- ¹⁸ The current version may be found at the FDA website, Regulatory Information, <http://www.fda.gov/regulatoryinformation/legislation/ucm148717.htm> (last visited Sept. 17, 2013).
- ¹⁹ See generally FDA website, FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List, <http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm150485.htm> (last visited Sept. 17, 2013).
- ²⁰ 21 C.F.R. § 1271.3(d) (2006).

- ²¹ Food and Drug Administration, *Proposed Approach to Regulation of Cellular and Tissue-Based Products*, Docket Number 97N-0068 (Feb. 28, 1997), available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf>.
- ²² 21 U.S.C. § 331(a).
- ²³ 21 U.S.C. § 331 (2013).
- ²⁴ 21 U.S.C. § 321(b) (2013). For purposes of the FFDCa, “Territory” is further defined as “any Territory or possession of the United States, including the District of Columbia and excluding the Canal Zone.” *Id.* at 321(a).
- ²⁵ 21 U.S.C. § 321(g)(1).
- ²⁶ *Id.* at 42, note 1; Colo. Rev. Stat. § 25-1.5-102 (2013) (establishing that the Colorado Department of Public Health has the power “[t]o investigate and control the causes of epidemic and communicable diseases affecting the public health”). For a measure of the extent of the program, see Colorado Department of Public Health and the Environment, Health Facilities, <http://www.colorado.gov/cs/Satellite/CDPHE-HF/CBON/1251583470236> (last visited Sept. 8, 2013), citing Section 264(e).
- ²⁷ *Id.* at 46.
- ²⁸ See *Katzenbach v. McClung*, 379 U.S. 294 (1964) (holding that Ollie’s Barbecue was subject to the public accommodations provisions of the Civil Rights Act of 1964 because it received some \$70,000 worth of food that had previously moved in interstate commerce).
- ²⁹ 514 U.S. 549 (1995).
- ³⁰ *Regenerative Sciences*, 878 F. Supp. 2d at 256 (quoting *United States v. Lopez*, 514 U.S. 549, 558–559 (1995)).
- ³¹ 317 U.S. 111 (1942).
- ³² 331 U.S. 432, 434 (1947).
- ³³ *Id.* at 434.
- ³⁴ *United States v. Dotterweich*, 320 U.S. 277, 278 (1944).
- ³⁵ *Walsh*, 331 U.S. at 435.
- ³⁶ Note, for instance, that 21 U.S.C. § 331(g) prohibits “[t]he manufacture within any Territory of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.” The statute’s focus on giving the FDA authority over manufacturing within Territories but not states clearly suggests that the statutory language in question was written to grant authority consistent with the Supreme Court’s pre-*Wickard* line of constitutional jurisprudence limiting congressional powers under the Constitution’s Commerce Clause.
- ³⁷ 331 U.S. at 434 (1947).
- ³⁸ *Walsh*, 331 U.S. at 434.
- ³⁹ *Id.* at 436.
- ⁴⁰ *Id.* at 437.
- ⁴¹ *Developments in the Law – The Federal Food, Drug, and Cosmetic Act*, 67 HARV. L. REV. 632, 699 (1954).
- ⁴² Pure Food and Drug Act, Pub. L. No. 59-384, ch. 3915, §1, 34 Stat. 768, 768-772 (1906).
- ⁴³ *Id.* at § 2.
- ⁴⁴ 156 U.S. 1 (1895).
- ⁴⁵ 188 U.S. 321 (1903).
- ⁴⁶ 21 U.S.C. § 331(k) (2013).
- ⁴⁷ 332 U.S. 689 (1948).
- ⁴⁸ *Id.* at 691.
- ⁴⁹ 161 F.2d 629 (5th Cir. 1947).
- ⁵⁰ Act of June 24, 1948, Pub. L. No. 80-749, ch. 613, 62 Stat. 582.
- ⁵¹ *Sullivan*, 161 F.2d 629 (5th Cir. 1947).

- ⁵² Sullivan, 332 U.S. at 696.
- ⁵³ *Id.* at 693.
- ⁵⁴ Final Brief for Plaintiff-Appellee in *Regenerative Sciences*, *supra* note 30, at 16.
- ⁵⁵ *Regenerative Sciences*, 878 F. Supp. 2d at 258 (quoting *United States v. Evers*, 643 F.2d 1043, 1052 (5th Cir. 1981)).
- ⁵⁶ 643 F.2d 1043.
- ⁵⁷ *Id.* at 1046; see Final Brief for Plaintiff-Appellee in *Regenerative Sciences*, *supra* note 30, at 23 (“doctors may therefore hold drugs for sale within the meaning of [21 U.S.C. § 331(k)]”); see also *Regenerative Sciences*, 878 F. Supp. 2d at 258, quoted above.
- ⁵⁸ *Evers*, 643 F.2d at 1045 (“Chelation is a chemical reaction which occurs between certain drugs and various harmful metals which are in the bloodstream”).
- ⁵⁹ FFDCA, 21 U.S.C. § 352 (2012). Its key provision reads:
A drug or device shall be deemed to be misbranded ... (f) Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users.
- ⁶⁰ *Evers*, 643 F.2d at 1054.
- ⁶¹ Even if one were to assume, contrary to the Court’s actual language, that *Evers*’s decision to stockpile standard drugs that had moved in interstate commerce for patient use counted as holding them for sale, the *Evers* case would not apply neatly to *Regenerative Sciences*. First, these stem cell extracts are a far cry from stockpiling inventory. There is no reasonable prospect that the physicians in *Regenerative* could “sell” stem cells that, in all likelihood, are still owned by the patient, who had never sold them to *Regenerative* or abandoned them to the first taker. Second, *Evers* does not relax the requirement that the statute applies only to a drug that “is held for sale after shipment in interstate commerce.” 643 F.2d at 1044.
- ⁶² James R. Copland & Paul Howard, *Off-Label, Not Off-Limits: The FDA Needs To Create a Safe Harbor For Off-Label Drug Use*, Issue Brief No. 15, 2 (Manhattan Inst. for Pol’y Res., Dec. 2012), available at http://www.manhattan-institute.org/pdf/ib_15.pdf (“Pharmaceuticals that are available for use and marketing under FDA regulations are also commonly prescribed for uses and indications beyond those listed on the drug’s FDA-approved label.”).
- ⁶³ 643 F.2d, at 1049 (stating that “[t]he district court agreed with Dr. Evers and held that no misbranding could result from a doctor’s prescription of a lawful drug to his own patients”).
- ⁶⁴ *Id.* at 1048 (quoting *United States v. Evers*, 453 F. Supp. 1141, 1147–48 (D.C. Ala. 1978)).
- ⁶⁵ 21 U.S.C. 321(g)(1) (2009).
- ⁶⁶ Brief for the petitioner, in *Gonzalez v. Raich*, 546 U.S. 243 (2006) (citing Oxford English Dictionary, 546 (2d ed. 1989)). The quoted passage is followed up by references to Webster’s Third New International Dictionary, 1402 (1966), and the Random House Dictionary of the English Language, 1194 (2d ed. 1987), with similar import.
- ⁶⁷ Colo. Rev. Stat. § 12-36-106(1).
- ⁶⁸ American Law Institute, Restatement (Second) of Torts, § 402A. Special Liability of Seller of Product for Physical Harm to User or Consumer (1966).
- ⁶⁹ 710 P.2d 247 (Cal. 1985).
- ⁷⁰ *Id.* at 251.
- ⁷¹ 150 P.2d 436 (Cal. 1944).
- ⁷² *Id.* at 444.
- ⁷³ On the shift to foreseeable use, see, e.g., *Larsen v. General Motors*, 391 F.2d 495 (8th Cir. 1968) (distinguishing *Evans v. General Motors Corp.*, 359 F.2d 822 (7th Cir. 1966), the last of the cases to reject a crashworthiness theory).

⁷⁴ 668 A.2d 521 (Pa. 1995).

⁷⁵ *Id.* at 523-24.

⁷⁶ Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG L. J. 285 (2011).

⁷⁷ 394 U.S. 784 (1969).

⁷⁸ *Id.* at 785.

⁷⁹ *Id.* at 791-792.

⁸⁰ Final Brief for Plaintiff-Appellee at 15-16, *U.S. v. Regenerative Sciences, LLC*, No. 12-5254 (C.A.D.C. March 13, 2013) (arguing that the “FDA is entitled to substantial deference in interpreting its own regulations regarding what cellular and tissue products are subject to regulation solely under part 1271.”).

⁸¹ *Bacto-Unidisk*, 394 U.S. at 793, 801 (considering the “drug-device dichotomy” at the initial application of the FFDA and quoting the definition in § 201(h) that “[t]he term ‘device’ ... means instruments, apparatus, and contrivances ... for use in the diagnosis ... of disease in man”). Note that this definition, too, is ambiguous in that it does not specify whether the device has to be used on the person. Remove that constraint, and a teaspoon is a medical device when used to determine dosage.

⁸² 529 U.S. 120 (2000).

⁸³ *Id.* at 132.

⁸⁴ Judicial deference to FDA interpretations, as with other agencies, is cabined by the Court’s pronouncement in *Chevron U.S.A. v. National Resources Defense Council, Inc.*, 467 U.S. 837 (1984), that no deference is owed to an agency interpretation “when Congress has directly spoken to the precise question at issue: the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.” *Id.* at 842-43. The fact that *Brown & Williamson* was decided after *Chevron* shows the utter futility of finding any coherence in Supreme Court cases and has led—quite properly, in my view—to claims that the entire doctrine be scrapped in favor of an approach that seeks to resolve questions by looking at the ordinary meaning of the statutory terms in light of the context, structure, and purpose of the act in question. See, e.g., Brief for the Petitioners in *Gonzales v. Raich*, *supra* note 66.

⁸⁵ 42 U.S.C. § 264(a) (2012); see also Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26744, 26745-47 (May 14, 1998) (amending 21 CFR Parts 207, 807, and 1271).

⁸⁶ See 42 U.S.C. § 264(a); 69 Fed. Reg. at 68,613..

⁸⁷ Brief for the Petitioners, *Gonzales v. Oregon*, 546 U.S. 243 (2006), available at 2005 U.S. S. Ct. Briefs LEXIS 354, 40-42, cited in briefs for Appellant in this case at 29 (citing *Asgrow Seed Co. v. Winterboer*, 513 U.S. 179, 187 (1995); *FDIC v. Meyer*, 510 U.S. 471, 476 (1994)).

⁸⁸ For the ordinary sense, see, e.g., Mayo Clinic, Infectious disease: Definition, <http://www.mayoclinic.com/health/infectious-diseases/DS01145> (last visited Sept. 8, 2013).

⁸⁹ *Proposed Approach to Regulation of Cellular and Tissue-Based Products*, *supra* note 21, at 12.

⁹⁰ *Id.* at 10.

⁹¹ *Id.*

⁹² *Id.*

⁹³ Final Brief for Plaintiff-Appellee at 26, *U.S. v. Regenerative Sciences, LLC*, No. 12-5254 (C.A.D.C. March 13, 2013).

²⁴ *Id.* at 26 (citing 21 C.F.R. § 210.3(b)(3) (2011)).

⁹⁵ *Id.* at 37.

⁹⁶ *Id.* at 32.

⁹⁷ *Id.* at 42.

⁹⁸ *Id.* at 12 (emphasis added).

⁹⁹ *Id.* at 13.

¹⁰⁰ See Colorado Department of Public Health and the Environment, Health Facilities, <http://www.colorado.gov/cs/Satellite/CDPHE-HF/CBON/1251583470236>, for a measure of the extent of the program. See generally Colo. Rev. Stat. §25-1.5-101 to §25-1.5-304.

¹⁰¹ RICHARD A. EPSTEIN, *OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION* (Yale University Press 2006); Epstein, *Cambridge v. Chicago: An Answer to Dr. Arnold Relman's New Republic Review of Overdose*, POINTOFLAW BLOG (Apr. 22, 2007), <http://www.pointoflaw.com/columns/archives/004194.php> (criticizing Arnold S. Relman, *To Lose Trust, Every Day*, THE NEW REPUBLIC, July 23, 2007).

¹⁰² Copland & Howard, *supra* note 62, at 2.

¹⁰³ *Id.*

¹⁰⁴ Halme & Kessler, *supra* note 10, at 1731.

¹⁰⁵ Chirba & Garfield, *supra* note 5, at 235–36 (footnotes omitted).

¹⁰⁶ See generally FRIEDRICH HAYEK, *THE ROAD TO SERFDOM* (1944).

¹⁰⁷ Munzer, *supra* note 12, at 759–60.

¹⁰⁸ *Id.* at 775 (citing Richard A. Epstein, *Against Permittitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 25–29 (2009)).

¹⁰⁹ Public Citizen, Health and Safety, <http://www.citizen.org/hrq> (last visited September 17, 2013).

¹¹⁰ Barbara von Tigerstrom, *The Food and Drug Administration, Regenerative Sciences, and the Regulation of Autologous Stem Cell Therapies*, 66 FOOD & DRUG L.J. 479, 479 (2011).

¹¹¹ *Id.* at 491.

¹¹² Munzer, *supra* note 12, at 759 n. 64.

¹¹³ FDA, www.fda.gov (last visited Sept. 17, 2013).

¹¹⁴ Abigail Alliance for Better Access to Developmental Drugs, www.abigail-alliance.org (last visited Sept. 17, 2013).

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