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FOCUS AT THE FDA:

**ALLOWING THE MARKET TO DETERMINE EFFECTIVENESS
COULD LEAD TO BETTER HEALTH OUTCOMES WHILE
ENSURING THE FOOD AND DRUG ADMINISTRATION
PRECLUDES THE DISTRIBUTION OF UNSAFE PRODUCTS**

by Geoff Lawrence

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INTRODUCTION

Many people are born with or develop very serious medical problems that threaten to shorten their lives or severely reduce their quality of life. This tragedy can be avoided or ameliorated with innovative pharmaceutical treatments. Simply put, pharmaceuticals can help people lead happier, longer, and more productive lives.

But pharmaceutical innovation in the United States has slowed in recent decades while pharmaceutical costs have skyrocketed, placing many vulnerable individuals beyond the hope of receiving life-changing drugs. Between the 1970s and 2000s, the average cost of bringing a new pharmaceutical to market increased by an order of magnitude, even after adjusting for inflation.¹ This has occurred over the same period that major technological breakthroughs have been made in the fields of computer processing, telecommunications, engineering, and even the practice of medicine more broadly. Indeed, most U.S. industries have been able to create innovative new products and push down costs since the mid-20th century. So why has pharmaceutical development become slower and more costly? After all, big screen panel televisions are nice but not nearly as critical as health and life itself.

The U.S. government clearly understands how important pharmaceutical development and innovation are. Congress has established and financed a vast bureaucracy to oversee pharmaceutical development and passed many laws intended to spur innovation and reduce costs. Yet, it seems the more efforts Congress makes, the higher prices climb and

¹ Jorge Mestre-Ferrandiz, J. Sussex, and Adrian Towse, "The R&D Cost of a New Medicine," Monographs, Office of Health Economics, No. 000135, <https://econpapers.repec.org/bookchap/ohemonogr/000135.htm>.

the slower innovation becomes, imposing negative consequences on both the quantity and quality of human life. Many observers find this result understandably frustrating.

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What if the way we choose to regulate pharmaceutical development contributes to these frustrating results? Most industrialized nations have created national or supranational regulatory authorities to oversee pharmaceutical development, but not all work the same way. Comparing the U.S. Food and Drug Administration (FDA)—the agency with primary responsibility for regulating pharmaceuticals—with corresponding agencies in other countries offers key insights. Even comparing today’s FDA to the FDA at different points in time reveals how the agency’s regulatory apparatus and relationship with industry have evolved, often with consequences for the health of private individuals. From these insights, it is possible to imagine different methods of pharmaceutical regulation that would better serve society’s needs by encouraging widespread availability of life-saving drugs at prices individuals can better afford.

This brief reviews the regulatory apparatus governing pharmaceutical development in the United States. Part 1 examines the historical cost trends—for both time and money—of bringing an approved pharmaceutical to market. Part 2 examines the effect of pharmaceutical regulation on human life and considers both the benefits and costs of that regulation on Americans’ health. Part 3 explains the basic regulatory process for pharmaceutical development and examines key policy issues and economic trends that influence pharmaceutical development. Part 4 highlights emerging special topics in pharmaceutical regulation, such as medical research into the cannabis plant and its derivatives, and the FDA’s growing scope of powers, including previous attempts to regulate common food items. Part 5 concludes with recommendations for how best to reform the FDA’s mission to achieve the broad public goal of improving the lives and health of all Americans.

PART 1

HISTORICAL COST TRENDS IN PHARMACEUTICAL DEVELOPMENT

In the late 1950s, a new sleeping pill called thalidomide produced by a German pharmaceutical company became popular in many countries around the world. Unlike most sleeping pills on the market at the time, thalidomide contained no barbiturates, leading many medical professionals to believe the pill was safer than alternatives. Within a few years, an Australian obstetrician discovered the pill also reduced morning sickness for pregnant women and began a pattern of prescribing it for this off-label use. Tragically, thousands of the children to whom these women would later give birth suffered severe physical deformities of the arms and legs.

Thalidomide was quickly removed from the market by regulators in Germany and other nations where the product had been sold. Fortunately, the U.S. Food and Drug Administration (FDA) had never permitted thalidomide to be marketed within the United States, although the American manufacturer, Richardson-Merrell, had submitted an application to market the drug and began clinical trials in which the drug was distributed to

about 600 pregnant women.² The FDA refused to approve marketing or distribution of the drug to the general public because it believed there was insufficient data to support the drug maker's safety claims, particularly regarding the drug's impact on fetal development.³

Although participants in the Richardson-Merrell clinical trials sadly gave birth to 17 American babies with congenital deformities,⁴ the FDA's requirements that drug makers demonstrate the safety of their products before they could be marketed prevented a more widespread tragedy. By any measure then, the FDA had succeeded in its mission of protecting the public from the risks of an unsafe drug like thalidomide.

Congress originally created the agency beginning in 1906 with passage of the Pure Food and Drug Act to ban interstate or foreign commerce in mislabeled food and drug products. Passage of the Food, Drug and Cosmetic Act in 1938 created the requirements that drug makers demonstrate the safety of their products through regulated clinical trials administered as part of a New Drug Application submitted to the FDA. The agency could not conclude, based on the data from these trials, that thalidomide was safe. Consequently, the FDA's regulatory procedures averted a mass tragedy by preventing distribution of the drug. Nonetheless, President Kennedy held a press conference to warn about the dangers of thalidomide, and legislation drafted by the FDA was introduced to Congress that the FDA still maintains was "designed to prevent a disaster like thalidomide."⁵ The legislation passed unanimously and was quickly signed into law by Kennedy.

Given that the agency's existing duties had already averted a thalidomide disaster, it's questionable why the agency helped to draft and support this legislation, called the Kefauver-Harris Amendments of 1962 to the Food, Drug and Cosmetic Act. The 1962 Amendments expanded the agency's scope by adding a new charge for the agency to police not only drug safety, but also drug effectiveness. Whereas thalidomide was considered dangerous and had been precluded from widespread distribution within the United States

² Leila McNeill, "The Woman Who Stood Between America and a Generation of 'Thalidomide Babies,'" *Smithsonian Magazine*, March 8, 2017, <https://www.smithsonianmag.com/science-nature/woman-who-stood-between-america-and-epidemic-birth-defects-180963165/>.

³ U.S. Food and Drug Administration, "Kefauver-Harris Amendments Revolutionized Drug Development," September 10, 2012, <https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development>; See also: Bara Fintel, Athena T. Samaras, and Edson Carias, "The Thalidomide Tragedy: Lessons for Drug Safety and Regulation." *Helix Magazine*, July 28, 2009, <https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation>.

⁴ McNeill, "The Woman Who Stood Between America and a Generation of 'Thalidomide Babies.'"

⁵ Ibid.

because it failed the agency's safety standards, the 1962 Amendments did not expand the agency's safety protocols, but instead directed the agency to also determine if a drug would be an effective treatment for a specified condition. Thus, the 1962 Amendments went in a direction different from addressing the public warnings issued by Kennedy and other concerned parties.



Prior to the 1962 Amendments, assessments of drug effectiveness were reserved to the medical community. Professional associations like the American Medical Association reviewed drugs and provided recommendations to medical practitioners, who could make informed choices along with their patients as to which pharmaceuticals might best treat an individual's particular symptoms.



Prior to the 1962 Amendments, assessments of drug effectiveness were reserved to the medical community. Professional associations like the American Medical Association reviewed drugs and provided recommendations to medical practitioners, who could make informed choices along with their patients as to which pharmaceuticals might best treat an individual's particular symptoms. The 1962 Amendments would require bureaucratic approval before any drug could be offered or prescribed in the United States.

It was unclear from the statutory language what standards the agency would use to evaluate or determine "effectiveness," and these standards have been left for the agency to clarify through rulemaking. The FDA eventually developed a framework of multi-staged clinical trials culminating in the demonstration, through two separate large-scale human trials, that a drug is more effective than a placebo for 95% of patients. If a drug fails to achieve this standard, even if it's a total cure for half the patients who try but not the remaining half (due to genetic or physiological variation, for instance), then that drug will

not be permitted for sale in the United States.⁶ These regulatory stages leading to approval are detailed in Part 3.



These new steps imposed significant new costs and delays on pharmaceutical researchers and manufacturers that have had demonstrable and devastating effects on human wellbeing.



These new steps imposed significant new costs and delays on pharmaceutical researchers and manufacturers that have had demonstrable and devastating effects on human wellbeing. Between 1948 and 1961, it took a pharmaceutical manufacturer about four years, on average, from the time of discovery to satisfy the FDA's safety protocols and bring a new drug to market. By the 1980s, that timeline stretched to more than 14 years.⁷ The additional decade of development time has meant that Americans suffering from severe illnesses were delayed from receiving potentially life-saving treatments.

By 1976, for instance, the President's Biomedical Research Panel warned, "...there is a different kind of hazard to public health posed by the prolonged delays and great costs of developing new and potentially useful drugs which the FDA's own protective systems have imposed. In some respects the agency has become a formidable roadblock."⁸

Indeed, the additional costs of meeting the FDA's new regulatory processes under the 1962 Amendments can be measured in both time and money, each of which has serious implications for the development of potentially life-saving treatments. Cost estimates have varied widely, although academic studies have generally shown the costs have increased over time. There are multiple components of costs that drug makers must consider. First, the cost of discovering or identifying a new chemical compound that could be potentially useful in combatting a known disease or health condition is open-ended. Generally, these

⁶ Mary J. Ruwart, *Death by Regulation*, Sunstar Press (2018): Kalamazoo, MI, 52-53.

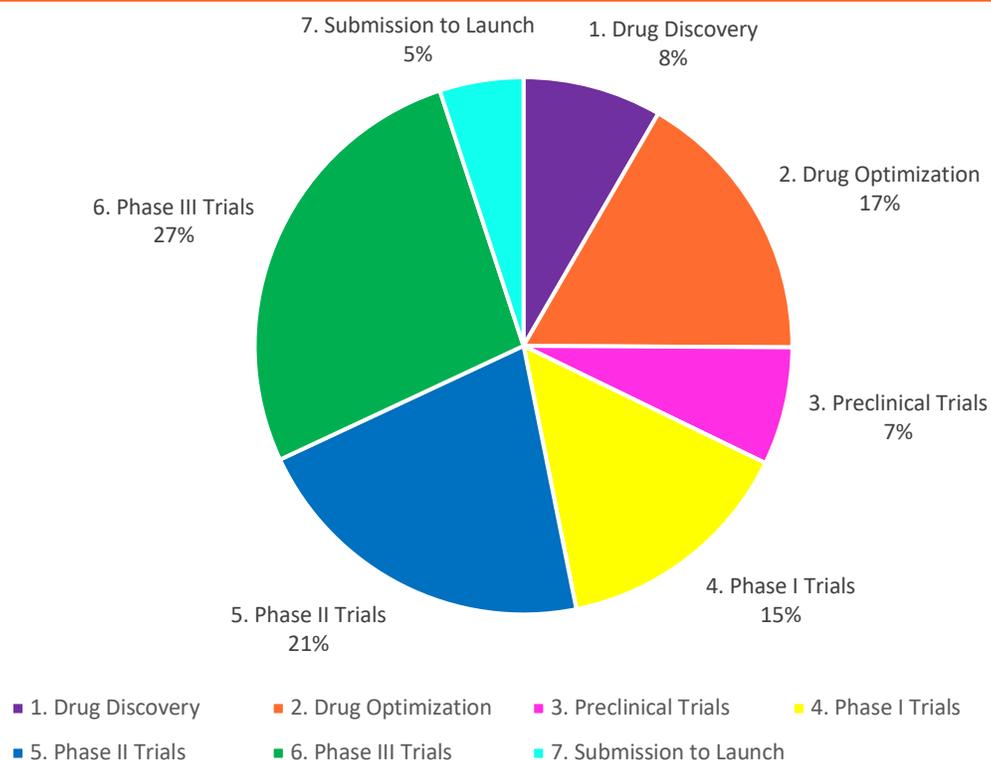
⁷ *Ibid*, 29.

⁸ Quoted by William M. Wardell, "A Close Inspection of the 'Calm Look' Rhetorical Amblyopia and Selective Amnesia at the Food and Drug Administration," *JAMA* 239 (1978): 2004-11, <https://jamanetwork.com/journals/jama/article-abstract/1722202>.

costs are understood as traditional research and development costs and are thus not necessarily driven by regulation.

Second, drug makers must take a selected drug through successive trials on laboratory animals and then limited human trials to determine safety. Subsequently, the drug maker must organize much larger human clinical trials in an effort to demonstrate efficacy up to the 95% confidence threshold and wait for the FDA to review the results of those studies between each stage. Although drug makers conducted versions of these studies prior to enactment of the 1962 Amendments, the costs and timelines involved today are effectively regimented by the FDA’s requisite processes and backlog of review times. Estimates indicate that clinical development during the period of regulatory review accounts for 63% of the total cost of drug development, and the final stages of pre-market clinical trials to determine efficacy alone account for 53% of drug costs.⁹

FIGURE 1: DRUG DEVELOPMENT COSTS BY PHASE



Source: Steven M. Paul et al., “How to Improve R&D Productivity: The Pharmaceutical Industry’s Grand Challenge,” *Nature*, Vol. 9 (March 2010), 203-214, <https://www.nature.com/articles/nrd3078.pdf>

⁹ Steven M. Paul, et al., “How to Improve R&D Productivity: The Pharmaceutical Industry’s Grand Challenge,” *Nature*, Vol. 9 (March 2010), 203-214, <https://www.nature.com/articles/nrd3078.pdf>.

Third, only in a small minority of cases is a drug deemed worthy of continuing from one stage to the next. To limit losses, most drug makers abandon projects early if they believe the drug will either be unsafe or deemed ineffective, either by the FDA during effectiveness trials or by the market if the medical profession believes the drug does not hold value. Thus, drug makers must account for the cost of high failure rates and amortize the cost of failures into their development costs for the few successful drugs they bring to market. Estimates indicate that roughly 8% of new drugs to enter FDA-supervised clinical trials will ultimately advance to market. This narrowing occurs after pharmaceutical companies internally eliminate drug candidates they believe are unlikely to be successful on a market basis or secure regulatory approval.¹⁰ Among those drugs that are placed in FDA trials and fail to win approval, a large majority are refused access to the market for failure to pass the FDA's definition of efficacy rather than safety. In other words, the FDA recognizes these drugs as safe for human consumption, but doesn't allow patients to try them. A review of 640 drugs to enter Phase III trials found that only 17% of failed Phase III trials were due to safety issues.¹¹

TABLE 1: MAJOR COST COMPONENTS OF DRUG DEVELOPMENT

1.	Discovery of a potentially beneficial molecule
2.	FDA-supervised pre-clinical and clinical trials
3.	Amortized cost of failures
4.	Cost of attracting capital to bring a drug to market
5.	Post-approval studies and marketing expense

Fourth, a pharmaceutical company must recognize the long and costly road from drug discovery to regulatory approval and market introduction, and secure adequate capital to ensure it can complete that journey. This means a company's cost of capital can significantly escalate the overall cost of a project that may take 14 years or more. Over that time frame, it must pay interest on borrowed funds or offer returns to equity investors in order to attract the capital needed to make the project a reality.

¹⁰ Ibid.

¹¹ Thomas J. Hwang, et al., "Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results," *JAMA Internal Medicine*, Vol. 176, No. 12 (Dec. 2016), 1826-1833, <https://pubmed.ncbi.nlm.nih.gov/27723879/>.

Finally, after a drug has been approved by the FDA and introduced to market, the drug maker is responsible for conducting follow-on studies to evaluate the drug's ongoing safety and effectiveness in addition to the marketing and selling costs that any company would bear to inform customers of what its products can do.

Academics have struggled to produce accurate estimates of all these cost components because not all pharmaceutical companies make this information readily available. Some researchers have been granted confidential access to proprietary data by certain companies,¹² while others have relied on the financial statements reported to the U.S. Securities and Exchange Commission by publicly traded companies.¹³ In each instance, estimates are computed using only a sampling of data since few researchers can gain access to proprietary information of all companies, and not all drug manufacturers are publicly traded.

Regardless, the all-in cost estimates of bringing a new drug to market in the United States have both increased over time and remained relatively consistent when researchers have analyzed similar time periods. A summary of results is detailed in Table 2.

These costs, in terms of both money and time, are a major disincentive for the development of innovative new drugs in the United States. Within just six years of passage of the 1962 Amendments, the number of firms bringing new drugs to market declined by 44%,¹⁴ limiting competition and allowing the predominantly large firms that remained to more easily raise prices in order to recapture development costs.

¹² See, e.g., Joseph A. DiMasi, "The Value of Improving the Productivity of the Drug Development Process: Faster Times and Better Decisions," *Pharmacoeconomics*, Vol. 20 (2002), 1-10. Available at: <https://pubmed.ncbi.nlm.nih.gov/12457421/>.

¹³ See Olivier J. Wouters, Martin McKee, and Jeroen Luyten, "Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018," *JAMA*, Vol. 323, No. 9 (March 2020), 844-853. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7054832/>.

¹⁴ Joseph M. Jadow, *The Economic Effects of the 1962 Drug Amendments*, (Charlottesville: University of Virginia), 38, 158, 160-161, 175-188.

TABLE 2: ESTIMATED CAPITALIZED COST OF DRUG DEVELOPMENT, BY STUDY

<i>Study</i>	<i>Cost Estimate</i>	<i>Time Period Examined</i>
DiMasi (2003) ¹⁵	\$802 million	1980-1999
Adams (2006) ¹⁶	\$868 million	1989-2002
DiMasi (2007) ¹⁷	\$1,138 million	1980-2004
Gilbert (2003) ¹⁸	\$1,700 million	2000-2002
Paul (2010) ¹⁹	\$1,778 million	1997-2007
Wouters (2020) ²⁰	\$1,336 million	2009-2018

Not only did the 1962 Amendments push nearly half of drug makers out of the market in a short time, but the additional costs of drug development have made these potentially life-saving expenditures unattractive to market participants who are wary of both risk and lengthy timelines. When Merck announced it would increase its research spending to develop new drugs and drive revenue growth in 2011, Wall Street responded with a sell-off of Merck stock that sent its market capitalization tumbling. Analysts complained, “Merck could end up wasting billions of dollars.”²¹ In other words, markets now sometimes punish drug companies that pour money into developing beneficial new drugs because of the additional risks and costs imposed by government regulation. Since drug development is the core business of these enterprises, and drug development also bears broad public benefits, this is a tragically perverse effect of the U.S. regulatory approach.

¹⁵ Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, “The Price of Innovation: New Estimates of Drug Development Costs,” *Journal of Health Economics*, Vol. 22 (2003), 141-185, <https://pubmed.ncbi.nlm.nih.gov/12606142/>.

¹⁶ Christopher P. Adams and Van V. Brantner, “Estimating the Cost of New Drug Development: Is It Really \$802 Million?” *Health Affairs*, Vol. 25 (2006), 420-428, <https://www.healthaffairs.org/doi/10.1377/hlthaff.25.2.420>

¹⁷ Joseph A. DiMasi and Henry G. Grabowski, “The Cost of Biopharmaceutical R&D: Is Biotech Different?” *Management Decision Economics*, Vol. 28 (2007), 469-479, <https://www.jstor.org/stable/25151529?seq=1>

¹⁸ James Gilbert, Preston Henske and Ashish Singh, “Rebuilding Big Pharma’s Business Model,” *In Vivo*, Vol. 21 (2003), 1-10, <https://www.bain.com/insights/rebuilding-big-pharmas-business-model/>

¹⁹ Paul, et al., “How to Improve R&D Productivity.”

²⁰ Wouters, McKee, and Luyten, “Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018.”

²¹ Jonathan D. Rockoff, “Pfizer, Merck Take Different R&D Tacks,” *The Wall Street Journal*, February 4, 2011, <https://www.wsj.com/articles/SB10001424052748703652104576122433479575072>.

PART 2

REGULATIONS INTENDED TO PROTECT US ARE ACTUALLY KILLING US

Many advocates of drug regulation consider it mundane to focus narrowly on the costs of drug development in terms of dollars and cents. Perhaps they're right. After all, the purpose of pharmaceuticals is to prolong or enhance human life, and regulation is intended to save lives. How can anyone compare financial costs to the lives and health of ourselves and our loved ones?

Unfortunately, drug regulation doesn't only make drugs more costly to produce. Analyses have shown the lengthy timelines involved actually result in far more people dying from preventable causes than are saved from potentially harmful drugs.

According to research from Frank Lichtenberg, Columbia University professor of health care management, drugs approved between 1970 and 1991 were responsible for saving an average of 18,800 American life-years each year by 1991 and new drugs were responsible

for 45% of the decline in disease-related deaths during that time.²² Many of these drugs prevented or aided recovery from leading causes of death such as heart attack and stroke, with the average beneficiary gaining 11 years of life. Biophysicist and pharmaceutical scientist Mary Ruwart builds off Lichtenberg's calculations to estimate that delays from introducing these drugs to market because of the 1962 Amendments resulted in a loss of five million years of life in the 1960s alone and this figure grew to 57.8 million years of life by the 1990s as regulatory timelines increased. This loss of life was due primarily to the increased delays imposed by FDA's new effectiveness standards, which prevented these drugs from reaching patients sooner and resulted in some patients dying while a potentially life-saving drug remained in regulatory review. As Ruwart concludes, "[D]eath by regulation far exceeds consumer protection, even if the estimates of deaths caused by the Amendments are 100 times too high."²³



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It's more difficult to measure the lives possibly saved by preventing drugs from coming to market altogether as pharmaceutical companies made internal decisions to avoid the expense of placing a drug through FDA-supervised trials. However, Stanford University drug scholar Dale Gieringer compared drugs approved in the United Kingdom to those in the United States. Gieringer estimates that 5,000-10,000 American lives could have been lost due to side effects of some of these drugs if they had been approved and marketed in the

²² Frank R. Lichtenberg, "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth," In *Measuring the Gains from Medical Research: An Economic Approach* (2003), Eds. Kevin M. Murphy and Robert H. Topel, (Chicago: University of Chicago Press), 74-109.

²³ Ruwart, *Death by Regulation*, 46-47.

United States. However, those same drugs could have saved 120,000 American lives if Americans had gained access (Gieringer's focus includes drugs that may have failed the FDA's safety standards *in addition* to those that may have failed its efficacy rules).²⁴ Similarly, University of Chicago economist Sam Peltzman has estimated that the delays and lack of access resulting from the 1962 Amendments has led to the loss of four lives for every life they spare.²⁵

In other words, the risk of adverse effects has been dwarfed by the risk of forbidden access. Regardless, as the thalidomide episode demonstrates, FDA processes were already more effective at preventing unsafe pharmaceuticals from coming to market than European regulators even prior to the 1962 Amendments.

This historical American advantage has not increased in the wake of the 1962 Amendments. There is even evidence that it may have waned following their passage. Under the modern regulatory structure, discontinuations of drugs approved by the FDA for subsequent discovery of their dangers have closely mirrored discontinuations in developed nations that impose far less strenuous pre-market regulatory screening. In the two decades following passage of the 1962 Amendments, more drugs were approved in the United Kingdom than in the United States. Yet, each country has similar records of discontinuations for safety concerns discovered after the fact and, in more recent years, regulators in the United States had to recall more drugs than did regulators in the United Kingdom.²⁶ This indicates that the FDA's modern regulatory structure requiring prior approval and effectiveness testing before a drug can be marketed to the public may have diverted the agency's attention from its historical role of ensuring drug safety. Medical researchers and practitioners can determine effectiveness through peer-reviewed studies, but safety monitoring is generally viewed as falling within the proper realm of government regulation.

²⁴ Dale H. Gieringer, "The Safety and Efficacy of New Drug Approval," *Cato Journal*, Vol. 5, No. 1 (Summer 1985), 177-201, <https://www.cato.org/sites/cato.org/files/serials/files/cato-journal/1985/5/cj5n1-10.pdf>.

²⁵ Sam Peltzman, *Regulation of Pharmaceutical Innovation: The 1962 Amendments*, (Washington, DC: American Enterprise Institute for Public Policy Research. Distributed by National Book Network: Blue Ridge Summit, PA) 13-18, 53-54. Available at: https://www.aei.org/wp-content/uploads/2014/05/-regulation-of-pharmaceutical-innovation-the-1962-amendments_1101223883.pdf?x91208.

²⁶ Olav M. Bakke, William M. Wardell, and Louis Lasagna, "Drug Discontinuations in the United Kingdom and the United States, 1964 to 1983: Issues of Safety," *Clinical Pharmacology & Therapeutics*, Vol. 35, No. 5 (May 1984), 559-567. Available at: <https://pubmed.ncbi.nlm.nih.gov/6713769/>.



... by preventing or substantially delaying promising drugs that meet the agency's safety standards from coming to market, the FDA's modern regulatory structure places millions of lives at risk. Large majorities of medical practitioners in the United States agree with this claim.



Instead, by preventing or substantially delaying promising drugs that meet the agency's safety standards from coming to market, the FDA's modern regulatory structure places millions of lives at risk. Large majorities of medical practitioners in the United States agree with this claim. In a 2002 national survey of American oncologists, 60% agreed that the "additional time it takes for the FDA to approve medical drugs and devices cost lives by forcing people to go without potentially beneficial therapies." More than three-fourths of respondents said the FDA's approval process had hurt their ability to treat their own patients and 70% said the FDA fails to understand the "human cost" of the delays created by its approval processes.²⁷ Similar surveys of emergency room physicians,²⁸ neurosurgeons²⁹ and orthopedic surgeons³⁰ have all revealed comparable opinions among physicians.

²⁷ Competitive Enterprise Institute, "A National Survey of Oncologists Regarding the Food and Drug Administration," April 30, 2002, <https://cei.org/wp-content/uploads/2010/10/CEI-Staff-A-National-Survey-of-Oncologists-Regarding-The-Food-And-Drug-Administration.pdf>.

²⁸ Competitive Enterprise Institute, "A National Survey of Emergency Room Physicians Regarding the Food and Drug Administration," October 1999, <http://cei.org/sites/default/files/Greg%20Conko%20-%20A%20National%20Survey%20of%20Emergency%20Room%20Physicians%20Regarding%20The%20Food%20And%20Drug%20Administration.pdf>.

²⁹ Competitive Enterprise Institute, "A National Survey of Neurologists and Neurosurgeons Regarding the Food and Drug Administration," October 1998, <https://cei.org/studies/a-national-survey-of-neurologists-and-neurosurgeons-regarding-the-food-and-drug-administration/>.

³⁰ Competitive Enterprise Institute, "A National Survey of Orthopedic Surgeons Regarding the Food and Drug Administration and the Availability of New Therapies," January 30, 2007, <https://cei.org/studies/a-national-survey-of-orthopedic-surgeons-regarding-the-food-and-drug-administration-and-the-availability-of-new-therapies/>.

A key frustration with both medical professionals and patients alike is that Americans are barred by law from accessing treatments that could save their own lives. Although the FDA has created nominal pathways for severely ill individuals to access drugs that are still in review, strong incentives exist to block these pathways. The FDA must grant approval for each specific individual to access these drugs on a “compassionate use” basis and the application procedures require a physician to spend around 100 man-hours with no certainty approval will be granted.³¹ In the case of Abigail Burroughs, a college student suffering from squamous cell carcinoma, and thousands of others in similar circumstances, the FDA has denied these applications for compassionate use and allowed the patients to die without receiving access even to exploratory treatments that may have helped. Burroughs’ father subsequently sued the FDA and prevailed in the U.S. Court of Appeals only to see the Court reverse its own decision a year later at the beckoning of the FDA, ruling that Americans have no constitutional right to try and save their own lives using drugs not approved by the FDA.³²

³¹ Ruwart, *Death by Regulation*, 35.

³² 495 F.3d 695, “Abigail Alliance for Better Access to Developmental Drugs and Washington Legal Foundation, Appellants v. Andrew Von Eschenbach, in His Capacity as Commissioner, Food and Drug Administration.” No. 04-5350, U.S. Court of Appeals, District of Columbia Circuit, August 7, 2007. Available at: <https://caselaw.findlaw.com/us-dc-circuit/1323520.html>.

PART 3

THE REGULATORY APPROVAL PROCESS AND ITS POLITICAL ECONOMY

Parts 1 and 2 examined the monetary and time costs of the current U.S. approach to pharmaceutical regulation due to slowed innovation and lives lost while individuals await access to treatments still under review. Neither the FDA nor the lawmakers who enshrined that agency or expanded its powers pursuant to the 1962 Amendments are inherently evil and we shouldn't expect them to have preferred these results. All these parties intended to protect—and not endanger—the health of Americans by enshrining a federal agency with broad powers to issue prior restraint in the trade or marketing of wide classes of goods. So, what specifically about the regulatory structure has produced these adverse results? Developing an understanding of these shortcomings is essential for building the informed recommendations for improvement presented in Part 5.

3.1

OUTLINE OF REGULATORY PROCESS

Pharmaceutical companies can spend years or decades researching how human cell samples or laboratory animals react to various chemical compounds to identify compounds that could have some potential health benefit. Drug makers have incurred these

exploratory research and development costs as a normal course of business throughout the history of that industry. Prior to passage of the 1962 Amendments, a drug maker would need to conduct toxicity studies for review by the FDA to ensure a drug's safety. Drug makers would generally also conduct extensive research into a drug's effectiveness so they could efficiently market their products to the public, although this wasn't necessarily required if the FDA concluded the product was safe for human use.



Prior to passage of the 1962 Amendments, a drug maker would need to conduct toxicity studies for review by the FDA to ensure a drug's safety. Drug makers would generally also conduct extensive research into a drug's effectiveness so they could efficiently market their products to the public, although this wasn't necessarily required if the FDA concluded the product was safe for human use.



The 1962 Amendments changed this market process by adding a series of FDA evaluations of effectiveness a drug maker would need to satisfy prior to bringing any new drug to market. Upon discovery of a molecule that could be beneficial in the treatment of some known health condition, a drug maker has always needed to file an application with the FDA to list that molecule as an Investigational New Drug (IND) if the drug maker has determined it holds enough promise to warrant the time and expense of moving through the regulatory process. The 1962 Amendments made the odds of an IND translating into a successful commercial drug so low—for reasons described herein—that manufacturers began to discontinue research on a drug early to limit cost exposure. The number of IND applications filed with the FDA fell by more than 50% within the first decade of the Amendments' passage.³³

³³ Joseph A. DiMasi, Mark A. Seibring, and Louis Lasagna, "New Drug Development in the United States, 1963 to 1992," *Clinical Pharmaceutical Industry*, 1999, (Washington, D.C.: Pharmaceutical Research and Manufacturers of America), 113-115.

Once a drug has been filed within an IND application, regulations promulgated by the FDA to implement its charge require a manufacturer to pass through three stages of clinical trials prior to introducing a drug to market, along with ongoing research requirements that the agency may request at any time post-approval. Phase I trials are limited in scope (often to fewer than 100 test subjects) and aim to ensure a drug's safety by confirming that toxicity levels greatly exceed amounts needed for effective treatment. Prior to submission of an IND, a drug maker will have already determined a range of likely toxicity levels through treatment in mice or other laboratory animals, but the FDA has never allowed human trials to begin without its supervision. Although this portion of the regulatory process existed prior to the 1962 Amendments, the FDA has nonetheless slowed these Phase I trials by disallowing dose-ranging within a trial or limiting all participants to a single dose of a treatment intended to include multiple doses.³⁴ As a result of such agency determinations, a drug maker may need to conduct multiple instances of trials within each phase in order to produce the needed results. This lengthens both the timeline and financial costs of drug development. This is one example of how the way the agency has chosen to interpret its statutory charge has lengthened the development process beyond what is apparent from reading the statutes themselves.



Prior to submission of an IND, a drug maker will have already determined a range of likely toxicity levels through treatment in mice or other laboratory animals, but the FDA has never allowed human trials to begin without its supervision.



The effect of the 1962 Amendments begins to be seen more broadly at the stage of Phase II clinical trials and beyond. Phase II trials are the first exposure of a new drug to the targeted human population—those who suffer from the specific health condition the drug is intended to improve. During this phase, drug makers and regulators alike look to establish an idea of the drug's effectiveness and potential side effects. Phase II trials are limited in scope from a few dozen to a few hundred test subjects, so drug makers typically use this

³⁴ Henry I. Miller, *To America's Health: A Proposal to Reform the Food and Drug Administration*, 2000, (Stanford University: Hoover Institution Press), 19.

trial phase to minimize their cost exposure while collecting initial data on a drug's effectiveness prior to undertaking the vastly more expensive Phase III trials.

Only about one in three INDs is selected to continue onto Phase III trials, which can cost hundreds of millions or even billions of dollars and take many years to complete.³⁵ FDA regulations require Phase III trials to demonstrate that an IND is a more effective treatment for a specified condition than a placebo in two separate, well-designed studies that are statistically significant at the 95% level. The implications of this requirement are important.



FDA regulations require Phase III trials to demonstrate that an IND is a more effective treatment for a specified condition than a placebo in two separate, well-designed studies that are statistically significant at the 95% level.



First, it's noteworthy that variations in genetics and biochemistry across individuals mean that some drugs could be highly effective for some individuals and minimally effective for others. The statistical significance level the FDA has adopted by rule effectively forces drug makers to cast aside treatments that could be total cures for some individuals if that treatment holds no benefit for others. The requirement alters the economics of drug development such that drug makers are incentivized to pursue drugs that promise only a mild alleviation of a particular symptom so long as that result can be replicated across a wide population.

In 2011, for example, Phase II trials of a potential new treatment for women with triple-negative breast cancer showed highly promising results. The drug, called Iniparib, nearly doubled the progression-free survival time of these women and produced few or no side effects. When the drug progressed to Phase III trials, some of the women who took it experienced similar survival advantages relative to those who received placebos. Although the FDA acknowledges that Iniparib did increase progression-free cancer survival on average, the Phase III trial did not meet the agency's statistical threshold of efficacy

³⁵ Pharmaceutical Research and Manufacturers of America, "New Drug Approvals," January 1998, 22.

because some women who took it didn't see any gains.³⁶ Subsequent reviews have suggested that this was likely due to heterogeneity in the study group—some women may have had biological differences that made them less receptive to the treatment even if it was highly effective for others.³⁷ After more than two decades of development, the company that made Iniparib finally ceased development in 2013. The FDA's interpretation of effectiveness ensures that no women suffering from triple-negative breast cancer will see their survival advantage doubled from taking Iniparib because it cannot be sold in the U.S. even after clearing the agency's safety protocols.

Second, the statistical significance threshold implies that drug makers need to design trials that include thousands of test subjects in the hopes that large numbers will overwhelm potential outliers. Phase III trials are intended to ascertain:

1. A drug's effectiveness across a wide spectrum of patients;
2. Types and frequency of side effects in a heterogenous population;
3. Potential for long-term use;
4. Possible adverse interactions with other drugs; and
5. Other information that could be useful for labeling.

Some of these goals further imply that Phase III trials need to be conducted over a prolonged period of continuous treatment with ongoing monitoring and data collection over each participant's condition. The trials themselves may take four to five years to complete and then the drug maker must compile all the information together, document the clinical results, perform statistical analyses, and submit a packet of documentation that would amount to a literal truckload of paper (if printed) to the FDA for review. This constitutes a New Drug Application (NDA) and it is unlawful in the United States to market any item that claims health benefits without successful approval of an NDA. The information produced from these trials is so voluminous that it often takes the FDA two years just to read through and approve the application.³⁸

³⁶ U.S. Food and Drug Administration, "22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results," January 2017, <https://www.fda.gov/media/102332/download>.

³⁷ Denise A. Yardley, "Iniparib: The Fairy Tale Dream Comes to an End," *The ASCO Post*, February 25, 2015, <https://ascopost.com/issues/february-25-2015/iniparib-the-fairy-tale-dream-comes-to-an-end/>.

³⁸ Miller, *To America's Health: A Proposal to Reform the Food and Drug Administration*, 80.

A common misperception is that the FDA completes the clinical trials itself. It does not—these trials are conducted and financed entirely by the sponsoring drug maker. The FDA simply reads through the documentation to determine if the studies satisfy the agency’s interpretations of its statutory charge to ensure effectiveness. If the agency determines any aspect of the study is insufficient to check the necessary boxes, it may require certain trials to be repeated, assuming the applicant retains the wherewithal to do so.



A common misperception is that the FDA completes the clinical trials itself. It does not—these trials are conducted and financed entirely by the sponsoring drug maker.



There has been wide dispute within the pharmaceutical industry about exactly what those boxes should look like. For instance, a pharmaceutical called Isoprinosine intended to help fight the effects of AIDS was shown in clinical trials to raise the count of T-cells within patients’ blood, indicating that the HIV virus was not destroying these patients’ immune systems. Although the clinical evidence was compelling, the FDA has not historically been receptive to “surrogate markers,” or interim indications in the treatment of a disease, such as an increase in T-cell counts. In the case of Isoprinosine, the FDA deemed these clinical studies irrelevant in 1986 because the specified condition within the IND that Isoprinosine was supposed to treat was AIDS. Although the clinical trials demonstrated patients’ immune systems were not deteriorating after receiving Isoprinosine, thereby averting the primary symptom of AIDS, the trials did not directly show that AIDS disappeared and the FDA would not accept a surrogate marker such as a rise in T-cell counts that indirectly implies AIDS symptoms were dissipating. The drug maker was instructed it would need to show directly that AIDS itself disappeared. Unfortunately, the drug maker didn’t possess the financial wherewithal to undergo a second round of Phase III trials. Years later, a separate research group bore the cost of re-doing the Isoprinosine trials and showed a high success rate of forestalling the progression from contracting the HIV virus to the development of AIDS with minimal side effects compared to alternative treatments.³⁹

³⁹ Ruwart, *Death by Regulation*, 75-76.

3.2

FDA CREATES A DISCOORDINATION OF KNOWLEDGE WITHIN THE MEDICAL FIELD

The FDA's historical unwillingness to accept surrogate markers as an indication of a drug's effectiveness underscores the importance of the specified condition detailed in the original IND application. Not only must clinical trials generally be designed to measure the specified condition directly, but once a drug has been approved by the FDA to go to market, it may only be marketed as a treatment for that specified condition. In the event a drugmaker discovers the drug has additional benefits and could treat other illnesses, it is forbidden from making this information public unless it again takes the drug through clinical trials with a different specified condition listed on the IND application. For example, in the 1960s, the Squibb Chemical Company discovered that a small daily dose of the common pain reliever aspirin could significantly decrease the likelihood and severity of heart attacks and strokes. However, the company was legally forbidden from making that information public. Moreover, the company faced adverse incentives for placing aspirin back through expensive clinical trials because aspirin had been around for so long that there was no longer any patent protection that would allow the company to recover the costs of these trials. It was not until the 1990s that a publicly funded trial by the National Institutes of Health investigated this connection and found overwhelming results. This trial finally allowed the information to be made public so that physicians could know aspirin was highly effective in reducing the effects of heart attack and stroke. The twenty-plus year gag order on this information is estimated to have cost 1.7 million American lives as Americans died from heart attacks whose lives could have been prolonged if they had been given something as simple as aspirin.⁴⁰

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In the event a drugmaker discovers the drug has additional benefits and could treat other illnesses, it is forbidden from making this information public unless it again takes the drug through clinical trials with a different specified condition listed on the IND application.

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⁴⁰ Ibid, 75-77.

Subsequent research has determined that a daily dose of aspirin can yield harmful side effects such as stomach ulceration and, therefore, presents a net benefit only to individuals who have previously suffered a heart attack. Yet, the FDA's suppression of clinical information delayed the public's understanding of aspirin for decades when the agency was intended to safeguard public health. Aspirin is only one known example of this suppression of clinical information. How many others could there be?



Although physicians are allowed to prescribe medications the FDA has approved for conditions other than the specified condition for which it was approved, physicians have few systematic methods for obtaining information about a drug's potential off-label uses.



Although physicians are allowed to prescribe medications the FDA has approved for conditions other than the specified condition for which it was approved, physicians have few systematic methods for obtaining information about a drug's potential off-label uses. Pharmaceutical companies like Squibb are prohibited by law from communicating this information and could face severe penalties for doing so. Off-label use of a drug only becomes common, then, when a physician haphazardly discovers a drug is effective at treating a symptom for a particular patient or set of patients and makes that discovery known to other physicians. This word-of-mouth network of medical information makes the aggregation of this knowledge and coordination of its benefits for medical patients highly inefficient. Essentially, the FDA's regulatory structure has short-circuited the efficient distribution of knowledge within the medical profession.⁴¹ Some physicians in some places may be aware of the potential off-label benefits of some medications, but this knowledge is only partially understood and unevenly distributed. As a result, people with serious medical conditions receive recommendations for medical treatment that include only haphazard fragments of the information that would be needed to generate the best decision for that

⁴¹ Nobel-laureate economist Friedrich Hayek is known for his explanation of how markets serve to coordinate dispersed knowledge across society whereas government interventions can sometimes disrupt this important feature. See: Friedrich A. Hayek, *The Use of Knowledge in Society*, (Menlo Park, CA: Institute for Humane Studies, 1945).

patient. This inefficiency is not the result of a market process (in which the information might be presented and evaluated across peer-reviewed medical journals), but entirely a result of the FDA's regulatory approval process and the way in which it suppresses valuable information.

3.3

POLITICAL ECONOMY OF DRUG REGULATION

To win regulatory approval to bring a new drug to market or identify additional uses of a previously approved drug, pharmaceutical companies are at the mercy of the FDA. If a company is convinced its trials demonstrate a drug's effectiveness but the FDA says otherwise, there is no recourse or appeals process to contest the FDA's opinion. This discourages pharmaceutical companies from criticizing the FDA's decisions because such criticisms could adversely affect future FDA decisions and instead encourages these companies to try and develop cozy relationships with the FDA. A figurative carousel has emerged in response in which pharmaceutical companies attempt to hire or otherwise woo former FDA regulators in an effort to strengthen these relationships. Before 1963, only 10% of officials leaving the FDA went into the private pharmaceutical industry. By 1969, that proportion had grown to 76%.⁴² Compliance departments at major pharmaceutical companies have enlarged, creating economies of scale for large firms that have pushed smaller companies out of the market and resulted in less competition and increasing cartelization of the industry. Moreover, regulation has produced its own interest groups as those working in these compliance departments are fully aware their livelihoods depend on continued regulation. Similarly, regulators are aware that high future salaries may await them within the companies they regulate and so they have an interest in both preserving

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Compliance departments at major pharmaceutical companies have enlarged, creating economies of scale for large firms that have pushed smaller companies out of the market and resulted in less competition and increasing cartelization of the industry.

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⁴² Ruwart, *Death by Regulation*, 33.

relationships with those entities while also ensuring that the level of regulation is large enough to continue to warrant expansive compliance departments.

For its part, the FDA faces its own perverse incentives. If regulatory processes fail to exclude from the market a particular drug that winds up producing serious side-effects, regulators will be hauled before Congress and publicly shamed and may be stripped of their livelihoods. On the other hand, they face no penalties for preventing a highly effective drug that could save millions of lives from coming to market. The public is generally unaware of the costs associated with these failures, in part because drug makers are prohibited from informing the public what they believe their products can do unless the FDA has approved those statements. So, regulators have every incentive to make the regulatory process as restrictive as possible because there is almost no accounting for the number of lives lost due to excluding a promising drug from the market.

Only in particular cases have ordinary citizens had any effect in moving the FDA's restrictive positions. Chief among these was a group of vocal sufferers of a common disease—AIDS—for which the FDA was preventing treatment.



In other words, FDA regulations have been sufficiently strict as to foster vibrant black markets for pharmaceuticals when a disease becomes relatively common and its effects are severe.



There were enough sufferers of AIDS in the 1980s, and the ultimate result of that disease so severe, that it made sense for these sufferers to invest significant resources into making each other aware of potential treatments and criticizing the FDA for refusing to permit those treatments. Sufferers began to identify treatments used in other countries and developed informal black-market networks, or “buyers clubs,” to smuggle these potentially life-saving drugs into the country and distribute them. In some instances, members of these networks have even attempted to manufacture the drugs in their home kitchens.⁴³ In other

⁴³ Amy D. Marcus, “Frustrated ALS Patients Concoct Their Own Drug,” *The Wall Street Journal*, April 15, 2012, <https://www.wsj.com/articles/SB10001424052702304818404577345953943484054>.

words, FDA regulations have been sufficiently strict as to foster vibrant black markets for pharmaceuticals when a disease becomes relatively common and its effects are severe. The movie *Dallas Buyers Club* told the story of one such black-market network of AIDS sufferers who were forced by FDA obstinance to act as international drug traffickers in pharmaceuticals that were completely legal in other countries.

Instances like this, in which the public became aware of the FDA's denial of life-saving treatments for known conditions, are rare but they do exist.

PART 4

MISSION CREEP AND OTHER CHALLENGES IN PHARMACEUTICAL REGULATION

Although the FDA was originally created to monitor the safety of food, drug, and cosmetic products and ensure those products are manufactured free of harmful contaminants, the agency has aggressively interpreted its expanded mandate under the 1962 Amendments to include a much broader scope of intervention into the marketplace. This mission creep unproductively diverts agency resources away from the agency's core mission and into fields of regulation that most Americans would likely find shocking.

4.1

FDA ATTEMPTS TO REGULATE COMMON FOOD ITEMS AS PHARMACEUTICALS

The FDA has interpreted its expanded mission to regulate the effectiveness of pharmaceuticals under the 1962 Amendments as applying to any product that makes a marketing claim about potential health benefits. The implications of this interpretation have reached absurd proportions in recent years as the FDA has informed producers of common food items they could not make health claims on their packaging unless they

submitted an IND application and took their food items successfully through all phases of clinical trials and secured FDA approval on those claims for each specified condition.

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In 2005, the FDA sent letters to 29 cherry producers warning that the labeling on their packages informed consumers that cherries could relieve arthritis and inflammation or lower rates of certain cancers.

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In 2005, the FDA sent letters to 29 cherry producers warning that the labeling on their packages informed consumers that cherries could relieve arthritis and inflammation or lower rates of certain cancers. The FDA’s warning letters informed the cherry growers, “These claims cause your products to be drugs...a new drug may not be legally marketed in the United States without an approved New Drug Application.”⁴⁴ Even though the cherry growers had relied on studies reviewed in medical journals for making these claims, they did not place their products into an IND and spend the money and time for the FDA to approve these claims, and so the FDA told cherry producers they had to destroy all packaging containing these claims and not make consumers aware of these potential health benefits.

This was not an isolated incident. In 2009, the FDA sent General Mills a warning letter stating the following:

Based on claims made on your product’s label we have determined that your Cheerios® Toasted Whole Grain Oat Cereal is promoted for conditions that cause it to be a drug because the product is intended for use in the prevention, mitigation and treatment of disease. Specifically, your Cheerios® product bears the following claims on its label:

“Did you know that in just 6 weeks Cheerios can reduce bad cholesterol by an average of 4 percent? Cheerios is...clinically proven to lower cholesterol. A clinical

⁴⁴ U.S. Food and Drug Administration, “Warning Letter to Cherry Republic,” October 17, 2005, <http://www.fda.gov/iceci/enforcementactions/warningletters/2005/ucm075633.htm>.

study showed that eating two 1 ½ cup servings daily of Cheerios cereal reduced bad cholesterol when eaten as part of a diet low in saturated fat and cholesterol.”

These claims indicate that Cheerios® is intended for use in lowering cholesterol and, therefore, in preventing, mitigating, and treating the disease hypercholesterolemia.⁴⁵

Even if General Mills had paid for or reviewed clinical studies to support its claims, it did so outside the context of an IND application supervised by the FDA, which made its claims illegal, according to the agency. The FDA has made similar enforcement actions against producers of walnuts and other common food items believed to hold health benefits.⁴⁶

It's highly doubtful Congress ever intended this level of scrutiny even when it agreed to enshrine the 1962 Amendments into law. But these examples illustrate that the agency has taken an aggressive approach toward interpreting its mission and expanding its powers accordingly.

4.2

CANNABIS AND HEMP-DERIVED CANNABINOIDS LIKE CBD

Much interest has arisen in recent years regarding the potential medical benefits of cannabis and even certain hemp-derived cannabinoids. In its 2018 Agricultural Act, Congress fully legalized the production of industrial hemp and extraction of hemp-derived cannabinoids within the United States. However, the FDA has made numerous enforcement actions against the makers of products containing these cannabinoids and asserted they are not approved for inclusion in interstate commerce. In fact, interest in a particular non-inebriating cannabinoid widely believed to hold anti-inflammatory and anti-spasticity benefits, cannabidiol (CBD), has inspired the FDA to create a unique page on its website to aggregate all the enforcement actions it has sent to producers of CBD products.⁴⁷

The FDA acknowledges widespread interest in the use of CBD and other cannabinoids to treat known medical conditions, but informs producers while it is now legal to produce these cannabinoids, it is unlawful to offer them for sale as an ingredient in any food

⁴⁵ U.S. Food and Drug Administration, “Warning Letter to General Mills,” May 5, 2009, <http://www.fda.gov/iceci/enforcementactions/warningletters/2009/ucm162943.htm>.

⁴⁶ Ruwart, *Death by Regulation*, 188-191.

⁴⁷ U.S. Food and Drug Administration. “Warning Letters and Test Results for Cannabidiol-Related Products.” <https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products>.

product, as a dietary supplement, or pharmaceutical without filing an IND. As the agency states on its website:

There is a significant interest in the development of therapies and other consumer products derived from cannabis and its components, including cannabidiol (CBD). FDA recognizes the potential opportunities that cannabis or cannabis-derived compounds may offer and acknowledges the significant interest in these possibilities. However, FDA is aware that some companies are marketing products containing cannabis and cannabis-derived compounds in ways that violate the Federal Food, Drug and Cosmetic Act (FD&C Act) and that may put the health and safety of consumers at risk.⁴⁸

The only instances in which the FDA has fully permitted the sale of products containing cannabinoids is in the few cases where a pharmaceutical company has paid to place an isolated cannabinoid through the IND application process. These cases include the approval of Epidiolex by GW Pharmaceuticals as a pure extract of CBD approved for treatment of two specified conditions—both of which are rare forms of epilepsy—and Marinol, a synthetic version of THC produced by Aklem Labs and approved for treatment of nausea associated with chemotherapy and appetite loss suffered by those with HIV infection. Clearly, then, the FDA has agreed in the past that certain cannabinoids hold undisputed medical value, but the agency continues to disallow medical claims about cannabis products or cannabinoids in general. The agency has historically been averse to trialing combinations of drugs as well, meaning that the supposed “entourage effect” created when multiple cannabinoids work in concert to create medical benefits are unlikely to successfully survive an FDA-supervised IND process. As increasing evidence accumulates in medical journals examining the effectiveness of cannabis and its derivatives in treating a wide array of medical conditions,⁴⁹ the regulatory process for drug approval in the United States will struggle to keep pace absent massive changes in approach.

⁴⁸ U.S. Food and Drug Administration. “FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD).” <https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd>.

⁴⁹ See, e.g., Zadalla Mouslech and Vasiliki Valla, “Endocannabinoid System: An Overview of Its Potential in Current Medical Practice.” *Neuro Endocrinology Letters*, Vol. 30, No. 2 (2009), 153-179. Available at: <https://pubmed.ncbi.nlm.nih.gov/19675519/#:~:text=The%20role%20of%20endocannabinoids%20in%20mammalian%20reproduction%20is,to%20improve%20infertility%20and%20reproductive%20health%20in%20humans>.

PART 5

CONCLUSION AND RECOMMENDATIONS

The costs and delays created by the FDA's drug approval process are responsible for a tremendous loss of life both within the United States and around the world, which looks heavily to the United States for the development of innovative new products. People die from treatable diseases while the FDA delays the availability of those treatments to the public, and the FDA has even prosecuted individuals who try to gain access to unapproved treatments in an attempt to save their own lives or the lives of loved ones. Likewise, the substantial cost barriers and low likelihood of success for securing approval to market a new drug has led to less frequent innovation and less competition within the pharmaceutical industry as firms consolidate to create larger economies of scale. The result is fewer innovative new treatments that could save lives and higher prices as drug makers try to recover their costs. Moreover, both regulators at the FDA and workers at regulated pharmaceutical companies can easily recognize that these bureaucratic costs to society may serve their own individual interests by creating stable and lucrative income opportunities as they migrate back and forth between the FDA and pharmaceutical companies' compliance departments.



There are few areas of public policy where the results have been as diametrically opposed to the intentions as pharmaceutical regulation in the United States.



There are few areas of public policy where the results have been as diametrically opposed to the intentions as pharmaceutical regulation in the United States. Most of these problems have arisen not as a result of the original incarnations of the Food and Drug Administration, which was quite efficient, but as a result of the 1962 Amendments to the Food, Drug and Cosmetic Act. Those amendments first gave the FDA the charge to ensure the “effectiveness” of new drugs in addition to their safety. The proximate motivation for that change was a concern about the safety of a drug (thalidomide) that the FDA had never determined was safe and had already excluded from the market.

Yet, recent developments have shown the FDA has the capacity to accelerate and encourage drug development in particular cases. When COVID-19 began to circulate in the United States in early 2020, the agency participated in an initiative known as Operation Warp Speed with the goal of making a vaccine available within 12 months. For its part of Operation Warp Speed, the FDA agreed to place promising vaccine candidates directly into large-scale Phase III trials and to analyze the data on these trials as it was collected rather than requiring drug makers to conduct multiple expensive and time-consuming studies and then criticizing those studies long after they have been completed. This process allowed regulators to give real-time feedback to researchers so that processes could be changed or improved on the fly as needed to ensure a reliable result. Manufacturing of the vaccines was also allowed to occur simultaneous to the ongoing clinical trials so that distribution could begin as soon as the FDA concluded the accelerated Phase III trial process was a success and issued an Emergency Use Authorization for the vaccines.⁵⁰

In other words, the agency has shown an ability to accelerate development of critical pharmaceutical products in moments of extreme political expediency. But this resolve has

⁵⁰ U.S. Department of Defense, “Operation Warp Speed: Accelerated Vaccine Process,” August 12, 2020, <https://media.defense.gov/2020/Aug/12/2002475961/-1/-1/1/WARP-SPEED-VACCINE-TIMELINE.PDF>.

been absent from the development of other pharmaceuticals that also may have the potential to save lives. Application of the Operation Warp Speed process to pharmaceutical development more broadly might be a notable improvement over the FDA's default regulatory process, although pharmaceutical development could be encouraged to an even greater extent if the FDA simply returned to its original purpose and evaluated the safety of a pharmaceutical while allowing the medical community to evaluate effectiveness.

#1 Repeal the 1962 Efficacy Amendment. An easy and obvious reform to the FDA's process that could again accelerate new drug development and make drugs more affordable for the public would be a repeal of the 1962 efficacy Amendments while preserving the FDA's powers to ensure that drugs are safe. Medical professional and professional associations, after all, are likely best positioned to determine a drug's potential effectiveness, both in the aggregate and for any particular patient. In fact, physicians already do this today by prescribing medications for off-label use. A key difference in off-label use is that physicians cannot gain access to the types of information they need to make fully informed choices because drug makers are forbidden by law from communicating the results of any clinical trials they may have conducted unless those trials were submitted to and approved by the FDA, even if those trials were rigorous and could withstand critical peer review. In the case of aspirin, many American lives might have been saved if the drug maker had been allowed to share its clinical research regarding the drug's potential to alleviate heart attack and stroke (although subsequent discoveries of potential side effects from daily dosage maintain relevance despite being unknown by both the FDA and the drug maker at the time of discovery).

If the United States elected to focus its regulation on safety rather than an evolving bureaucratic standard of effectiveness, it would not be the only industrialized nation to do so. The United Kingdom, for instance, focuses its pre-market regulatory efforts on safety and requires pharmaceutical manufacturers to determine effectiveness based largely on after-market studies of patients who take the drug. This approach has many benefits because it allows the manufacturer to draw its conclusions based on a wider and more diverse pool of subjects and also allows it to begin recapturing costs much sooner, which holds down the capitalized cost of development and allows the drug to be offered more cheaply.

#2 Encourage private actors that bear the financial liability to exercise greater oversight powers directly. Repeal of the 1962 Amendments is likely necessary, but it's not the only reform that could effectively streamline the FDA and make drug development more vibrant.

Former FDA official Henry Miller, for instance, has made several meaningful suggestions that would fundamentally transform the FDA's role in drug approval and streamline the process. Miller notes that the FDA assumes no legal liability for its decisions anyway, and so the decision-making authority would be used more efficiently if it were passed to parties that do bear financial liability. This might include insurers or managed care agencies that recommend certain courses of treatment. The pharmaceutical manufacturers' carriers of product liability insurance, for instance, would have a direct interest in ensuring the safety of any product sold by an insured company. Likewise, managed care organizations already retain their own in-house pharmacoeconomics departments to evaluate the effectiveness of different courses of treatment in relation to their costs.⁵¹ Each of these private parties is arguably best positioned to evaluate the effectiveness of a pharmaceutical product, while the FDA continues to evaluate the safety of those products for human consumption.

#3 Make the FDA a certifier of certifiers. Another option is to privatize much of the hands-on work currently performed by the FDA while allowing the agency to retain official oversight of those functions.⁵² Private certification agencies could set up their own review processes for the medical information generated by the clinical trials that drug makers administer. Underwriters Laboratories, for instance, provides standards and conducts quality certifications for any number of advanced products in the marketplace. Government regulation works this way in many other industries such as public accounting, wherein the Public Company Accounting Oversight Board reviews the processes followed by private certified public accountants in auditing public company financial records, but does not complete those audits directly. Similarly, the FDA could promulgate standards for private reviewers of clinical trial data and randomly check the records of these reviewers to ensure the proper standards were followed without conducting every review itself. This would significantly speed the process of drug approval and quickly eliminate the FDA's backlog and staffing needs.

#4 Reciprocity. As yet another option, the FDA could reciprocally recognize the approvals issued by regulatory authorities in other advanced nations, such as the United Kingdom or the European Union. Henry Miller, a physician and molecular biologist who spent 15 years as a reviewer of study data for the FDA, has heaped praise on the alternative approach used by the European Medicines Agency, for instance. As he notes, the mission of that agency is to "provide useful and clear information to users and health professionals," whereas the FDA suppresses much useful information. The EMA outsources much of its review work to a

⁵¹ Miller, *To America's Health: A Proposal to Reform the Food and Drug Administration*, 29.

⁵² *Ibid*, 89.

pool of thousands of topical experts rather than completing all reviews in-house and boasts faster and more knowledgeable reviews. Surveys of medical researchers show much higher degrees of satisfaction with the approach of the EMA than the FDA.⁵³ A policy of reciprocity among pharmaceutical regulatory agencies in advanced nations would allow U.S. drug makers to conduct clinical trials in other nations where the regulatory apparatus remains robust, but also flexible and bears in mind the human cost of preventing or delaying seriously ill individuals' access to potentially life-saving treatments.

Failure by Congress or the FDA to adopt any of these alternative approaches would mean costs and timelines for new drug development will continue to escalate, leading many individuals to grow increasingly desperate to secure the drugs they need to save their own lives. In lieu of well-researched and documented medical innovations, growing swaths of patients may resort to the sort of black-market or homemade concoctions to which AIDS patients were drawn in the 1980s and 1990s. This result is neither conducive to an orderly and lawful market nor likely to produce the safest and most innovative health solutions. However, this is the route to which the FDA will ultimately relegate many desperate individuals if it continues along its current path of pharmaceutical regulation.

⁵³ Ibid, 35.

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