Health Options Foreclosed

How the FDA Denies Americans the Benefits of Medical Research

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Abstract

In recent decades, the Food and Drug Administration (FDA) has assumed increasing premarket authority for drugs and devices. Given how the FDA's regulatory stance has inhibited breakthroughs in the development of medical products, it appears that the agency will stand in the way of emerging technologies such as nanotechnology, synthetic biology, nanorobotics, virally delivered telomerase, and cellular therapy. These new technologies represent not only the means to prevent and cure diseases, but also the key to helping people live longer and healthier lives. We conclude, therefore, that an incremental approach to reform—one that would keep the FDA as the sole arbiter of new medical technologies—is unlikely to work. Rather, we think that a regulatory system based on competitive market approval of drugs and devices is more likely to strike the appropriate benefit-risk balance, including that inherent in the compassionate use of experimental medical treatments.

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Health Options Foreclosed:

How the FDA Denies Americans the Benefits of Medical Research

Richard Williams, Marc Joffe, and Ariel Slonim

During the past century, the premarket approval processes for drugs and devices used by the Food and Drug Administration (FDA) have become increasingly restrictive in response to a small number of adverse events. Recently, we have observed multiple cases in which the FDA has denied or retarded the development of new innovations, thereby blocking the availability of tremendous scientific breakthroughs that promise us much longer and much healthier lives.

On a daily basis, FDA regulations either prevent or hinder patient access to new medications and other treatments. In some cases, Americans thwart FDA regulations by obtaining treatments in foreign countries or by using unauthorized drugs illegally at home; however, the costs and risks associated with both international travel and illegal activity undoubtedly limit the use of such unapproved treatments. And it goes without saying that drugs that are never developed cannot help anyone.

Advocates of current FDA pharmaceutical regulation see these restrictions as the necessary cost of keeping Americans safe from inadequately tested and potentially dangerous drugs. They argue that the absence of regulation could result in mass poisonings, such as those attributed to Elixir Sulfanilamide in 1937, or in birth defects, such as those caused by thalidomide in the late 1950s and early 1960s. For supporters of the current FDA regime, those incidents demonstrate the dangers of unregulated access to drugs and have been used to justify increased powers for the FDA, including the power to evaluate treatment effectiveness.

When considering the social benefits of drug regulation, it is important to recognize that no single regulatory regime can guarantee absolute safety. Nor is it possible for a regulatory regime to guarantee drug effectiveness. Adverse reactions to a treatment or failure of a treatment to perform may be caused by improper use, prescription error, built-up tolerance to a drug, or safety problems that occur over time (beyond the clinical trial period). They may also occur because the population of actual users is significantly more heterogeneous than the population of a clinical trial.

Because absolute safety and universal effectiveness are impossible to achieve, a more plausible goal for FDA regulation would be minimizing deaths and illnesses that result from both (1) adverse drug reactions and (2) denial or inhibition of access to drugs and therapies that could be beneficial to patients. These two types of regulatory error run counter to each other: a stricter regulatory regime reduces the number of medical incidents caused by maladministration of drugs at the expense of preventing some types of drug use that could be beneficial to patients. A more relaxed regime affords patients greater opportunity to cure their illnesses and avoid death while simultaneously increasing patients' likelihood of adverse reactions to treatments. As we illustrate in this study, the relatively strict regime in place today is imposing great harm; therefore, we suggest that a more relaxed regime is called for.

The 21st Century Cures Act, which is currently pending, intends to address some of the concerns raised in this paper.[1] However, if the act passes, the rate of innovation in development of medical products will likely stay virtually the same. The act perpetuates what Robert Graboyes calls a "hub-and-spoke mechanism, with data conveyed from all over into a centralized machine, processed and analyzed there, and shipped outward, along with some

[1] 21st Century Cures Act, H.R. 6, 114th Cong. (2015).

mandates."[2] Daniel Carpenter, professor of government at Harvard University, describes this model as the FDA using its veto authority over "the pharmaceutical marketplace, global clinical research, multimillion dollar advertising and sales campaigns, everyday medical practice, and other realms of the modern world."[3] He goes on to say that the FDA owns pharmaceutical companies "body and soul" and exercises its influence over scientific research as well as related sectors, including financial markets.[4] All the information goes into the FDA and decisions go out, a hub-and-spoke model. One thing the 21st Century Cures Act does not appear to do is fundamentally alter this model to match the current potential rate of innovation in the health product sphere with new innovative regulatory structures.

First, the 21st Century Cures Act authorizes the government to determine and award prizes for new discoveries. A huge portion of the bill is directed toward new authority and requirements for the FDA. Other agencies affected include the Centers for Disease Control and Prevention, the Centers for Medicare and Medicaid Services, and the National Institutes of Health. Authors of the legislation assume that commanding the FDA to have more meetings, conduct more consultations, publish more guidelines, develop more special product pathways, perform more training, and produce more congressional reports—and that ordering the FDA to operate more "efficiently"—will somehow improve the rate of innovation in health products. Although some parts of the bill clearly would improve the existing process (e.g., by making better use of available information using Bayesian statistics), the act largely leaves in place the FDA's current regulatory authority.

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[2] Robert Graboyes, "Steampunk Regulation, Medical Technology, and the IT Revolution," *Real Clear Technology*, March 12, 2015.
[3] Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton, NJ: Princeton University Press, 2010), 10.
[4] Ibid., 9.

Thus, the legislation continues to reinforce the model of the FDA as the center of medical product innovation—a model that has prevailed for over half a century. For most of the FDA's history, medicine and device development became increasingly national in scope, while data sharing among medical practitioners remained limited. Because of such limited communication among practitioners, problems with new therapies did not typically surface until a fairly large number of people had already experienced adverse effects. When problems like these occurred, a government agency needed to gather data, take action, and ultimately be held accountable. But each major problem prompted both the FDA and Congress to further regulate the amount of information required before a drug could go on the market—in hopes of avoiding future large adverse events. And as long as attenuating health product innovation was less of a concern—simply because the underlying science was not moving that fast—this model of the FDA worked relatively well. Furthermore, most scientific advances focused on ameliorating symptoms, not on curing people. Certainly advances at that time were not about enhancing human function.

But the information arena and the science underlying health care have changed. With the sharp increase of data available to patients, physicians, and insurers, neither unsafe nor ineffective products—as well as the companies that produce such products—can escape the rigor of market information and judicial remedies. Even more important is the tremendous potential for rapid advancement of human health that simply was not possible in the 20th century. In this paper, we will show that these improvements are scientifically possible but that current FDA institutions may be unreasonably blocking them.

We begin this paper with a history of FDA laws and regulations through the current FDA regime. Next, we discuss relatively new scientific breakthroughs that have the potential to revolutionize medical technology and treatments. We then provide examples of applications that

the FDA has delayed. Finally, we consider reform alternatives that may strike a better balance between the two types of regulatory risk described earlier. We argue that there is likely to be a huge lag between what is possible in terms of new technologies that can improve health and what is likely to happen if we continue with the current regime.

History of FDA Laws and Regulation

Virtually no federal drug regulation existed before 1903, leaving consumers and patients essentially free to self-medicate. By 1962, Congress had given the FDA sweeping powers to control pharmaceutical research, drug availability, and drug labeling. The fairly rapid transition from laissez-faire to federal control was driven by a series of individual crises that advocates leveraged to justify the new legislation. In some cases, the legislative solution did not even directly address the problem at hand.

Stimulated by the work of Louis Pasteur in the 1880s, the practice of artificial immunization for infectious diseases spread throughout Europe and to the United States during the late 19th century and early 20th century.[5] The commercial development of vaccines in the United States was unregulated at that time.[6] Two 1901 vaccine-related tragedies precipitated the first federal legislation to regulate the interstate trafficking of serums, viruses, antitoxins, and similar products.[7] In St. Louis, Missouri, 13 children died from a diphtheria antitoxin that had been contaminated with tetanus. Investigators found that officials of the St. Louis municipal

[5] Pasteur developed the first laboratory vaccine in 1879. Immunization itself goes back much further. The Chinese are reported to have used inoculation as far back as the 11th century. See the Timelines section of *The History of Vaccines* (College of Physicians of Philadelphia), specifically "Diseases and Vaccines" and "Pioneers: Pasteur," accessed July 8, 2016, http://www.historyofvaccines.org/content/timelines/all.
[6] "Vaccine Development, Testing, and Regulation," *The History of Vaccines*, College of Physicians of Philadelphia, last modified July 31, 2014.
[7] The Biologics Control Act, Pub. L. No. 57-244, 32 Stat. 728 (1902).

health authority were at fault for not destroying all the serum produced from a diseased horse.[8] In Camden, New Jersey, that same year, nine children died from smallpox vaccines that had been contaminated with tetanus.[9] After these two incidents, Congress concluded that the United States needed to control the production and sale of antitoxins, serums, and other similar products through strict regulation. But Congress, limited by the Commerce Clause of the US Constitution, could regulate only the interstate and foreign trade of vaccines.[10] In the St. Louis case, the contaminated antitoxin had been produced and administered in Missouri by the St. Louis Board of Health. It had also been distributed within the state, and therefore regulation of the vaccine was outside the scope of federal law.

At the time, not everyone agreed that the remedy to the problem was federal regulation. Two editorials on the St. Louis incident appeared in the journal *The Medical Brief*; both articles suggested that the problem happened because the antitoxin had been produced in a government-run facility. In addition to asserting that "a city has no right to manufacture anything in competition with an individual," one editorial insisted that city-run health boards "have not the facilities, the experience nor the incentive to furnish products equal to those of the individual proprietor."[11] One editorial suggested the following remedy: "If we must have antitoxin, let its manufacture be restricted to those whom we can hold responsible, whose business interests are at stake and who will, consequently, exert every known precaution to avert disaster."[12]

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[8] College of Physicians of Philadelphia, "Vaccine Development."
[9] Ibid.
[10] At the time the law was passed, the Supreme Court maintained that local manufacturing was not interstate commerce and was therefore outside the scope of Commerce Clause jurisprudence. See United States v. E.C. Knight Co., 156 U.S. 1, 12 (1895). For a discussion on the development of Commerce Clause expansion, see Robert H. Bork and Daniel E. Troy, "Locating the Boundaries: The Scope of Congress's Power to Regulate Commerce," *Harvard Journal of Law and Public Policy* 25 (2001): 849–93.
[11] J. J. Lawrence, "Encroachments on Individual Rights," *Medical Brief* 30, no. 1 (1902): 65–78, 65.
[12] J. J. Lawrence, "Editorial," *Medical Brief* 30, no. 4 (1902): 545–58, 549.

Interestingly, the first commercial producer of the diphtheria antitoxin, H. K. Mulford, had already adopted strategies to minimize the occurrence of tragic situations akin to the one in St. Louis. For the first two years of its antitoxin production, 1895–1897, Mulford sent every batch of antitoxin to the University of Pennsylvania's Laboratory of Hygiene for testing.[13] The company advertised that it dated and labeled all its merchandise and that it invited medical professionals to inspect its facilities to ensure the highest-quality merchandise.[14] Despite these precautions, however, the smallpox vaccine in Camden that was contaminated with tetanus is thought to have come from Mulford, although authorities never confirmed the source of contamination.[15]

The Biologics Control Act of 1902, which was passed in response to the two vaccine-related tragedies of the previous year, required licensing for the production of all antitoxins and vaccines, as well as the labeling of all products with the product name, license number, and expiration date. The act vested the secretary of the Treasury with licensing authority and created a board comprising the secretaries general of the US Army, Navy, and Marine hospitals.[16] The board was charged with developing regulatory standards for licensing as well as for the sale of antitoxins, serums, and other products. In 1903, the Hygienic Laboratory of the Public Health issued the first regulations promulgated under the law.[17]

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[13] Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895–1995* (Cambridge, UK: Cambridge University Press, 1997), 17n21.
[14] Ibid., 18.
[15] David E. Lilienfeld, "The First Pharmacoepidemiologic Investigations: National Drug Safety Policy in the United States, 1901–1902," *Perspectives in Biology and Medicine* 51, no. 2 (2008): 188–98, 193.
[16] "1902 Biologics Control Act," US Pharmocopeia, October 7, 2010.
[17] Center for Biologics Evolution and Research (CBER), "Science and the Regulation of Biological Products," Food and Drug Administration, September 2002, 13.

1906 Pure Food and Drug Act

The popular account of the 1906 Pure Food and Drug Act[18] is that it was enacted as a result of Upton Sinclair's *The Jungle*, a fictionalized story of horrendous conditions in the meatpacking industry.[19] Although *The Jungle* is part of the story, the efforts of Harvey Wiley, Samuel Hopkins Adams, and Senators P. J. McCumber (R-ND) and Weldon Heyburn (R-ID) also played a significant role in the passage of the act.

Dr. Harvey Washington Wiley, at the time the chief chemist at the Bureau of Chemistry, worked so diligently to promote and ensure the passage of the Pure Food and Drug Act that the law, which was originally referred to as the Heyburn Act, was renamed the Wiley Act.[20] Wiley began his work on "pure" food long before 1906. In 1883, working within the Department of Agriculture's Division of Chemistry, Wiley began expanding the department's ongoing investigation of adulterated agricultural products. Diligent and publicity savvy, Wiley publicized his famous "poison squad" experiment in which healthy men consumed varying levels of food additives to determine their effect on the human body.[21] His efforts brought about increased public awareness of the problem and significant political pressure for new legislation.[22]

Concurrent efforts by muckrakers, particularly Samuel Hopkins Adams and Upton Sinclair, to expose the practices of the patent medicine and meatpacking industries, respectively, rallied public opinion behind the Pure Food and Drug Act.[23]

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[18] Pure Food and Drug Act, Pub. L. No. 59-384, 34 Stat. 768 (1906).
[19] Upton Sinclair, *The Jungle* (New York: Doubleday, Page, 1906). See also CBER, "Science and the Regulation of Biological Products," and US Food and Drug Administration (FDA), "FDA History—Part I: The 1906 Food and Drugs Act and Its Enforcement," June 18, 2009.
[20] John P. Swann, "FDA's Origin," US Food and Drug Administration, last updated June 23, 2014.
[21] Ibid.
[22] Wiley's work was not as unbiased as many make it out to be. For instance, Wiley favored straight whiskey over blended whiskey in his "truth-in-labeling" campaign, without providing a chemical basis for his argument. Jack High and Clayton Coppin, "Wiley and the Whiskey Industry: Strategic Behavior in the Passage of the Pure Food Act," *Business History Review* 62, no. 2 (1988): 286–309.
[23] FDA, "FDA History—Part I."

Beginning in 1905, Samuel Hopkins Adams wrote a series of articles titled "The Great American Fraud" in *Collier's Weekly* magazine. The first article lambasted the curative properties of patent medicines; the unethical advertising practices and fake testimonials employed by manufacturers of patent medicines; the complicit activity of the US Patent Office, which issued trademarks to the manufacturers, and the US Post Office, which was used for distribution; and the reticence of some health boards, particularly the Health Department of New York City, to publish their analyses of patent medicines.[24] The second article in the series, "Peruna and the Bracers," detailed the use of Peruna, essentially an inexpensive cocktail that was marketed as a medicine. Although Peruna was advertised as a tonic, its users, including Native Americans and temperance advocates, were becoming alcoholics.[25] Seven of the articles in Adams's series appeared before the 1906 passage of the Pure Food and Drug Act, and all focused on effectiveness claims in relation to the patent medicines' contents—primarily alcohol, cocaine, and opium.[26]

As a result of the attention drawn to patent medicines, Congress incorporated drug labeling requirements for alcohol and poisons into the Pure Food and Drug Act, despite objections that such actions were the proper domain of state police powers.[27] Many states had already adopted laws prohibiting adulterated food and drugs, but such laws were viewed as inadequate because they could not apply to food or drugs imported from other states.[28] Indeed, as a writer for the *Chicago Eagle* newspaper lamented, "If the State cannot protect the individual

[24] Adams applauded the states that adopted labeling laws but highlighted the ability of proprietary interests to thwart the efficacy or passage of such laws. Samuel Hopkins Adams, *The Great American Fraud*, reprinted from *Collier's Weekly*, October 7, 1905 (Chicago: American Medical Association, 1907), 14–15.
[25] Samuel Hopkins Adams, "Peruna and the Bracers," in *The Great American Fraud*, reprinted from *Collier's Weekly*, October 28, 1905 (Chicago: American Medical Association, 1907), 12–22.
[26] Samuel Hopkins Adams, *The Great American Fraud* (Chicago: American Medical Association, 1907), 1–84.
[27] "House Votes to Expose Secrets of Drug Trade: Strong Patent Medicine Label Clause in Pure Food Bill," *New York Times*, June 23, 1906, 3.
[28] John Callan O'Laughlin, "Pure Food Bill Will Pass Today: House and Senate Conferees Finally Agree on a Compromise Measure Satisfactory to Both," *Chicago Daily Tribune*, June 28, 1906, 1, 7.

against such swindling—and the State commissions confess their impotence—one naturally looks to the Federal government for protection and to his representative in Congress to provide statutory means for such protection."[29]

The congressional sponsors promoting the bill to the public framed the Pure Food and Drug Act campaign as a fight against fraud. The cosponsors of the Pure Food and Drug Act, Senators Heyburn and McCumber, gave an interview in January 1906 in which they stated that the goals of the bill were the following: (1) prevention of fraudulent sales so that consumers would know what they were buying, (2) protection of honest manufacturers from dishonest competitors, and (3) establishment of consistent food and drug standards to replace the patchwork legislation of several states. Heyburn and McCumber insisted that the law neither determined what could be shipped between states nor established a board or committee under the Department of Agriculture for the purpose of determining which foods could be sold; the law provided only definitions of *adulterated* and *misbranded* for use in court cases.[30]

In the House, Representative James Mann (R-IL) dramatically displayed fraudulent food products. He showcased a multitude of adulterated and misbranded substances, including fake peppercorns, dyed cherries, and canned goods whose labels misrepresented their contents.[31] Mann's argument resonated with the general public, especially with journalists. According the *New York Times*, "There is not, so far as we know, one valid argument to be made against a reasonable restriction of the possibilities of fraud in the manufacture of foods and medicines, and even as it stands the Heyburn bill errs only on the side of leniency to swindlers and poisoners."[32]

[29] "Beef Trust Fowl," *Chicago Eagle*, April 7, 1906, 1.
[30] W. W. Jermane, "Pure Food Bill's Outlook Hopeful," *Minneapolis Journal*, January 29, 1906, 3.
[31] Clifford S. Raymond, "'Pure Food' Show Sets House Agape," *Chicago Daily Tribune*, June 22, 1906, 1.
[32] "Topics of the Times," *New York Times*, June 6, 1906, 8.

Signed on June 30, 1906, the law in its final form provided labeling standards for drugs and food; prohibited false or misleading labels; and required that certain drug ingredients, among them cocaine, heroin, and opium, be printed on product labels.[33] The law was heralded by the *New York Times*:

> The Pure Food bill brings up with a round turn a multitude of the country's meanest swindlers—the detestable wretches who sell all manner of alimentary and medicinal preparations under lying labels, who adulterate drugs and compound food products of deleterious or worthless substances. This and the Meat Inspection bill are instances of paternalism in legislation demanded and made necessary because of the wholesale practice of shameless frauds. They will protect the public pocket and the public health.[34]

The 1906 law formed the basis for what would later become the FDA. Although the Pure Food and Drug Act was originally designed to provide consumers with truthful labeling, the paternalistic intentions behind the law later burgeoned into a desire to protect consumers from themselves.

Proponents of the 1906 Pure Food and Drug Act soon discovered the limitations of the law. In 1911, the Supreme Court determined that the law "did not prohibit false therapeutic claims, but only false and misleading statements about the ingredients or identity of a drug."[35] The ruling prompted Congress to pass the Sherley Amendment in 1912, which prohibited false claims intended to defraud the user, but the standard was difficult to prove in court.[36] Two years after the passage of the Sherley Amendment and eight years after the passage of the 1906 Pure Food and Drug Act, Congress enacted the first law to restrict access to a particular class of drugs. Attempting to combat growing narcotics use, Congress passed the Harrison Narcotics Tax Act of

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[33] FDA, "FDA History—Part I."
[34] "The Federal Power Exalted," *New York Times*, June 6, 1906, 6.
[35] CBER, "Science and the Regulation of Biological Products," 13. See also Suzanne White Junod, "FDA and Clinical Drug Trials: A Short History," in *A Quick Guide to Clinical Trials*, ed. Madhu Davies and Faiz Kermani (Washington, DC: Bioplan, 2008), 25–55.
[36] CBER, "Science and the Regulation of Biological Products."

1914, thereby creating the "first statutory requirement for prescription drugs in the United States."[37] The act required a prescription for pharmacies to dispense narcotics, and it also required dispensing pharmacies to register with and pay a fee to the IRS. The act also prohibited drug refills, instead requiring a new prescription for each dispersal of medication.[38]

1938 Federal Food, Drug, and Cosmetic Act

In the early 1930s, pressure started building for a new food and drug bill to protect consumers from false claims and harmful products. The FDA created an exhibition of products that were still allowed under the 1906 law but that were harming consumers, either by promising treatments that the products did not deliver or by actually causing injury. Such products included eye drops that caused blindness, a fake cure for diabetes, and a tonic containing radium.[39]

The eventual 1938 Food, Drug, and Cosmetic Act began as a bill introduced in 1933.[40] The bill lacked support until 1937, when a drug called Elixir Sulfanilamide killed more than 100 people. The intended active ingredient of the elixir, sulfanilamide, was already widely used as an antibiotic, appearing in both tablet and powder form.[41] Demand for the drug in liquid form, primarily for children, prompted the company Massengill to develop Elixir Sulfanilamide. In this liquid version, sulfanilamide, which has low solubility, was dissolved in diethylene glycol. The company added raspberry flavoring to the drug and tested for its "flavor, appearance, and fragrance"—but not for safety—before manufacturing and widely

[37] "This Week in FDA History—Dec. 17, 1914," US Food and Drug Administration, last updated June 18, 2009.
[38] John P. Swann, "FDA and the Practice of Pharmacy: Prescription Drug Regulation before the Durham-Humphrey Amendment of 1951," *Pharmacy in History* 36, no. 2 (1994): 55–70, 59.
[39] FDA, "FDA History—Part II: The 1938 Food, Drug, and Cosmetic Act," September 24, 2012.
[40] The Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938). See Peter Temin, "The Origin of Compulsory Drug Prescriptions," *Journal of Law and Economics* 22, no. 1 (1979): 91–105, 96.
[41] Carol Ballentine, "Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident," *FDA Consumer Magazine*, June 1981.

distributing the drug.[42] Prescribed primarily to children for sore throats and available over the counter, the elixir quickly killed more than 100 patients before it was recalled. The drug's solvent, diethylene glycol, which is now used in some antifreeze, is highly toxic and caused "metabolic acidosis, kidney failure, and dangerous neurological complications."[43]

Massengill and the FDA worked quickly to recall the substance, but the FDA's only authority to seize the product lay in the fact that Elixir Sulfanilamide was mislabeled as an elixir, which was defined as an alcohol solution. In court, the FDA was forced to rely on the same mislabeling authority, because safety requirements were not part of the 1906 Pure Food and Drug Act. Had Massengill labeled the elixir as a "solution," the FDA would have had no authority to seize the liquid or to prosecute Massengill, despite the company's lack of basic animal testing and the medical literature on diethylene glycol, both of which would have revealed the substance's toxicity. Recalls were also difficult; the FDA relied on radio announcements to provide recall information to consumers, but some segments of the population did not have access to a radio.[44] Outrage over the incident rallied public support for food and drug law reform, including the required safety testing outlined in the 1938 Federal Food, Drug, and Cosmetic Act.[45]

The 1938 act significantly increased the formal regulatory scope of the FDA. Most notably, the law expanded the FDA's authority to regulate medical devices and cosmetics, and it also gave the FDA the authority to postpone the introduction of new drugs to the market until the agency certified the drugs as safe.[46] However, the law did contain a provision that awarded the

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[42] Ibid.
[43] Kristin Jarrell, "Regulatory History: Elixir Sulfanilamide," *Journal of GXP Compliance* 16, no. 3 (2012): 12–14, 13.
[44] Donna Young, "Documentary Examines Sulfanilamide Deaths of 1937," American Society of Health-System Pharmacists, December 5, 2003.
[45] Ballentine, "Taste of Raspberries, Taste of Death."
[46] FDA, "FDA History—Part II; Temin, "Compulsory Drug Prescriptions," 94–95.

drug de facto approval if the FDA did not act on the manufacturer's application within a certain time frame.[47]

The Federal Food, Drug, and Cosmetic Act also revised and increased labeling standards for drugs, which were now required under section 502 to include directions for use, warnings regarding misuse, and ingredient lists. The law also required that drug labels could not be false or misleading, and it stipulated that a drug was mislabeled if it was dangerous to health in the dosage recommended. Nonetheless, these labeling requirements did not apply to drugs that were to be repackaged before sale or to drugs whose labels included the following warning: "to be used only by or on the prescription of _____ (doctor, dentist, veterinarian)."

The stated goal of the Food, Drug, and Cosmetic Act, according to Walter Campbell, then chief of the FDA, was "to make self-medication safe."[48] The effect, however, of this exemption for prescription medications appears to have been the opposite. There were two reasons for the problem. First, within two months of the law's passage, the FDA began exercising its power to curtail the sale of some drugs that had previously been available over the counter by requiring a prescription.[49] By 1941, the FDA had classified more than 20 different drugs and drug groups as too dangerous to sell without a prescription.[50] Second, drug producers used the exemption for prescription drugs as a way to avoid the labeling requirements, thus curtailing the supply of over-the-counter drugs available to citizens.[51]

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[47] Michelle Meadows, "The Food, Drug, and Cosmetic Act of 1938: Promoting Safe and Effective Drugs for 100 years," *FDA Consumer Magazine*, Centennial Edition/January–February 2006.
[48] Temin, "Compulsory Drug Prescriptions," 96.
[49] FDA, "FDA History—Part III: Drugs and Foods under the 1938 Act and Its Amendments," last updated June 18, 2009.
[50] John K. Crellin, *A Social History of Medicines in the Twentieth Century* (Binghamton, NY: Pharmaceutical Products Press, 2004), 128.
[51] Ibid. See also Swann, "FDA and the Practice of Pharmacy," 60.

1951 Durham-Humphrey Amendment

Confusion regarding the legal status of prescription drugs prompted the 1951 Durham-Humphrey Amendment, which defined a prescription-only drug as "any habit-forming substance, any substance so toxic or harmful that it required the supervision of a practitioner for its administration, or any new substance approved under the safety provision of the 1938 act that had to be used under supervision."[52] The amendment codified 13 years of FDA regulation and enforcement, especially in regard to distinguishing prescription from nonprescription drugs.[53] Historically, the primary purpose of prescription enforcement had been to curtail the sale of barbiturates and amphetamines, addictive drugs that were legally marketed as sleeping pills and antidepressants and were frequently refilled indiscriminately by pharmacists or sold illicitly at truck stops.[54]

Although the FDA already enforced a two-tier system of prescription and over-the-counter drugs, professional pharmacists, the American Medical Association (AMA), and the drug industry strongly opposed legislation codifying the FDA's authority to determine the prescription-only list.[55] While the AMA likely viewed the law as an encroachment on its members' freedom to practice medicine, the Proprietary Association (representing the patent medicine industry) attacked the law as a "handmaid of socialized medicine [and] . . . the most famous threat to freedom of medical care in America since the famous Tugwell bill of 1933. . . . [The proposed amendment] jeopardizes the traditional right of self-medication and choice of remedies."[56] Although pharmacists, the AMA, and drug manufacturers surely had vested

[52] Crellin, *Social History of Medicines*, 128.
[53] Swann, "FDA and the Practice of Pharmacy," 65.
[54] FDA, "FDA History—Part III.
[55] Swann, "FDA and the Practice of Pharmacy," 60.
[56] W. Stephen Pray, *A History of Nonprescription Product Regulation* (Binghamton, NY: Pharmaceutical Products Press, 2003), 143.

interests in the law, their dislike of the Durham-Humphrey Amendment revealed that not everyone was keen to consolidate authority in the FDA, which—as those groups accurately predicted—would come to limit the freedom of doctors to practice, the ability of companies to develop drugs, and consumers' ability to choose for themselves.

1962 Kefauver-Harris Amendments

In 1959, the Antitrust and Monopoly Subcommittee, headed by Senator Estes Kefauver (D-TN), began hearings on drug pricing. The primary issues raised in the hearings were (1) that new drugs on the market were priced "unusually high" and (2) that institutional structures allowed companies to use patents to excessively profit from only minor changes to a drug.[57] If drug companies aggressively promoted such drugs, physicians might overprescribe them and consumers might end up overpaying. Kefauver suggested that government regulation of a manufacturer's claims of drug effectiveness would be cheaper in hindsight.[58]

Stricter regulation of drug manufacturers gained popular support after thalidomide, an over-the-counter sedative, caused severe birth defects—primarily limb deformities—in thousands of children born in Europe in the mid-20th century.[59] Although thalidomide was not approved by the FDA for use in the United States, trial samples of the drug were available.

Pharmaceutical company Chemie Grünenthal first marketed thalidomide in West Germany in 1956 after limited human testing. In their book *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine*, Trent Stephens and Rock Brynner suggest that

[57] Sam Peltzman, "An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments," *Journal of Political Economy* 81, no. 5: 1049–91, 1050.
[58] Ibid.
[59] James H. Kim and Anthony R. Scialli, "Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease," *Toxicological Sciences* 122, no. 1 (2011): 1–6.

the company's failure to test more diligently was born of the callous attitude toward drug experimentation during the Nazi era.[60] Because the drug did not cause similar effects in animals and because it triggered fetal deformities only when taken in early pregnancy, the relationship between thalidomide and birth defects was hard to identify. Thalidomide usage spread widely through Europe, Canada, and Australia before its devastating side effects were conclusively documented.

The thalidomide incident attracted attention to the FDA after Kefauver leaked to the *Washington Post* the story of FDA officer Dr. Frances Kelsey's denial of approval for marketing of thalidomide in the United States. The story boosted the public's confidence in the work of the agency, resulting in a bill that invested considerably more power in the agency.[61] Although the scandal prompted stricter drug regulation, it is not clear if such regulation would have prevented the drug from reaching the market, because "other countries with regulatory approval processes, such as Sweden and Canada, had approved the drug," and also because Dr. Kelsey had withheld US approval of thalidomide on the basis of concerns about peripheral neuropathy, not phocomelia (a limb deformity).[62]

The Kefauver-Harris Amendments fundamentally changed the way the FDA regulated drugs. The law required manufacturers to demonstrate the effectiveness—not just the safety—of new drugs, and it required them to report any serious side effects after a drug's release on the market. The law eliminated default drug approval after 60 days and instead instituted a 180-day process that required positive FDA approval before a drug could be marketed. The law also

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[60] Trent Stephens and Rock Brynner, *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine* (Cambridge, MA: Perseus, 2001).
[61] Bridget Henig, "50th Anniversary of the Kefauver-Harris Drug Amendments of 1962: Interview with FDA Historian John Swann," US Food and Drug Administration, last updated September 26, 2012.
[62] Kim and Scialli, "Thalidomide," 1.

required a retrospective evaluation of effectiveness for drugs that had been approved under the 1938 law. Furthermore, the law (1) granted the FDA authority to regulate drug manufacturing practices; (2) mandated regular facilities inspections; and (3) transferred authority to the FDA to regulate drug marketing, including the marketing of generics.[63] The most influential of these new requirements, the requirement for "adequate and well-controlled studies," established the randomized double-blind controlled clinical trial, which came to be considered the gold standard method for demonstrating drug effectiveness.[64] Ultimately, though, the result of the law was the opposite of what Kefauver had hoped; the drug approval process became longer and more intense, drugs became more expensive, and new drugs reached the US market more slowly.[65]

The thalidomide tragedy also revealed the dangers of an overly aggressive regulatory policy. Such dangers include impeding medical discovery and limiting access to treatments that may be appropriate for some classes of patients. In 1964, an Israeli doctor, Jacob Sheskin, was attempting to sedate a leprosy patient who was in extreme pain. The doctor administered two thalidomide pills that remained in the Israeli hospital's infirmary.[66] The medication not only enabled the patient to sleep, but also reversed the disease's symptoms. Access to thalidomide pills from the drug's initial rollout thus allowed the physician to discover a successful treatment for leprosy. Later, continued access to thalidomide provided the opportunity for practitioners to test the drug as a treatment for AIDS and cancer. Both of these tests eventually proved successful. By managing the risks associated with thalidomide, physicians can safely use the

[63] "Kefauver-Harris Amendments Revolutionized Drug Development," US Food and Drug Administration, last updated February 19, 2015.
[64] Henig, "50th Anniversary of the Kefauver-Harris Amendments."
[65] Jeremy A. Greene and Scott H. Podolsky, "Reform, Regulation, and Pharmaceuticals: The Kefauver-Harris Amendments at 50," *New England Journal of Medicine* 367, no. 16 (2012): 1481–83.
[66] Kim and Scialli, "Thalidomide," 2.

drug to treat patients with certain serious diseases. Today, thalidomide is approved for use in the United States to treat Hansen's disease (leprosy) and multiple myeloma.[67]

Without recognizing the benefits of thalidomide, many people are likely to assume that stricter drug testing is always better. However, this assumption ignores the cost of missed opportunities and treatment discoveries that occur only when doctors and patients decide that the potential benefits of a "dangerous" drug outweigh its risks. Thus, when formulating a drug safety regime, policymakers should be mindful that overreactions to safety concerns can be as costly as underreactions.

Legislative Reforms and Amendments after 1962

Legislative reforms after 1962 focus predominantly on mitigating the adverse consequences of the Kefauver-Harris Amendments, including increased drug costs and longer development and approval processes. Recognizing that these increased costs significantly decreased incentives for pharmaceutical companies to develop drugs for relatively small disease populations, Congress passed the Orphan Drug Act of 1983.[68] The act created financial incentives—including tax breaks and seven-year monopoly grants—for companies to develop medicines for rare diseases.[69]

In 1984, Congress recognized the impact of longer trials on the price of drugs. The 1984 Drug Price Competition and Patent Term Restoration Act extended patents by the length of the FDA approval process and expanded the list of drugs eligible for an abbreviated approval process in an effort to encourage generic drug manufacturing.[70] The Prescription Drug User Fee

[67] Ibid.
[68] Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).
[69] Meadows, "Promoting Safe and Effective Drugs for 100 Years."
[70] Ibid. See Drug Price Competition and Patent Term Restoration Act, Pub L. No. 98-417, 98 Stat. 1585 (1984).

Act of 1992 authorized the FDA to collect user fees from applicants filing a New Drug Application or Biologics License Application;[71] these fees were then used to fund review staff. The act has been renewed every five years since its adoption, including as part of the Food and Drug Modernization Act of 1997.[72]

The Medical Device Amendments of 1976 did not follow the same trend as the other acts, which were efforts to counteract the effects of increased costs and longer approval processes. The amendments expanded the FDA's authority over medical devices and established a three-tiered system to identify different market pathway requirements and clinical investigation requirements. The amendments also created advisory panels to classify and evaluate medical devices according to the tiered system established by the law.[73] A more recent law, the Food and Drug Administration Safety and Innovation Act, is addressed later in the policy section.[74]

The history of the FDA reveals that, over time, the purpose of the agency has shifted from ensuring honest and accurate drug information to providing strict regulatory drug oversight. This stricter regulatory scheme imposes significant costs, which are generally justified by claims that such a system ensures consumer safety. But the general legislative trend for the past 30 years suggests the possibility that not all these costs are justified. Both delayed access to available drugs and drugs that never even become available because of the cost and time for approvals suggest that there are more efficient means of achieving the FDA's consumer safety goal. In the

[71] Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992).
[72] Food and Drug Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (1997).
[73] See Richard A. Rettig, Laurence E. Earley, and Richard A. Merrill, eds., *Food and Drug Administration Advisory Committees: Committee to Study the Use of Advisory Committees by the Food and Drug Administration* (Washington, DC: National Academy Press, 1992), 63–65. See also "Overview of Medical Devices and Their Regulatory Pathways," US Food and Drug Administration, March 6, 2014.
[74] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012).

following sections, we provide evidence that the costs imposed by the FDA's current regulatory scheme remain higher than is socially optimal.

Future Science and the FDA

The examples in this section represent just a few of the changes that are possible in the ways we seek to live healthier and longer lives. Throughout history, humans have been driven to extend our lifespans, increase our quality of life, or both. In the 21st century, opportunities to positively affect both length and quality of life seem more numerous than at any other time in human history. Singularity University studies *exponential medicine*—that is, technology in the field of medicine that is accelerating at exponential rates. It describes its exponential medicine program as follows:

> This unique program focuses on breakthrough developments ranging from 3D printing to personalized stem cell lines, artificial intelligence, point-of-care lab-on-a-chip diagnostics to large-scale bioinformatics and synthetic biology and the implications of low cost genomics. All of these rapidly developing technologies and more are discussed in the context of the current explosions of digital information, big data and connected and distributed healthcare.[75]

In his book *Radical Evolution*, Joel Garreau describes what he calls *GRIN* (genetic, robotic, information, and nano) technologies, which we discuss later.[76] Garreau noted back in 2004 that these technologies were "creating a curve of change unlike anything we humans have ever seen."[77] Garreau writes that, in a world where science is allowed to progress, the following would be reality:

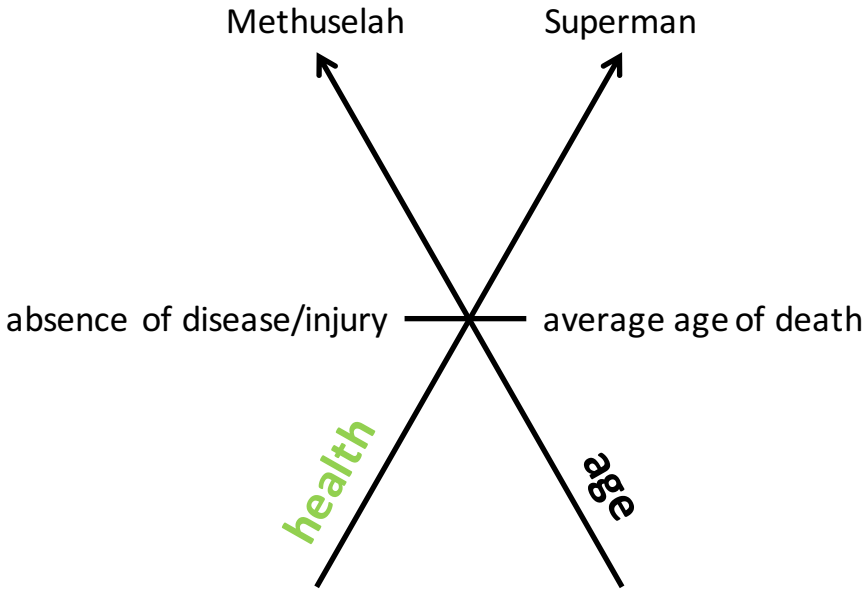
> Aging has slowed dramatically. Most disease can be prevented or reversed. Drugs are individually tailored to an individual's DNA, so there is nothing like the 100,000 annual

[75] Singularity Education Group, "About Exponential Medicine," Exponential Medicine, 2016, https://exponential.singularityu.org/medicine/about/#overview.
[76] Joel Garreau, *Radical Evolution: The Promise and Peril of Enhancing Our Minds, Our Bodies—and What It Means to Be Human* (New York: Doubleday, 2004), 4.
[77] Ibid., 5.

> deaths even from properly used prescription drugs that had been common in the United States. Robots the size of blood cells—nanobots, as they are called—are routinely injected by the millions into people's bloodstreams. They are used primarily as diagnostic scouts and patrols, so if anything goes wrong in a person's body, it can be caught extremely early.[78]

The difference between the goals of modern medicine and radical evolution are illustrated in figure 1. Note that the goals of modern medicine currently end at the intersection of the two arrows. Until fairly recently, the purpose of health care has been to try to restore human health after disease or injury and to allow people to live to or beyond the average age of death. It is with this approach that we have established medical institutions as we know them, specifically (1) public health agencies, such as the FDA, to approve drugs and medical devices; (2) insurance companies, including government agencies, to pay for medical treatments; and (3) doctors to prescribe drugs and perform surgery.

Figure 1. The New Age–Health Paradigm



[78] Ibid.,102.

The top half of figure 1, where people seek to live much longer lives and to achieve bodies of above-average health (not simply absent of diseases and injuries), represents the new frontier of health care. Currently, no public or private institutions regulate or reimburse patients for such cutting-edge treatments. Eventually, as concerns emerge regarding the safety, effectiveness, and fairness of these treatments, the question will be whether we will simply graft current healthcare regulations onto these new applications or whether we will look for something entirely new.

Additionally, many people are beginning to question the multiple and expensive permissions that inhibit access to the best possible medical treatments (see the bottom half of the chart). Newer technologies (discussed below), which could eventually allow humans to enjoy the benefits of the upper range of figure 1, may be leading some patients to question the efficacy of the our current "hub and spoke" regime.[79] Particularly, restrictions on such treatments become a more salient issue as scientific discovery opens doors to new treatment possibilities, which the older regulatory institutions of the United States would undoubtedly attenuate.

James Watson, co-winner of the 1953 Nobel Prize for his discovery of the structure of DNA, asked the following: "No one really has the guts to say it, but if we could make better human beings by knowing how to add genes, why shouldn't we?"[80] If humanity is truly serious about curing disease, preventing disease, and making longer lives possible, the next question is, what conditions are necessary for the translation of GRIN technologies into actual human health improvements? The answer to that question, in turn, lies in whether government can restructure

[79] See, for example, Peter Bach, "The FDA May No Longer Exist in 25 Years—Here's Why," *Wall Street Journal*, December 23, 2015; Tenth Amendment Center, "Time to Get Rid of the FDA," May 16, 2007.
[80] As quoted by Gregory Stock, *Redesigning Humans: Choosing Our Genes, Changing Our Future* (New York: Houghton Mifflin, 2003), 12.

the FDA's role into one that (1) allows for more innovation and (2) relies more heavily on both market forces and physicians to ruthlessly monitor risks and benefits of innovative treatments in an effort to minimize harm. The next section briefly examines some of the emerging scientific technologies that are likely to have an effect on health care and aging within the next several decades—particularly if the technologies are not subjected to onerous regulatory burdens.

Robotics

Robotics is likely to play a role in, for example, diagnostics, medical devices, and drug delivery. Remote robotic surgery, which may be regulated in the same manner as medical devices, is just beginning to see promise, and it may have the ability to perform much more precise, targeted procedures than are currently possible. Other possibilities for robotics include robot nurses (for elderly patients and patients with transmissible diseases), robotic limbs, and even exoskeletons (an example of the "superman" possibilities alluded to in figure 1).[81] One type of exoskeleton currently in development can read an EEG (electroencephalogram) to help paralyzed individuals walk.[82] Other exoskeletons are designed to enhance human speed and strength.[83]

Nanotechnology

Nanotechnology uses nanomaterials, which are roughly the size of three atoms strung together. Nanomaterials have characteristics that differ (e.g., color, charge, and strength) from those of

[81] Robot Nurses are already being developed. In Japan, it has been estimated that such nurses could save $21 billion in in healthcare costs. "Robotic Nurses (Ethics of Robot Decisions under Uncertainty of Human Interaction)" (Stanford University Computer Science Department), accessed July 18, 2016.
[82] Brady Dale, "A New Industry Flexes Its Servos," *Fortune*, August 27, 2014.
[83] Samuel Gibbs, "The Future for Augmented Humans: 'In Five Years You'll See Exoskeletons on the Building Site,'" *Guardian*, January 7, 2015.

macrosized elements.[84] Areas with the greatest potential for revolutionary changes from nanotechnology are medicine, computer science, and environmental science.[85]

Nanotechnology may revolutionize virtually all aspects of medicine, including drug delivery, diagnostics, cell repair, and antimicrobial functions.[86] In a cross between robotics and nanotechnology, nanorobots are just starting to emerge. For example, nanorobots constructed from DNA may be programmed to find and kill (through a delivery of small drug molecules) targeted leukemia cells without affecting surrounding healthy cells.[87] Nanorobots may also be used to deliver vaccines efficiently, to dissolve blood clots, to release insulin for diabetics, or to block virus reproduction. Nanorobots may be used for screening purposes; by routinely scouring the body, they would allow much earlier detection than is currently possible. Conceivably, when the nanorobot detected a problem, it could send a signal to a device worn by the patient. Other potential nanoproducts include nanosponges that would soak up toxins or absorb free radicals in the bloodstream and nanotubes that would replace invasive surgery by blasting tumors with sound waves.[88]

Cellular Therapy

Perhaps the most promising of the new technologies goes beyond managing patients' symptoms to find cures that (1) address diseases' root causes and (2) promise to extend lifespans by

[84] Richard Williams, review of *Nanotechnology: Health and Environmental Risks*, by Jo Anne Shatkin, *Risk Analysis* 29, no. 2 (2009): 312–13.
[85] Richard Williams et al., "Risk Characterization for Nanotechnology," *Risk Analysis* 30, no. 11 (2010): 1671–79, 1677.
[86] "Nanotechnology in Medicine—Nanomedicine," *Understandingnano.com*.
[87] Sarah Griffiths, "Nanorobots Trial to Begin in Humans: Microscopic DNA Devices Could Be Injected into a Leukaemia Patient in a Bid to Destroy Abnormal Cells," *Daily Mail*, March 18, 2015.
[88] UnderstandingNano.com discusses these and other uses of nanotechnology in medicine on its website at http://www.understandingnano.com/medicine.html.

decades.[89] Also known as *regenerative medicine*, cellular therapy uses living tissue—either a person's own tissue (autologous) or someone else's (allogenic)—to stimulate tissues or organs to heal themselves.[90] More specifically, regenerative medicine is the "use of natural human substances such as genes, proteins, cells and biomaterials to regenerate diseased or damaged human tissue."[91] These substances can come from the same tissue or organ to which they are applied (homologous), or they can come from a different tissue or organ (nonhomologous). Right now, about 18,000 clinical trials of regenerative therapies are being conducted in the United States.[92] As Robert Freitas states, "One conceptually simple form of basic cell repair is chromosome replacement therapy (CRT), in which the entire chromatin content of the nucleus in a living cell is extracted and promptly replaced with a new set of prefabricated chromosomes which have been artificially manufactured as defect-free copies of the originals."[93]

Another possibility of regenerative medicine is the prevention of inherited diseases caused by mitochondrial DNA (mtDNA) mutations. A newly developed technique known as *mtDNA transfer* replaces in vitro–fertilized mutated genes with a third party's healthy mtDNA. This technique may lead to longer lifespans, improved health, and even elimination of some diseases.[94]

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[89] Bipartisan Policy Center, "Advancing Regenerative Cellular Therapy: Medical Innovation for Healthier Americans," December 2, 2015.

[90] The postgenomic perspective challenges that of the older genome revolution, which assumed a static one-to-one relationship between the genome (as a collection of genes) and a disease. In particular, it now appears as though the genome adapts and responds to different signals that it receives from its environment. See Evelyn Fox Keller, "The Postgenomic Genome," in *Postgenomics: Perspectives on Biology after the Genome*, ed. Sarah S. Richardson and Hallam Stevens (Durham, NC: Duke University Press, 2015).

[91] Giuseppe Orlando et al.,"Regenerative Medicine and Organ Transplantation: Past, Present and Future," *Transplantation* 91 (2011):1310–17, as cited in Margaret Foster Riley, "Twenty-First-Century Technology with Twentieth-Century Baggage: FDA Regulation of Regenerative Medicine," *FDA in the 21st Century: The Challenges of Regulating Drugs and New Technologies*, ed. Holly Fernandez Lynch and I. Glenn Cohen (New York: Columbia University Press, 2015), 456.

[92] Bipartisan Policy Center, "Advancing Regenerative Cellular Therapy," 4.

[93] Robert Freitas, "The Ideal Gene Delivery Vector: Chromallocytes, Cell Repair Nanorobots for Chromosome Replacement Therapy," *Journal of Evolution and Technology* 16, no. 1 (2007): 1–97, 1.

[94] Jonathan Govette, "Biggest Innovations in Health Care Technology in 2015 and 2016," referralMD, October 2, 2015.

Currently, even if cells are transplanted back into the person from whom they were taken, the FDA regulates those very cells as biologics (i.e., in a manner similar to its regulation of drugs). But cellular therapies are *not* drugs developed for use by thousands of people; rather, they are medical treatments for specific individuals. Regenerative medicine therapies fall under one of the FDA's three tiers of regulatory approval for biologics. The strictest of these tiers requires the biologics license application, which costs "hundreds of millions of dollars to compile 'substantial clinical evidence' demonstrating [a therapy's] safety and effectiveness before [the therapy can receive] market approval."[95]

Most of the controversy surrounding cellular therapy is associated with the use of neonatal stem cells. But use of adult stems cells (found in adults and children) and of other types of stem cells (e.g., pluripotent cells created using viral vectors) should not carry the same level of controversy or FDA scrutiny. To date, stem cell products have been regulated differently in different countries (e.g., regulated as drugs, regulated as devices, or simply unregulated). Further complicating regulation, stem cell products are often classified as mixtures of drugs, devices, and biologics.[96] One issue is whether the FDA even has the authority to regulate procedures that appear to be simply extensions of the practice of medicine, even when tissues are manipulated.[97] A more in-depth discussion on cultured stem cells appears later.

Some analysts have pointed out that if the FDA continues to crack down on cellular therapies, therapy providers will simply move offshore, thereby boosting the medical tourism industry.[98] In fact, this very phenomenon is happening right now, as the FDA has not

[95] Bipartisan Policy Center, "Advancing Regenerative Cellular Therapy," 9.
[96] Riley, "Twenty-First-Century Technology with Twentieth-Century Baggage."
[97] Ibid.
[98] Richard Williams, Robert Graboyes, Adam Thierer, "US Medical Devices: Choices and Consequences" (Mercatus Working Paper, Mercatus Center at George Mason University, Arlington, VA, 2015).

approved a single one of these regenerative technologies in the past 15 years (as of December 2015).[99]

Big Data and the Internet of Things

As Daniel Kraft noted in 2011, "Many aspects of health care and disease management will become cheaper and more effective as our mobile phones and other, similar technology platforms become smaller, Web-enabled and interconnected. In essence, these smartphones will become health platforms. They already contain a wide array of sensors."[100] Current smartphone-connected activity and sleep trackers, like those marketed by Fitbit,[101] herald such future possibilities, which might include, for example, digestible sensors that transmit real-time information to people about their physical condition.[102] What has been called *digital health*, ranging from remote sensing and diagnostics to perhaps even treatment, has the potential to both improve the quality and lower the costs of medical treatment.

Citing an example of the future of digital health, Adam Thierer notes that South Korean scientists have already developed a flexible electronic "skin patch that's thinner than a sheet of paper and can detect subtle tremors, release drugs stored inside nanoparticles on-demand, and record all of this activity for review later."[103] Having received real-time knowledge of their health and DNA, people can learn what diseases they are susceptible to. People can also

[99] Kevin McCormack, "Doing Nothing Is Not OK: A Call for Change at the FDA," *Stem Cellar* (California Institute for Regenerative Medicine), December 16, 2015.
[100] Quoted in Vivek Wadhwa, "The Future of Medicine," *Washington Post*, July 28, 2011.
[101] For information about range of fitness tracking devices available from Fitbit, see the company's website at https://www.fitbit.com/.
[102] Brian Honigman, "The Seven Biggest Innovations in Health Care Technology in 2014," referralMD, November 17, 2013.
[103] Adam Thierer, "The Internet of Things and Wearable Technology Addressing Privacy and Security Concerns without Derailing Innovation" (Mercatus Working Paper, Mercatus Center at George Mason University, Arlington, VA, November 2014), 18.

determine how to best treat those diseases by using their own genetic profile to access "crowd-sourced, data-driven, participatory genomics-based [pharmacogenomics], medicine."[104] IBM's Watson platform can access more data instantaneously than can any individual physician, a fact that highlights the potential of big data to positively affect the lives of patients.[105] Despite releasing some initial guidance, however, the FDA is still trying to figure out how and where to regulate these new technological developments.[106]

Synthetic Biology

Going well beyond traditional cellular therapies, synthetic biology combines the fields of biology, computer engineering, and genetic engineering to "design and construct novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems."[107] Synthetic biology allows scientists to take genetic information from one organism and apply it to the next, but its ultimate goal is to create life from nonorganic materials. Nonorganic origins would alter the human genome, effectively making humans immune to all diseases. As George Church and Ed Regis put it, "If synthetic genomics were used to enhance our immune response, we would possess a deliberately engineered superimmunity to a vast array of diseases."[108] The big idea behind synthetic biology is that humans no longer need to wait for the long process of evolution; rather, they can accelerate evolution for themselves.

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[104] Wadhwa, "Future of Medicine."
[105] "IBM's Watson," slide, from Susan Scutti, "Medical Robots Are Not Just the Future of Health Care, but Part of the Present," *Medical Daily*, January 22, 2015.
[106] InfoLawGroup, "The Internet of Things: FDA Releases Guidance on Securing Wireless Medical Devices—What Medical Device Manufacturers Should Know," October 2, 2013.
[107] Scott A. Edelstein and Lindsay P. Holmes, "Seeking Novel Treatments Abroad: Stem Cell Tourism—Risks, Legal Issues and Mitigation; Proceeding of the STEMSO Conference," *CellR4* 2, no. 1 (2014): e700.
[108] George Church and Ed Regis, *Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves* (New York: Basic Books, 2012), 132.

3-D–Printed Biological Materials

In time, 3-D printers could begin to print organs, cartilage, and tissues.[109] One potential use for 3-D printers that the FDA is currently struggling with is the "printing" of prosthetic hands. Parts for the 3-D–printed hands generally cost around $5 to $10, as opposed to FDA-approved prosthetics, which can run over $20,000.[110] However, a layperson such as a family member can assemble the 3-D–printed hands for children who have missing or deformed limbs. The FDA has so far determined that it will not regulate 3-D–printed hands unless they have some sort of electrical component.

Case Studies of Treatments Delayed or Denied Approval by the FDA

With such tremendous potential improvements for medical treatments, it seems unlikely that a drug approval regime conceived in 1962 can keep up in the future. In this section, we examine five therapies whose availability is being retarded or denied by FDA regulation. These case studies are not limited to individual drugs; we also discuss genetic testing and a treatment involving reinjection of a patient's own cells (cellular therapy). The common thread connecting the example therapies is that they would all be more widely or more immediately available under a more liberal regulatory regime.

Cultured Stem Cells: Regenexx, Precision Stem Cell

Cultured stem cell procedures offer a nonsurgical alternative for the treatment of orthopedic injuries, including sports injuries, joint pain, and degenerative joint conditions.[111] Other uses of

[109] Honigman, "Seven Biggest Innovations in Health Care Technology in 2014."
[110] Robert Graboyes, "How to Print Yourself a New Hand," *CNN*, October 24, 2014.
[111] The physician network Regenexx discusses these procedures on its website, http://www.regenexx.com/.

cultured stem cells include treatment for neurodegenerative diseases such as ALS (amyotrophic lateral sclerosis).[112] On the whole, orthopedic stem cell procedures promise recovery times that are quicker than traditional surgery, as well as more sustained benefits over time, but companies seeking to use stem cell treatments face significant regulatory hurdles from the FDA. These hurdles have caused some companies to limit certain stem cell treatments to offshore facilities.

Cultured stem cell procedures for orthopedic purposes generally use adult stem cells. These cells are *multipotent*, or able to differentiate themselves in limited ways based on tissue type.[113] These cells are typically drawn from fat or bone marrow and are then reinserted into the same patient.[114] From the 1990s until 2005, the FDA maintained the position that regulations regarding human cells as biological products did not apply to cells or tissue taken from and reinserted into the same patient.[115] But the FDA modified its rule in 2006 without providing any public notice or opportunity for comment. The agency changed title 21, part 1271 of the *Code of Federal Regulations* from applying to "human cells and tissue intended for implantation, transplantation, infusion or transfer into *another human*" to applying to "implantation, transplantation, infusion or transfer into *a human* recipient."[116] The new rule significantly broadened the scope of the FDA's authority and reversed the agency's position on autologous (same-person) human tissue and cells.

Following this regulatory change, Regenerative Sciences, LLC challenged the expansion of the FDA's regulatory authority to include autologous tissue. Regenerative Sciences had

[112] For information about ALS, also known as *Lou Gehrig's disease*, see the National Stem Cell Foundation's website at http://www.nationalstemcellfoundation.org/amyotrophic-lateral-sclerosis-als/.
[113] Mary Anne Chirba and Stephanie M. Garfield, "FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?," *Journal of Health and Biomedical Law* 7 (2011): 33–272, 234.
[114] Ibid.
[115] Ibid., 236.
[116] Ibid., 253–54.

received a letter from the FDA informing the company that its "Cultured Regenexx Procedure" fell under the regulatory authority of the FDA as both a drug and a biological product and was therefore subject to the same requirements as a mass-produced commercial drug.[117] Regenerative Sciences argued that the stem cell procedure in question was a medical procedure, not a drug or a biological product subject to FDA authority. Both the US District Court and US Court of Appeals in Washington, DC, ruled in favor of the FDA and affirmed its authority to classify the cultured stem cell procedure as a drug and a biologic because the cells used in the procedure were intended for treatment of a disease.[118]

The FDA argued that the cultured stem cell mixture was unsafe,[119] despite any hard evidence to substantiate the claim with respect to the Regenexx procedure. At that time, Regenerative Sciences had published two safety reports on the cultured treatment, one that studied 227 patients and another that studied 339 patients. Neither study showed evidence of neoplastic complications or malignant transformations in vivo.[120] Despite these publications, the FDA asserted that no adequate and well-controlled studies existed.[121] Furthermore, the Regenerative Sciences lab followed International Cellular Medicine Society guidelines and used an independent lab-auditing service, Reglera, to ensure the quality of its medical practices.[122] The court, however, determined that the Regenexx stem cell mixture was adulterated because the

[117] Ibid., 236–37.
[118] United States v. Regenerative Sciences, LLC, 741 F.3d 1314 (D.C. Cir. 2014).
[119] Ibid., 7.
[120] Christopher J. Centeno et al., "Safety and Complications Reporting on the Re-implantation of Culture-Expanded Mesenchymal Stem Cells Using Autologous Platelet Lysate Technique," *Current Stem Cell Research and Therapy* 5, no. 1 (2010): 81–93; Christopher J. Centeno et al.,, "Safety and Complications Reporting Update on the Re-implantation of Culture-Expanded Mesenchymal Stem Cells Using Autologous Platelet Lysate Technique," *Current Stem Cell Research and Therapy* 6, no. 4 (2011): 368–78.
[121] Chirba and Garfield, "FDA Oversight of Autologous Stem Cell Therapies," 158.
[122] Regenerative Sciences, "Regenexx Procedure: Imaging Case Reports and Medical Provider Information," http://www.regenexx.com/wp-content/uploads/2009/10/regenexx_medical-provider_information-1.pdf.

clinic did not conform to federal manufacturing regulations, regardless of other safety procedures that the clinic implemented. Thus, the FDA did not have to actually show that the mixture was contaminated for it to be deemed unsafe.[123]

As a consequence of this ruling, any stem cell procedure that cultivates cells before reinserting them into the same patient is prohibited, unless a company undertakes the lengthy and expensive process of premarket approval, which is estimated to cost an average of $2.6 billion dollars.[124] Because the cultured stem cell mixtures are developed individually, not mass-produced like most drugs, recouping the costs of premarket approval is substantially more difficult. The effect, then, of the FDA's policy of treating cultured stem cells as drugs is not a delay in the availability of a promising medical treatment, but rather the likely elimination of the treatment's availability in the United States.

As an alternative to spending billions on premarket approval in the United States, Regenerative Sciences opened an independent facility, Regenexx Cayman, in the Cayman Islands, where the company is able to offer its cultured stem cell procedure to patients.[125] Although the facility is open to US residents, the time and cost of travel limit treatment access to those who can afford it. The location of the facility also complicates insurance coverage for US residents. Regenerative Sciences still operates in the United States, but the company is limited to providing same-day stem cell procedures that comply with FDA regulations according to 21 C.F.R. 1271.15(b).

[123] United States v. Regenerative Sciences, 14.
[124] Tufts Center for the Study on Drug Development, "Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion," news release, November 18, 2014.
[125] For more information about Regenexx Cayman, see the company's website at http://regenexxcayman.ky/faq/.

Comparisons of the same-day stem cell procedure and the cultured stem cell procedure indicate that the latter is generally more effective. Data reporting patients' levels of knee pain showed that patients who opted for the cultured stem cell treatment experienced a decrease in pain of at least 75 percent.[126] For hand arthritis, the data suggest that the cultured stem cell procedure is significantly more effective than the same-day procedure, yielding approximately 80 percent improvement compared with 40 percent. However, the data were collected at different times after patients' respective procedures (an average of 26.4 months after the cultured stem cell procedure, versus 10.2 months after the same-day procedure), and this discrepancy could account for some of the differences in results.[127] Differences in results of the cultured stem cell treatment for ankle arthritis appear less stark than those for hand arthritis, but the cultured stem cell treatment still achieves better outcomes than does the same-day treatment.[128] Although the cultured stem cell procedure is more costly, the difference in results could make it worthwhile for some patients.

Prohibiting these two procedures in the United States limits treatment options for the 52.5 million adults with doctor-diagnosed arthritis and especially impacts the 22.7 million who report limitations because of their arthritis.[129] Cultured stem cells have potential to treat diseases and conditions beyond orthopedic ailments. The National Stem Cell Foundation lists 67 conditions that can be treated with stem cells, including ALS, various autoimmune diseases, multiple sclerosis, and Parkinson's disease.[130] However, stem cell treatments

[126] Chris Centeno, "How Does Regenexx-sd or -ad Compare to Regenexx-C?," Regenexx, May 29, 2011.
[127] "Hand/Wrist Arthritis (CMC) and Regenexx-sd vs -C Outcome," Regenexx, accessed November 23, 2015.
[128] "Foot/Ankle, Same Day vs. Cultured," Regenexx, accessed November 23, 2015.
[129] These figures are for 2015 and are from the Centers for Disease Control and Prevention's website at http://www.cdc.gov/chronicdisease/resources/publications/aag/arthritis.htm.
[130] For the list, see the National Stem Cell Foundation website at http://www.nationalstemcellfoundation.org/list-of-conditions/.

designed to address these conditions are limited by the same FDA regulations that treat cultured stem cells as drugs.

The "Medicines in Development: Biologics, 2013" report published by the Pharmaceutical Research and Manufacturers and of America listed 69 cell therapies that were in clinical trials under review by the Food and Drug Administration."[131] Of the 15 cell therapies in phase 3 trials, 3 involved the use of autologous stem cells.[132] Aastrom Biosciences, which is developing a cultured stem cell product, announced in 2013 that it was cutting its workforce in half, choosing instead to switch its focus from the use of ixmyelocel-T as a treatment for critical limb ischemia (CLI), a severe obstruction of the arteries, to use as a treatment for dilated cardiomyopathy (DCM), a decreased ability of the heart to pump blood. The company made the decision to both reduce its number of employees and scale back its clinical trials because of the relative costs of clinical trials for CLI and DCM treatments.[133] The FDA designated both treatments as orphan drugs—that is, drugs for small populations that lack good treatment alternatives. Unfortunately, people suffering from CLI will have to wait longer for treatment because the cost of premarket drug development priced the CLI drug out of the market.

Some drug companies choose to circumvent either parts or all of the FDA approval process by developing or testing products overseas before beginning the FDA approval process. One company that has taken this route is Precision StemCell, currently operating in Bogotá, Colombia. In partnership with Neuralgene, Precision StemCell is investigating the effectiveness of PRCN-829 as a gene therapy treatment in combination with cultured stem cell

[131] Cited in Brandy Sargent, "Fifteen Cell Therapies/Stem Cell Therapies in Phase III Clinical Trials," Cell Culture Dish, accessed November 23, 2015.
[132] Ibid.
[133] Vrinda Manocha, "Aastrom Biosciences Ends Drug Trial, to Cut Half Its Workforce," *Reuters*, March 27, 2013.

treatment for ALS.[134] In a press release, Neuralgene stated, "After initial testing of PRCN-829 in Colombia, Neuralgene plans to seek approval from the FDA for trials in the United States."[135] Though promising, testing of clinical treatments in foreign countries creates an additional step that further delays delivery of potentially beneficial treatments to Americans. Thus, the FDA needs to balance drug safety considerations with the interests of those patients who are unable to take advantage of certain treatment options because of the costs and delay associated with premarket approval.

23andMe

After the completion of the Human Genome Project in 2003, genomics emerged as a promising new field of biomedical research that would expedite identification of (1) genetic mutations that are responsible for certain diseases, (2) genetic predispositions for disease, and (3) probable adverse reactions to medications.[136] Together with improving data-analysis technology, genomics opens up possibilities for individuals to learn about their own genetic predispositions, thereby expanding opportunities for preventive treatment and early diagnosis that can significantly affect both the length and the quality of their lives.

Capitalizing on this new medical frontier, Anne Wojcicki founded 23andMe, a direct-to-consumer genetic-testing operation that won the *Time Magazine* Invention of the Year award in 2008.[137] Envisioning the possibilities of a large DNA database for genetic research and data

[134] For information about this research, see Precision StemCell's website at http://www.precisionstemcell.com /research.cfm.
[135] Neuralgene, "Gene Therapy Developed for ALS Treatment: New Biotech Company Neuralgene Enters Evaluation Phase," press release, April 12, 2013.
[136] Francis S. Collins et al., "A Vision for the Future of Genomics Research," *Nature* 422, no. 6934 (2003): 835–47, http://www.genome.gov/11007524.
[137] Anita Hamilton, "1. The Retail DNA Test," *Time*, October 29, 2008.

analysis—as well as the benefits of individuals knowing their own genetic predispositions for disease and adverse reactions to medications—23andMe began offering genetic-testing kits for as low as $99. The price of the kit included analysis of 600,000 genetic markers to evaluate an individual's genetic predispositions for more than 90 medical conditions, responsiveness to particular medications, and ancestry.[138]

Inquiries soon arrived from the FDA, which expressed concern about the accuracy of the testing and the ability of consumers to fully understand their test results.[139] 23andMe struggled to satisfy the FDA's inquiries because the company had neither a legal nor a regulatory expert to decode the FDA's communications and to satisfactorily respond to the agency.[140] 23andMe met 14 times with the FDA, which approved initial marketing efforts for the genetic-testing kits, but 23andMe then failed to meet many of the FDA's deadlines and did not submit an additional marketing campaigns for review.[141] In May 2013, 23andMe stopped responding to FDA inquiries. The company then received a letter in November of that same year, which prohibited it from selling its genetic health–testing kits.[142]

From November 2013 to October 2015, the FDA restricted sales of 23andMe testing kits to those intended for determining ancestry. On October 21, 2015, 23andMe issued a press release stating that the company had received FDA authorization to market its direct-to-consumer genetic tests, results of which included limited health information, more than 35 carrier trait reports, and four wellness reports. Although 23andMe provides the first direct-to-consumer genetic testing to have been approved by the FDA, the company's ability to provide health

[138] Elizabeth Segran, "How CEO Anne Wojcicki Turned 23andMe Around after Falling Out with the FDA," *Fast Company*, October 21, 2015.
[139] Ibid.
[140] Ibid.
[141] Robert Safian, "Exclusive: What Really Drove 23andMe and the FDA Apart," *Fast Company*, December 5, 2013.
[142] Segran, "How CEO Anne Wojcicki Turned 23andMe Around."

information to consumers has been significantly curtailed, compared with the information it offered before November 2013.[143] Among those tests still not approved are genetic screenings for breast cancer and Alzheimer's disease, as well as tests for reactions to certain medicines, such as blood thinners.[144]

By limiting consumer access to 23andMe's full array of health reports, the FDA is preventing individuals from proactively addressing identifiable and preventable health concerns. The FDA's presumption is that 23andMe's genetic testing is unsafe because informed consumers may request unnecessary and life-changing procedures or forgo further screening. A 2013 study conducted by researchers at both 23andMe and the genetics department at the Stanford University School of Medicine indicated that the FDA's fears may be unfounded. Indeed, recipients of 23andMe test results indicating that those individuals were carriers for the *BRCA* mutations associated with breast and ovarian cancers not only did not exhibit severe emotional distress, but also sought further medical advice after receiving their results. For example, men who received positive carrier results for gene mutations associated with cancer shared their information with female relatives, who then tested for their own carrier information. These subsequent test results revealed 13 more carriers. Noncarriers did not forgo cancer screenings based on their results.[145] The study suggests that protecting consumers from receiving adverse health assessments restricts their ability to anticipate future health risks.

An additional cost of stifling the direct-to-consumer genetic-testing industry is fewer opportunities to gather genetic data for research. Genetic research can be particularly beneficial

[143] 23andMe, "23andMe Launches New Customer Experience: Reports Include Carrier Status That Meet FDA Standards, Wellness, Traits, and Ancestry," press release, October 21, 2015.
[144] Segran, "How CEO Anne Wojcicki Turned 23andMe Around."
[145] Uta Francke et al., "Dealing with the Unexpected: Consumer Responses to Direct-Access *BRCA* Mutation Testing," *PeerJ* 1 (2013): e8.

for understanding genetic diseases such as Parkinson's. By researching the genetic information of consenting customers and by recruiting more than 11,000 individuals diagnosed with Parkinson's disease, 23andMe has been able to identify new genes and genetic regions that are associated with Parkinson's, all in a fraction of the time and at a fraction of the cost of traditional research.[146] But when the FDA hampers consumer access to direct-to-consumer genetic-testing alternatives such as 23andMe, the growth and research potential of such alternatives declines. Although it is impossible to predict where that research might lead, there is almost certainly a cost associated with retarding its growth.

Heberprot-P: A Treatment for Diabetic Foot Ulcers

About 6 percent of diabetics suffer from foot ulcers that do not heal naturally and that, in many cases, can lead to amputation.[147] J. Bradford Rice and colleagues estimate that the cost of treating diabetic foot ulcers in the United States is between $9 billion and $13 billion annually.[148] Research published in the *International Wound Journal*[149] and in *Diabetic Foot and Ankle*[150] suggests that recombinant epidermal growth factor (EGF), known commercially as either Heberprot-P or Epiprot, is an effective treatment for this condition. Because the EGF treatment

[146] For information about 23andMe's work on Parkinson's disease, see the company's website at https://www.23andme.com/pd/. See also Mara Grunbaum, "#56: Private DNA Companies Tap Crowds to Speed Disease Research," *Discover*, January–February 2012.
[147] David J. Margolis et al., "Incidence of Diabetic Foot Ulcer and Lower Extremity Amputation among Medicare Beneficiaries, 2006 to 2008" (Data Point no. 2, Agency for Healthcare Research and Quality, Rockville, MD, February 17, 2011).
[148] J. Bradford Rice et al., "Burden of Diabetic Foot Ulcers for Medicare and Private Insurers," *Diabetes Care* 37, no. 3 (2014): 651–58.
[149] José I. Fernández-Montequín et al., "Intra-lesional Injections of Recombinant Human Epidermal Growth Factor Promote *Granulation* and Healing in Advanced Diabetic Foot Ulcers: Multicenter, Randomised, Placebo-Controlled, Double-Blind Study," *International Wound Journal* 6, no. 6 (2009): 432–43.
[150] Bulent M. Ertugrul et al., "Intralesional Epidermal Growth Factor for Diabetic Foot Wounds: The First Cases in Turkey," *Diabetic Foot and Ankle* 6 (2015).

for foot ulcers was developed in Cuba, it has faced substantial barriers to acceptance in the United States. According to Gail Reed of the nonprofit organization Medical Education and Cooperation with Cuba, EGF has been used to treat 165,000 patients in 26 countries, but it has not begun clinical trials in the United States.[151]

Physicians in Ecuador began treating patients with Heberprot-P in 2012.[152] The year before the drug became available, 500 of the 700 patients in Ecuador who presented with severe diabetic foot ulcers required amputations.[153] In early 2015, the Ecuador's Ministry of Public Health used Heberprot-P to treat 802 patients in 5 of Ecuador's 24 provinces. The vast majority of these patients responded well to treatment and avoided an amputation.[154] Similar benefits—on a much larger scale—would be possible if Heberprot-P were available in the United States, but the drug's access is blocked by a combination of the Cuba trade embargo and the costs of the FDA approval process.

In 2010, the US Treasury Office of Foreign Assets Control (OFAC), tasked with enforcing the Cuban embargo, prohibited both sales and clinical trials of Heberprot-P in the United States. In 2013, 111 members of the House of Representatives sent OFAC a letter asking it to reconsider its stance. In June 2014, OFAC authorized clinical trials of EGF, but the office has not issued a license for commercial sales in the event of FDA approval of the drug. The firm that owns the US marketing rights to EGF, France-based Healiance Pharmaceuticals, is reluctant to spend the millions of dollars needed to run US clinical trials without such a license.[155] If the

[151] Gail Reed, "Renewed US-Cuba Relations: Saving American Lives and Limbs," *Huffington Post*, January 24, 2015.
[152] Ecuador Ministry of Public Health, "500 pacientes con pie diabético se beneficiarán con el medicamento Heberprot-P."
[153] "Los afiliados al IESS reciben tratamiento para pie diabético," *El Telégrafo*, March 8, 2015. *El Telégrafo* is an Ecuadorian state-owned newspaper based in Guayaquil.
[154] "La Calidad de Vida de las Personas con Pie Diabético Mejora," *El Telégrafo*, March 22, 2015.
[155] Gail Reed, "Renewed US-Cuba Relations: Saving American Lives and Limbs," *Huffington Post*, January 24, 2015.

FDA trial process were less costly, it is possible that Healiance would take the risk and begin testing in the United States in hopes that successful results would trigger OFAC approval for commercial sales. Meanwhile, tens of thousands of diabetics in the United States continue to face amputations that could well be avoided if they had access to Heberprot-P.

Antiaging Therapies

Telomeres are repeating sequences of DNA at the end of every human chromosome. Research shows a correlation between telomere length and aging. The Shay/Wright Lab at the University of Texas Southwestern provides the following description:[156]

> Telomeres function by preventing chromosomes from losing base pair sequences at their ends. They also stop chromosomes from fusing to each other. However, each time a cell divides, some of the telomere is lost (usually 25–200 base pairs per division). When the telomere becomes too short, the chromosome reaches a "critical length" and can no longer replicate. This means that a cell becomes "old" and dies by a process called apoptosis.

An enzyme called *telomerase* extends the length of telomeres and thus may be able to slow or reverse aging. The Shay/Wright Lab continues:

> Telomerase, also called telomere terminal transferase, is an enzyme made of protein and RNA subunits that elongates chromosomes by adding [repeating base pair] sequences to the end of existing chromosomes. Telomerase is found in fetal tissues, adult germ cells, and also tumor cells. Telomerase activity is regulated during development and has a very low, almost undetectable activity in somatic (body) cells. Because these somatic cells do not regularly use telomerase, they age. The result of aging cells is an aging body. If telomerase is activated in a cell, the cell will continue to grow and divide.[157]

Three US-based scientists—Elizabeth H. Blackburn of the University of California, San Francisco; Carol W. Greider of the Johns Hopkins University School of Medicine; and Jack W. Szostak of Harvard Medical School, Massachusetts General Hospital, and the

[156] UT Southwestern Medical Center Shay/Wright Lab, "Facts about Telomeres and Telomerase."
[157] Ibid.

Howard Hughes Medical Institute—won the 2009 Nobel Prize in Physiology or Medicine for their "discovery of how chromosomes are protected by telomeres and the enzyme telomerase."[158] Science writer Josh Mitteldorf summarizes the recent telomerase research, concluding that "telomerase activation is a field that offers the most potential for human life extension in the next few years."[159]

Research conducted at the Spanish National Cancer Research Center and at Dr. Robert de Pinho's Harvard laboratory shows an increase of up to 24 percent in the lifespan of mice as a result of telomerase treatments at an early age. The research also indicates a reversal of organ-system degeneration when the telomerase is administered to older mice. One concern regarding use of the enzyme is that telomerase treatments could backfire by increasing the longevity of cancer cells,[160] but the studies that Mitteldorf cites do not support this fear. Mitteldorf notes that, despite its promise, telomerase research receives limited government funding because the enzyme is not considered a medicine. Private companies could potentially fill the gap in funding, but they would need to overcome FDA barriers to do so.

In 2007, T.A. Sciences began marketing a plant-based compound, TA-65, that activates the telomerase enzyme.[161] TA-65 is derived from the root of a plant known as *Astragalus membranaceus*, which occurs naturally in China, Mongolia, and Korea, and which is used in traditional Chinese medicine. Because of the compound's plant origins, T.A. Sciences has been able to market TA-65 as a *nutraceutical*—essentially a type of dietary supplement that the FDA presumes to be safe.[162] Recent studies have shown that TA-65 increases telomere length and

[158] Nobel Media, "The Nobel Prize in Physiology or Medicine 2009."
[159] Josh Mitteldorf, "Telomerase Therapies in Our Future," *Aging Matters*, accessed November 24, 2015.
[160] Jalees Rehman, "Aging: Too Much Telomerase Can Be as Bad as Too Little," *Scientific American*, July 5, 2014.
[161] For information about the company, see its home page at https://www.tasciences.com/.
[162] Michael Fossel, *The Telomerase Revolution* (Dallas, TX: BenBella Books, 2015).

even provides some users with moderate improvements in immune function, blood pressure, cholesterol levels, glucose levels, insulin levels, bone density, and other measurements of health.[163] Although these results are promising, benefits of TA-65 are limited. Thus, a true telomerase pharmaceutical is needed to radically affect the aging process.

As is the case for any medication, running clinical trials on a telomerase activator that conforms to FDA standards would be very expensive. Furthermore, an antiaging therapy may be unable to obtain FDA approval because the agency may not consider aging a disease that requires treatment. Although we could not find specific FDA pronouncements on this issue, pharmaceutical researchers assume that approval could be held up for this reason.[164] If the FDA does not view aging as a disease, FDA analysts may decide that even successful antiaging treatments fail to meet standards of effectiveness.[165] Entrepreneurs hoping to commercialize telomerase drugs thus have two broad options: either (1) position telomerase as a treatment for a specific aging-related disease and then undergo the FDA approval process or (2) develop telomerase therapies offshore.

Telocyte, a start-up founded by Dr. Michael Fossel, has chosen the first alternative. The company intends to run clinical trials on a telomerase-based product for the purpose of curing Alzheimer's disease.[166] Given the severity of Alzheimer's, Fossel believes that the FDA may agree to designate its treatment as a "breakthrough therapy"—thereby making it eligible for an expedited FDA review process. However, because the FDA rejects most requests for

[163] Links to these studies may be found on TAsciences website at https://www.tasciences.com/clinical-research/.
[164] Kate Kelland, "Is Aging a Disease?," *Reuters*, May 20, 2010. A similar view was presented by Jason Pontin, "An Age-Defying Quest (Red Wine Included)," *New York Times*, July 8, 2007.
[165] Recently, the Albert Einstein College of Medicine of Yeshiva University began an antiaging clinical trial of Metformin, a diabetes drug that has been widely used since the late 1950s. See "Metformin in Longevity Study (MILES)," ClinicalTrials.gov, US National Institutes of Health, NCT02432887, December 2015.
[166] See Telocyte's home page at http://www.telocyte.com/.

breakthrough therapy designation, earning one could prove to be an uphill battle for Telocyte. As of early June 2016, the FDA had denied 415 breakthrough therapy designation requests and granted 130 since the program began in 2012. Of these 130, 49 products had been approved.[167]

If Telocyte is able to obtain the breakthrough therapy designation, it may be allowed to file a new drug application after completing phase 2 trials. Doing so would enable the Telocyte to begin realizing significant revenue from its drug while conducting phase 3 trials, which are the most expensive part of the FDA approval process.

One company pursuing the offshore alternative is BioViva USA.[168] The company's chief medical officer, Dr. Jason Williams, also operates Precision StemCell, an offshore clinic discussed earlier. In September 2015, BioViva's founder, Elizabeth Parrish, received "an intravenous dose of viruses containing genetic material to produce telomerase" at a facility outside the United States. She also "received injections into her muscles containing the gene follistatin, which in animal experiments is shown to increase muscle mass by blocking myostatin."[169] The injections could not be provided legally in the United States.

In an interview for this study, Parrish said that the cost of the FDA clinical trial process for a telomerase therapy could be $1 billion or more. Her assessment of the FDA is that it is too risk averse. She remarked that "if we're too risk averse, we're going to die waiting for treatments already proven in the lab." Parrish went on to note that many of today's new therapies do not involve new molecules, as new therapies did in the past, and thus tend to pose less risk of causing unexpected side effects.[170]

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[167] Friends of Cancer Research, "Breakthrough Therapies," accessed July 12, 2015.
[168] For information about BioViva USA, see the company's home page at http://bioviva-science.com/.
[169] Antonio Regalado, "A Tale of Do-It-Yourself Gene Therapy," *MIT Technology Review*, October 14, 2015.
[170] Phone interview of Elizabeth Parrish by Marc Joffe, November 6, 2015.

Telocyte's Michael Fossel shares Parrish's belief that the FDA is risk averse, but he also notes the difficult politics that affect FDA commissioners.[171] Historically, the biggest challenges facing FDA management have involved appearing before a congressional committee to defend approval of a drug that caused injuries or fatalities. Conversely, the FDA has faced less political fallout for declining a potentially effective therapy. The best way for the FDA to avoid negative publicity, then, has been to emphasize drug safety over drug effectiveness. However, Fossel also thinks that pressure from patient groups has created a growing incentive for drug approvals, which may ultimately balance the FDA's tendency toward risk aversion. If patient groups encourage a member of Congress to ask the FDA commissioner why a promising drug has not been approved, they can create an incentive to change this balance toward granting approval.

The FDA may eventually move in the right direction, but the speed with which it does so makes a difference for the large number of Americans who die every year from age-related diseases. The news outlet Disabled World estimates that two-thirds of worldwide deaths are attributable to age.[172] Assuming that same proportion applies to the 2.6 million annual deaths in the United States, a drug that either slows or reverses aging could delay more than 1.7 million deaths each year.

Sarepta Therapeutics

In April 2016, the FDA's panel of experts recommended to the FDA that it not approve eteplirsen, a drug manufactured by Sarepta Therapeutics for treatment of Duchenne muscular

[171] Phone interview of Michael Fossel by Marc Joffe, November 11, 2015.
[172] Disabled World, "Aging: Associated Diseases and Information," March 7, 2015.

dystrophy. The panel "conclude[ed] that there wasn't sufficient evidence the drug was effective."[173] Duchenne muscular dystrophy is a fatal genetic mutation that causes its victims, mostly males, to die by the age of 25. But the disease is also rare, so eteplirsen was tested (successfully) on only 12 patients. It is estimated that fewer than 1,600 boys in the entire United States might benefit from the drug.[174]

For the FDA to ultimately approve eteplirsen, Sarepta would have to run a trial in which results of those patients who received the drug were compared with results of control group of patients who did not receive the drug. The FDA even expressed concern that perhaps Sarepta's drug *appeared* to work because "biased parents or doctors might have coached boys ahead of a walking test or otherwise infected the [trial's] results," thus implying that drug recipients could have simply willed themselves to recover.[175] Another reason the panel voted against approval of eteplirsen was the wording of questions such as the following: "Question 2: Has the Applicant [Sarepta] provided substantial evidence from adequate and well-controlled studies that Eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit?"[176] Obviously, a trial with only 12 patients could not represent a "well-controlled" study. At present, the director of the FDA's Center for Drug Evaluation and Research is charged with making the ultimate decision regarding eteplirsen approval.

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[173] *Wall Street Journal*, "Mental Dystrophy at the FDA," April 28, 2016.
[174] Author calculations based on 13 percent of the 12,000 reported in *Wall Street Journal* article. The 13 percent estimate comes from Annemieke Aartsma-Rus et al., "Theoretic Applicability of Antisensemediated Exon Skipping for Duchenne Muscular Dystrophy Mutations," *Human Mutation* 30, no. 3 (2009): 293–99.
[175] *Wall Street Journal*, "Mental Dystrophy at the FDA."
[176] Ken Kam, "Sarepta: FDA Policy Forced AdCom to Vote against Patients' Interests," *Forbes*, April 29, 2016.

Policies Needed

Before considering policy options, it is important to recognize that consumers and patients are becoming increasingly dissatisfied with the FDA's current regulatory system. Eric Topol has written about that dissatisfaction in his book *The Patient Will See You Now*.[177] As Topol observes, many people are now monitoring their own health; generating their own health data; seeking remote treatment via telemedicine or going to other countries for therapies currently banned in the United States; and ultimately diagnosing, treating, and enhancing themselves. In times to come, people may even be 3-D–printing their own organs. Such individuals are effectively acting as the water going around the FDA "boulder."

We have discussed how the FDA's current regulatory system prevents Americans from accessing cultured stem cell treatments, diabetic ulcer medications, and genetic testing, while simultaneously impeding the development of antiaging drugs. These cases are just a sampling of the medical treatments being impeded by FDA regulation.

Although the FDA tries to regulate drug safety and effectiveness, evidence suggests that the current system will never be able to achieve universal safety or universal effectiveness. Additionally, given the potential of medical treatments that are currently in development, the FDA errs on the side of being far too restrictive. For example, the FDA's effectiveness standards limit the availability of better medicine, and its "gold standard" clinical trials toss out information that could lead to more personalized treatments. The effectiveness standards required for current clinical trials essentially enforce a "one-size-cures-all" policy. Such a policy accounts neither for subpopulations that respond to treatments in markedly different ways than do average patients, nor for medicines that use a patient's own biologic material to target

[177] Eric Topol, *The Patient Will See You Now* (New York: Basic Books, 2015).

diseases or injuries.[178] Nor does such a policy properly address the needs of small disease populations, which typically cannot produce the two large sample groups required for randomized controlled trials.

A 2007 report by the FDA Science Board's Subcommittee on Science and Technology found that, "[w]hile the world of drug discovery and development has undergone revolutionary change—shifting from cellular to molecular and gene-based approaches—FDA's evaluation methods have remained largely unchanged over the last half century."[179] The FDA's failure to keep pace with technological advancements is preventing innovative medicines from saving the lives of American people. The nature of FDA regulation is such that it will always lag scientific discovery. Thus, a regulatory system that is designed to minimize the impact of this knowledge gap should (1) broaden the types of treatment outcomes considered to be successful and (2) reduce the current stringency of premarket drug-effectiveness testing. Such a change would allow doctors and patients to choose from a wider variety of medicines that are better suited to address an individual patient's specific needs and preferences for risk. In the next section, we review a number of policy alternatives that would liberalize the FDA's current regulatory regime, thereby making a more expansive array of medical treatments possible.

Pending Legislation

Congress is considering new regulatory reform measures, the most prominent of which is H.R. 6, the 21st Century Cures Act.[180] The second part of the proposed law includes reforms intended to

[178] See Peter W. Huber, *The Cure in the Code: How 20th Century Law Is Undermining 21st Century Medicine* (New York: Basic Books, 2013).
[179] Subcommittee on Science and Technology, "FDA Science and Mission at Risk," FDA Science Board, November 2007, 3.
[180] Energy and Commerce Committee, "21st Century Cures: A Call to Action," White Paper, May 1, 2014.

expedite drug development and approval. The act calls for updated and finalized guidance on (1) qualifying drug-development tools, such as biomarkers, precision medicine, Bayesian statistics, and adaptive clinical trials; (2) expanded access to information (especially regarding adverse drug events); and (3) dissemination of off-label marketing information. The act also requires that data on patient experiences be added to the FDA's benefit-risk framework for new drug approval. Furthermore, the act encourages expedited review of certain antibacterial and antifungal drugs, as well as expedited labeling approval for antibiotics.

In regard to medical devices, the 21st Century Cures Act (1) provides a priority review for breakthrough devices; (2) allows third-party approval for alternative uses of medical devices; (3) removes the requirement that institutional review boards be local;[181] and (4) expands the term *valid scientific data* to include well-documented case studies, peer-reviewed journals, and other relevant data.[182]

The real issue is not whether the FDA will approve a few more drugs and devices in any given year, but whether the 21st Century Cures Act or any other legislation will attempt to create institutions to open the floodgates for applications for new products and treatments based on new medical technologies. Present application numbers do not reflect the potential for new products. In fact, in both the drug and the medical device fields, application numbers have remained fairly consistent despite quicker review times and significantly more funding for the FDA.[183] Thus,

[181] A problem arises when institutional review boards must be local but many jurisdictions must be appeased such that multiple institutional review boards become necessary.
[182] Judith Johnson, Susan Thaul, and Erin Bagalman, "H.R. 6: The 21st Century Cures Act," CRS Report 5-5700, Congressional Research Service, Washington, DC, August 10, 2015.
[183] Richard Williams, Jason Briggeman, and Ethan Roberts, "How Productive Is the FDA's Human Drugs Program?," Mercatus Center at George Mason University, March 7, 2017; Richard Williams, Jason Briggeman, and Ethan Roberts, "How Productive Is the FDA's Devices Program?," Mercatus Center at George Mason University, April 4, 2016.

unleashing the power of modern science to further reduce the incidence of human disease and injury will require even more radical institutional change.

It is not surprising that this somewhat incremental approach to FDA reform has received widespread bipartisan support. Most policy analysts—and most members of the public—seem to agree that it is the government's responsibility to protect consumers from unsafe and ineffective drugs. In other words, most people support the FDA's historical regulatory stance, which has been to exercise restraint in regard to new medical treatments. However, it is not clear whether preserving the current "hub and spoke" system of governance with FDA at the center (mentioned earlier in this paper), as the 21st Century Cures Act would do, will strike the proper balance between guarding against the potential risks and allowing the public to benefit from new medical technologies.

Policies for Future Innovation

Two approaches to regulation of medical treatment have the potential to radically alter the FDA's "hub-and-spoke" model: (1) approval of treatments by private firms and (2) compassionate use of as-yet unapproved treatments.

Approving firms. The disaggregated nature of emerging medical technologies that will affect both drugs and medical devices points to a need for disaggregated governance, particularly by private firms. As the paper "US Medical Devices: Choices and Consequences" points out, the European market already relies on private companies to approve low- to medium-risk medical devices.[184] Similar organizations in the United States could approve applications for low-risk

[184] Richard Williams, Robert Graboyes, and Adam Thierer, "US Medical Devices: Choices and Consequences" (Mercatus Working Paper, Mercatus Center at George Mason University, Arlington, VA, October 2015).

devices and even some drugs, including those designated as "orphan" drugs and those that pose little risk to the general population. In some cases, these organizations would approve different products than would the FDA; in other cases, the organizations would function as FDA competitors.

Daniel Klein and Alex Tabarrok emphasize the potential roles of "knower organizations" and middlemen.[185] Klein and Tabarrok define a *knower organization* as "a private organization that knows more than the consumer about a seller's reputation or about the quality and safety of the seller's products." Knower organizations "often inspect quality and safety, and grant a certification mark or seal of approval." Examples include Underwriters Laboratories, Good Housekeeping, the American Dental Association, and credit rating agencies (we address concerns about this last group later). Unlike monopoly government agencies, these third-party organizations compete with each other on price, quality, and timeliness and are paid by the companies themselves, much as FDA now receives user funding.[186] As Klein and Tabarrok note, however, knower organizations are relatively underdeveloped in the pharmaceutical sector because of the power of the FDA.

Undoubtedly, third-party organizations in the pharmaceutical sector would specialize in terms of the types of drugs and devices reviewed. Thus, rather than impaneling different specialists for every product review, knower organizations in the pharmaceutical sector would develop their own specialties. Insurance companies, whose business models require minimizing adverse consequences, would clearly have an interest in ensuring that drugs and devices are safe and effective and would monitor the approving organizations.

[185] Daniel Klein and Alex Tabarrok, "The Sensible Alternative: The Voluntary Provision of Assurance," FDAreview.org.
[186] "PDUFA and MDUFA History" (California Healthcare Institute), accessed July 18, 2016.

These private organizations would, of course, also be monitored by postmarket entities, including retailers—such as Walgreens—and drug and device manufacturers themselves, both of which have reputations to protect. In every sector, market stories exist of firms that have produced dangerous products that either incur great losses for a company or force that company to go out of business. The pharmaceutical sector is no different.

Tort liability can further deter fraudulent marketing of dangerous or ineffective medications. During the past 15 years, three pharmaceutical liability cases have resulted in settlements of over $1 billion. In one case, Baycol, a cholesterol-lowering statin manufactured by Bayer, caused numerous—sometimes fatal—muscle disorders, triggering litigation that was ultimately settled for $1.17 billion. In a second case, Vioxx, a pain-relief medication developed by Merck, caused a large number of strokes and heart attacks, resulting in a $4.85 billion payout. The third case involved the diet pill combination Fen-Phen, which caused heart valve problems, costing Wyeth (now part of Pfizer) $6.44 billion.[187]

As previously noted, analogies between private drug adjudicators and credit rating agencies are legitimate cause for concern. Credit rating agencies, including Standard & Poor's, Moody's, and the Fitch Group, were blamed for exacerbating the 2008 financial crisis by assigning excessively lenient ratings to subprime mortgage-backed securities.[188] Several years earlier, those same agencies had been accused of incorrectly rating Enron and WorldCom by maintaining relatively high ratings of both firms until shortly before their respective bankruptcies.[189]

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[187] Han W. Choi and Jae Hong Lee, "Pharmaceutical Product Liability," in *Principles and Practice of Pharmaceutical Medicine*, 3rd ed., ed. Lionel D. Edwards, Anthony W. Fox, and Peter D. Stonier (Boston: Blackwell, 2011), 688–702.
[188] Financial Crisis Inquiry Commission, *The Financial Crisis Inquiry Report* (Washington, DC: US Government Printing Office, 2011).
[189] Lawrence J. White, "A New Law for the Bond Rating Industry," *Regulation* 30, no. 1 (2007): 48–52.

A common criticism of credit rating agencies is that—because they are paid by bond issuers—they have a strong incentive to lower their standards to gain market share. Theoretically, credit rating agencies should be concerned with their reputations, but opportunities to obtain near-term revenue often eclipse such concerns. As Marc Joffe and Anthony Randazzo suggest, this problem is exacerbated when there are relatively few customers purchasing a given rating service.[190] This was the case with subprime mortgage-backed securities, which were marketed by a relatively small number of financial institutions. A single decision to assign a low rating to one of Goldman Sachs's deals could have led to the investment bank's taking all its business elsewhere.

Competitive drug adjudicators could face a similar dynamic. A review of the FDA's new drug approvals for 2014 shows that six companies had four or more approvals during the calendar year.[191] This finding suggests the presence of a number of "regular customers," each of whom would be costly to disappoint. However, if drug companies were to compete with each other over price, speed, and quality of approval, more drug companies would likely enter the market (particularly small- and medium-sized companies), as well as more drugs.

A number of regulatory options would better align the incentives of competitive drug evaluators with consumer preferences. One option is stepped-up supervision. Congressional legislation enacted in 2006 and 2010 gave the Securities and Exchange Commission (SEC) more power over credit rating agencies. Since 2013, the SEC has sanctioned three different credit

[190] Marc Joffe and Anthony Randazzo, "Restoring Trust in Mortgage Backed Securities" (Policy Study 402, Reason Foundation, Los Angeles, CA, May 2012).
[191] Mylan and AstraZeneca each received six approvals, Merck received five, and Gilead Sciences and Boehringer Ingelheim each received four. We did not see a list of NDA denials. FDA, "CY 2014 CDER Drug and Biologic Calendar Year Approvals," December 31, 2014.

rating agencies for operational failures and misrepresentations.[192] However, there have been no high-profile credit rating failures akin to those uncovered by the 2008 financial crisis.

Changes to market structure could also improve incentive alignment. During the debate over the Dodd-Frank financial reform legislation, Senator Al Franken (D-MN) proposed a measure that would have prevented an investment bank from selecting the rating agency that would analyze the bank's bonds. Instead, a government entity would have selected the credit rating agency. This arrangement would have removed the rating agency's incentive to compete for market share by relaxing standards. Franken's approach was not adopted, perhaps because of industry pressure. In the case of private drug approval, no industry currently exists, nor do prospects for incumbent lobbying of private approval companies. Unfortunately, however, the solution is imperfect. Imposing a third-party selector may remove not only the potentially damaging effects of competition between drug manufacturers, but also the potential advantages of such competition. Private adjudicators would have limited incentive to innovate and could ultimately come to resemble bureaucratic entities.

One issue may be dispositive; that is, observing the failures of the rating agencies was difficult, at least until the financial meltdown of 2008 happened. A comparable meltdown of the drug industry would be unlikely, however, as any safety or effectiveness failures observed for individual products would be unlikely to lead to a societywide medical breakdown. Drug or medical device failures would be discovered much, much faster than financial failures. In

[192] Securities and Exchange Commission, "Administrative Proceeding File No. 3-14856: In the Matter of Egan-Jones Ratings Company and Sean Egan, Respondents," January 22, 2013; Securities and Exchange Commission, "Administrative Proceeding File No. 3-16348: In the Matter of Standard & Poor's Rating Services, Respondent," January 21, 2015; Securities and Exchange Commission, "Administrative Proceeding File No. 3-16922: In the Matter of DBRS Inc. Respondent," October 26, 2015.

addition, there are laws against individuals who accept favors for favorable approvals, and these laws could be further enhanced.

Another approach to avoiding negative incentives would require that independent evaluators be not-for-profit organizations. Consumers Union, the not-for-profit that publishes *Consumer Reports*, has maintained a good reputation and substantial influence during its 80-year history. This example suggests that not-for-profit drug evaluators could be successful over the long term, though industry interests could corrupt evaluation standards. For instance, if an evaluator had an opportunity for higher-paying employment at a pharmaceutical firm, that evaluator could potentially lose his or her sense of objectivity.

Finally, although effective institutional design could check the behavior of private drug and device adjudicators, the medical marketplace provides checks as well. This marketplace comprises patients, families, physicians, other healthcare professionals, and, as mentioned earlier, insurance companies. These stakeholders span a wide range of benefit-risk preferences and are becoming more connected to each other through the web. In addition, for those insurers, physicians, and patients who want the evidence-based medical products that have gone through all phases of FDA approval (that are more expensive and take much longer), the FDA would be a competitive alternative to the private approval system.

Historically, the FDA has struggled to regulate *combination products*—that is, products that act both as medical devices and as drugs—and the agency's current guidelines are an attempt to determine how best to manage these products.[193] Given the potential of new technologies, combination products are likely to become much more complex and to evolve at a much faster

[193] Office of Combination Products, "Guidance and Regulatory Information," US Food and Drug Administration, http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm109110.htm.

pace, creating even more regulatory difficulties. As Larry Downes notes, "Technology changes exponentially, but social, economic and legal systems change incrementally."[194]

Imagine that, one day, 3-D printers "print" synthetically derived organs and tissues. Perhaps these organs and tissues use human stem cells or even machine parts that are built from nanomaterials. The organs may also contain sensors that can, when necessary, either chemically (with drugs that are specifically targeted toward an individual's DNA) or mechanically (with nanorobots) heal themselves. No protocol currently exists for such technologies, and the idea of a fixed set of premarket approval tests for treatments that employ such technologies seems inadequate and old-fashioned. Although standards—perhaps even those that are set or approved by the FDA—are necessary, they should be minimal and subject to change as new medical products and performance tests emerge. Evidence of drug and device performance should be drawn from all available sources of information, which could eventually include new types of tests and perhaps even artificial human systems designed to evaluate both safety and effectiveness of medical treatments. An artificial human system would have redundant safety and effectiveness controls built into it. As they are today, medical products of the future should be tried slowly at first by those who need or want the products most and who have willing physicians to prescribe them. As time goes on, and more and more information is generated through experience and the product either catches on or fails.

Compassionate use. In addition to private approval of drugs and devices, the issue of compassionate use must be addressed. The FDA created the expanded access option to provide

[194] Larry Downes, *The Laws of Disruption: Harnessing the Forces That Govern Life and Business in the Digital Age* (New York: Basic Books, 2009), 2, as quoted in Adam Thierer, *Permissionless Innovation: The Continuing Case for Comprehensive Technological Freedom* (Arlington, VA: Mercatus Center at George Mason University, 2016), 109.

patients with access to investigational new drugs (INDs) that have not yet been approved by the agency. Between 2011 and 2014, the FDA approved more than 99 percent of the almost 6,000 expanded access applications it received.[195]

Although the approval rate for expanded access is high, the relatively low number of applications suggests that the program's requirements may be deterring some patients. To be considered eligible for single-patient expanded access,[196] an applicant must have a serious or life-threatening condition for which there is currently no satisfactory or comparable alternative treatment. That applicant must also be ineligible for a clinical trial involving the prescribed treatment.[197] The rationale of expanded access, then, is that the unknown risks of taking an IND far outweigh the unknown benefits. In other words, patients are safer when taking medicine that has been approved despite any known side effects than when taking a potentially better treatment whose risks and benefits are uncertain. Although some risk aversion is certainly reasonable, it may be unreasonable for the FDA to impose its own stance on risk aversion on patients, who may have their own perceptions about treatment risks and benefits. The courts, however, have upheld the FDA's interest in ensuring patients' safety.[198]

Furthermore, applying for the expanded access program can be onerous. As the *New York Times* pointed out in a February 2015 editorial, the application form required doctors to provide

[195] Elizabeth Richardson, "Right-to-Try Laws (Updated)," Health Policy Brief, April 9, 2015.
[196] The FDA has also expanded access programs for intermediate-sized patient populations and for widespread use. See "What Are the Different Types of Expanded Access/Compassionate Use?," in "Expanded Access: Information for Patients," on the FDA website at http://www.fda.gov/ForPatients/Other/ExpandedAccess/ucm20041768.htm#different-types.
[197] US Food and Drug Administration, "Expanded Access (Compassionate Use)."
[198] In 2009, *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach* (495 F.3d 695 [D.C. Cir. 2007], cert. denied 552 U.S. 1159 [2008]) overturned the 2006 ruling of a three-judge panel. The 2009 ruling determined that patients do not have a right to access inaccessible drugs. See Valarie Blake, "The Terminally Ill, Access to Investigational Drugs, and FDA Rules," *Virtual Mentor* 15, no. 8 (2013): 687–91.

26 types of information and to include seven attachments.[199] That same month, however, the FDA issued draft regulations that would greatly simplify the form.[200] The draft guidance for individual use makes the form shorter and easier to use.[201] The simpler form still acts as an obstacle, though, requiring a brief clinical history of the patient (age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy), as well as the reason for seeking treatment with the IND and an extensive list of proposed treatment information.[202]

The FDA draft guidance seems to be a response to the passage of "right-to-try" laws, which have been considered in 40 state legislatures and enacted in 26. Such laws allow patients to take INDs without obtaining prior FDA approval. The state-based right-to-try concept has been actively promoted by the Goldwater Institute, which has issued a policy report supporting the concept and has developed model legislation.[203]

Both the FDA's expanded access program and state right-to-try laws apply only to those INDs that manufacturers make available for patient use. Those INDs treat only a limited range of diagnoses. Also, as mentioned earlier, the expanded access program is available only to patients who have a serious or immediately life-threatening disease or condition.[204] Similarly, the model right-to-try laws apply to patients with terminal conditions that, if not treated, would soon result in death. The expanded access program and right-to-try laws would thus not apply to most of the

[199] New York Times Editorial Board, "Quicker Access to Experimental Drugs," *New York Times*, February 12, 2015.
[200] US Food and Drug Administration, "Individual Patient Expanded Access Applications: Form FDA 3926; Draft Guidance for Industry; Availability," 80 Fed. Reg. 7318 (proposed February 10, 2015) (to be codified at 21 C.F.R. pt. 312).
[201] US Food and Drug Administration, "Individual Patient Expanded Access Applications: Form FDA 3926; Guidance for Industry," June 2016.
[202] Ibid.
[203] For the policy report, see Christina Corieri, "Everyone Deserves the Right to Try: Empowering the Terminally Ill to Take Control of their Treatment" (Policy Report 266, Goldwater Institute, Phoenix, AZ, February 11, 2014). For the model legislation, see Goldwater Institute, "Right to Try Model Legislation," Goldwater Institute.
[204] FDA, "Expanded Access (Compassionate Use)."

treatment examples discussed earlier. Cultured stem cell and antiaging treatments (at least when undergone by otherwise healthy individuals) would probably not meet the FDA's standard for serious conditions. Although diabetic foot ulcers necessitating amputation might meet this standard, Heberprot-P is not considered an IND. Perhaps the rationale behind expanded access and right-to-try may one day apply to drugs approved in other countries that are not yet INDs in the United States.

The FDA's expanded access program and state right-to-try laws would require substantial broadening before they could apply to the treatments reviewed in this paper. However, major relaxation of expanded access and right-to-try criteria would effectively eliminate the FDA's power to regulate new drugs. Even today, the FDA ultimately controls right-to-try laws. If a drug manufacturer allows a dying patient to try an IND, and that patient either dies or has a setback, then the FDA can put ongoing clinical trials for that IND on hold. Manufacturers of INDs are likely to lose millions of dollars in such cases and are therefore reluctant to part with drugs during trial periods, which can last well more than a decade. This is just one instance where the decision regarding compassionate use should lie with physicians and their patients. A scenario in which a drug company either sells or provides an IND for compassionate use, and in which both patient and physician believe that the potential benefits of the drug are worth its risks, does not seem like a scenario that should be regulated by the federal government.

Conclusion

Concerns about contaminated vaccines, the tragedies caused by Elixir of Sulfanilamide and thalidomide, and the unethical marketing of patent medicines triggered legislation that, while initially designed to protect consumers, now hinders the transformation of medical insights into

beneficial medical therapies. FDA regulation has prevented the marketing of some unsafe and ineffective treatments. However, FDA regulation has also stifled the rate of innovation and prevented patients from accessing breakthrough treatments. Many of these patients—especially when they seek the counsel of qualified medical professionals—are able to rationally determine whether a treatment's potential benefits are worth its associated costs and risks. Denying these patients the freedom to choose newer medical alternatives effectively limits the ability of people to maximize their individual welfare, while also slowing overall medical progress.

A recent book, *FDA in the 21st Century: The Challenges of Regulating Drugs and New Technologies*, which was edited by two Harvard researchers, includes a section in which several authors list their ideas about regulating new medical technologies. One author, Margaret Foster Riley, says that most of today's FDA critics are looking for what Riley calls a "middle way" to balance the need for innovation with the incentives to seek offshore treatments and to ensure consumer safety.[205] This "middle" view aligns with recommendations of the Bipartisan Policy Center's Advancing Medical Innovation for a Healthier America initiative and with the Manhattan Policy Institute's aptly named Project FDA.

But it is not clear that a middle way will ultimately solve the problem. Newly emerging sciences may make it possible to detect diseases even before they develop, to use targeted drug therapies to treat or cure people, and to print medical devices (on a 3-D printer) that people can rapidly improve within Internet-based collaboration. These capabilities could lead not only to much longer lives, but also to lives of higher quality. Are we content, then, to subject these promising medical advancements to the same precautionary, slow, expensive, and innovation-stifling regulation exercised by the FDA, even with "middle way" improvements?

[205] Riley, "Twenty-First-Century Technology," 455–69.

Accelerated approval, expanded access, and right-to-try laws are welcome steps in the direction of greater patient access to potentially life-saving drugs. However, these reforms are less relevant to treatments for nonfatal chronic conditions (such as cultured stem cell therapies and Heberprot-P) or to initiatives that promise long-term improvement in overall health and longevity (such as 23andMe and telomerase research). Additional regulatory reforms should include disaggregated competitive governance, manifested in private drug and device evaluators and rating agencies, and the return of compassionate use to medicine. Such reforms will be better suited to effectively balance the risks and benefits of emerging technologies than is the current regulatory system employed by the FDA.

The incomplete nature of human medical knowledge makes it impossible for government regulators to perfectly balance the risks of "bad" drugs with the benefits of "good" drugs. Consider the case of thalidomide. What was a "bad" drug for pregnant women was found to be a "good" option for people with leprosy, AIDS, and cancer, and those findings would not have been made if thalidomide had not passed through Germany's very lenient regulatory regime.

A regulatory environment that relies more on the input of premarket middlemen, information from raters and insurers, postmarket consumer monitoring, physician expertise, and the tort system than it does on centrally imposed precautionary restraint would allow more medical discoveries—including accidental ones—to benefit American consumers, and to do so more quickly. Such a system would employ redundant checks that can best be described as *engineering redundancy* and would be a great deal more robust than the FDA's current regulatory regime. The benefits of transitioning to such a system in terms of both life expectancy and quality of life could be enormous.