

## The Fall of FDA Review

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Abstract:

The U.S. Food and Drug Administration (FDA) is in crisis. FDA can hardly go a single day without an investigation, negative news story, or scholarly critique of the agency's work. We have increasingly entrusted FDA—today, to the tune of 25% of the U.S. economy—with vetting the products we put in and on our bodies. But the array of problems facing the agency raises questions about whether it is equipped to succeed in the 21st century.

FDA's core function is to oversee a special legal regime called "premarket review." Congress has prohibited all marketing of certain types of products (like drugs) until FDA reviews and approves an application from the manufacturer. This system allows consumers to depend on the foods they ingest, the pills they swallow, and the health care they receive—in theory. But critics have documented how FDA review failures have produced, or contributed to, public health crises, including those related to opioids, e-cigarettes, trans fats, sugar, and, most recently, the COVID-19 pandemic.

Leveraging five FDA product areas, this Article argues that premarket review is faltering. The reasons vary somewhat across FDA's regulatory regimes. However, the bottom line is the same: longstanding efforts to undermine FDA governance by corporations and financial power writ large. Corporate deregulatory efforts have operated through courts, Congress, the President, and the agency's leadership itself. In some cases, premarket review has been so hollowed out that all that remains is the illusion of regulation, nothing more. These developments reflect the ascendancy of neoliberalism, a system in which core social guarantees devolve to decisions by individual consumers.

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We need not accept this state of affairs. Learning from the mechanisms behind premarket review's erosion, this Article proposes a suite of structural solutions to build a revitalized FDA: one that is dutifully empowered, inside and out, to safeguard the public health.

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## INTRODUCTION

Laurie asked her son for a bite of his apple. Puzzled, he asked why—she hated apples. “I’m tasting metal again.” For several months a metal taste had crept across her tongue into the corners of her mouth. Her son was concerned. Through doctors’ appointments, Laurie learned she had elevated levels of multiple metal ions in her blood. Doctors traced these ions to her metal-on-metal hip replacement, which had a ball and socket made of metal. The metal-on-metal hip had been advertised to her as offering an easier surgery with quicker recovery. Yet over the years, it was revealed that patients with metal-on-metal hips suffered pain, metal taste in their mouths, cognitive losses, and other problems stemming from heavy metals in the bloodstream.<sup>1</sup> Laurie had been experiencing memory loss, brain fog, and difficulty processing information. Her device was soon recalled, requiring another hip replacement just to remove the defective device.<sup>2</sup> Laurie has cognitive symptoms to this day. Laurie is my mother, and I shared the apple with her.

How did such a dangerous device clear the U.S. Food and Drug Administration’s (FDA’s) regulatory hurdles to come to market? Not through traditional FDA review. Instead, despite a new design and new materials, FDA cleared it as “substantially equivalent” to prior models, thus avoiding the premarket approval process.<sup>3</sup>

Premarket review is a regulatory system with significant public cachet. Though most Americans would not know premarket review by name, we generally consume items like foods and drugs with some assumptions about their quality. FDA stands for the guarantee that these items will help us, will nourish us, will not kill us.

However, experts have increasingly observed gaps in premarket review.<sup>4</sup>

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1 Carl Heneghan et al., *Ongoing Problems with Metal-on-Metal Hip Implants*, BMJ, Feb. 28, 2012, at 1.

2 She received a more traditional ceramic hip. See Stephen Richard Knight, *Total Hip Arthroplasty—Over 100 Years of Operative History*, 3 ORTHOPEDIC REVS. 72, 73 (2011).

3 Brent M. Ardaugh, Stephen E. Graves & Rita F. Redberg, *The 510(k) Ancestry of a Metal-on-Metal Hip Implant*, 368 NEW ENG. J. MED. 97, 97 (2013); Heneghan et al., *supra* note 1, at 2.

4 See, e.g., Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 432 (2008) (“In terms of both personnel and the money to support them, the agency is barely hanging on by its fingertips.”); Mason Marks, *Automating FDA Regulation*, 71 DUKE L.J. 1207, 1279 (2022); Daniel G. Aaron, *Tobacco Reborn: The Rise of E-Cigarettes and Regulatory Approaches*, 25 LEWIS & CLARK L. REV. 827 (2021); Donald W. Light, Joel Lexchin & Jonathan J. Darrow, *Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs*, 41 J. L., MED & ETHICS 590 (2013); Ezekiel J. Emanuel, *A Middle Ground for Accelerated Drug Approval—Lessons From Aducanumab*, 326 JAMA 1367 (2021); Alexandra Maulden, *Ignoring the Experts: Implications of the FDA’s Aduhelm Approval*, 48 AM. J. L. & MED. 108 (2022); Jerry Avorn & Aaron S. Kesselheim, *Up Is Down — Pharmaceutical Industry Caution vs.*

These critiques have described how premarket review failures have produced, or contributed to, some of the largest public health crises of the day. Many premarket review stories have reached popular media. Elizabeth Holmes of Theranos skirted FDA approval of a blood-testing device.<sup>5</sup> Purdue Pharma's OxyContin, after being approved on a thin reed of evidence, ignited the opioid crisis.<sup>6</sup> Vaping companies have addicted scores of U.S. youth under FDA's watch.<sup>7</sup> Other modern crises to which premarket review has contributed include multiple tobacco epidemics, the obesity epidemic, and the COVID-19 pandemic. Table 1 provides examples of products within FDA's premarket areas that have nonetheless caused an alarming number of deaths. Over the past ten years, FDA has announced investigations into broad swaths of its regulatory portfolio, suggesting it is well aware of the structural cracking of premarket review.<sup>8</sup>

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*Federal Acceleration of Covid-19 Vaccine Approval*, 383 *NEW ENG. J. MED.* 1706 (2020); Aaron P. Mitchell, Niti U. Trivedi & Peter B. Bach, *The Prescription Drug User Fee Act: Much More Than User Fees*, 60 *MED. CARE* 287 (2022); Matthew Herder, *Pharmaceutical Drugs of Uncertain Value, Lifecycle Regulation at the US Food and Drug Administration, and Institutional Incumbency*, 97 *MILBANK Q.* 820 (2019); Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *FDA Regulation and Approval of Medical Devices: 1976-2020*, 326 *JAMA* 420 (2021); William Chanes Martinez, *Attack of the Clones: An Examination and Critique of FDA's Medical Device Regulatory Scheme*, 15 *TENN. J. L. & POL'Y* 344 (2021); Benjamin N. Rome et al., *FDA Approval of Cardiac Implantable Electronic Devices via Original and Supplement Premarket Approval Pathways, 1979-2012*, 311 *JAMA* 385, 385 (2014); Cameron Faustman et al., *Ten Years Post-GAO Assessment, FDA Remains Uninformed of Potentially Harmful GRAS Substances in Foods*, 61 *CRITICAL REVS. IN FOOD SCI. & NUTRITION* 1260 (2020); Laurie J. Beyranevand, *Generally Recognized as Safe?: Analyzing Flaws in the FDA's Approach to GRAS Additives*, 37 *VT. L. REV.* 887 (2013); Andrew Kolodny, *How FDA Failures Contributed to the Opioid Crisis*, 22 *AMA J. ETHICS* 743 (2020); Yaniv Heled, Ana Santos Rutschman & Liza Vertinsky, *Regulatory Reactivity: FDA and the Response to COVID-19*, 76 *FOOD & DRUG L.J.* 318 (2021).

<sup>5</sup> O. Hayden Griffin III, *Promises, Deceit and White-Collar Criminality Within the Theranos Scandal*, *J. WHITE COLLAR & CORP. CRIME*, Sept. 2, 2020, at 7.

<sup>6</sup> See *infra* notes 257–257

<sup>7</sup> See *infra* Section II.C.2.

<sup>8</sup> In 2018, FDA announced it was overhauling its medical device review program to respond to new evidence of public health harms from devices. *FDA Vows to Overhaul Decades-Old System for Approving Medical Devices*, CBS (Nov. 26, 2018), <https://www.cbsnews.com/news/fda-vows-to-overhaul-decades-old-medical-device-system-today-2018-11-26>. In July 2022, FDA announced it would “conduct a comprehensive evaluation” for its entire food and tobacco programs. *FDA Conducting Evaluation of Key Agency Activities to Strengthen Operations*, U.S. FOOD & DRUG ADMIN. (July 19, 2022), <https://www.fda.gov/news-events/press-announcements/fda-conducting-evaluation-key-agency-activities-strengthen-operations>. In August 2022, FDA declared that it was reviewing its prior opioid decisions and hoping to learn from its mistakes. *FDA's Overdose Prevention Framework Aims to Prevent Drug Overdoses and Reduce Death*, U.S. FOOD & DRUG ADMIN. (Aug. 30, 2022), <https://www.fda.gov/news-events/fda-voices/fdas-overdose-prevention-framework-aims-prevent-drug-overdoses-and-reduce-death>. In addition, FDA's regulation of medical products has been on the Government Accountability Office's (GAO's) high-risk list since 2009, a serious designation for issue-laden federal programs. *Protecting Public Health Through Enhanced Oversight of Medical Products*, GOV'T ACCOUNTABILITY OFF. (Accessed Sept. 3, 2022),

Though scholarly critiques of premarket review exist, most authors target a distinct area of law, such as foods or devices.<sup>9</sup> This Article is the first to examine premarket review across FDA’s product areas to synthesize conclusions about the effectiveness of premarket review as a legal regime.<sup>10</sup>

Health Threat	Category of Premarket Review	Time Period of Data	Number of Deaths Attributable to Threat	Ref.
Opioids	Drugs	1999–2020	>500,000	11
Trans Fats	Food Additives <sup>12</sup>	2003–2014	>84,000	13
Vioxx (Rofecoxib)	Drugs	1999–2004	56,000	14
Sleeping Pills	Drugs	Around 2010	320,000–507,000/year <sup>15</sup>	16
Sugar-Sweetened Drinks	Food Additives	2012	>51,694/year	17
Salt	Food Additives	Around 2014	57,578/year	18

<https://www.gao.gov/highrisk/protecting-public-health-through-enhanced-oversight-medical-products>. However, it is true GAO has recently appeared to narrow its high-risk designation for FDA. *Id.*

<sup>9</sup> See *supra* note 4.

<sup>10</sup> Adam I. Muchmore has compared FDA’s authorization pathways using a more theoretical lens. Adam I. Muchmore, *Marketing Authorization at the FDA: Paradigms and Alternatives*, 74 ADMIN. L. REV. 539 (2022).

<sup>11</sup> Daniel G. Aaron, *Public Health in the Opioid Litigation*, 53 LOY. U. CHI. L. REV. 11, 17 (2021). This figure includes deaths due to illicit opioids, too, given the illicit component of the current opioid crisis was precipitated by prescription opioids. *Id.* at 21–22. The toll of prescription opioids alone is more than 263,000. *Drug Overdose*, CTRS. FOR DISEASE CONTROL & PREVENTION (May 18, 2022), <https://www.cdc.gov/drugoverdose/deaths/prescription/overview.html>.

<sup>12</sup> “Food additives” per its plain meaning, not the statutory definition.

<sup>13</sup> See Faustman et al., *supra* note 4, at 1262.

<sup>14</sup> Thomas H. Maugh, *Banned Report on Vioxx Published*, L.A. TIMES (Jan. 25, 2005), <https://www.latimes.com/archives/la-xpm-2005-jan-25-sci-vioxx25-story.html>.

<sup>15</sup> The source notes this estimate is rough, but this value would be significant even if lower. Daniel F. Kripke et al., *Hypnotics’ Association with Mortality or Cancer: A Matched Cohort Study*, BMJ OPEN, Feb. 27, 2012, at 1, 6.

<sup>16</sup> *Id.*

<sup>17</sup> Renata Micha et al., *Association Between Dietary Factors and Mortality from Heart Disease, Stroke, and Type 2 Diabetes in the United States*, 317 JAMA 912, 916–17 (2017).

<sup>18</sup> Dariush Mozaffarian et al., *Global Sodium Consumption and Death from Cardiovascular Causes*, 371 NEW ENG. J. MED. 624, supp. at 54 (2014).

Medical Devices, generally	Devices	2008–2017	83,000	19
Drug Adverse Events	Drugs	Around 2011	128,000/year	20
Cigarettes	Tobacco Products	2009–2022	>480,000/year	21

Table 1: Deaths arguably caused, at least in part, by faltering premarket review.<sup>22</sup> If this table included illness and injuries, the toll would be far more, and other products would be included.

This Article makes the unnerving claim that premarket review is crumbling—and we are losing its attendant public health benefits. Part II substantiates this claim across five FDA regulatory areas, showing that premarket review is dramatically weakened, and, in some cases, near-eliminated for certain classes of products.

What explains the fall? The traditional story is that the weakening of premarket review reflects the intentional embrace of “lifecycle” approaches, in which FDA shifts its regulation *postmarket* because it allows faster patient access concurrent with regulatory study.<sup>23</sup> However, this story does not hold up as a matter of regulatory history. Rather, I point largely to corporate power. Lessons from five FDA regulatory regimes bear out an analytical framework demonstrating how corporate influence eroded premarket review using five structural mechanisms: (1) the president, (2) Congress, (3) courts, (4) resource control, and (5) ideological capture.<sup>24</sup> These elements worked in concert, though in different ways for different FDA programs, to erode the core promise that FDA will evaluate products intimately connected to human life before they enter the market.

19 *Medical Devices Harm Patients Worldwide as Governments Fail on Safety*, INT’L CONSORTIUM OF INVESTIGATIVE JOURNALISTS (Nov. 25, 2018), <https://www.icij.org/investigations/implant-files/medical-devices-harm-patients-worldwide-as-governments-fail-on-safety>.

20 Light et al., *supra* note 4, at 593. Many of these drug adverse events may be unavoidable, but even a fraction of these annual deaths raises serious concerns.

21 *Tobacco-Related Mortality*, CTRS. FOR DISEASE CONTROL & PREVENTION (Apr. 28, 2020), [https://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/health\\_effects/tobacco\\_related\\_mortality/index.htm](https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm).

22 Does not indicate sole cause, but many or most of these deaths would likely have been avoided if premarket review were operating well. The table also does not indicate that FDA was responsible for these failures.

23 Holly Fernandez Lynch & I. Glenn Cohen, *Introduction*, in *FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* 1, 9–10 (Holly Fernandez Lynch and I. Glenn Cohen eds., 2015); Herder, *supra* note 4, at 820.

24 *See infra* Figure 1.



Throughout this paper, I highlight the serious consequences of premarket review's fall. As Part III explains, FDA scholars have acknowledged premarket review's role not just in public health, but also in requiring product manufacturers to generate reliable information about the utility of their products. In fact, the evidentiary basis for our medical system—the information doctors need to diagnose and treat patients—depends on FDA. Premarket review's erosion breeds a less reliable market, which costs billions of dollars in wasted payments, engenders mistrust of our government, and disrupts innovation by inundating markets with low-value products.<sup>25</sup>

We need not live with the status quo. Drawing from the reasons behind premarket review's fall, Part IV offers cross-substantive solutions to repair it moving forward. Predictable but important solutions include infusing FDA with sorely needed funding and repairing statutory loopholes. More broadly, this Article identifies the use of enforcement discretion as a core problem that interferes with premarket review. That is, if FDA does not take legal enforcement action, it can nullify statutory requirements for premarket review through inaction. I advance granting FDA independent litigating authority to insulate enforcement decisions from the U.S. Department of Justice, which controls most federal law enforcement. In addition, it is high time for Congress to curb FDA's enforcement discretion by laying out a statutory framework that does not depend on FDA's goodwill for enforcement. Premarket review is statutorily required, and FDA should not be able to easily part with it by administrative fiat.

This Article makes one additional contribution: situating premarket review's erosion in what some scholars have described as neoliberalism.<sup>26</sup> Neoliberalism is a mode of governance that erodes core social guarantees in favor of market ordering.<sup>27</sup> This idea carries significant explanatory power as to why important scientific decisions intended to be made by FDA are devolving to individual consumers. I do not use neoliberalism purely in an ideological sense, but rather, to refer to systems where individual decisions—about which products work and are safe—replace government guarantees. Throughout this Article, I illustrate how corporate power has driven FDA's adoption of market-driven approaches to

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<sup>25</sup> See *infra* Section III.A.

<sup>26</sup> See, e.g., Jedediah Britton-Purdy et al., *Building a Law-and-Political-Economy Framework: Beyond the Twentieth-Century Synthesis*, 129 YALE L.J. 1784 (2020); Kate Andrias & Benjamin I. Sachs, *Constructing Countervailing Power: Law and Organizing in an Era of Political Inequality*, 130 YALE L.J. 546 (2021); David Singh Grewal & Jedediah Purdy, *Introduction: Law and Neoliberalism*, 77 LAW & CONTEMP. PROBS. 1 (2014); Tayyab Mahmud, *Debt and Discipline: Neoliberal Political Economy and the Working Classes*, 101 KY. L.J. 1 (2013); Amy Kapczynski, *The Lochnerized First Amendment and the FDA: Toward a More Democratic Political Economy*, 118 COLUM. L. REV. ONLINE 179, 189 & n.66 (2018); DAVID HARVEY, A BRIEF HISTORY OF NEOLIBERALISM (2018).

<sup>27</sup> Britton-Purdy et al., *supra* note 26, at 1789 n.21.

regulation. Understanding these mechanisms leads to a more robust solution set for restoring FDA's ability to respond to the panoply of public health crises facing the United States in the years and decades to come.

Now is the time for a reorientation of legal scholars' understanding of FDA. Only by grappling with the real-world influences on FDA can we understand this secretive institution and attempt to repair it.

## I. THE RISE OF FDA REVIEW

This part offers the building blocks needed to understand premarket review. Briefly, it will discuss premarket review's rise, the role of FDA review, and the concept of neoliberalism in the FDA context.

### A. *Premarket Review*

FDA was born in an era of broad public awakening about corporations selling fraudulent and unsafe foods and drugs.<sup>28</sup> Crisis after crisis in public health led Congress to steadily entrust FDA with increasing power over products intimately connected with human welfare.<sup>29</sup> However, premarket review largely did not exist until 1938;<sup>30</sup> before then, companies inventing new drugs, potions, or elixirs could simply bring them to market. Of course, FDA had some enforcement powers, but they were postmarket in nature.<sup>31</sup>

In 1937, the elixir sulfanilamide disaster, involving mass poisonings due to use of the solvent diethylene glycol in a therapeutic potion, killed more than 100 people in 15 states.<sup>32</sup> This suggested to Congress that if FDA assessed products before sale, FDA could prevent harms rather than respond to them.<sup>33</sup> In 1938, Congress vested FDA with a gatekeeping role over new drugs to ensure they were safe before marketing.<sup>34</sup> The Federal Food, Drug and Cosmetic Act (FDCA) of 1938, together with later amendments, gave birth to modern premarket review.<sup>35</sup> And over the next 80 years, FDA gained increasing authority over an array of product categories. Rising concerns about industrially produced chemicals in foods in the 1950s, which were transforming the American diet, led

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28 See Kapczynski, *supra* note 26, at 183.

29 See Robert M. Califf, *Now Is the Time to Fix the Evidence Generation System*, CLINICAL TRIALS, Jan. 17, 2023, at 1, 3.

30 The exception is for biologics. Biologics Control Act of 1902, Pub L. No. 57-244.

31 Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1761 (1996).

32 *Id.*; Carol Ballentine, *Sulfanilamide Disaster*, FDA CONSUMER (June 1981), <https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf>.

33 Merrill, *supra* note 31, at 1761.

34 *Id.* at 1761–62.

35 *Id.*

Congress to vest FDA with premarket review over food additives.<sup>36</sup> Congress added an efficacy requirement for drugs in 1962 after thalidomide, taken for pregnancy-related nausea, caused congenital anomalies of newborns around the world.<sup>37</sup> FDA first obtained jurisdiction over medical devices in 1938, but after serious safety issues from devices like the Dalkon Shield contraceptive and cardiac pacemakers, Congress gave FDA premarket review authority over devices in 1976.<sup>38</sup> And there is tobacco. With U.S. lung cancer deaths peaking around 1990,<sup>39</sup> FDA asserted jurisdiction over tobacco in 1996, lost it in 2000 via *FDA v. Brown & Williamson Tobacco Corp.*,<sup>40</sup> and received statutory premarket review authority in 2009 once Barack Obama became president.<sup>41</sup>

Although FDA has gained increasing premarket responsibilities over the U.S. health marketplace, formal increases in authority were often paired with other forms of disempowerment. As I will discuss, FDA's regulatory power has made it a target of corporations, laissez-faire thinkers, and anti-government activists,<sup>42</sup> who have found channels through which to attack FDA.<sup>43</sup> Corporations, in particular, are incentivized to avoid or erode premarket review because it is the gateway to marketing products to hundreds of millions of people.

### B. *The Role of FDA*

One's understanding of premarket review depends on the role of FDA as a regulatory agency. FDA is most commonly understood to serve the dual purposes of public health and consumer protection. Seven former FDA Commissioners frame FDA as the "modern consumer safety net."<sup>44</sup> According to FDA itself, the mission of FDA is "protecting the public health by ensuring the safety, efficacy, and security" of FDA-regulated products.<sup>45</sup> Current FDA Commissioner Dr.

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36 See Maricel V. Maffini, Thomas G. Neltner & Sarah Vogel, *We Are What We Eat: Regulatory Gaps in The United States That Put Our Health at Risk*, 15 PLOS BIOLOGY, Dec. 20, 2017, at 1, 1.

37 See PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, *FOOD AND DRUG LAW* 642–43 (4th ed., 2014).

38 *Id.* at 1201.

39 Aaron, *supra* note 4, at 856.

40 529 U.S. 120, 160–61 (2000).

41 See *infra* Section II.C.

42 See Kapczynski, *supra* note 26, at 183.

43 See *infra* Sections I.C, II.F.

44 Robert M. Califf et al., *Seven Former FDA Commissioners: The FDA Should Be an Independent Federal Agency*, 38 HEALTH AFFS. 84, 84 (2019).

45 *What We Do*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), <https://www.fda.gov/about-fda/what-we-do>. In addition, FDA includes as part of its mission "helping to speed innovations that make medical products more effective, safer, and more affordable." *Id.* While this objective contains the word "innovation," it does not suggest FDA aims to lower the evidentiary bar or

Robert M. Califf asserts that FDA “preserves and protects the public health” through regulation.<sup>46</sup>

On the other hand, FDA is increasingly called an “innovation institution”—part of the arrangements that “structure the production and allocation of knowledge goods.”<sup>47</sup> While premarket review may affect the development rate and reliability of new products, FDA’s role is traditionally not “innovation.”<sup>48</sup> However, there are two ways in which FDA is increasingly being connected with innovation. First, there has been pressure from industry to hurry products to market in order to expedite access to new products (“innovation”) for patients.<sup>49</sup> As we will see, FDA has sometimes internalized these exhortations by allowing products on the market before they are vetted—sometimes at serious public health cost.<sup>50</sup> Alternatively, the evidentiary bar new products must meet can also be conceived as pro-innovation. That is, by guarding against the sale of “quack products,” FDA can protect market space for new products that are truly innovative.<sup>51</sup>

### C. *Neoliberalism Disguised as Innovation*

It is hard to miss the drumbeat of some advocates and authors who portray premarket review as anti-innovation. For many years, politicians have prioritized “FDA reform” on the grounds that FDA is responsible for delaying access to new products.<sup>52</sup> One article in the *Food and Drug Law Journal* observes that “[w]hile FDA does not intend to stifle innovation or access, its premarket approval

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hasten access to new products.

<sup>46</sup> Robert M. Califf, *The FDA and the Clinical Community*, 328 JAMA 1043, 1043 (2022). Similarly, former Commissioner Margaret Hamburg and former Deputy Commissioner Joshua Sharfstein have written that the agency’s overriding purpose is protecting public health. Margaret A. Hamburg & Joshua M. Sharfstein, *The FDA as a Public Health Agency*, 360 NEW ENG. J. MED. 2493, 2493 (2009).

<sup>47</sup> Daniel J. Hemel & Lisa Larrimore Ouellette, *Innovation Institutions and the Opioid Crisis*, 7 J. L. & BIOSCIENCES 1, 4 (2020).

<sup>48</sup> However, in 1997, a Republican Congress added speed to FDA’s statutory mission: “taking appropriate action on the marketing of regulated products in a timely manner.” Federal Food, Drug and Cosmetic Act (FDCA) § 1003. One could read this vague mission statement as pro-innovation or simply pro-efficiency (or maybe both).

<sup>49</sup> Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *FDA Approval and Regulation of Pharmaceuticals, 1983-2018*, 323 JAMA 164, 168 (2020). Some might view innovation as strictly referring to an increased pace of product development incentivized through reducing regulatory barriers. However, earlier access is often viewed as innovation because patients are accessing new products faster. Informally, I believe the latter definition is more common, although there is overlap between these definitions.

<sup>50</sup> See, e.g., *infra* Sections II.B–II.E.

<sup>51</sup> For further discussion of FDA and innovation, see *infra* Section III.B.

<sup>52</sup> Merrill, *supra* note 31, at 1755–56.

programs accomplish this end through their very existence.”<sup>53</sup> Another prominent article notes “the growing recognition that the realities of modern drug development mean that a heavy focus on premarket approval is no longer sufficient,” in part because clinical trials “create[] delays” and “keep[] patients from accessing” new drugs.<sup>54</sup> Dr. Califf has said, “Americans have told their Congresspeople we would rather take more risk and have earlier access [to medical products].”<sup>55</sup> Others are more measured; for example, Peter Barton Hutt has said that FDA “must continually change” to “provide a reasonable balance between fostering innovation and protecting the public health.”<sup>56</sup>

What these views share is an unexplained belief in a spectrum in which more stringent premarket review leads to less innovation, and vice versa. However, this assumption is easily debunked. After all, a world of no premarket review would have free availability of products with little knowledge about how to use them. In the words of Dr. Rita Redberg, “True innovations are welcomed, but cannot be recognized as such without clinical trial evidence to show that new technologies are beneficial for patients.”<sup>57</sup> In other words, without knowledge, there is no innovation. Rebecca Eisenberg recognized this problem years ago when she noted that pharmaceutical innovation requires “the development of credible information about the effects of drugs.”<sup>58</sup> As this Article will argue, premarket review is generally pro-innovation.<sup>59</sup> However, I will submit that premarket review is in tension with access to products—products which may or may not be innovative.

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53 Bonnie Scott, *Oversight Overhaul: Eliminating the Premarket Review of Medical Devices and Implementing a Provider-Centered Postmarket Surveillance Strategy*, 66 FOOD & DRUG L.J. 377, 378 (2011).

54 W. Nicholson Price II, *Introduction*, in FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 247, 247, *supra* note 23. As I explain above, *supra* note 49, I view this as a type of innovation argument.

55 In the Bubble with Andy Slavitt, *Exclusive: FDA Commissioner on COVID-19 Vaccine for Kids 0-5 (with Robert Califf)*, STITCHER, at 15:30 (Apr. 28, 2022), <https://www.stitcher.com/show/in-the-bubble-with-andy-slavitt/episode/exclusive-fda-commissioner-on-covid-19-vaccine-for-kids-0-5-with-robert-califf-202759879>.

56 Peter Barton Hutt, *Historical Themes and Developments at FDA over the Past Fifty Years*, in FDA IN THE 21<sup>ST</sup> CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 17, 17, *supra* note 23.

57 *FDA Medical Device Approval: Is There a Better Way?: Hearing Before the Subcomm. on Health Care*, 112th Cong. (2011) (testimony of Dr. Rita Redberg), <https://www.youtube.com/watch?v=iu4gHoa42So>.

58 Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 349 (2007).

59 See *infra* Section III.B; see also Daniel Carpenter, Jeremy Greene & Susan Moffitt, *The Drug Efficacy Study and Its Manifold Legacies*, in FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 306, 321, *supra* note 23 (describing the argument that premarket review helps remove “lemons” from the marketplace, which increases the “quality-weighted amount of innovation”).

What explains the lack of critical interrogation of what innovation *is*? Why is premarket review often counterposed with innovation as an unquestionable fact? I would posit that beneath some innovation claims lies neoliberalism. Neoliberalism is a mode of governance that prioritizes market ordering, weakens social responsibilities and guarantees, and devolves decisions to the individual consumer level.<sup>60</sup> In the FDA context, I believe there is a common assumption that we should release “innovative” products sooner,<sup>61</sup> leaving individuals to make expert decisions about which drugs, lab tests, foods, and tobacco products to consume. This assumption likely stems in part from years of effort by industry to address “regulatory overkill at the FDA” and promote more rapid approvals<sup>62</sup>—suggesting industry has successfully reshaped the narrative of FDA.

I am not the first to suggest that neoliberalism has damaged FDA. Rather, I credit this observation to Amy Kapczynski;<sup>63</sup> some news articles have also discussed this possibility.<sup>64</sup> Kapczynski notes FDA’s regulatory power has made it a target of laissez-faire thinkers and anti-government activists.<sup>65</sup> Other scholars have alluded to neoliberalism, albeit indirectly. For example, Daniel Hemel and Lisa Ouellette argue that “innovation institutions,” such as FDA, are “politically produced” and politicians are not incentivized to design them effectively<sup>66</sup>—likely due to political, especially corporate, influence.

An “emphatic turn” toward neoliberalism began in the 1970s, largely as a project to “re-establish the conditions for capital accumulation and to restore the power of economic elites.”<sup>67</sup> Economist Milton Friedman’s famous 1970 *New York Times* opinion piece described the “ideal free market” as a place where “all cooperation is voluntary,” and there “are no ‘social’ values, no ‘social’ responsibilities in any sense.”<sup>68</sup> Friedman’s free-market approach took hold in the 1970s amid a crisis of inflation and the establishment of market-minded think

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60 Jedediah Britton-Purdy et al., *supra* note 26, at 1789 n.21; Jason J. Czarnecki & Katherine Fiedler, *The Neoliberal Turn in Environmental Regulation*, 2016 UTAH L. REV. 1, 2–3 (2016).

61 As noted, Dr. Califf believes Americans think “we would rather take more risk and have earlier access.” STITCHER, *supra* note 55.

62 John Abraham & Rachel Ballinger, *The Neoliberal Regulatory State, Industry Interests, and the Ideological Penetration of Scientific Knowledge: Deconstructing the Redefinition of Carcinogens in Pharmaceuticals*, 37 SCI., TECH., & HUM. VALUES 443, 449–51 (2012).

63 See Kapczynski, *supra* note 26, at 183.

64 See, e.g., Efthimios Parasidis, *The Trump Administration’s FDA Is Both Victim and Villain*, BARRON’S (Aug. 26, 2020, 08:00 PM), <https://www.barrons.com/articles/the-trump-administrations-fda-is-both-victim-and-villain-51598478351>.

65 See Kapczynski, *supra* note 26, at 183.

66 Hemel & Ouellette, *supra* note 47, at 48.

67 DAVID HARVEY, *A BRIEF HISTORY OF NEOLIBERALISM* 2, 19 (1st ed., 2005).

68 Milton Friedman, *A Friedman Doctrine-- The Social Responsibility of Business Is to Increase Its Profits*, N.Y. TIMES (Sept. 13, 1970), <https://www.nytimes.com/1970/09/13/archives/a-friedman-doctrine-the-social-responsibility-of-business-is-to.html>.

tanks.<sup>69</sup> In addition, Lewis Powell, Jr.’s famous 1971 Powell Memorandum laid out a multi-pronged blueprint to protect “business and the enterprise system” from those who “preferred socialism or some form of statism (communism or fascism).”<sup>70</sup>

FDA was caught in this storm. Although its power greatly increased in the 1960s, in the following decade, drug companies became “eager to push new drugs to market as quickly as possible to start generating revenue.”<sup>71</sup> Regulated industry rebuked FDA for being too slow<sup>72</sup> and advanced numerous attacks on premarket review.<sup>73</sup> Deregulation, an “essential element of the neoliberal edifice,”<sup>74</sup> became a useful ally. The Reagan Administration loosened FDA enforcement and sought to make FDA a “partner” of industry.<sup>75</sup> Within a decade, a report found that FDA was “operating on a threadbare budget, close to impotence and badly in need of expanded powers.”<sup>76</sup> As I will show, however, the erosion continued, increasingly leaving individuals in the position of making expert decisions about what is appropriate to put in and on their bodies.

Yet it is precisely this market ordering that some scholars, and sometimes FDA itself,<sup>77</sup> believe will invite innovation. This “innovation agenda” reflects the dedicated efforts of regulated industry to shape national discourse about FDA—often through the mouthpiece of sponsored patient groups who have clamored for faster access.<sup>78</sup> Because some industry players have used “innovation” arguments

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69 KEAN BIRCH & VLAD MYKHENKO, *THE RISE AND FALL OF NEOLIBERALISM: THE COLLAPSE OF AN ECONOMIC ORDER?* 50 (2010).

70 Lewis Powell, *Attack on American Free Enterprise System* (Aug. 23, 1971), <https://scholarlycommons.law.wlu.edu/cgi/viewcontent.cgi?article=1000&context=powellmemo>.

71 See Sarah S.P. DiMaggio et al., *Accelerated Approval of Cancer Drugs—Righting the Ship of the US Food and Drug Administration*, 179 *JAMA INTERNAL MED.* 922, 922 (2019).

72 Darrow, Avorn & Kesselheim, *supra* note 49.

73 See *infra* Part II. Corporations do not always oppose premarket review, however. For example, pharmaceutical companies that developed COVID-19 vaccines intentionally withheld applying for authorization to avoid shoddy review influenced by President Trump. Avorn & Kesselheim, *supra* note 4, at 1706.

74 NICHOLAS FREUDENBERG, *AT WHAT COST: MODERN CAPITALISM AND THE FUTURE OF HEALTH* 27 (2021).

75 Herbert Burkholz, *A Shot in the Arm for the F.D.A.*, *N.Y. TIMES* (June 30, 1991), <https://www.nytimes.com/1991/06/30/magazine/a-shot-in-the-arm-for-the-fda.html>.

76 Burkholz, *supra* note 75.

77 See, e.g., *infra* Section II.C.2; Rachel E. Sachs, W. Nicholson Price II & Patricia J. Zettler, *Rethinking Innovation at FDA*, *B.U. L. REV.*, at 1, 3–5 (forthcoming 2023) (describing FDA, after approving a drug of questionable effectiveness and safety, justifying its decision based on spurring more research and innovation).

78 Alice Fabbri et al., *Industry Funding of Patient and Health Consumer Organisations: Systematic Review with Meta-Analysis*, *BMJ*, Jan. 22, 2020, at 1, 11; Susannah L. Rose et al., *Patient Advocacy Organizations, Industry Funding, and Conflicts of Interest*, 177 *JAMA INTERNAL MED.* 344, 347 (2017). Of course, there are exceptions to this trend. For example, some patient groups have supported premarket review. See *infra* Section III.B (describing HIV patients wanting

to support a neoliberal agenda, we should not be surprised that these arguments have proliferated. But these arguments are dangerous and backwards: in the view of myself and many others, premarket review is pro-innovation.<sup>79</sup> So we should be cautious of *innovation* arguments that are a mere disguise for neoliberalism. The danger is that we feel optimistic about the erosion of FDA's core regulatory regime—that we *delight in our own destruction*. As several top FDA scholars have noted, when FDA considers innovation in an approval decision, it paradoxically impairs later innovation.<sup>80</sup>

In this Article, I will support the proposition that premarket review's erosion is not a deliberate, carefully conceived thrust toward innovation but is better explained by external and internal influences on FDA. External forces include presidential interference (as advanced by the current Supreme Court),<sup>81</sup> control over FDA officials through the appointment process, congressional fiscal austerity,<sup>82</sup> corporate influence over FDA's budget, corporate lobbying for amendments to the FDCA, and expensive litigation often leading to curtailments of agency authority.

Internal forces are the permeation of an "innovation" ideology favoring rapid market entry, installation of ideologically acceptable leaders into the agency through politics and the revolving door,<sup>83</sup> and internal legal wrangling over enforcement among FDA staff, agency lawyers, and the Department of Justice (DOJ). These dynamics are complex and frequently take place beyond the public's eye. It is likewise difficult to associate these internal forces with particular FDA decisions, and while I have tried to decipher them, they represent one limitation of this Article.

Viewing the cumulative effects of these forces across five different regulatory areas (Figure 1), I submit that corporations have eroded premarket review and returned many heavily regulated areas to market ordering. The general trend across all surveyed product areas is an increasing ability of manufacturers to bring products to market faster and with less, little, or sometimes no oversight. These trends exemplify neoliberal governance, which E.

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new treatments but seeking to preserve premarket review).

<sup>79</sup> See *infra* Section III.B.

<sup>80</sup> Sachs, Price & Zettler, *supra* note 77, at 55.

<sup>81</sup> Cass R. Sunstein & Adrian Vermeule, *The Unitary Executive: Past, Present, Future*, 2020 SUP. CT. REV. 83, 117 (arguing that the current Supreme Court has shown a "firm insistence on firm presidential control").

<sup>82</sup> Former FDA Commissioner Andrew Von Eschenbach has described Congress as starving FDA of resources. Thomas Sullivan, *Former FDA Commissioner Calls for End of FDA Conflict of Interest Rules*, POL'Y & MED. (May 6, 2018), <https://www.policymed.com/2012/05/former-fda-commissioner-calls-for-end-of-fda-conflict-of-interest-rules.html>.

<sup>83</sup> See, e.g., Jeffrey Bien & Vinay Prasad, *Future Jobs of FDA's Haematology-Oncology Reviewers*, BMJ (Sept. 27, 2016), at 1, 1.



Melanie DuPuis & Brian J. Gareau define as: “[P]olitical actors have abandoned the idea of central state decision making and instead rely on market processes, individual self-sufficiency and responsibility, devolution of decision making down to local scales, and the concomitant ‘hollowing out’ of the nation-state.”<sup>84</sup> If one takes seriously my analysis of five categories of premarket review, I believe it is difficult to deny that developments in premarket review carry the signs and symptoms of neoliberalism. The hollowing out of FDA’s central decision making via premarket review reduces the role of the state in surveilling consumer products coming to market and devolves health decisions to individual consumers.

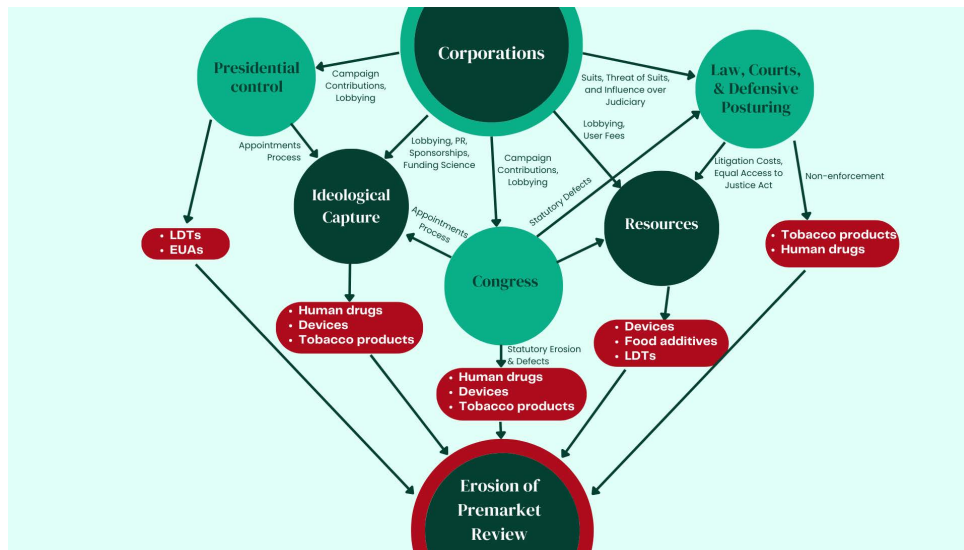


Figure 1: Corporate contributions to the erosion of premarket review.

Notably, the framework of neoliberalism is used intentionally, as opposed to its cousins deregulation and regulatory capture. Deregulation usually refers to removing or repealing agency rules.<sup>85</sup> But this Article describes something more complex than deregulation. In some cases, there is no active regulatory regime (despite statutory requirements), and so corporate influence has maintained the

84 E. Melanie DuPuis & Brian J. Gareau, *Neoliberal Knowledge: The Decline of Technocracy and the Weakening of the Montreal Protocol*, 89 Soc. Sci. Q. 1212, 1213 (2008) (citations omitted).

85 See Jody Freeman & Sharon Jacobs, *Structural Deregulation*, 135 HARV. L. REV. 585, 588 (2021) (referring to traditional “substantive” deregulation as “weaken[ing] or rescind[ing] particular agency rules or policies”); *Deregulation*, Merriam-Webster (2023), <https://www.merriam-webster.com/dictionary/deregulation> (“the act or process of removing restrictions and regulations”).

status quo.<sup>86</sup> In others, Congress created special premarket pathways that, while adding complexity and rules, nonetheless allowed products to market with less vetting.<sup>87</sup> Because the fall of FDA review is not strictly a story about reducing regulations, “deregulation” is not an ideal descriptor. Recently, Jody Freeman and Sharon Jacobs have identified the broader concept of “structural deregulation,” referring to a president attacking an agency’s “core capacities” to undermine it.<sup>88</sup> This definition is closer, but FDA’s story is not just about the president. Indeed, there is a complex interplay of institutions. This Article chiefly describes the ideology and practice of replacing the federal FDA guarantee with individual consumption “decisions”<sup>89</sup>—i.e., neoliberalism.<sup>90</sup>

Likewise, regulatory capture is a helpful but imperfect term. Dorit Rubinstein Reiss has defined regulatory capture as the “intentional influence” of an agency’s decisions.<sup>91</sup> Influence may sometimes be so strong as to become control.<sup>92</sup> But a neoliberal outcome does not always stem *directly* from corporate influence. The erosion of premarket review occurs on several levels and is effectuated through multiple intermediary institutions. Regulatory capture—usually a story of the industry and the agency—misses the interplay of mechanisms that has eroded the social guarantee of FDA approval. This Article describes neoliberal erosion, not strictly capture or control.<sup>93</sup>

There are broader definitions of regulatory capture, of course, but they too are an imperfect fit. Most prominently, Daniel Carpenter and David A. Moss define regulatory capture as “the result or process by which regulation, in law or application, is consistently or repeatedly directed away from the public interest and toward the interests of the regulated industry, by the intent and action of the industry itself.”<sup>94</sup> Certainly, industry has at times co-opted FDA review for its

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86 See *infra* Section II.A (laboratory-developed tests).

87 See *infra* Section II.B (human drugs).

88 Freeman & Jacobs, *supra* note 85, at 587.

89 I place “decision” in quotation marks because (1) the vast majority of consumers would be unable to scientifically evaluate manufacturer products and claims, and (2) without FDA, the scientific evidence behind products would likely not exist. See *infra* notes 578–583 and accompanying text.

90 This point is somewhat semantic, and a broader understanding of “structural deregulation” than that described by Freeman and Jacobs is closer to my use of neoliberalism—albeit without the ideological valence.

91 Dorit Rubinstein Reiss, *The Benefits of Capture*, 47 WAKE FOREST L. REV. 569, 579 (2012) (reviewing definitions of regulatory capture and settling on “intentional influence”).

92 *Id.*

93 Some scholars might place the fall of FDA review into the bucket of regulatory capture. See Daniel Carpenter & David A. Moss, *Introduction*, in PREVENTING REGULATORY CAPTURE: SPECIAL INTEREST INFLUENCE AND HOW TO LIMIT IT 1, 12 (DANIEL CARPENTER & DAVID A. MOSS EDS., 2013) (defining “weak capture” as “compromis[ing] the capacity of regulation to enhance the public interest”).

94 *Id.* at 13.

own benefits.<sup>95</sup> But a results-based definition of capture misses that premarket review often benefits industry.<sup>96</sup> As Reiss points out, the public interest is amorphous,<sup>97</sup> and what benefits one company in the short-term may delegitimize an industry, occupy market space, or cause other long-term harms to business interests.<sup>98</sup> Indeed, FDA creates strange bedfellows. And regulatory capture may refer to something less systemic and less ideological than neoliberalism. Being a systemic concept, neoliberalism can describe the ongoing fraying of premarket review while leaving space for heterogeneity of mechanisms and industry goals.<sup>99</sup> The uniting feature is the devolution of decisions to individual consumers—often paired with an individual-choice ideology.

With these building blocks in place, I will evaluate five premarket review regimes FDA administers. These are likely the most significant—in terms of industry size and public health impact—of FDA’s premarket review areas.

## II. EROSION OF PREMARKET REVIEW ACROSS FIVE PRODUCT AREAS

This Part will examine the nature, history, and law of premarket review’s erosion across five FDA areas. The goal is to substantiate the claim that premarket review is eroding and to illuminate why.

### A. *Laboratory-developed tests (LDTs)*

A laboratory-developed test (LDT) is a clinical test developed in a lab for the lab’s own use.<sup>100</sup> Laboratory-developed tests fit squarely within the FDCA’s definition of medical devices.<sup>101</sup> While medical devices will be discussed later,<sup>102</sup>

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<sup>95</sup> See, e.g., *infra* Section II.A (describing industry successfully reorienting FDA premarket review of laboratory-developed COVID-19 tests away from public health and toward liability shields and insurance reimbursement).

<sup>96</sup> See, e.g., Avorn & Kesselheim, *supra* note 4, at 1706 (describing pharmaceutical company efforts to preserve premarket review of COVID-19 vaccines); Citizen Petition, RAI Services Company, February 6, 2023, at 2, [https://downloads.regulations.gov/FDA-2023-P-0430-0001/attachment\\_1.pdf](https://downloads.regulations.gov/FDA-2023-P-0430-0001/attachment_1.pdf) (RJ Reynolds, a major tobacco company, petitioning FDA to ramp up enforcement against unauthorized tobacco products).

<sup>97</sup> Reiss, *supra* note 91.

<sup>98</sup> See *infra* notes 576–581 and accompanying text.

<sup>99</sup> Nonetheless, both deregulation and regulatory capture are helpful terms that describe many of the phenomena in this Article, and I use them frequently.

<sup>100</sup> *Laboratory Developed Tests*, U.S. FOOD & DRUG ADMIN. (Sept. 27, 2018), <https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests>.

<sup>101</sup> See FDCA § 201(h)(1) (defining “device” as, in brief, “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or . . . intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action.”).

LDTs are treated separately here because FDA regulates them as a distinct category, and they raise unique issues of failed regulatory oversight.

Despite the 1976 statutory amendment requiring devices to have premarket authorization,<sup>103</sup> FDA has admitted it “has generally not enforced premarket review” of LDTs for most of the last 40 years.<sup>104</sup> It is concerning that FDA *sua sponte* excluded an entire class of medical devices from premarket review requirements. The predictable result is that some products that are not safe or effective would be brought to market. Nonetheless, FDA had less concern initially because of the small scope of use of LDTs (i.e., for a single medical establishment in one state) and because physicians would generally use and interpret the tests directly.<sup>105</sup> In addition, FDA may have sought to limit its own responsibilities in response to fiscal austerity and an increasingly dominant logic from the 1970s to the 2000s of favoring small government.<sup>106</sup>

In 2010, FDA became increasingly concerned about the public health impact of LDTs. LDTs had grown in complexity and were being used for an increasing number of illnesses, including life-threatening ones.<sup>107</sup> With the rise of overnight shipping, they were also being offered on the national and international levels.<sup>108</sup>

One particularly harrowing example of the failure of LDTs involved two women tested at Creighton University for the BRCA gene, associated with breast and ovarian cancer. One received a false positive result (i.e., it should have been negative) and proceeded to have both of her breasts removed via double mastectomy at age 23.<sup>109</sup> She was therefore unable to breastfeed her three kids.<sup>110</sup> The other woman tested negative for BRCA, but twenty years later discovered she was positive on retest.<sup>111</sup> The false negative result deprived her of key years

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102 See *infra* Section II.E.

103 *Id.*

104 *Laboratory Developed Tests*, *supra* note 100; Jonathan R. Genzen, Regulation of Laboratory-Developed Tests: A Clinical Laboratory Perspective, 152 AM. J. CLINICAL PATHOLOGY 122, 122 (2019).

105 See U.S. FOOD & DRUG ADMIN., FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS (LDTs) 7 (2014); *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market*, PEW (Oct. 22, 2021), <https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market>.

106 See *supra* Section I.C.

107 See U.S. FOOD & DRUG ADMIN., *supra* note 105, at 8.

108 *Id.*

109 Christa Dubill, *She Tested Positive for Breast Cancer and Got a Double Mastectomy. The DNA Test Was Wrong*, WMAR (Mar. 26, 2019), <https://www.wmar2news.com/news/national/she-tested-positive-for-breast-cancer-and-got-a-double-mastectomy-the-dna-test-was-wrong>.

110 *Id.*

111 Katie Kosko, *Two Women Given the Wrong BRCA Results Are Now Bound by a Blunder*, CURE (Apr. 9, 2020), <https://www.curetoday.com/view/two-women-given-the-wrong-brca-results-bound-by-a-blunder>.

in which to take prophylactic steps to reduce her cancer risk.<sup>112</sup>

In its report describing twenty case studies on the threat of LDTs to public health, FDA documented many risks.<sup>113</sup> These include abortion based on false genetic test results of a fetus, unnecessary antibiotics based on false positive bacterial tests, incorrect drug use to treat cancer, and unnecessary removal of a woman’s ovaries due to KRAS gene testing.<sup>114</sup> These risks continue today. For example, a test of the KRAS gene offered by Mira Dx, predicated on a likely spurious association between the KRAS gene and ovarian cancer, remains on the market.<sup>115</sup> Further, a 2022 *New York Times* exposé revealed that many fetal genetic LDTs remain on the market despite abysmal efficacy—for these tests, a positive result for a fetal abnormality is wrong 85% of the time, despite touting the test as providing “information you can trust” that can give you “peace of mind.”<sup>116</sup> A 2015 *Wall Street Journal* article named LDTs the “wild west” of medicine.<sup>117</sup>

Amidst these concerns, in 2010, FDA announced its intent to reconsider its enforcement discretion policy that allows LDTs to be marketed without premarket review.<sup>118</sup> Four years later, after a workshop and internal discussion, FDA issued a draft guidance laying out a plan to establish premarket review to “ensure [the] safety and effectiveness” of LDTs.<sup>119</sup>

FDA’s regulatory push drew the ire of industry and “intense lobbying.”<sup>120</sup> The American Clinical Laboratory Association (ACLA) spent \$1.6 million on lobbying between 2014 and 2015.<sup>121</sup> It also hired two world-famous lawyers—Paul Clement, former solicitor general and a known industry favorite,<sup>122</sup> and

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112 Most likely these tests were LDTs given they were performed out of a Creighton University laboratory. *See id.*

113 U.S. FOOD & DRUG ADMIN., THE PUBLIC HEALTH EVIDENCE FOR FDA OVERSIGHT OF LABORATORY DEVELOPED TESTS: 20 CASE STUDIES (2015).

114 *Id.* at 11–12, 12–14, 16–18.

115 *KRAS-Variant Testing*, MIRADx (2022), <https://miradx.com/kras-variant-testing>.

116 Sarah Kliff & Aatish Bhatia, *When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong*, N.Y. TIMES (Jan. 6, 2022), <https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html>.

117 Thomas M. Burton, *Is Lab Testing the ‘Wild West’ of Medicine?*, WALL STREET J. (Dec. 10, 2015, 9:25 PM), <https://www.wsj.com/articles/is-lab-testing-the-wild-west-of-medicine-1449800707>.

118 *Laboratory Developed Tests*, *supra* note 100.

119 U.S. FOOD & DRUG ADMIN., *supra* note 105, at 10.

120 Jeffrey N. Gibbs, *LDTs: The Saga Continues*, FOOD & DRUG L. INST. (Apr. 2017), <https://www.fdpi.org/2017/04/ldts-saga-continues>.

121 Burton, *supra* note 117.

122 *See, e.g.*, Jason Zengerle, *How Paul Clement Won the Supreme Court’s Oral Arguments on Obamacare*, INTELLIGENCER (Mar. 27, 2012), <https://nymag.com/intelligencer/2012/03/how-paul-clement-won-the-obamacare-oral-arguments.html> (representing industry against the Affordable Care Act); Ryan J. Reilly, *Dog the Bounty Hunter and a Top Conservative Lawyer Are*

Laurence Tribe, renowned Harvard law professor<sup>123</sup>—to fend off FDA. The duo wrote an aggressive memo arguing that LDTs are the “practice of medicine” and therefore cannot be regulated as medical devices.<sup>124</sup> This argument is dubious given studying the intricacies of lab tests is distant from the core duties of doctoring, such as speaking with patients, ordering diagnostics and treatments, and documenting visits. Still, the document may have been a strategic success. ACLA released the memo the day before FDA held a workshop about LDT regulation,<sup>125</sup> seemingly to preempt FDA. The memo, combined with industry litigation threats,<sup>126</sup> likely gave the agency pause. Rumors circulated that FDA would finalize a new policy.<sup>127</sup> Instead, faced with resistance to the 2014 proposal, FDA did not or could not act before the election of Donald Trump.<sup>128</sup>

In November 2016, just after Donald Trump was elected president, FDA backed off its plan to initiate premarket review of LDTs.<sup>129</sup> The likely reason is that, in order to follow through on the draft guidance, FDA would have needed to take a “significant” regulatory action that would trigger review by the Office of Information and Regulatory Affairs—an office in the Executive Office of the President.<sup>130</sup> Rather than take regulatory action that would be “vetoed” by the Administration, FDA issued a 2017 “discussion paper” laying out some tentative ideas for a premarket review regime that would “balance patient protection with

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*Trying to Save the Bail Industry*, HUFFPOST (Feb. 13, 2017), [https://www.huffpost.com/entry/bail-industry-unconstitutional\\_n\\_58adf025e4b05ca474a04011](https://www.huffpost.com/entry/bail-industry-unconstitutional_n_58adf025e4b05ca474a04011) (representing the American Bail Coalition, a trade association for the bail bond industry).

123 *ACLA Retains Attorneys Paul D. Clement and Laurence H. Tribe to Represent ACLA in Opposing the FDA’s Proposal to Treat Laboratory Developed Tests (LDTs) as Medical Devices*, AM. CLINICAL LABORATORY ASS’N (Nov. 18, 2014), <https://www.acla.com/acla-retains-attorneys-paul-d-clement-and-laurence-h-tribe-to-represent-acla-in-opposing-the-fdas-proposal-to-treat-laboratory-developed-tests-ldts-as-medical-devices>.

124 Paul D. Clement & Laurence H. Tribe, *Laboratory Testing Services, As the Practice of Medicine, Cannot Be Regulated as Medical Devices* (2015), <https://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf>.

125 Mary K. Caffrey, *Arguments Taking Shape for and Against FDA Regulation of Diagnostic Tests*, AJMC (Feb. 16, 2015), <https://www.ajmc.com/view/arguments-taking-shape-for-and-against-fda-regulation-of-diagnostic-tests>.

126 Damian Garde, *The Most Influential People in Biopharma Today*, FIERCE BIOTECH (Mar. 15, 2016), <https://www.fiercebiotech.com/special-report/most-influential-people-biopharma-today> (describing “CDRH’s issuance of a draft guidance that would regulate the lab-developed test (LDT) segment of the diagnostics industry. LDT providers have threatened to sue the FDA via the American Clinical Laboratory Association (ACLA).”).

127 Gibbs, *supra* note 120.

128 Sheila Kaplan, *FDA Puts Off Closing Lab-Test ‘Loophole,’ Leaving Decision to Congress and Trump*, STAT (Nov. 18, 2016), <https://www.statnews.com/2016/11/18/fda-lab-test-loophole>.

129 See Thomas M. Burton, *FDA Backs Off Plans to Issue Rules Governing Lab-Developed Tests*, WALL STREET J. (Nov. 21, 2016, 8:41 A.M.), <https://www.wsj.com/articles/fda-backs-off-plans-to-issue-rules-governing-lab-developed-tests-1479529259>.

130 Cass R. Sunstein, *The Office of Information and Regulatory Affairs: Myths and Realities*, 126 HARV. L. REV. 1838, 1845 (2013).

continued access and innovation.”<sup>131</sup> The LDT space remained quiet until 2020, reflecting the President’s quiet authority blocking premarket review despite a compelling public health rationale, FDA’s public health mission, and statutory requirements.

However, in 2020, COVID-19 struck the world and FDA became sandwiched between its desire that new viral tests be safe and effective and the immediate need for tests. As political pressure mounted, Vice President Mike Pence and FDA Commissioner Stephen Hahn promised tens of thousands to even a million tests in short order.<sup>132</sup> On February 29, 2020, FDA issued a policy to expedite test development in which labs could validate their own tests and immediately market them, with an emergency use authorization (EUA) request to be submitted later.<sup>133</sup> (The EUA pathway allows FDA, during an emergency, to temporarily clear health products with less evidence.<sup>134</sup>) For lab-developed *antibody* tests, no EUA was required.<sup>135</sup> Because this regime was stronger than *enforcement discretion*, it was a step closer toward premarket review of LDTs,<sup>136</sup> even as it allowed tests on the market without premarket review.

The predictable result of a weak premarket regime was, again, a flood of tests of questionable efficacy onto the market. House Representative Raja Krishnamoorthi lamented that four antibody test makers received an EUA, compared with 107 companies which simply brought their tests to market.<sup>137</sup> According to two top FDA officials in May 2020, including Dr. Jeffrey Shuren, the top device official, “[F]lexibility never meant we would allow fraud. We unfortunately see unscrupulous actors marketing fraudulent test kits and using the pandemic as an opportunity to take advantage of Americans’ anxiety.”<sup>138</sup>

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131 *Discussion Paper on Laboratory Developed Tests (LDTs)*, U.S. FOOD & DRUG ADMIN. 10 (2017), <https://www.fda.gov/media/102367/download>.

132 Katie Thomas & Knvul Sheikh, *Estimates Fall Short of F.D.A.’s Pledge for 1 Million Coronavirus Tests*, N.Y. TIMES (Mar. 3, 2020), <https://www.nytimes.com/2020/03/03/health/coronavirus-tests-fda.html>.

133 *Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics*, U.S. FOOD & DRUG ADMIN. (Feb. 29, 2020), <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-help-expedite-availability-diagnostics>.

134 FDCA § 564.

135 U.S. FOOD & DRUG ADMIN., POLICY FOR DIAGNOSTIC TESTS FOR CORONAVIRUS DISEASE-2019 DURING THE PUBLIC HEALTH EMERGENCY 9 (Mar. 2020).

136 Whereas FDA has little role in a full enforcement discretion regime, the February policy at least allowed FDA to conduct scientific review of some LDTs after the fact.

137 Hannah Hagemen, *Antibody Tests Go to Market Largely Unregulated, Warns House Subcommittee Chair*, NPR (Apr. 26, 2020, 3:18 P.M.), <https://www.npr.org/sections/coronavirus-live-updates/2020/04/26/845164212/antibody-tests-go-to-market-largely-unregulated-warns-house-subcommittee-chair>. Of note, there is likely some, but not complete, overlap with the category of antibody tests and LDTs.

138 *Insight into FDA’s Revised Policy on Antibody Tests: Prioritizing Access and Accuracy*,

Concurrent with this statement, the agency laid out a stronger policy for LDTs, stating “FDA recommends” submission of an EUA request within 10 days of notifying FDA of validation of an antibody-based LDT, although it would not object to marketing without EUA given it would rather focus on commercial manufacturers, which likely have larger distribution networks.<sup>139</sup> For other COVID-19 LDTs, FDA stated that companies should notify FDA if their tests are validated in order to be placed on FDA’s website, and if they do not submit an EUA request within 15 days of validation, they will be removed from FDA’s online list of tests.<sup>140</sup> In practice, many companies complied. The policy was efficient and low-cost. One study of the first 14 EUAs issued for COVID-19 LDTs found that FDA took an average of 17 days to review each EUA request, and the process cost labs between \$1,800 and \$7,800 per submission.<sup>141</sup> FDA even provided a 20-page template for EUA requests.<sup>142</sup>

The Trump Administration was not pleased with FDA’s oversight of LDTs, however limited and efficient. In August 2020, the Department of Health and Human Services (HHS), in a stunning paragraph, “determined” that FDA “will not require premarket review of laboratory developed tests” unless FDA engages in notice-and-comment rulemaking.<sup>143</sup> While FDA had attempted to offer some flexibility through nuanced policies, HHS discarded all prior regulatory work and ended premarket review for LDTs (except for voluntary submissions). HHS accomplished this by “undelegating” authority over LDTs; indeed, the FDCA gives premarket review authority to HHS, not to FDA.<sup>144</sup> This move sent shockwaves through FDA. HHS purported to end premarket review that by statute FDA was supposed to be conducting and that was integral to addressing a public health crisis. The move triggered “wide-ranging expressions of

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U.S. FOOD & DRUG ADMIN. (May 4, 2020), <https://web.archive.org/web/20200504170131/https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy>.

139 U.S. FOOD & DRUG ADMIN., POLICY FOR DIAGNOSTIC TESTS FOR CORONAVIRUS DISEASE-2019 DURING THE PUBLIC HEALTH EMERGENCY 15–16 (May 2020).

140 *Id.* at 8–9.

141 Hetal D. Marble et al., *Temporary Regulatory Deviations and the Coronavirus Disease 2019 (COVID-19) PCR Labeling Update Study Indicate What Laboratory-Developed Test Regulation by the US Food and Drug Administration (FDA) Could Look Like*, 23 J. MOLECULAR DIAGNOSTICS 1207, 1211 (2021).

142 U.S. FOOD & DRUG ADMIN., *supra* note 135, at 21–41.

143 *Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests*, DEP’T OF HEALTH & HUM. SERVS. (Aug. 19, 2020), <http://web.archive.org/web/20200820212750/https://www.hhs.gov/coronavirus/testing/recission-guidances-informal-issuances-premarket-review-lab-tests/index.html>.

144 See James A. Boiani & Megan Robertson, *The VALID Act: Senate Action Brings FDA Regulation of LDTs Closer to Fruition*, NAT’L L. REV. (May 20, 2022), <https://www.natlawreview.com/article/valid-act-senate-action-brings-fda-regulation-ltds-closer-to-fruition>.



concern.”<sup>145</sup>

Unfortunately, the time needed to engage in notice-and-comment rulemaking all but prevented FDA from actuating premarket review for LDTs to address COVID-19. Even worse, HHS officials clarified that the decision was intended to be broader than COVID-19—implying FDA did not have jurisdiction over LDTs.<sup>146</sup> Former FDA Commissioner Scott Gottlieb scribed a scathing Twitter thread rebuking the new “[s]weeping medical device policy” advanced mid-public-health crisis.<sup>147</sup> Rachel Sachs described the change as aligned with the Trump Administration’s “deregulatory bent.”<sup>148</sup> Congressman Frank Pallone warned that the Trump Administration was “[f]looding the market with unregulated and potentially inaccurate tests.”<sup>149</sup> In October 2020, the FDA fully capitulated and stated it would end all review of EUA requests, even voluntary ones, explaining that it was not worth its resources,<sup>150</sup> likely because the highest-risk labs would not submit EUA requests, thus diminishing the public health value of continued review. By September 2021, 47% of COVID-19 tests on the market known to FDA were unauthorized.<sup>151</sup> As an indicator of poor-quality tests on the market, as of December 2021, FDA had issued import alerts for 348 COVID-19 tests.<sup>152</sup>

The next phase of the saga was even more stunning and revealed how premarket review of LDTs in some ways served regulated parties more than the public health. The ACLA, which earlier had hired Laurence Tribe and Paul Clement to argue FDA did not have authority over LDTs, said FDA’s ending of premarket review “creates unnecessary confusion” and the agency should allow *voluntary* submission of EUA requests.<sup>153</sup> In other words, industry wanted a

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145 Eli Y. Adashi & I. Glenn Cohen, *SARS-CoV-2 Laboratory-Developed Tests: Integrity Restored*, 327 JAMA 1229, 1230 (2022).

146 David Lim & Zachary Brennan, *Trump Administration Limits FDA Review of Some Coronavirus Tests*, POLITICO (Aug. 19, 2020), <https://www.politico.com/news/2020/08/19/trump-fda-review-coronavirus-tests-398924>.

147 Scott Gottlieb (@ScottGottliebMD), Twitter (Aug. 22, 2020, 8:43 AM), <https://twitter.com/ScottGottliebMD/status/1297152402773233666>.

148 Lim & Brennan, *supra* note 146.

149 *Pallone Demands Briefing on HHS Decision to Bypass FDA and Allow Lab Developed COVID-19 Tests to Come to Market Without Review* (Aug. 20, 2020), <https://energycommerce.house.gov/newsroom/press-releases/pallone-demands-briefing-on-hhs-decision-to-bypass-fda-and-allow-lab>.

150 See Greg Salbodkin, *FDA Takes Hands Off EUA Review for COVID-19 Lab Developed Tests*, MEDTECHDIVE (Oct. 8, 2020), <https://www.medtechdive.com/news/fda-will-no-longer-review-eua-submissions-for-lab-developed-tests/586647>.

151 U.S. GOV’T ACCOUNTABILITY OFF., *FDA TOOK STEPS TO HELP MAKE TESTS AVAILABLE; POLICY FOR FUTURE PUBLIC HEALTH EMERGENCIES NEEDED 21–22* (2022).

152 *Id.* at 31.

153 *ACLA Statement on FDA Accouchement Regarding EUA Reviews*, AMERICAN CLINICAL LABORATORY ASS’N (Oct. 7, 2020), <https://www.acla.com/acla-statement-on-fda-announcement->

voluntary premarket review regime. Likely, many labs wanted to take advantage of liability protections for EUA-authorized tests under the Public Readiness and Emergency Preparedness (PREP) Act,<sup>154</sup> as well as mandatory reimbursement by insurers under the Coronavirus Aid, Relief, and Economic Security (CARES) Act.<sup>155</sup>

On a November 2020 media call, Brett Giroir, Assistant Secretary for Health, stated that FDA does not have “regulatory jurisdiction” over LDTs and that EUAs are not required, but nonetheless directed FDA to review EUA requests for COVID-19 LDTs.<sup>156</sup> This perverted execution of food and drug regulation meant that FDA was forbidden from reviewing LDTs based on public health risk; rather, it would do so at the White House’s demand, strictly for those labs that would benefit financially from an EUA. Therefore, FDA resources and staff would be dedicated to analyses and paperwork for the benefit of corporations.

In November 2021, President Biden’s HHS withdrew the Trump Administration “policy,”<sup>157</sup> and FDA issued fresh guidance pushing labs to submit EUA requests within 60 days (or otherwise expecting them to pull their LDTs from the market).<sup>158</sup> FDA noted the importance of accurate tests to avoid under- and over-treatment, waste of resources, and further spread—exactly why premarket review might be important for tests for a severe and often lethal disease like COVID-19.<sup>159</sup> While this new policy was a positive development for the quality of COVID-19 LDTs, it did not address concerns with other types of LDTs, leaving many of the previously discussed public health issues unresolved. On June 14, 2023, FDA announced its intent to issue a proposed rule making clear that LDTs are devices under the FDCA, signaling it may be finally trying to

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regarding-eua-reviews.

154 Kyle Y. Faget, *EUAs for LDTs No Longer Required, But at the Expense of PREP Act Immunity*, 12 NAT’L L. REV. (Aug. 24, 2020), <https://www.natlawreview.com/article/euas-ldts-no-longer-required-expense-prep-act-immunity>.

155 See Coronavirus Aid, Relief, and Economic Security Act (2020) § 3201–02.

156 Joyce Frieden, *HHS Pushes FDA to Speed Up EUAs for Some COVID-19 Tests*, MEDPAGE TODAY (Nov. 17, 2020), <https://www.medpagetoday.com/infectiousdisease/covid19/89726>; Greg Slabodkin, *In Shift, FDA Ordered to Provide ‘Timely’ EUA Reviews for COVID-19 Lab Developed Tests*, MEDTECHDIVE (Nov. 17, 2020), <https://www.medtechdive.com/news/giroir-directs-fda-to-provide-timely-eua-reviews-for-covid-19-lab-develop/589159>.

157 *Statement by HHS Secretary Xavier Becerra on Withdrawal of HHS Policy on Laboratory-Developed Tests* (Nov. 15, 2021), <https://www.hhs.gov/about/news/2021/11/15/statement-hhs-secretary-xavier-becerra-withdrawal-hhs-policy-laboratory-developed-tests.html>.

158 U.S. FOOD & DRUG ADMIN., POLICY FOR DIAGNOSTIC TESTS FOR CORONAVIRUS DISEASE-2019 DURING THE PUBLIC HEALTH EMERGENCY (REVISED) 13 (Nov. 2021), <https://web.archive.org/web/20211201210146/https://www.fda.gov/media/135659/download>.

159 *Id.* at 5. The administration’s ability to review COVID-19 LDTs benefitted from \$500 million in extra funding provided by the American Rescue Plan Act. American Rescue Plan Act of 2021, Pub. L. No. 117-2, § 2304.

end non-enforcement of premarket review for LDTs.<sup>160</sup> If FDA continues to pursue premarket review of LDTs, it will likely face industry opposition, litigation, and the ticking clock of a possible change in administration.

### B. Human Drugs

America’s pharmaceutical system has been criticized for at least two decades by people at the top of their field. Ameet Sarpatwari, Michael S. Sinha, and Aaron S. Kesselheim have called the pharmaceutical market “broken.”<sup>161</sup> Andrew Kolodny has rebuked FDA for making numerous mistakes contributing to the opioid crisis, asserted FDA has failed to properly enforce the FDCA, and argued for oversight of FDA to “ensure that public health is consistently prioritized ahead of industry interests.”<sup>162</sup> Jacqueline Salwa and Christopher Robertson have made the stunning suggestion of reorganizing federal public health authority to allow a separate agency from FDA to review medical products—implying FDA would lose jurisdiction over its foundational area.<sup>163</sup> Prescription drugs themselves are a top cause of death in the United States today.<sup>164</sup> Yet only about 11 to 16 percent of new molecular entities carry a significant therapeutic gain, according to Donald W. Light, Joel Lexchin, and Jonathan Darrow.<sup>165</sup> While many drugs have entered popular American discourse for public health reasons, perhaps none is so salient as opioids, which have cost more than 500,000 American lives.<sup>166</sup>

Still, medicines do save lives,<sup>167</sup> and pharmaceutical companies have used the benefits of drugs to press the government for requiring too much evidence and working too slowly in approving new drugs.<sup>168</sup> These companies have successfully lobbied for a suite of special programs (Table 2) that make drug regulation fairly opaque to outside observers but advantageous to companies seeking quick time-to-market. Dr. Joshua Sharfstein has explained that FDA’s

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160 See Anna Clark, *Scores of Critical Lab Tests Fall into a Regulatory Void. The FDA Is Trying to Close It.*, PROPUBLICA (June 14, 2023), <https://www.propublica.org/article/fda-moves-to-regulate-lab-developed-tests>.

161 Ameet Sarpatwari, Michael S. Sinha & Aaron S. Kesselheim, *The Opioid Epidemic: Fixing a Broken Pharmaceutical Market*, 11 HARV. L. & POL’Y REV. 463 (2017).

162 Kolodny, *supra* note 4, at 746–47.

163 Jacqueline Salwa & Christopher Robertson, *Designing an Independent Public Health Agency*, 384 NEW ENG. J. MED. 1684, 1685 (2021).

164 Donald W. Light & Joel Lexchin, *The FDA’s New Clothes*, BMJ (2015), at 1.

165 Light et al., *supra* note 4, at 592.

166 Aaron, *supra* note 11, at 17.

167 The World Health Organization has a list of 591 essential medicines that should be available to all health systems at all times. *WHO Model List of Essential Medicines – 22nd List, 2021*, WORLD HEALTH ORG. (Sept. 30, 2021), <https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02>.

168 Avorn & Kesselheim, *supra* note 4, at 1706.

regulation of drugs “has evolved over time into a thicket of special programs, flexible review criteria, and generous incentives. As a result, it is challenging to understand the totality of these reforms on drug approval in the United States.”<sup>169</sup>

<b>Program</b>	<b>Year</b>
Orphan Drugs	1983
Fast Track	1988
Accelerated Approval	1992
Priority Review	1992
Softening of Two-Clinical-Trial Requirement	1997
Emergency Use Authorization	2004
Enriched Enrollment Randomized Withdrawal Trials	2006
Priority Review Vouchers	2007 <sup>170</sup>
Breakthrough Therapy	2012
Generating Antibiotic Incentives Now	2012
Limited Population Pathway for Antibacterial and Antifungal Drugs	2016
Real-World Evidence	2016
Regenerative Medicine Advanced Therapy	2016
Material Threat Medical Countermeasure	2016
Right to Try	2018

Table 2: Special Programs and Regulatory Changes Speeding Review or Lowering Evidentiary Burden for New Drugs

<sup>169</sup> Joshua M. Sharfstein, *Reform at the FDA—In Need of Reform*, 323 JAMA 123, 123 (2020).

<sup>170</sup> The original program, created in 2007, provided vouchers for priority review to manufacturers who developed therapies for neglected tropical diseases. See Oulu Wang, *Buying and Selling Prioritized Regulatory Review: The Market for Priority Review Vouchers as Quasi-Intellectual Property*, 73 FOOD & DRUG L.J. 383, 388 (2018). However, the program was expanded in 2012 and 2016 to include rare pediatric diseases and medical countermeasures. *Id.*

The overarching trend of drug regulation, however, is a shift away from the clinical trial, often considered the “gold standard” of medical evidence, in favor of data sources that are less reliable to show safety and efficacy but are more likely to suggest a drug works. Many drugs come to market with less evidence than would have been required twenty years ago, despite the fact that “[d]etermining the safety and efficacy of the therapies clinicians use and patients receive is at the heart of the medical system.”<sup>171</sup>

This Part will examine the state of premarket review for drugs, surveying areas such as fast track, accelerated approval, surrogate markers, clinical trial quantity and quality, and real-world evidence.

### 1. *Overarching View*

FDA’s regulation of drugs is probably its most iconic and historic responsibility. FDA’s premarket review of drugs emerged as a series of high-profile medical disasters from unregulated and dangerous products rattled the country.<sup>172</sup> Congress created a safety-based approval process for drugs in 1938 after deaths from sulfanilamide elixir, and added an efficacy requirement in 1962 after thalidomide caused congenital anomalies of newborns around the world.<sup>173</sup> FDA interpreted the 1962 statute’s requirement for “adequate and well-controlled investigations” to require *two* randomized controlled trials, the gold standard of evidence, to prove a drug’s efficacy.<sup>174</sup>

Since the 1960s, industry has complained about the time and cost needed to seek and obtain approval.<sup>175</sup> Thus began a decades-long campaign to pressure FDA to relax its approval standards. During the AIDS crisis, LGBTQ activists pressured FDA to allow patients to take antiretrovirals during the evidence-gathering process.<sup>176</sup> This movement provided industry both a venue for resistance *and* an easy-to-understand example with which to denounce premarket review.<sup>177</sup> The rise of Reaganomics, increasingly concentrated wealth during the 1970s and 1980s, and surging corporate power pushed against a high bar for market entry in favor of speedy approvals that would maximize economic growth

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171 Lindsay R. Baden et al., *The FDA and the Importance of Trust*, 383 *NEW ENG. J. MED.* e148, e149 (2020).

172 See HUTT ET AL., *supra* note 37; Lynch, *supra* note 23, at 35.

173 HUTT ET AL., *supra* note 37.

174 FDCA § 505(d) (emphasis added); *Development & Approval Process: Drugs*, U.S. FOOD & DRUG ADMIN. (Apr. 8, 2022), <https://www.fda.gov/drugs/development-approval-process-drugs>.

175 Darrow, Avorn & Kesselheim, *supra* note 49.

176 See *infra* notes 599–605.

177 See *id.*

and financial returns to industry, in the name of “patients” who need drugs.<sup>178</sup> Industry was heavily incentivized to drive FDA to review more quickly because time during which products were reviewed is time lost for sales, and the review period runs the clock on patents. There was also some concern that the United States was suffering from late access to new drugs, a phenomenon labeled the “drug lag.”<sup>179</sup>

For drugs, deregulatory statutes and ideological capture were more important than legal cases in undermining premarket review. Courts rebuffed a key attack on drug premarket review in *In re Barr Laboratories*.<sup>180</sup> Here, a company sought mandamus requiring FDA to “act promptly” on its generic drug applications, which were pending longer than the statutory timeline of 180 days; FDA admitted significant delays, but explained there was a “personnel crisis” (i.e., resource constraints).<sup>181</sup> If plaintiffs were successful, the one-two punch of fiscal austerity with a tight timeline could have undermined premarket review by requiring hasty, unconsidered decisions. But the D.C. Circuit recognized the foolishness of mandamus, which would allow litigating companies to jump the queue<sup>182</sup>—incentivizing more companies to litigate and waste government resources. In deference to the day-to-day administration of government, the court respected FDA’s review timelines and denied mandamus.<sup>183</sup>

Similarly, in *Abigail Alliance v. von Eschenbach*,<sup>184</sup> the conservative think tank Washington Legal Foundation tried, and failed, to establish a constitutional right among terminally ill patients to access untested drugs.<sup>185</sup> Legal commentators warned that such a right could collapse the “regulatory safety net” protecting patients from untested drugs, and ultimately reflected a “market-oriented, deregulatory perspective.”<sup>186</sup> The en banc D.C. Circuit held that

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178 See DiMugno et al., *supra* note 71, at 923; Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America’s Drug Constitution*, 42 AM. J. L. & MED. 687, 700 (2016).

179 Fredrik Andersson, *The Drug Lag Issue: The Debate Seen from an International Perspective*, 22 INT’L J. HEALTH SERVS. 53, 53 (1992). However, as discussed later, the number of drugs approved is an imperfect indication of the number of drugs that are safe and effective. See *infra* notes 609-618 and accompanying text.

180 930 F.2d 72 (D.C. Cir. 1991).

181 *Id.* at 73–74.

182 *Id.* at 75.

183 *Id.* at 73.

184 *Abigail All. for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006), *rev’d en banc*, 495 F.3d 695 (D.C. Cir. 2007), *cert. denied*, 552 U.S. 1159 (2008). The Washington Legal Foundation’s attempts to undermine premarket review through litigation are discussed further below. See *infra* Section II.B.4.

185 Elizabeth Weeks Leonard, *Right to Experimental Treatment: FDA New Drug Approval, Constitutional Rights, and the Public’s Health*, 37 J. L., MED. & ETHICS 269, 270 (2009).

186 See, e.g., Peter D. Jacobson & Wendy E. Parmet, *A New Era of Unapproved Drugs: The Case of Abigail Alliance v Von Eschenbach*, 297 JAMA 205, 207 (2007).

terminally ill patients do not have a constitutional right to access unapproved drugs.<sup>187</sup>

With courts generally unwilling to disturb premarket review of drugs,<sup>188</sup> industry took two approaches. First, rather than support more FDA appropriations, the drug industry advanced the first FDA user fee program under the Prescription Drug User Fee Act of 1992 (PDUFA).<sup>189</sup> It is difficult to overstate the benefits to industry of PDUFA, along with its parallel iterations for generic drugs, devices, biologics, and other product areas. While these programs allowed faster review of medical products ostensibly to protect the public health, these programs selectively funded only those FDA statutory mandates needed to bring products to market, and not those needed to improve science, conduct postmarket surveillance, or enforce the law.<sup>190</sup> As with other product review areas, then, user fee programs facilitated review on industry's terms. As to speed, FDA, as part of periodic negotiations, signs "commitment letters" promising industry expeditious review times.<sup>191</sup> And, more structurally, PDUFA negotiations create a regular *reopening* (i.e., opportunity for statutory amendment) of the FDCA that facilitates pro-industry changes to premarket review.<sup>192</sup> During these periodic reopenings, FDA's programs are in jeopardy if the new statute does not pass,<sup>193</sup> giving industry excessive leverage to reshape premarket review. Over time, the user fee legislation has increasingly required FDA to convene with industry, thus increasing industry influence.<sup>194</sup>

Concurrent with the shift to user fees, industry sought and obtained a number of expedited review programs. The Fast Track Program (1988) speeds reviews for drugs targeted to serious diseases with unmet treatment needs.<sup>195</sup>

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187 Abigail All. for Better Access to Developmental Drugs v. Von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007), *cert. denied*, 552 U.S. 1159 (2008).

188 *But see infra* Section II.B.4 (off-label marketing).

189 Pub. L. No. 102-571, 106 Stat. 4491 (1992).

190 *See* Hutt, *supra* note 4, at 452–54.

191 *See, e.g., PDUFA VII: Fiscal Years 2023–2027*, U.S. FOOD & DRUG ADMIN. (Jan. 26, 2023), <https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027>.

192 Mitchell, Trivedi & Bach, *supra* note 4, at 291.

193 *Id.*

194 Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *Speed, Safety, and Industry Funding—From PDUFA I to PDUFA VI*, 377 NEW ENG. J. MED. 2278, 2282 (2017).

195 FDCA § 506(b). While this article does not have the space for a full treatment of Fast Track, one drug merits a brief discussion. The story of the diabetes drug troglitazone (Rezulin) supports FDA's prioritization of drug commercialization over safety and effectiveness. Troglitazone came to market through the Fast Track Program in 1997. David Willman, *Fears Grow Over Delay in Removing Rezulin*, L.A. TIMES (Mar. 10, 2000), <https://www.latimes.com/archives/la-xpm-2000-mar-10-mn-7318-story.html> [hereinafter "*Fears Grow*"]. The company, Warner-Lambert, knew some patients in clinical studies had developed severe liver damage, but it asserted to FDA that the risk was trivial. Scott Gottlieb, *Company*

Accelerated approval (1992) allows approval of medically important products using unvalidated surrogate markers, subject to confirmatory trials.<sup>196</sup> Priority review (1992) preferences review of drugs for serious conditions that would provide a significant improvement in safety or effectiveness. The program aims to shorten review from the standard of 10 months to 6 months.<sup>197</sup> As of 2007, some drugs approvals are rewarded with a priority review voucher, which can be sold for tens of millions of dollars and redeemed to expedite FDA review of any drug.<sup>198</sup> The breakthrough therapy designation (2014), which automatically includes fast track, targets products for serious conditions where preliminary evidence suggests a clinically significant improvement on a clinically significant endpoint compared with available therapies. These and other pathways<sup>199</sup> constitute a “thicket of special programs”<sup>200</sup> that nudges FDA toward the role of speedy approver and away from the role of gatekeeper. In 2020, 68% of newly approved drugs passed through one or more of these expedited pathways.<sup>201</sup>

FDA drug leadership embraced these programs, particularly Janet Woodcock, head of the Center for Drug Evaluation and Research. During her long tenure starting in 1994, Woodcock established a “track record of

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*Played Down Drug’s Risks, Report Says*, 322 *BMJ* 696, 696 (2001). When an FDA reviewer developed concerns over both safety and effectiveness, see David Willman, *REZULIN: Fast-Track Approval and a Slow Withdrawal*, *L.A. TIMES* (Dec. 20, 2000, 3:00 A.M.), <https://www.latimes.com/nation/la-122001rezulin-story.html> [hereinafter “*Fast-Track*”], his boss told Warner-Lambert he would terminate the reviewer if the company was not pleased. Gottlieb, *supra*. The reviewer was removed from the case and his report was withheld from the advisory committee. *Id.* FDA granted the drug approval through the Fast Track Program in 1997, and within three years, the drug was linked to nearly 400 deaths, thousands of liver injuries, and \$2 billion in total revenue. Willman, *Fast-Track, supra*; David Willman, *The Rise and Fall of the Killer Drug Rezulin*, *L.A. TIMES* (June 4, 2000), <https://www.latimes.com/archives/la-xpm-2000-jun-04-mn-37375-story.html> [hereinafter “*Rise and Fall*”]. British authorities pulled the drug in the same year FDA approved it, and FDA was aware of this decision. Willman, *Rise and Fall, supra*. Under heavy pressure from the public and angry physicians within FDA, the agency sought withdrawal of the drug in 2000. *Id.* A total of 35,000 lawsuits settled for \$750 million. Jef Feeley, *Pfizer Ends Rezulin Cases With \$205 Million to Spare*, *BLOOMBERG* (Mar. 31, 2009), <https://tinyurl.com/4zhmasa4>. In its approval of troglitazone, FDA appeared influenced by the possible benefit of the drug to diabetes patients and only sought withdrawal when drugs in the same class without severe liver toxicity came to market. Willman, *Fears Grow, supra*. FDA repeatedly downplayed troglitazone’s risk of liver failure and death. Willman, *Rise and Fall, supra*. Troglitazone reveals an FDA caught up in innovation fever and willing to allow new drugs to market despite serious safety and effectiveness concerns. See Edwin A.M. Gale, *Troglitazone: The Lesson That Nobody Learned?*, 49 *DIABETOLOGIA* 1, 2 (2006).

196 See *infra* Section II.B.2.

197 U.S. FOOD & DRUG ADMIN., EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS 25 (2014), <https://www.fda.gov/media/86377/download>.

198 See discussion *supra* note 170; Wang, *supra* note 170, at 389, 395.

199 See *supra* Table 2.

200 Sharfstein, *supra* note 169, at 123.

201 Alex M. Ebied, *New Drugs Approved in 2020*, 134 *AM. J. MED.* 1096, 1096 (2021).



championing quick approval of new medicines” and was criticized for tolerating inferior evidence of safety and efficacy.<sup>202</sup> At a 2018 event with the Innovative Health Initiative, she lamented the “old problem that’s sort of holding us back, and that is our need for evidence generation—clinical evidence.”<sup>203</sup> To call the need for clinical evidence a “problem” suggests Woodcock views evidence generation as an obstacle, rather than a feature, of FDA review. She advocates for “adaptive designs,” and laments barriers to alternative trial designs such as “culture, habit, and loss of control.”<sup>204</sup> This rhetoric is directly opposed to numerous experts who believe randomized controlled trials to be the gold standard and greatly worry about FDA’s growing indifference toward clinical trials.<sup>205</sup> Similarly, FDA Commissioner Dr. Robert Califf has called for more “effective and efficient methods of evidence generation” than clinical trials.<sup>206</sup> He has also said, “Americans have told their Congresspeople we would rather take more risk and have earlier access,”<sup>207</sup> and called those critical of premarket review’s erosion “overly cautious.”<sup>208</sup>

## 2. Accelerated Approval & Surrogate Markers

Although drug clinical trials usually measure the impact on a clinical endpoint, i.e., a patient’s symptoms, body functioning, or survival,<sup>209</sup> the FDCA allows for surrogate markers, or substitutes, that are “known” to predict clinical benefit.<sup>210</sup> For example, blood pressure is sometimes used to measure clinical

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202 Sarah Owerhohle, Adam Cancryn & Lauren Gardner, *Controversial Drug Approval Stokes Concern About Lack of a Permanent FDA Chief*, POLITICO (June 11, 2021, 3:50 P.M. EDT), <https://www.politico.com/news/2021/06/11/fda-woodcock-controversial-drug-approval-493324>.

203 The Innovative Health Initiative, *Janet Woodcock, FDA, on Future Innovation in Drug Development*, YOUTUBE (Oct. 1, 2018), <https://www.youtube.com/watch?v=vcPMzHntLzY> (2:00)

204 *Id.* at 5:13.

205 See *infra* Section II.B.3; Mayookha Mitra-Majumdar et al., *Analysis of Supportive Evidence for US Food and Drug Administration Approvals of Novel Drugs in 2020*, JAMA NETWORK OPEN (May 17, 2022), at 8–9 (expressing concern about “reduced evidence requirements for marketing authorization” and calling for a “reexamination” of FDA’s approach); Caroline Chen, *FDA Increasingly Approves Drugs Without Conclusive Proof They Work*, PBS (June 26, 2018), <https://www.pbs.org/newshour/health/fda-increasingly-approves-drugs-without-conclusive-proof-they-work> (describing multiple experts’ criticism of FDA allowing drugs to market with less evidence).

206 Califf, *supra* note 29, at 4.

207 *In the Bubble with Andy Slavitt*, STITCHER (Apr. 28, 2022), <https://www.stitcher.com/show/in-the-bubble-with-andy-slavitt/episode/exclusive-fda-commissioner-on-covid-19-vaccine-for-kids-0-5-with-robert-califf-202759879> (15:38).

208 See Herder, *supra* note 4, at 842–43.

209 See Victor G. De Gruttola et al., *Considerations in the Evaluation of Surrogate Endpoints in Clinical Trials: Summary of a National Institutes of Health Workshop*, 22 CONTROLLED CLINICAL TRIALS 485, 487 (2001).

210 See FDCA § 507(e)(9)(A).

benefit, as opposed to the symptoms and sequelae of high blood pressure. Surrogate markers under the “known” standard encompass a wide variety of uses that are not necessarily controversial.<sup>211</sup>

However, the accelerated approval pathway tolerates several more levels of uncertainty. Launched in 1992 for serious unmet needs (such as cancer and HIV), it permits the use of surrogate measures “reasonably likely” to predict clinical benefit, although sponsors must conduct confirmatory trials after approval.<sup>212</sup> Unfortunately, we are likely to overestimate the validity of surrogate markers because most validation studies of surrogate markers review a biased subset of available trials.<sup>213</sup> Further, under accelerated approval, FDA has statutory authority to consider, in an approval decision, the severity and prevalence of the disease and the need for the drug<sup>214</sup>—considerations apart from safety and effectiveness. Therefore, although safety and effectiveness are still required, companies (and FDA) can stress other aspects of drugs and divert attention from serious effectiveness or safety issues during the approval process. The number of factors at play in accelerated approval arguably dilutes the salience of safety and effectiveness for drugs assessed under this pathway.

The most notorious example of accelerated approval is the story of aducanumab (Aduhelm) for Alzheimer’s disease, approved in June 2021. Previously, FDA’s nervous system drug advisory committee had recommended *against* approving the drug near-unanimously.<sup>215</sup> The drug did not show clinical benefit and caused potentially severe brain swelling.<sup>216</sup> Two clinical trials had been shut down in 2019 because an independent monitoring committee found aducanumab was not helping patients.<sup>217</sup> Some industry-funded patient groups supported the drug, in particular the Alzheimer’s Association, which partnered with Biogen to hire celebrities like Samuel Jackson to create buzz and build public support for approval.<sup>218</sup> And although aducanumab did not show clinical

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211 See *Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure*, U.S. FOOD & DRUG ADMIN. (Feb. 28, 2022), <https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure>.

212 FDCA § 506(c).

213 Vinay Prasad et al., *The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-Analyses*, 175 JAMA INTERNAL MED. 1389, 1395 (2015).

214 See FDCA § 507(e)(9)(B), 506(c)(1)(A).

215 See Pam Belluck, Sheila Kaplan & Rebecca Robbins, *How an Unproven Alzheimer’s Drug Got Approved*, N.Y. TIMES (July 19, 2021), <https://www.nytimes.com/2021/07/19/health/alzheimers-drug-aduhelm-fda.html>.

216 Pam Belluck & Rebecca Robbins, *Three F.D.A. Advisers Resign over Agency’s Approval of Alzheimer’s Drug*, N.Y. TIMES (June 10, 2021), <https://www.nytimes.com/2021/06/10/health/aduhelm-fda-resign-alzheimers.html>.

217 Belluck, Kaplan & Robbins, *supra* note 215.

218 Beth Snyder Bulik, *Celeb-Backed Alzheimer’s Association Campaign Aims to Build*

benefit, thus precluding traditional approval, FDA was moved by the drug's impact on amyloid plaque, a protein hypothesized to accumulate in the brain of Alzheimer's patients.<sup>219</sup> So FDA ignored the lack of clinical benefit and granted "accelerated" approval based on the surrogate marker of amyloid plaques—a move that spurred intense criticism.<sup>220</sup>

On approval, three members of the advisory committee resigned, drawing broad press coverage.<sup>221</sup> Under pressure, Acting FDA Commissioner Janet Woodcock called for an inspector general investigation.<sup>222</sup> Many of the country's most prestigious hospitals said they would not prescribe the drug.<sup>223</sup> In a surprising move, the Center for Medicare and Medicaid Services issued a decision denying coverage except in clinical trials,<sup>224</sup> thus undermining FDA's approval. When Biogen set the price tag at \$56,000 per year,<sup>225</sup> public curiosity arose about whether FDA was acting on behalf of public health or on the corporations it was built to regulate. Why else would FDA offer Biogen a massive windfall for little public benefit? FDA's embrace of aducanumab in spite of serious questions about effectiveness and safety suggests it was more concerned with addressing the unmet need of Alzheimer's disease rather than ensuring the drug was safe and effective.<sup>226</sup> Improper communications between FDA and Biogen suggested inappropriate corporate influence over the regulatory process.<sup>227</sup> FDA also made the bizarre move of pivoting to accelerated approval as a backdoor only after months of review suggested traditional approval was unlikely.<sup>228</sup> The story of aducanumab demonstrates how the malleable pathway of accelerated approval can lead to decisions that are misaligned with public health and with FDA's founding principles.

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*Grassroots Support for Biogen's Aducanumab Ahead of FDA Decision*, FIERCE PHARMA (May 14, 2021, 11:22 A.M.), <https://www.fiercepharma.com/marketing/alzheimer-s-association-campaign-more-time-supports-biogen-s-aducanumab-awaiting-fda>.

219 Maulden, *supra* note 4, at 110, 118, 130.

220 Emanuel, *supra* note 4, at 1367.

221 Belluck, Kaplan & Robbins, *supra* note 215.

222 *Id.*

223 Arthur Allen, *Inside the Tactical Tug of War over the Controversial Alzheimer's Drug*, KHN (Feb. 16, 2022), <https://khn.org/news/article/medicare-ruling-aduhelm-controversial-alzheimer-drug-critics>.

224 See CTR. FOR MEDICARE & MEDICAID SERVS., *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease* (Apr. 7, 2022), <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=305>.

225 Zachary B. Wolf, *The Hard Math on the New \$56,000 Alzheimer's Drug*, CNN (July 20, 2021, 8:11 P.M. EDT), <https://www.cnn.com/2021/07/20/politics/aduhelm-alzheimers-drug-cost-what-matters/index.html>.

226 See Maulden, *supra* note 4, at 132.

227 See HOUSE E&C COMM., *THE HIGH PRICE OF ADUHELM'S APPROVAL: AN INVESTIGATION INTO FDA'S ATYPICAL REVIEW PROCESS AND BIOGEN'S AGGRESSIVE LAUNCH PLANS 15–21* (2022).

228 *Id.* at 21.

A survey of the data suggests that accelerated approval is a partial end run around premarket review. A September 2022 report by the HHS Office of the Inspector General revealed that during accelerated approval's lifetime, 104 of all 278 approved drug applications under the program have not completed confirmatory trials, suggesting that accelerated approval tolerates significant uncertainty in the drugs sold on the U.S. market.<sup>229</sup> More than half of confirmatory trials are completed late.<sup>230</sup> Yet FDA has not once used its authority to issue civil monetary penalties against a manufacturer for a late trial.<sup>231</sup>

Even if all confirmatory trials were completed promptly—which they are not—they would be unlikely to confirm the safety and effectiveness of drugs granted accelerated approval. A 2019 review of the 93 cancer drug indications granted accelerated approval from 1992–2017 found only 58 indications had a “confirmed benefit” after confirmatory trial.<sup>232</sup> And, of these 58 indications, only 19 reported a survival benefit in confirmatory trials.<sup>233</sup> Another 19 reported improvement in the *same surrogate* as the preapproval trial, and 20 reported improvement in a different surrogate.<sup>234</sup> Arguably, the safety and efficacy of drugs coming to market under accelerated approval are far less reliable, even after confirmatory trials.

Although the laxity of accelerated approval should be paired with a rapid correction mechanism, FDA has no easy way to withdraw drugs granted accelerated approval that fail confirmatory trials.<sup>235</sup> FDA's fraught withdrawal of bevacizumab's (Avastin's) indication for breast cancer was understood to be the “first and last time” it would withdraw accelerated approval in the face of industry opposition.<sup>236</sup> Given the time and expense, one director called the bevacizumab episode “Armageddon.”<sup>237</sup> However, FDA recently accomplished a

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229 Jeff Craven, *OIG Raises Concerns About Accelerated Approval Pathway*, REGUL. FOCUS (Sept. 30, 2022), <https://www.raps.org/news-and-articles/news-articles/2022/9/oig-raises-concerns-about-accelerated-approval-pat>.

230 Anjali D. Deshmukh, Aaron S. Kesselheim & Benjamin N. Rome, *Timing of Confirmatory Trials for Drugs Granted Accelerated Approval Based on Surrogate Measures from 2012 to 2021*, JAMA HEALTH FORUM (Mar. 31, 2023), at 1.

231 Anthony Barraeta et al., *Restoring Provider Confidence in FDA-Approved Drugs*, HEALTH AFFS. (June 28, 2022), <https://www.healthaffairs.org/doi/10.1377/forefront.20220623.43556>; Steven Woloshin et al., *The Fate of FDA Postapproval Studies*, 377 NEW ENG. J. MED. 1114, 1116 (2017).

232 Bishal Gyawali, Spencer Phillips Hey & Aaron S. Kesselheim, *Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval*, 179 JAMA INTERNAL MED. 906, 908 (2019).

233 *Id.*

234 *Id.*

235 Daniel G. Aaron, I. Glenn Cohen & Eli Y. Adashi, *The FDA Struggle to Withdraw Makena: Problems with the Accelerated Approval Process*, 328 JAMA 2394, 2394 (2022).

236 Herder, *supra* note 4, at 849.

237 *Id.* at 841.

second accelerated approval withdrawal—for hydroxyprogesterone caproate (Makena), a drug used to prevent preterm birth that appears to have little clinical utility.<sup>238</sup> FDA had been trying to pull the drug since 2019 but had been stymied by the pandemic and cumbersome withdrawal requirements.<sup>239</sup> Hydroxyprogesterone caproate was responsible for more than \$700 million in federal healthcare spending and was discovered to increase cancer risk in exposed offspring.<sup>240</sup> Again, FDA was lulled into approving an ineffective drug by the promise of addressing the public health problem of preterm birth (which can have serious complications for the baby).<sup>241</sup> Recent changes to accelerated approval in the Food and Drug Omnibus Reform Act have made withdrawal marginally easier by removing the hearing requirement, but the process is still cumbersome when a manufacturer does not voluntarily withdraw its drug.<sup>242</sup> Therefore, once products are granted accelerated approval, the statutory framework discourages FDA from withdrawing approval for any “dud” products.

Inevitably, accelerated approval changes the balance of FDA regulation to favor earlier access over certainty in safety and efficacy. But these examples and data suggest more: accelerated approval has become the leaky faucet of drug approvals, with no easy way to correct errors. The program’s very existence incentivizes companies to target unvalidated surrogate markers, which may offer a surer pathway to market. Surrogate markers such as blood pressure are easier to target with a drug, yet, without measuring clinical outcomes (e.g., deaths), they can be misleading because they may fail to capture overall impact on health.<sup>243</sup> Beyond surrogate markers, the program vests discretion with FDA to allow drugs to market that meet a reduced standard, particularly when the need is great and political pressure and corporate influence are high. Therefore, it can be and has been misused to circumvent regular premarket review. Accelerated approval creates the discretion—and sets an ideological tone—for FDA to speed products

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238 *FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena*, U.S. FOOD & DRUG ADMIN. (Apr. 6, 2023), <https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena>; Christina Jewett, *F.D.A. Panel Recommends Pulling Preterm Birth Drug from the Market*, N.Y. TIMES (Oct. 19, 2022), <https://www.nytimes.com/2022/10/19/health/fda-preterm-birth-drug.html>.

239 Aaron, Cohen & Adashi, *supra* note 235. Recent statutory amendments to accelerated approval struck the hearing requirement and may facilitate withdrawal somewhat. *See Consolidated Appropriations Act, 2023* § 3210(a)(1)(A), Pub L. No. 117–328.

240 Aaron, Cohen, & Adashi, *supra* note 235, at 2395.

241 *Id.* at 2394.

242 *See* Jeff Craven, *FDA Withdraws Pre-Term Birth Drug Makena*, REGUL. FOCUS (Apr. 6, 2023), <https://www.raps.org/news-and-articles/news-articles/2023/4/fda-withdraws-pre-term-birth-drug-makena>.

243 Oriana Ciani et al., *Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward*, 20 VALUE IN HEALTH 487, 489 (2017).

to market in conflict with its gatekeeper role.

### 3. *Erosion of the Clinical Trial Requirement: Quantity and Quality*

Imagine a world where drug access was freely provided without premarket review. In this world, it would be nearly impossible to measure efficacy. A group of patients with brain cancer trying a new drug might almost all die—but we would not know whether the patients lived longer or better because of the drug. Or a group of patients with a virus might all improve—but such is the natural course of most viruses. Clinical trials, which take place under carefully planned circumstances, help ensure that FDA’s approvals are a reliable indication of drugs’ safety and effectiveness.

But since the 1990s, FDA feared that clinical trial “failures” (i.e., null findings) were obstructing innovation.<sup>244</sup> Of course, some drugs are bound to have no clinical benefit, but FDA saw this as a problem. In addition, clinical trials became seen as too cumbersome and expensive,<sup>245</sup> a view heavily espoused by new industry-oriented leadership.<sup>246</sup> With these concerns in mind, industry, FDA, and Congress set out to “moderniz[e]” the clinical trial requirement.<sup>247</sup>

Traditionally, FDA required two randomized clinical trials to support the effectiveness of new drugs.<sup>248</sup> However, in the Food and Drug Administration Modernization Act (1997), a fully conservative Congress abolished the requirement for two clinical trials under certain circumstances, such as when a single trial coupled with confirmatory evidence could establish effectiveness.<sup>249</sup> This broad exception encourages FDA to accept any additional evidence submitted in addition to one randomized clinical trial. Between 1995 and 1997, 80.6% of indications for new drugs and biologics were supported by at least two pivotal trials.<sup>250</sup> Between 2015 and 2017, by comparison, 52.8% of indications were supported by at least two trials.<sup>251</sup> For opioids, which arguably should have

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244 Jonah Campbell & Nicholas B. King, “Unsettling Circularity”: *Clinical Trial Enrichment and the Evidentiary Politics of Chronic Pain*, 12 *BIOsocieties* 191, 196–97 (2017) (describing FDA concerns about slowing of the drug pipeline and FDA’s belief that even drugs with “literally thousands of years of clinical experience” were seeing clinical trial “failures”).

245 *Id.*

246 *See supra* notes 202–208.

247 Campbell & King, *supra* note 244, at 197.

248 FDCA § 505(d)(5); U.S. FOOD & DRUG ADMIN., DEMONSTRATING SUBSTANTIAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 4 (Dec. 2019), <https://www.fda.gov/media/133660/download>.

249 *Id.*; FDCA § 505(d).

250 Audrey D. Zhang et al., *Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017*, *JAMA NETWORK OPEN*, Apr. 21, 2020, at 5.

251 *Id.*

a higher bar for approval, only 29/48 of approved applications between 1997 and 2018 had at least *one* pivotal trial.<sup>252</sup> (A pivotal trial is a very significant trial that would count as one of the “two” traditionally required trials. Those opioids approved with zero pivotal trials likely piggybacked on published data or data submitted for other applications.<sup>253</sup>) These data suggest that the previous gold standard of two pivotal trials per indication has been eroded.<sup>254</sup> This change is important because studies can have serious blind spots or undetected biases, so the existence of two trials provides insurance that findings of a drug’s effectiveness are real.<sup>255</sup> For example, the approval of OxyContin, the drug that ignited the opioid crisis,<sup>256</sup> was based on a single two-week trial.<sup>257</sup>

In addition, the data quality FDA considers acceptable has declined. Well-designed clinical trials should have several features: (1) randomization to make sure the groups exposed to different treatments do not have significant differences; (2) a control group; (3) double-blinding; (4) clinical endpoints;<sup>258</sup> and (5) proper accounting for study problems such as dropouts (Table 3).

Drug Category	Randomized	Controlled	Double-Blinded
All	89%	87%	80%
Cancer	47%	47%	27%
Orphan Drug	54%	50%	38%
Accelerated Approval	45%	45%	30%

Table 3: Features of clinical trials serving as basis for FDA approvals of novel therapeutic agents, 2005–2012 (rounded).<sup>259</sup>

252 James Heyward et al., *Key Evidence Supporting Prescription Opioids Approved by the U.S. Food and Drug Administration, 1997 to 2018*, 173 ANNALS OF INTERNAL MED. 956, 958 (2020). One might point out that all but one of these applications were for previously approved molecular entities. *Id.* at 960. However, given opioids’ risks and the tenuous evidence they provide benefit as a whole, one would expect a higher bar for efficacy for new indications, not a lower one.

253 *Id.* at 957; see FDCA § 505(b)(2).

254 Some of this change may be due to increased development of orphan drugs, which are defined by a small patient population and thus for which two trials may be infeasible. However, the trend nevertheless exists and is not limited to orphan drugs, as shown in Table 3.

255 See Darrow et al., *supra* note 49, at 167.

256 Aaron, *supra* note 11, at 17–19; Daniel Aaron, *Opioid Accountability*, 89 TENN. L. REV. 611, 619 (2022) [hereinafter “*Opioid Accountability*”].

257 Kolodny, *supra* note 4, at 745.

258 See *supra* Section II.C.2.

259 Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012*, 311 JAMA 368, 372 (2014).

These data suggest that FDA is willing to forego essential clinical trial features for certain drug categories. The fact that FDA adheres to these features for most drugs suggests their importance. For comparison, 100% of neurology trials for novel therapeutic agents approved between 2005 and 2012 were randomized and double-blinded.<sup>260</sup>

Also concerning is a relatively new and biased trial method specifically for pain drugs. The “enriched enrollment randomized withdrawal” (EERW) trial has been used since 2006 to address high “failure rates” of pain management trials and to boost measurements of efficacy.<sup>261</sup> From 1997 to 2018, more than 40% of new opioid drug applications approved by FDA had no pivotal trial submitted, and of those with a pivotal trial, 59% had at least one EERW trial.<sup>262</sup> The EERW method includes an initial phase in which all patients receive the drug and “non-responders” (those who experience no benefit or who suffer severe adverse events) are removed. In the second phase, the “responders” are divided between a treatment and a placebo arm.<sup>263</sup> The rationale for measuring efficacy in responders is that, in “personalized medicine,” people respond differently to drugs.<sup>264</sup> This type of trial leverages the rhetoric of individualism to create a biased sample that boosts efficacy and safety measures and generates evidence inapplicable to the population at large. Further, because many patients become dependent on opioids during the first phase, those who are randomly assigned to placebo in the second phase are prone to experience opioid withdrawal (including pain sensitivity),<sup>265</sup> which artificially boosts efficacy. EERW trials, which experts have called “cheating,”<sup>266</sup> are a derogation of FDA’s standards.

FDA’s acceptance of EERW trials began with private industry-funded meetings through the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a private industry-sponsored group aimed at improving pain drug trial designs.<sup>267</sup> The meetings have been described as “pay-for-play” because pharmaceutical companies could pay as much as \$35,000 for the opportunity to meet with FDA regulators.<sup>268</sup> These meetings hold the risk of capturing FDA regulators and aligning FDA with industry interests. FDA has since launched a public-private partnership called the Analgesic, Anesthetic, and Addiction Clinical Trials Translations, Innovations, Opportunities, and Networks

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260 *Id.*

261 Campbell & King, *supra* note 244, at 191; Kolodny, *supra* note 4, at 745.

262 Heyward et al., *supra* note 252, at 959.

263 Campbell & King, *supra* note 244, at 193–94.

264 *Id.* at 194, 209.

265 Kolodny, *supra* note 4, at 746.

266 John Fauber, *FDA and Pharma: Emails Raise Pay-for-Play Concerns*, MEDPAGETODAY (Oct. 7, 2013), <https://www.medpagetoday.com/painmanagement/painmanagement/42103>.

267 *Id.*

268 *Id.*



Initiative (ACTTION), which absorbed IMMPACT and is led by IMMPACT's founders.<sup>269</sup> In founding ACTTION, FDA released a statement making it clear that it wanted opioids to be proven effective to be consistent with “literally thousands of years of clinical experience.”<sup>270</sup> Because of its close ties with industry as part of ACTTION, FDA may be ignoring the possibility that the “frequent failures of clinical efficacy trials of opioid drug products”<sup>271</sup> might indicate the drugs were ineffective for many types of pain.

FDA's growing skepticism toward clinical trials<sup>272</sup> raises questions about the agency's ability to produce reliable information about the products it regulates. The most reliable information source for FDA approvals has become, at least in some instances, one of FDA's sworn enemies. Surely, this development cannot be good for protecting the public health through premarket review.

#### 4. *Off-Label Marketing*

Off-label marketing represents a court-created path to evade premarket review. FDA generally approves drugs for a particular indication listed in a drug's labeling. After approval, physicians may prescribe the drug for so-called “off-label use,” a long-accepted and important part of the practice of medicine. However, FDA for years prohibited “off-label marketing,” given a history of manufacturers promoting approved drugs for unproven and unsafe uses.<sup>273</sup> For example, in 2000, Eli Lilly obtained approval for olanzapine (Zyprexa) to treat schizophrenia and bipolar disorder.<sup>274</sup> However, DOJ reached a \$1.4 billion settlement in 2009 on the grounds that Eli Lilly was marketing the drug for dementia, Alzheimer's disease, depression, anxiety, sleep problems, and behavioral symptoms.<sup>275</sup> Patients could therefore be subjected to ineffective treatment coupled with serious risk: olanzapine is notorious for causing premature death through weight gain and diabetes.<sup>276</sup>

The conservative group Washington Legal Foundation (WLF), which receives funding from pharmaceutical companies, realized off-label marketing

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<sup>269</sup> Campbell & King, *supra* note 244, at 196.

<sup>270</sup> *Id.*

<sup>271</sup> *Id.*

<sup>272</sup> See Califf, *supra* note 29.

<sup>273</sup> Aaron S. Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection* 183, 186, in LYNCH & COHEN, *supra* note 23.

<sup>274</sup> *Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, U.S. DEP'T JUST. (Jan. 15, 2009), <https://www.justice.gov/opa/pr/eli-lilly-and-company-agrees-pay-1415-billion-resolve-allegations-label-promotion-zyprexa>.

<sup>275</sup> *Id.*

<sup>276</sup> See Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308, 309 (2007).

was a chance to undermine premarket review using the First Amendment. Beginning in the late 1990s, WLF pursued a series of cases challenging FDA authority to regulate off-label marketing as infringing on “commercial speech” of pharmaceutical companies.<sup>277</sup> The major breakthrough occurred in *United States v. Caronia*,<sup>278</sup> in which the Second Circuit overturned—under First Amendment grounds—the conviction of Alfred Caronia, who marketed the risky psychotropic drug Xyrem (gamma-hydroxybutyrate, or GHB) off-label for a hodgepodge of mental disorders.<sup>279</sup> GHB is also used as a date rape drug because of its strong nervous system effects, can cause life-threatening central nervous system and respiratory depression, and can trigger dependence and life-threatening withdrawal.<sup>280</sup> Caronia’s marketing of the drug for so many uses raised safety and effectiveness concerns.

The Second Circuit overturned Caronia’s conviction as an unconstitutional infringement of free speech,<sup>281</sup> despite the government’s interest in “preserving the effectiveness and integrity of the FDCA’s drug approval process.”<sup>282</sup> Ultimately, the court believed it was not damaging premarket review because physicians could already prescribe drugs off-label, and therefore it was only liberalizing *speech*—and speech always promotes health in medical spaces by promoting “intelligent treatment decisions.”<sup>283</sup> Further, prohibiting off-label speech, the court stressed, is “paternalistic[.]”<sup>284</sup> The image of a sophisticated consumer evaluating choices on full information; the idea of government as an overbearing paternal figure; and the kneecapping of regulatory review on behalf of individual decisions are neoliberal ideas that stand in direct opposition to public health. The fact that the court thought it had a better grasp of what would preserve the integrity of premarket review than FDA itself<sup>285</sup> is a loud expression of judicial hubris and lack of deference to agency expertise.

WLF scored another victory in *Amarin Pharma, Inc. v. FDA*.<sup>286</sup> There, the

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<sup>277</sup> See Kapczynski, *supra* note 26, at 189 n.66.

<sup>278</sup> 703 F.3d 149 (2d Cir. 2012).

<sup>279</sup> *Id.* at 152, 155.

<sup>280</sup> Leo J. Schep et al., *The Clinical Toxicology of Gamma-Hydroxybutyrate, Gamma-Butyrolactone and 1,4-Butanediol*, 50 *CLINICAL TOXICOLOGY* 458, 459, 463 (2012).

<sup>281</sup> *Caronia*, 703 F.3d at 168–69.

<sup>282</sup> *Id.* at 166.

<sup>283</sup> *Id.*

<sup>284</sup> *Id.*

<sup>285</sup> *Id.* The court reasoned that off-label *use* is legal, so “it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government’s goal[] of preserving the efficacy and integrity of the FDA’s drug approval process.” *Id.* “[I]n the fields of medicine and public health, where information can save lives,” ensuring accurate decisions through more speech—even commercially motivated, biased speech—“only furthers the public interest.” *Id.* at 167 (internal quotation marks omitted).

<sup>286</sup> 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

U.S. District Court for the Southern District of New York held that FDA cannot sustain a criminal enforcement action based on “truthful promotional speech alone,”<sup>287</sup> and it substituted its own analysis for FDA’s of whether the defendant company’s statements were truthful and non-misleading.<sup>288</sup> Of course, misleading speech carries the risk of fostering uses of a drug that FDA has not approved. Because premarket review is expert-based, the “misleadingness inquiry should operate to preserve agency authority over an assessment that the agency is most qualified to make.”<sup>289</sup> WLF gloats on its website that *Amarin* “is a major milestone in WLF’s two-decades-long effort to require FDA to abide by the First Amendment.”<sup>290</sup>

After *Caronia* and its progeny, it is far easier for companies to market drugs for a range of conditions without generating the evidence for that use.<sup>291</sup> FDA has taken a soft enforcement approach through the issuance of non-binding guidance for off-label marketing.<sup>292</sup> Of course, FDA can still attempt to prove manufacturer claims are false or misleading,<sup>293</sup> but that places the burden on FDA to support an enforcement action when the burden was supposed to be placed on the manufacturer as part of premarket review.

The judicially created hole in premarket review through off-label promotion creates concrete risks to Americans’ health. Off-label marketing invites the trifecta of health harm, little or unknown health benefits, and unaccountable corporate marketing; examples include gabapentinoids,<sup>294</sup> various psychiatric

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287 *Id.* at 224.

288 *Id.* at 230–36.

289 *Amarin Pharma, Inc. v. FDA*, 129 HARV. L. REV. 2021, 2028 (2015).

290 *Amarin Pharma, Inc. v. FDA*, WASH. LEGAL FOUND. (June 12, 2015), <https://www.wlf.org/case/amarin-pharma-inc-v-fda>.

291 *But see* United States v. Facticeau, Case No. 1:15-cr-10076-ADB (D. Mass. 2020), *under appeal*; *U.S. v. Facticeau: District Court Finally Upholds Misdemeanor Convictions for Off-Label Promotion*, FOOD & DRUG LAW INST. (2021), <https://www.fdpi.org/2021/06/u-s-v-facticeau-district-court-finally-upholds-misdemeanor-convictions-for-off-label-promotion> (“After a string of losses dating back over fifteen years, *Facticeau* is the first time the government has overcome a First Amendment defense to score a (partial) victory in an off-label promotion case.”). Also, anti-fraud laws may have mitigated increases in off-label use stemming from *Caronia*, but this effect is not clear. *See generally* Aaron S. Kesselheim et al., *False Claims Act Prosecution Did Not Deter Off-Label Drug Use in the Case of Neurontin*, 30 HEALTH AFFS. 2318 (2011) (using a case study to discuss whether fraud cases have helped deter off-label use).

292 *See* U.S. FOOD & DRUG ADMIN., DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES — RECOMMENDED PRACTICES 2 (Feb. 2014), <https://www.fda.gov/media/88031/download> (“[G]uidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations.”); U.S. FOOD & DRUG ADMIN., MEDICAL PRODUCT COMMUNICATIONS THAT ARE CONSISTENT WITH THE FDA-REQUIRED LABELING QUESTIONS AND ANSWERS 2 (June 2018), <https://www.fda.gov/media/133619/download> (same).

293 Kapczynski, *supra* note 26, at 192.

294 *See* Alyssa M. Peckham et al., *Gabapentin for Off-Label Use: Evidence-Based or Cause for Concern?*, 12 SUBSTANCE ABUSE 1, 1–2, 7 (2018); Christopher W. Goodman & Allan S. Brett,

drugs including antipsychotics and antidepressants,<sup>295</sup> thalidomide and its analogues,<sup>296</sup> and direct oral anticoagulants.<sup>297</sup> 60% of U.S. physicians believe FDA should “definitely not” or “probably not” allow off-label marketing to physicians; 93% of the same group believe FDA should not allow off-label marketing to patients.<sup>298</sup> A Canada study found that off-label uses had 44% more adverse drug events compared with approved uses.<sup>299</sup> As former FDA Commissioner Margaret Hamburg has noted, liberation of off-label marketing threatens to provide a loophole for companies to seek approval for a trivial indication and then market broadly, and may sow confusion by incentivizing effectiveness claims even when other drugs are proven to be effective for the same use.<sup>300</sup> However, to the two judges on the Second Circuit siding with Caronia, public health benefits from more “information,” and premarket review is paternalistic.

### 5. *Real-World Evidence*

In 2016, Congress passed the 21st Century Cures Act, which requires FDA to establish a program to allow the use of “real-world evidence” for two purposes: (1) for new indications of an already approved drug, and (2) for postapproval study requirements, such as confirmatory trials for drugs receiving accelerated approval.<sup>301</sup> Real-world evidence is data “from sources other than traditional clinical trials.”<sup>302</sup> It is hard to think of a clearer expression of congressional intent to erode clinical trials than by defining a catchy new term

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*A Clinical Overview of Off-label Use of Gabapentinoid Drugs*, 179 JAMA INTERNAL MED. 695, 695 (2019).

295 See Lisa E. Smilan, *The Off-Label Loophole in the Psychopharmacologic Setting: Prescription of Antipsychotic Drugs in the Nonpsychotic Patient Population*, 30 HEALTH MATRIX 233, 266–84 (2020); Aishwarya Vijay, Jessica E. Becker & Joseph S. Ross, *Patterns and Predictors of Off-Label Prescription of Psychiatric Drugs*, 13 PLOS ONE (2018), at 1, 2, 9; Jenna Wong et al., *Off-Label Indications for Antidepressants in Primary Care: Descriptive Study of Prescriptions from an Indication Based Electronic Prescribing System*, 356 BMJ (2017), at 1, 1–3.

296 Y. Tony Yang et al., *Thalidomide, Drug Safety, and Off-Label Prescribing: Lessons Learned from Celgene’s Settlement*, 4 JAMA ONCOLOGY 915, 915 (2018).

297 Ann Marie Nevar & Roxana Mehran, *High Rates of Off-Label Prescribing and the Urgent Need for a Randomized Clinical Trial*, 5 JAMA CARDIOLOGY 692, 692–93 (2020); JOY C. ECKERT ET AL., MILKEN INSTIT. OF PUB. HEALTH AT GEORGE WASHINGTON U., *THE MARKETING AND PRESCRIBING OF ANTICOAGULANTS IN THE DISTRICT OF COLUMBIA* 35 (2018).

298 See Aaron S. Kesselheim et al., *Physicians’ Perspectives on FDA Approval Standards and Off-label Drug Marketing*, 179 JAMA INTERNAL MED. 707, 708 (2019).

299 Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERNAL MED. 55, 55, 58 (2015).

300 Margaret A. Hamburg, *Innovation, Regulation, and the FDA*, 363 NEW ENG. J. MED. 2228, 2230 (2010).

301 FDCA § 505F(a).

302 FDCA § 505F(b).

encompassing all evidence *other than* clinical trials. Further, “real-world evidence” is a “god term,” that is, a phrase that seems so obviously good as to inspire immediate loyalty.<sup>303</sup> Yet one study found that only 15% of clinical trials published in high-impact journals could be replicated using observational data.<sup>304</sup> Clinical trials, and their coveted randomization component, are irreplaceable.

This is not to say that other types of evidence are useless. But congressional requirements that FDA rely less on clinical trials solidify a troublesome trend. FDA had already used real-world evidence in certain instances, such as for some cancer drugs;<sup>305</sup> however, FDA has now considerably expanded its use and developed a regulatory framework.<sup>306</sup> As FDA has explained on its website under the heading “Why is this happening now?”, FDA points to the use of computers and devices to “gather and store huge amounts of health-related data” and “sophisticated, new analytical capabilities.”<sup>307</sup> Therefore, FDA is helping to justify this shift away from the gold-standard method of determining safety and efficacy.

## 6. *The Fall of Drug Review*

The erosion of drug premarket review began with lobbying of Congress to (1) create a “tangled thicket” of approval pathways, (2) pare back on randomized clinical trials, and (3) transition funding from appropriations to user fees paid by the pharmaceutical industry. Ideological capture, represented by the belief that patients would benefit from faster access to less tested drugs, eroded the drug vetting process. Over the past ten years, FDA has sidelined its major source of outside expertise: advisory committees. According to one study, committee meetings on initial approvals declined from 26 in 2012 to 8 in 2021.<sup>308</sup> Commissioner Dr. Califf has even suggested ending committee votes

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303 See RICHARD M. WEAVER, *THE ETHICS OF RHETORIC* 212 (1953).

304 Victoria L. Bartlett et al., *Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence*, *JAMA NETWORK OPEN* (Oct. 9, 2019), at 1, 7; see also Shirley V. Wang et al., *Using Real-World Data to Extrapolate Evidence from Randomized Controlled Trials*, 105 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 1156, 1162 (2020) (finding utility in real-world evidence for filling evidence gaps for underrepresented patient groups in clinical trials, but noting that “these methods are not a substitute” for randomized clinical trials that welcome these groups).

305 U.S. FOOD & DRUG ADMIN., *FRAMEWORK FOR FDA’S REAL-WORLD EVIDENCE PROGRAM* 9 (Dec. 2018), <https://www.fda.gov/media/120060/download>.

306 See generally *id.* (describing FDA’s framework for real-world evidence).

307 *Real-World Evidence*, U.S. FOOD & DRUG ADMIN. (Jan. 31, 2023), <https://web.archive.org/web/20230307111003/https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>.

308 C. Joseph Ross Daval et al., *Association of Advisory Committee Votes with US Food and Drug Administration Decision-Making on Prescription Drugs, 2010-2021*, *JAMA HEALTH F.* (July 7, 2023), at 1, 4.

altogether.<sup>309</sup> According to Genevieve Kanter, “FDA appears to have been looking for reasons to approve drugs,”<sup>310</sup> and so committee votes may be an obstacle to the goals of FDA leadership.

As to litigation, the judiciary was largely a bystander to the erosion of drug review, with two caveats. The first is off-label promotion, which courts turned into a substantial hole in premarket review.<sup>311</sup> The second is recent court intrusions into FDA’s approval of mifepristone.<sup>312</sup> Courts may be increasingly willing to tread on scientific decisions—despite FDA’s longstanding expertise in drug approvals. Of course, the judiciary may have had a more indirect role in undermining FDA by empowering the corporation, lubricating the flow of money in politics, and disempowering agencies.<sup>313</sup>

Together, these mechanisms of erosion largely reflect corporate influence on premarket review of drugs. It is pharmaceutical companies that complained about slow reviews,<sup>314</sup> lobbied for pro-business changes to the FDCA,<sup>315</sup> and have sought to ensure FDA commissioners are business-friendly. For example, current FDA Commissioner Dr. Robert Califf has received millions of dollars from life sciences companies,<sup>316</sup> believes the American public wants earlier access to drugs despite the risks,<sup>317</sup> and is a “big fan” of accelerated approval.<sup>318</sup> Dr. Califf

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309 Genevieve P. Kanter, *The Real Question the FDA Is Asking Its Advisory Committees*, JAMA HEALTH F. (July 7, 2023), at 1, 2.

310 *Id.*

311 *See supra* Section II.B.4.

312 Daniel G. Aaron, Teneille R. Brown & Michael S. Sinha, *Court Intrusion into Science and Medicine—The Mifepristone Decisions*, 329 JAMA 1735, 1735 (Apr. 26, 2023).

313 *See infra* Section IV.B.

314 *See* Darrow, Avorn & Kesselheim, *supra* note 49.

315 Between 1999 and 2018, the pharmaceutical and health products industry spent \$4.7 billion on lobbying. Olivier J. Wouters, *Lobbying Expenditures and Campaign Contributions by the Pharmaceutical and Health Product Industry in the United States, 1999-2018*, 180 JAMA INTERNAL MED. 688, 690 (2020). Between 1998 and 2005, the pharmaceutical and health products industry hired about 3,000 lobbyists and lobbied more than 1,400 federal bills. M. Asif Ismail, *Prescription for Power*, CTR. FOR PUB. INTEGRITY (Apr. 28, 2005), <https://publicintegrity.org/politics/lobby-watch/prescription-for-power>. More recently, the 21st Century Cures Act, which required FDA to use real-world evidence and weakened device regulation, *see infra* Section II.E.1, was one of the most-lobbied bills in the 114th Congress. According to one former representative, “[A] lot of groups have a lot of interest in every line in that bill.” Sydney Lupkin, *Legislation That Would Shape FDA and NIH Triggers Lobbying Frenzy*, NPR (Nov. 25, 2016), <https://www.npr.org/sections/health-shots/2016/11/25/503176370/legislation-that-would-shape-fda-and-nih-triggers-lobbying-frenzy>.

316 Sarah Owerhohle & Adam Cancryn, *Califf’s Profitable Industry Ties Spark Fresh Criticism*, POLITICO PULSE (Nov. 23, 2021), <https://www.politico.com/newsletters/politico-pulse/2021/11/23/califfs-profitable-industry-ties-spark-fresh-criticism-799053>

317 *See supra* Section I.C.

318 Samantha Sault, *FDA Commissioner on Accelerated Approval, Misinformation, and Food*, BIO.NEWS (June 16, 2022), <https://bio.news/bio-convention/fda-commissioner-on-accelerated-approval-misinformation-and-food>.

prevailed over another potential nominee, Dr. Joshua Sharfstein—a public health professor—likely because of industry opposition.<sup>319</sup> Industry continues to fund 75% of FDA’s drug budget, and even Dr. Califf admits that he “wish[es] the taxpayer paid for all the F.D.A. and there weren’t user fees.”<sup>320</sup> The user fee process has served as a “legislative vehicle” that has “favored industry through decreasing regulatory standards, shortening approval times, and increasing industry involvement in FDA decisionmaking.”<sup>321</sup> Industry influence over FDA has eroded the agency’s consumer protection role and increasingly allowed drugs to market with an inferior understanding of their safety and effectiveness.

Importantly, this Section has offered only a sampling of serious problems damaging the integrity of FDA’s premarket review of drugs. It does not address special antibiotic pathways,<sup>322</sup> biologics, compounded drugs, generic drugs,<sup>323</sup> and “breakthrough” drugs. However, some of the critiques here apply to those programs as well. FDA has increasingly accepted a lower standard for drugs on the grounds that its role is predominantly speeding products to market, rather than consumer protection and evidence generation. One can wonder whether the opioid crisis and other serious drug-related harms could have been avoided through a properly functioning premarket-review regime.

### C. Tobacco Products

The Family Smoking Prevention and Tobacco Control Act (TCA) of 2009<sup>324</sup> was a landmark statute that provided FDA premarket review authority over tobacco products. FDA had earlier asserted jurisdiction over tobacco products

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319 See Matthew Perrone, *New FDA Chief Can’t Come Soon Enough for Beleaguered Agency*, AP NEWS (Oct. 8, 2021), <https://apnews.com/article/coronavirus-pandemic-joe-biden-science-business-health-62291dd94de2ec922bd9a76cbf389d66>. During his prior tenure at FDA, Dr. Sharfstein “often clashed with drug and device makers over tougher regulations.” Beth Snyder Bulik, *Woodcock to Step Up to Interim FDA Chief as She and Sharfstein Are Vetted for Permanent Job: Reports*, FIERCE PHARMA (Jan. 14, 2021), <https://www.fiercepharma.com/pharma/woodcock-to-step-interim-fda-commissioner-under-biden-sharfstein-waiting-wings-media-reports>. Dr. Sharfstein has stated that FDA’s increasing rate of drug approvals necessitates “changes . . . to make sure the medicines are worthwhile for patients.” Sydney Lupkin, *FDA Approves Drugs Faster Than Ever but Relies on Weaker Evidence, Researchers Find*, NPR (Jan. 14, 2020, 11:03 A.M.), <https://www.npr.org/sections/health-shots/2020/01/14/796227083/fda-approves-drugs-faster-than-ever-but-relies-on-weaker-evidence-researchers-fi>.

320 Christina Jewett, *F.D.A.’s Drug Industry Fees Fuel Concerns over Influence*, N.Y. TIMES (Sept. 15, 2022), <https://www.nytimes.com/2022/09/15/health/fda-drug-industry-fees.html>.

321 Mitchell, Trivedi & Bach, *supra* note 4, at 287.

322 Spencer Phillips Hey et al., *Influence, Integrity, and the FDA: An Ethical Framework*, 357 SCIENCE 876, 876 (2017).

323 See generally KATHERINE EBAN, *BOTTLE OF LIES: THE INSIDE STORY OF THE GENERIC DRUG BOOM* (2019) (describing serious problems with FDA oversight of generic drugs).

324 Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified as amended in scattered sections of 15 U.S.C. and 21 U.S.C.).

under the “1996 rule,” but the Supreme Court held in 2000 that FDA may not regulate cigarettes as drugs or devices.<sup>325</sup> The TCA brought hope that the federal government would reign in a persistent top cause of death and disease in the United States—tobacco use and associated nicotine addiction<sup>326</sup>—largely through premarket review. With tobacco review, FDA may only authorize new tobacco products that are “appropriate for the protection of the public health.”<sup>327</sup>

### 1. *Statutory Defects*

Despite hopes that premarket review might tackle the public-health harm from tobacco, the statute suffered from at least two defects. The first defect is that Congress exempted from review all tobacco products already on the market as of February 15, 2007.<sup>328</sup> Only new tobacco products required FDA review.<sup>329</sup> Therefore, cigarettes, which kill approximately 480,000 Americans each year,<sup>330</sup> were allowed to remain on the market. Of course, *premarket* review for these cigarettes was impossible since they were already marketed, but other premarket review regimes have applied post-hoc, such as premarket review of drugs (with the Drug Efficacy Study Initiative, or DESI<sup>331</sup>) and devices.<sup>332</sup> And although post-hoc review is laborious, cigarettes are also uniquely dangerous and in need of review.

It does not end there. The TCA provides a “substantial equivalence” pathway, analogous to device substantial equivalence,<sup>333</sup> that has allowed new cigarette (and other tobacco) products to come on the market despite serious public health harms simply because they resemble their predecessors.<sup>334</sup> Therefore, cigarettes, even new ones, can largely avoid premarket review.<sup>335</sup>

Still, the TCA was a compromise, evident in tobacco companies like Philip

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325 *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 161 (2000).

326 In this paper, tobacco use refers to the use of products containing materials made or derived from tobacco, including nicotine from any source.

327 FDCA § 910(c)(2)(A).

328 *Id.* § 910(a).

329 *Id.* § 910(a)(2).

330 *Tobacco-Related Mortality*, CTRS. FOR DISEASE CONTROL & PREVENTION (Apr. 28, 2020), [https://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/health\\_effects/tobacco\\_related\\_mortality/index.htm](https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm).

331 Carpenter, Greene & Moffitt, *supra* note 59, at 307–08.

332 HUTT ET AL., *supra* note 37, at 1204–05.

333 *See infra* Section II.E.1.

334 FDCA § 910(a)(2)(A)(i).

335 Not only does the TCA essentially carve out cigarettes, but it sanctioned a dangerous baseline. To be approved, new tobacco products must be “appropriate for the protection of the public health.” FDCA § 910(c)(2)(A). The presence of cigarettes increased the likelihood that other tobacco products that are incrementally less harmful would enter the market even if they, too, carry significant harms.



Morris supporting it.<sup>336</sup> Therefore, it is possible the public health value of premarket review would derive from review not of existing products, but of truly new products. However, the TCA had one more exception: it provided authority over only four named categories of tobacco products.<sup>337</sup> Therefore, as a practical matter, FDA did not have jurisdiction over new types of tobacco products coming to market, such as e-cigarettes.<sup>338</sup>

A full-blown epidemic of youth e-cigarette use has emerged over the past ten years. At the 2019 peak, 27.5% of U.S. high schoolers used e-cigarettes.<sup>339</sup> E-cigarettes have become the new public-relations off-ramp for tobacco companies, allowing them to shift marketing resources to a “public health-promoting” product while addicting a new generation of youth.<sup>340</sup> As nearly all tobacco use begins in youth,<sup>341</sup> e-cigarettes have been a substantial boon to the business model of tobacco companies. And yet FDA did not have jurisdiction over them in order to conduct premarket review.

So, Congress exempted existing tobacco products from premarket review, but it did not provide FDA with jurisdiction over new types of tobacco products. These carveouts essentially negated the public health value of premarket review. This premarket framework is clearly concessionary to the tobacco industry. While FDA was not left without options,<sup>342</sup> these examples illustrate clear statutory erosion of premarket review and symbolize the difficulty in passing truly progressive legislation with a Congress heavily influenced by corporate power.

## 2. *Ideological Capture and E-Cigarettes*

Despite statutory defects in the TCA, FDA had one ray of hope to secure premarket review over tobacco products: the deeming provision.<sup>343</sup> Through this provision, Congress permitted FDA to “deem” other tobacco products subject to the statute.<sup>344</sup> It took seven years, until 2016, for FDA to deem e-cigarettes

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336 Duff Wilson, *Philip Morris’s Support Casts Shadow over a Bill to Limit Tobacco*, N.Y. TIMES (Mar. 31, 2009), <https://www.nytimes.com/2009/04/01/business/01tobacco.html>.

337 FDCA § 901(b) (“cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco”).

338 FDA did have a hand in shaping the TCA and might have asked more questions about why it was only granted partial authority over tobacco products.

339 Aaron, *supra* note 4, at 870.

340 *Id.* at 880–85.

341 *Id.* at 874.

342 *See infra* Section II.C.2.

343 FDCA § 901(b) (“This chapter shall apply to all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco and to *any other tobacco products that the Secretary by regulation deems* to be subject to this chapter.”) (emphasis added).

344 *Id.*

subject to its authority, during which time e-cigarette use surged.<sup>345</sup> By 2016, the U.S. Centers for Disease Control and Prevention (CDC) had warned that youth e-cigarette use was “a major public health concern,” having risen 900% between 2011 and 2015 among high school students.<sup>346</sup>

As FDA obtained authority over e-cigarettes in 2016, a major question emerged: how would it approach e-cigarettes? The plain text of the TCA requires all new tobacco products introduced after February 15, 2007 to undergo premarket review for being “appropriate for the protection of public health.”<sup>347</sup> Clearly, Congress intended to keep off the market products that would harm or be neutral toward public health. FDA seemed intent on honoring Congress’s words. The Deeming Rule laid the groundwork for premarket review, stating e-cigarette applications were due in 2018.<sup>348</sup>

However, shortly after the Deeming Rule took effect, President Trump took office and appointed Dr. Scott Gottlieb as FDA Commissioner. Shortly thereafter, Dr. Gottlieb announced a “comprehensive” approach to nicotine and tobacco,<sup>349</sup> pushing the due date for premarket applications to 2022 by guidance document.<sup>350</sup> He championed the potential of “innovation” to reduce tobacco harms, lauded how nicotine-delivering products are now “regulated” and present less risk, and extolled the value of science in the tobacco space.<sup>351</sup> Put simply, he believed in the power of e-cigarettes to displace traditional cigarettes, and so premarket review, paradoxically, could damage the public health.

Dr. Gottlieb’s postponement of scientific review of tobacco products while lauding science was deeply ironic. Arguably, Dr. Gottlieb’s claim to be following science in deferring premarket review is ideological capture dressed in the language of science. Indeed, FDA Commissioner Scott Gottlieb was the “most interest-conflicted commissioner in American history, by far,” in the words of Daniel Carpenter, based on his industry ties.<sup>352</sup> Although the public health

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345 Aaron, *supra* note 4, at 890.

346 U.S. SURGEON GEN., E-CIGARETTE USE AMONG YOUTH AND YOUNG ADULTS: A REPORT OF THE SURGEON GENERAL vii (2016) [https://ecigarettes.surgeongeneral.gov/documents/2016\\_sgr\\_full\\_report\\_non-508.pdf](https://ecigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf).

347 FDCA § 910(a).

348 81 Fed. Reg. 28,974, 29,045 (May 10, 2016).

349 Scott Gottlieb, *Protecting American Families: Comprehensive Approach to Nicotine and Tobacco*, U.S. FOOD & DRUG ADMIN. (June 28, 2017), <https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017>.

350 U.S. FOOD & DRUG ADMIN., EXTENSION OF CERTAIN TOBACCO PRODUCT COMPLIANCE DEADLINES RELATED TO THE FINAL DEEMING RULE 8 (Nov. 2017), <https://wayback.archive-it.org/7993/20180124142324/https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM557716.pdf>.

351 Gottlieb, *supra* note 349.

352 Julia Belluz, *Scott Gottlieb, the New FDA Chief, Explained*, VOX (May 10, 2017),

approach to tobacco is rooted in a zero-trust approach of tobacco companies given their legacy of deceit,<sup>353</sup> Dr. Gottlieb’s belief in e-cigarette innovation and trust in voluntary steps from e-cigarette companies<sup>354</sup> suggest a medicalized, privatized approach to regulation (which, arguably, is the opposite of regulation). Declaring his hope to “transform the tobacco marketplace,” Dr. Gottlieb wrote in 2017 that “FDA is committed to striking an appropriate balance between protecting the public and fostering innovation in less harmful nicotine delivery.”<sup>355</sup> The buzzwords “marketplace” and “innovation” highlight Dr. Gottlieb’s neoliberal approach of tackling tobacco use not through FDA premarket review, but by skirting statutory requirements in order to liberalize e-cigarette use.<sup>356</sup> Dr. Gottlieb’s preference for “deregulation” and making FDA authorization easier to secure likely won him the appointment from President Trump, who had stated his goal to “remake” the FDA.<sup>357</sup>

Dr. Gottlieb soon regretted the FDA policy postponing premarket review of e-cigarettes. Just one year later, he made a startling admission of his and the agency’s mistakes: “We didn’t predict what I now believe is an epidemic of e-cigarette use among teenagers. Today we can see that this epidemic of addiction was emerging when we first announced our plan last summer.”<sup>358</sup> These are

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<https://www.vox.com/2017/3/10/14887290/scott-gottlieb-fda-trump>. And, no doubt, Dr. Gottlieb’s 180-degree policy change from the deeming rule was fueled and enabled by trends in Supreme Court jurisprudence promoting the unitary executive and top-down control over agencies. *See, e.g., Seila Law, LLC v. CFPB*, 140 S. Ct. 2183, 2211 (2020).

353 *See* Kelly D. Brownell & Kenneth E. Warner, *The Perils of Ignoring History: Big Tobacco Played Dirty and Millions Died. How Similar Is Big Food?*, 87 MILBANK Q. 259, 259 (2009) (“The tobacco industry had a playbook, a script, that emphasized personal responsibility, paying scientists who delivered research that instilled doubt, criticizing the ‘junk’ science that found harms associated with smoking, making self-regulatory pledges, lobbying with massive resources to stifle government action, introducing “safer” products, and simultaneously manipulating and denying both the addictive nature of their products and their marketing to children.”).

354 *See* Stanton A. Glantz, *FDA Commissioner Scott Gottlieb Is Falling into an Old Industry Trap by Expressing Willingness to Partner on “Youth E-Cigarette Prevention”*, UCSF CTR. FOR TOBACCO CONTROL RSCH. & EDUC. (Nov. 5, 2018), <https://tobacco.ucsf.edu/fda-commissioner-scott-gottlieb-falling-old-industry-trap-expressing-willingness-partner-%E2%80%9Cyouth-e-cigarette-prevention%E2%80%9D>.

355 Scott Gottlieb & Mitchell Zeller, *A Nicotine-Focused Framework for Public Health*, 377 NEW ENG. J. MED. 1111, 1113 (2017).

356 Aaron, *supra* note 4, at 847.

357 Joe Neel, *Trump Chooses Dr. Scott Gottlieb to Head Food and Drug Administration*, NPR (Mar. 10, 2017), <https://www.npr.org/sections/health-shots/2017/03/10/519703946/trump-to-nominate-dr-scott-gottlieb-to-head-food-and-drug-administration>; Katie Thomas, *F.D.A. Nominee, Paid Millions by Industry, Says He’ll Recuse Himself If Needed*, N.Y. TIMES (Mar. 9, 2017), <https://www.nytimes.com/2017/03/29/health/fda-nominee-scott-gottlieb-recuse-conflicts.html>.

358 *Statement from FDA Commissioner Scott Gottlieb, M.D., on New Steps to Address Epidemic of Youth E-Cigarette Use*, U.S. FOOD & DRUG ADMIN. (Sept. 11, 2018), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb->

shocking admissions from an FDA Commissioner who one year earlier nixed premarket review while espousing the value of science and public health.

As gatekeeper, FDA shirked congressionally required premarket review by not enforcing the statutory mandate, thereby carving a gap between Congress's words and their enforcement.<sup>359</sup> Public health groups, which were alarmed by the CDC's reports about youth e-cigarette use,<sup>360</sup> sued FDA on the grounds that its guidance document postponing premarket review was a legislative rule and an abdication of FDA's responsibilities under the TCA.<sup>361</sup> The public health groups won, and the District of Maryland invalidated the guidance. The judge determined that FDA's policy was "tantamount to an amendment to the Tobacco Control Act," and that "these requirements . . . run 180 degrees counter to the plain meaning of the statute."<sup>362</sup> These are strong words from an Article III court and an indictment of FDA's hands-off approach to e-cigarettes. Indeed, FDA's approach reflects neoliberalism in that it returned the decision to use e-cigarettes to individual consumers despite a statutory responsibility to conduct premarket review.

Extraordinarily, the Court crafted specific injunctive relief to remedy FDA's illegal actions:

The issue is whether this case presents those "extraordinary circumstances" that call for more than a simple remand or vacatur. . . .

Given the uncertainty in the efficacy of e-cigarettes as smoking cessation devices, the overstated effects that a shorter deadline may have on manufacturers, the Industry's recalcitrance, the continued availability of e-cigarettes and their acknowledged appeal to youth, and the clear public health emergency, I find that a deadline is necessary.<sup>363</sup>

The judge ordered applications for new tobacco products covered by the Deeming Rule to be submitted within 10 months, and for the applications to be reviewed within an additional year (or else products must be "subject to"

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md-new-steps-address-epidemic-youth-e-cigarette-use.

359 Industry filed suit to avoid premarket review of e-cigarettes writ large. However, courts rebuffed this effort. *See Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 281 (D.C. Cir. 2019) (holding that the subjection of e-cigarettes to premarket review is congressionally mandated and therefore cannot be challenged under the APA).

360 Aaron, *supra* note 4, at 847.

361 *Am. Acad. of Pediatrics v. FDA*, 379 F. Supp. 3d 461, 469 (D. Md. 2019).

362 *See id.* at 497–98 (cleaned up).

363 *Am. Acad. of Pediatrics v. FDA*, 399 F. Supp. 3d 479, 481, 486–87 (D. Md. 2019).

enforcement action).<sup>364</sup> The judge’s strong relief for plaintiffs indicates the level of FDA’s deviation from the statute amid a public health emergency. This decision had an immediate effect on the e-cigarette market by subjecting e-cigarette companies to an expedited regime in which their products were analyzed for their public health merit. Therefore, companies that addicted youth could be at risk of market removal. E-cigarette use appeared to decline in 2020 and 2021, although the COVID-19 pandemic interfered with data tracking, making it difficult to ascertain youth levels of e-cigarette use.<sup>365</sup>

In sum, Dr. Gottlieb’s ideology appeared to displace the rule of law and public health concerns with e-cigarettes. Thankfully, by ordering FDA to institute premarket review as it was already required to do under the TCA, the court protected the American public from an e-cigarette wild west.

### 3. DOJ and Legal Wrangling

The *American Academy of Pediatrics v. FDA* lawsuit teed up the question of how premarket review would operate under a court order, but FDA’s actions were not more encouraging. Pursuant to the court order, a rush of applications arrived in September 2020, and FDA had one year of discretion before the court would expect enforcement. FDA needed to decide what would happen to products on the market in the interim. The agency could have enforced against youth-addicting products immediately for lack of marketing authorization under the TCA.<sup>366</sup> Further, most youth-appealing flavored e-cigarettes were immediate targets for enforcement under a 2020 FDA guidance.<sup>367</sup>

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<sup>364</sup> *Id.* at 487. The order requiring FDA to review applications within one year has important ambiguity. It states, “New Products for which applications have been timely filed may remain on the market without being subject to FDA enforcement actions for a period not to exceed one year from the date of application while FDA considers the application.” *Id.* This order does not *per se* require FDA to review applications within one year but requires that any new products with unreviewed applications must be “subject to” FDA enforcement actions after one year. Of course, “subject to” can be fairly general or literally mean *subjected to enforcement*. See *Merriam-Webster*, “subject to,” <https://www.merriam-webster.com/dictionary/subject%20to> (Accessed Aug. 25, 2023) (defining “subject to” as “affected by or possibly affected by (something)”). Because the judge wrote earlier in the opinion, “I will impose . . . a one-year deadline for approval,” 399 F. Supp. 3d at 481, and was perturbed by a pressing public health emergency, it is likely he intended for FDA to take action on products within a year. It is dubious that the judge would have been satisfied by the mere possibility of enforcement against e-cigarettes.

<sup>365</sup> *Youth E-cigarette Use Remains Serious Public Health Concern amid COVID-19 Pandemic*, U.S. FOOD & DRUG ADMIN. (Sept. 30, 2021), <https://www.fda.gov/news-events/press-announcements/youth-e-cigarette-use-remains-serious-public-health-concern-amid-covid-19-pandemic>.

<sup>366</sup> FDCA § 910(c)(1)(A).

<sup>367</sup> U.S. FOOD & DRUG ADMIN., ENFORCEMENT PRIORITIES FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (ENDS) AND OTHER DEEMED PRODUCTS ON THE MARKET WITHOUT PREMARKET AUTHORIZATION 31 (April 2020), <https://www.fda.gov/media/133880/download>.

Instead of enforcing, FDA took the approach that products with pending applications can remain on the market for one year while the application is reviewed.<sup>368</sup> However, this approach continued past the one-year period when the court expected FDA to earnestly begin enforcement. Even today, most of the top-market-share products (e.g., Juul) still have pending applications and have not been removed from the market. Therefore, FDA has essentially continued an enforcement discretion policy for e-cigarettes even after losing in *American Academy of Pediatrics v. FDA*. FDA has defended itself by issuing a statement, precisely on the one-year review deadline, that it had taken action on more than 90% of timely-submitted applications.<sup>369</sup> However, it admitted that 75% of all applications were from a single applicant and were disposed of through an administrative process for missing required contents.<sup>370</sup> And, again, actions were not taken on high-market-share products.

Frustrated, the plaintiffs in *American Academy of Pediatrics* moved to reopen the case in November 2021. They noted that “FDA has not issued a single PMTA [premarket tobacco product application] decision on any of the products with the largest market share in the market as a whole or in the youth market.”<sup>371</sup> Asking for periodic status reports, the plaintiffs noted that e-cigarette products “remain on the market for an indeterminate amount of time, despite receiving no FDA authorization.”<sup>372</sup> The court agreed, finding this status quo was “inconsistent” with the court’s previous judgment,<sup>373</sup> and ordered FDA to submit status reports every 90 days.<sup>374</sup> FDA has made progress since then, although some of the highest-market-share products remain on the market. In the absence of enforcement, e-cigarette companies now regularly ignore warning letters for

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368 *Id.* at 27; *Perspective: FDA’s Progress on Tobacco Product Application Review and Related Enforcement*, U.S. FOOD & DRUG ADMIN. (Sept. 9, 2021), <https://www.fda.gov/tobacco-products/ctp-newsroom/perspective-fdas-progress-tobacco-product-application-review-and-related-enforcement>; *Deemed New Tobacco Product Applications Lists*, U.S. FOOD & DRUG ADMIN. (Aug. 9, 2021), <https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/deemed-new-tobacco-product-applications-lists#list%20of%20deemed>.

369 *FDA Makes Significant Progress in Science-Based Public Health Application Review, Taking Action on Over 90% of More Than 6.5 Million ‘Deemed’ New Tobacco Products Submitted*, U.S. FOOD & DRUG ADMIN. (Sept. 9, 2021), <https://www.fda.gov/news-events/press-announcements/fda-makes-significant-progress-science-based-public-health-application-review-taking-action-over-90>.

370 *Id.*

371 *RE: American Academy of Pediatrics, et al., v. FDA* at 2, *Am. Acad. of Pediatrics v. FDA*, No. 8:18-cv-00883 (D. Md. Nov. 15, 2021), ECF No. 195.

372 *Id.* at 3.

373 Letter Order at 2, *Am. Acad. of Pediatrics v. FDA*, No. 8:18-cv-00883 (D. Md. Apr. 15, 2022), ECF No. 201.

374 Revised Remedial Order at 1, *Am. Acad. of Pediatrics v. FDA*, No. 8:18-cv-00883 (D. Md. Apr. 15, 2022), ECF No. 202.

failure to obtain marketing authorization.<sup>375</sup> Even so, FDA continues to assert that new tobacco products require premarket authorization for marketing.<sup>376</sup> Strong words, soft touch.<sup>377</sup>

What can explain the gap between FDA’s assertion that premarket review is required but a lack of enforcement of the premarket review requirement? The most likely cause is law. Enforcement is a legal mechanism that requires FDA lawyers to be on board. Further, as FDA lacks independent litigating authority, it must secure cooperation from DOJ to go to court. A recent unprecedented study of the FDA–DOJ interactions in enforcement has confirmed that DOJ vetoes numerous enforcement actions that FDA would otherwise bring.<sup>378</sup> Further, a recent report FDA commissioned of its tobacco center found that DOJ was a significant barrier to tobacco enforcement.<sup>379</sup> Most likely, lawyers at DOJ would rather premarket review decisions be made on the scientific level rather than as a matter of law, and therefore products with applications are allowed to remain on the market pending scientific review.

Indeed, a scientific decision is more likely to survive in court given judges’ limited expertise. Further, FDA is required to review applications within 180 days,<sup>380</sup> a timeline it could not meet given the millions of applications, and therefore a manufacturer could claim it was denied the opportunity to even go through premarket review before enforcement. While these arguments hold some merit, premarket review is legally binding and should be enforced as such. Recent statements by FDA officials support the theory that lawyers vetoed enforcement of premarket review requirements. In the words of Mitch Zeller, director of FDA’s tobacco regulatory efforts, “*technically*, for the newly deemed products, any product that is on the market without what is required by law to be a marketing authorization, *technically* that product is marketed unlawfully and subject to enforcement action at our discretion.”<sup>381</sup> That a center director would attend a major tobacco conference and repeat twice that the premarket review requirement is only *technical* is shocking and likely stems from DOJ lawyers not treating premarket review requirements as binding in letter or spirit.

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<sup>375</sup> Nicholas Florke & Elissa Welle, *The FDA Stands By as the Vaping Industry Flouts Its Orders*, STAT (Aug. 24, 2022), <https://www.statnews.com/2022/08/24/the-fda-stands-by-as-the-vaping-industry-flouts-its-orders>.

<sup>376</sup> *Perspective*, *supra* note 368.

<sup>377</sup> Still, FDA is trying to catch up with the millions of applications it received.

<sup>378</sup> C. Joseph Ross Daval, *Litigating Authority for the FDA*, 100 WASH. U. L. REV. 175, 192, 214 (2022).

<sup>379</sup> REAGAN-UDALL FOUNDATION, OPERATIONAL EVALUATION OF CERTAIN COMPONENTS OF FDA’S TOBACCO PROGRAM 22–23 (2022).

<sup>380</sup> FDCA § 910(c)(1)(A).

<sup>381</sup> SRNT PR, *SRNT 2022 FDA Special Session*, YOUTUBE (Mar. 16, 2022), <https://www.youtube.com/watch?v=NVvY1-luA4M> (19:07).

The inevitable consequence of FDA's and DOJ's non-enforcement is the marketing of tobacco products before FDA review. Despite clear congressional intent for *premarket* review, the future of e-cigarette use among youth will depend largely on postmarket action.

#### 4. *Litigation over Scientific Decisions*

Despite attempts to shield FDA decisions by making them on the scientific front—as opposed to the legal front—the deep financial resources of the tobacco industry and a willingness to litigate have hampered FDA review regardless. As of March 2022, seven cases led to stays of market denial orders, and thus essentially prevented FDA enforcement against these companies.<sup>382</sup> In addition, there were 48 cases for judicial review of specific market denial orders for tobacco products, 44 of which were pending.<sup>383</sup> This is a huge amount of litigation facing an agency that is trying to establish its tobacco premarket review program, and it no doubt drains staff resources, thus delaying premarket review even further. In June 2022, FDA denied marketing authorization to Juul, perhaps the biggest instigator of the youth e-cigarette epidemic, and one day later, a court administratively stayed the decision.<sup>384</sup>

As a result of litigation, FDA has taken the approach of staying its own market denial orders in order to buy more time to rereview its decisions, likely in the hopes of reducing the odds of a litigation loss. For example, in July 2022, FDA stayed its denial of Juul products, promising not to take enforcement action during the stay plus an additional thirty days.<sup>385</sup> Essentially, FDA is allowing Juul to remain on the market despite lack of authorization to minimize litigation risk, indicating the power of law to upend FDA decision making. Sure enough, Juul's D.C. Circuit case against FDA is now in abeyance<sup>386</sup>—but at what cost to public health? In 2022, FDA predicted it will clear its backlog of high-market-share applications (i.e., those filed by September 9, 2020) by June 30, 2023.<sup>387</sup> However, given litigation, those decisions may not be effective until years later.

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<sup>382</sup> *Id.* at 15:06.

<sup>383</sup> *Id.*

<sup>384</sup> Tom Murphy, *Juul Can Keep Selling E-cigarettes as Court Blocks FDA Ban*, AP NEWS (June 24, 2022), <https://apnews.com/article/science-politics-health-tobacco-industry-regulation-a52e9928a95908c3556a411a3738cef7>.

<sup>385</sup> *FDA Denies Authorization to Market JUUL Products*, U.S. FOOD & DRUG ADMIN. (June 23, 2022), <https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products>; Matthew Perrone, *Juul, FDA Suspend Court Case While E-Cigarette Ban on Hold*, AP NEWS (July 6, 2022, 8:06 PM EDT), <https://apnews.com/article/science-health-tobacco-industry-regulation-f0734a2149ac6578015901ee144ddc76>.

<sup>386</sup> Order, *Juul Labs, Inc. v. FDA*, No. 22-1123 (D.C. Cir. July 7, 2022), ECF No. 1953851.

<sup>387</sup> Status Report at 1–3, *Am. Acad. of Pediatrics v. FDA*, No. 8:18-cv-00883 (D. Md. May 13, 2022), ECF No. 205.



In an update to the court in January 2023, FDA described the challenges of facing “more than 50 lawsuits challenging its e-cigarette marketing decisions” and the resulting drain on agency resources.<sup>388</sup> It updated the expected date for clearing the backlog to December 31, 2023<sup>389</sup>—but “unauthorized e-cigarettes continue to launch.”<sup>390</sup>

### 5. *The Fall of Tobacco Review*

Premarket review of tobacco products is embattled. Thankfully, cigarette marketing and sales, one of the biggest killers of Americans, have waned over the past two decades in the wake of federal and state regulatory and litigation efforts.<sup>391</sup> On the other hand, e-cigarette use has become endemic among youth, peaking in 2019 and still high. Many unauthorized e-cigarettes remain on the market, with some companies representing the largest market shares among youth largely free from enforcement (including Juul and Puff Bar),<sup>392</sup> applications pending. Other available e-cigarettes likely do not have applications pending, including thousands of products “pouring into the US” from China, according to one news article<sup>393</sup>—the exact opposite of what premarket review is supposed to achieve. FDA is stuck on a never-ending treadmill, unable to catch up with new products, and apparently unwilling to boldly use its enforcement tools in the meantime. FDA has not authorized a single flavored e-cigarette (other than tobacco flavor),<sup>394</sup> yet it is flavored e-cigarettes that drive youth use.<sup>395</sup>

And while e-cigarette companies may have a temporary incentive to “lay

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<sup>388</sup> Status Report at 2, *Am. Acad. of Pediatrics v. FDA*, No. 8:18-cv-00883 (D. Md. Jan. 24, 2023), ECF No. 211.

<sup>389</sup> *Id.*

<sup>390</sup> Matthew Perrone, *FDA Warns Stores to Stop Selling Elf Bar, the Top Disposable E-Cigarette in the US*, AP NEWS (June 22, 2023, 1:02 PM EDT), <https://apnews.com/article/ecigarettes-elf-bar-vapes-4353becf747846b528ec2aea609ed2f9>.

<sup>391</sup> U.S. SURGEON GEN., *THE HEALTH CONSEQUENCES OF SMOKING—50 YEARS OF PROGRESS* 18 (2014).

<sup>392</sup> FDA has, however, issued an import alert for Elf Bar. *FDA Roundup: May 19, 2023*, U.S. FOOD & DRUG ADMIN. (May 19, 2023), <https://www.fda.gov/news-events/press-announcements/fda-roundup-may-19-2023>. Elf Bar is now the top disposable e-cigarette on the U.S. market. Perrone, *supra* note 390. Elf Bar may not have submitted an application to FDA, which could explain FDA’s use of enforcement tools, in contrast with Juul and Puff Bar.

<sup>393</sup> Matthew Perrone, *Thousands of Unauthorized Vapes Are Pouring into the US Despite the FDA Crackdown on Fruity Flavors*, AP NEWS (June 26, 2023, 7:43 PM EDT), <https://apnews.com/article/fda-vapes-vaping-elf-bar-juul-80b2680a874d89b8d651c5e909e39e8f>.

<sup>394</sup> *FDA Denies Marketing of Two Vuse Solo Menthol E-Cigarette Products*, U.S. FOOD & DRUG ADMIN. (Mar. 17, 2023), <https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-two-vuse-solo-menthol-e-cigarette-products>.

<sup>395</sup> Of youth e-cigarette users, 85% use flavored e-cigarettes. *More than 2.5 Million Youth Reported E-Cigarette Use in 2022*, CTRS. FOR DISEASE CONTROL & PREVENTION (Oct. 6, 2022, 1:00 P.M. ET), <https://www.cdc.gov/media/releases/2022/p1007-e-cigarette-use.html>.

low” while FDA reviews their applications, it is doubtful these companies will not push for more youth use if they receive marketing authorization. Indeed youth-oriented marketing has been a mainstay of e-cigarette manufacturers like Juul.<sup>396</sup> Senator Dick Durbin has criticized FDA for this status quo:

[A]ddictive e-cigarettes like JUUL are only on the store shelves because the FDA has given the tobacco companies a free pass to sell their vaping products. . . . So today, I am calling on the FDA to immediately halt its enforcement discretion and remove all unauthorized e-cigarettes from the market. Don’t allow JUUL and other tobacco companies one more day of endangering our children.<sup>397</sup>

While the Senator’s comments might be additionally targeted at Congress as well as FDA and DOJ lawyers for disfavoring enforcement,<sup>398</sup> he is not wrong to look to the failures of FDA review in attributing responsibility for youth e-cigarette addiction. The tobacco story is one of (1) statutory defects; (2) presidential control over selection of the FDA Commissioner, which placed the industry-friendly Dr. Gottlieb in that role; (3) Dr. Gottlieb’s faith in the goodwill of tobacco companies and the safety of new tobacco technology even without the regulatory guardrails of premarket review; and (4) law, lawyers, and judges preventing an agency from enforcing the law and clearing the market. In one case, a court insulated an entire category of tobacco products (premium cigars) from premarket review.<sup>399</sup> As FDA Commissioner Robert Califf has opined, the tobacco industry “has amazing capabilities on the legal front. If we make one single error in the process, we can be set back for years in these applications.”<sup>400</sup> Califf’s words point to the threat of lawsuits, and the resultant internal wrangling with FDA and DOJ lawyers, as the current problem undermining tobacco premarket review.

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396 Aaron, *supra* note 4, at 881–84.

397 Durbin: *I’m Calling on FDA to Immediately Halt Its Enforcement Discretion and Remove All Unauthorized E-Cigarettes from the Market*, DICK DURBIN: ILLINOIS (May 18, 2022), <https://www.durbin.senate.gov/newsroom/press-releases/durbin-im-calling-on-fda-to-immediately-halt-its-enforcement-discretion-and-remove-all-unauthorized-e-cigarettes-from-the-market>.

398 As discussed above, FDA continually asserts that products require premarket review to be legally marketed, and therefore the blockade is likely in terms of enforcement.

399 Cigar Ass’n of Am. v. FDA, 480 F. Supp. 3d 256, 281 (D.D.C. 2020); *see also* Memorandum Opinion and Order, Cigar Ass’n of Am. v. FDA, No. 1:16-cv-01460-APM (D.D.C. July 5, 2022), ECF No. 268 (holding that FDA’s deeming of premium cigars subject to the Tobacco Control Act was arbitrary and capricious).

400 Celine Castronuovo, *FDA Must Be ‘Judicious’ in Vaping Enforcement, Califf Says*, BLOOMBERG LAW (May 19, 2022), <https://news.bloomberglaw.com/health-law-and-business/fda-must-be-judicious-in-vaping-enforcement-califf-says>.

#### D. Food Additives

For substances that can be so harmful to human health, it is surprising how far the regulation of food additives<sup>401</sup> has fallen in the last six decades. Food additives by law require premarket review.<sup>402</sup> However, today, nearly all food additives avoid premarket review through a loophole known as “generally recognized as safe” (GRAS),<sup>403</sup> in which industry evaluates safety at its discretion and often brings new additives to market without FDA oversight or awareness.<sup>404</sup> There are two general types of GRAS substances of public health concern. First, many long-used GRAS substances have been proven toxic or directly harmful to human health, including sugar, trans fats, and salt.<sup>405</sup> Other GRAS substances may be lesser-known chemicals suspected of carcinogenicity or other harms. For example, butylated hydroxyanisole, widely added to fatty foods as a preservative, is “reasonably anticipated to be a human carcinogen,” according to the National Toxicology Program.<sup>406</sup>

Congress passed the Food Additives Amendment in 1958 in response to increasing concern about chemicals added to foods.<sup>407</sup> It was subtitled “An Act [t]o protect the public health by amending the FDCA to prohibit the use in food of additives which have not been adequately tested to establish their safety.”<sup>408</sup> It provided for premarket review of food additives.<sup>409</sup> Food additives were defined broadly: “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food.”<sup>410</sup> Industry carried the burden of showing a proposed additive was safe for a particular use.<sup>411</sup> Congress also recognized that some food additives were in such prevailing use that premarket review was unnecessary.<sup>412</sup> Therefore, it excluded from the statutory definition of food additive (and therefore from premarket review) any substance that is GRAS.<sup>413</sup> Arguably, Congress’s use of vague language vested a resource-

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401 In this article, I use “food additives” to refer to substances added to food, other than color additives. Legally, however, a substance that is generally recognized as safe (GRAS) is not a food additive.

402 FDCA § 409.

403 FDCA § 201(s).

404 Faustman et al., *supra* note 4, at 1261.

405 See, e.g., FREUDENBERG, *supra* note 74, at 46–48.

406 *Butylated Hydroxyanisole*, REP. ON CARCINOGENS, NAT’L TOXICOLOGY PROGRAM (15th ed., 2021), <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/butylatedhydroxyanisole.pdf>.

407 62 Fed. Reg. 18938 (Apr. 17, 1997).

408 Food Additives Amendment of 1958, Pub. L. No. 85-929, 52 Stat. 1041.

409 FDCA § 409.

410 FDCA § 201(s).

411 FDCA § 409(c)(3); 62 Fed. Reg. 18939.

412 *Id.* at 18938–39.

413 *Id.*

starved food center at FDA with discretion to swallow almost all food additive regulation into the GRAS exception.

At first, despite the GRAS exception, FDA exerted significant premarket authority. FDA generally knew what substances were added to food because, immediately after the Food Additives Amendment, FDA created a list of GRAS substances, which it updated consistently.<sup>414</sup> In 1974, FDA promulgated regulations creating a premarket petition process for GRAS status, which, as FDA later clarified, asked for the same scientific evidence as was required for food additive approval.<sup>415</sup> This uniform, high evidentiary bar reflected respect for premarket review. And although the petition program was technically not mandatory for marketing,<sup>416</sup> FDA carried significant authority over the market. It also conducted its own large study: between 1972 and 1982, an FDA-contracted committee created “detailed reports” on the safety of more than 400 GRAS substances.<sup>417</sup> And when FDA believed a substance was GRAS for certain uses, it sought notice and comment and, if encouraging, used rulemaking to affirm GRAS status.<sup>418</sup> Therefore, GRAS products were subject to significant premarket (and postmarket) oversight, and companies generally engaged with FDA before bringing new food substances to market.

FDA abandoned these efforts by 1997.<sup>419</sup> Faced with insufficient funding and a backlog of petitions for GRAS substances *and* for food additives, it abandoned its GRAS premarket petition regime, moving toward a voluntary notification process.<sup>420</sup> This change made the GRAS pathway vastly more lenient than the food additive pathway—an efficient but lax superhighway that could solve both backlogs at once. This sidelining of premarket review has led many to self-determine their products as GRAS without FDA awareness—a process that has been called “secret GRAS”—which is rife with conflicts of interest.<sup>421</sup> Through January 2011, approximately 1,000 substances are estimated to have entered the market as GRAS after secret deliberations by food companies,<sup>422</sup> though that number is larger today. Further, although GRAS status applies to a

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414 Beyranevand, *supra* note 4, at 898–99. Not all substances ended up on the list, but the list was broad and consistently updated. *Id.* at 899.

415 *Id.* at 903.

416 *Id.* at 899.

417 *GRAS Substances (SCOGS) Database*, U.S. FOOD & DRUG ADMIN. (Mar. 3, 2022), <https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database>; *History of the GRAS List and SCOGS Reviews*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), <https://www.fda.gov/food/gras-substances-scogs-database/history-gras-list-and-scogs-reviews>.

418 *History of the GRAS List and SCOGS Reviews*, *supra* note 417.

419 Peter Barton Hutt, *Historical Themes*, *supra* note 56, at 26; 62 Fed. Reg. 18941 (Apr. 17, 1997). The rule was finalized in 2016. 81 Fed. Reg. 54,960 (Aug. 17, 2016).

420 Hutt, *supra* note 56, at 26; Faustman et al., *supra* note 4, at 1261.

421 Faustman et al., *supra* note 4, at 1260 (citation omitted).

422 *Id.* at 2.

particular substance “under the conditions of its intended use,”<sup>423</sup> in practice, companies are free to devise new uses and creative combinations of additives.

We do not know the full scope of substances added to food in the United States, but very few food additives use the premarket review pathway.<sup>424</sup> The consequence is a flooding of unvetted food additives onto the market without oversight.<sup>425</sup> As concluded by the U.S. Government Accountability (GAO) office in 2010, “FDA’s Oversight Process Does Not Help Ensure the Safety of All New GRAS Determinations.”<sup>426</sup> The language “does not help” indicates the level of faith GAO had in FDA’s GRAS regime.

There is evidence that many substances deemed GRAS are harmful. Trans fats notably killed about 7,000 people per year until FDA revoked the GRAS status of partially hydrogenated oils (the main source) in 2015.<sup>427</sup> By the time FDA took action, at least 75% of trans fats were already removed from the food supply due to public pressure and state and local lawmaking.<sup>428</sup> Likewise, because caffeine is generally treated as GRAS, caffeinated concoctions are not reviewed before marketing.<sup>429</sup> Between 2004 and 2014, energy drinks with caffeine caused 34 deaths, and the combination of caffeine with alcohol was deemed particularly dangerous.<sup>430</sup> Four Loko famously combined alcohol and caffeine in a fruity youth-marketed drink, and it caused “scores of deaths and hospitalization” in youth.<sup>431</sup> Caffeinated alcohol drinks can create a “wide-awake

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423 FDCA § 201(s).

424 Kimberly Kindy, *Food Additives on the Rise as FDA Scrutiny Wanes*, WASH. POST (Aug. 17, 2014), [https://www.washingtonpost.com/national/food-additives-on-the-rise-as-fda-scrutiny-wanes/2014/08/17/828e9bf8-1cb2-11e4-ab7b-696c295ddf1\\_story.html](https://www.washingtonpost.com/national/food-additives-on-the-rise-as-fda-scrutiny-wanes/2014/08/17/828e9bf8-1cb2-11e4-ab7b-696c295ddf1_story.html).

425 It is true FDA has received more than 1000 voluntary GRAS notices. *See Gras Notices*, U.S. FOOD & DRUG ADMIN. (Apr. 3, 2023), <https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices>. However, a voluntary regime is not premarket review. It allows an unknown number of unknown products to market, and the very products that are most dangerous will be more likely to bypass a voluntary process.

426 FDA SHOULD STRENGTHEN ITS OVERSIGHT OF FOOD INGREDIENTS DETERMINED TO BE GENERALLY RECOGNIZED AS SAFE (GRAS), U.S. GOV’T ACCOUNTABILITY OFF. 8 (Feb. 2010).

427 Walter Willett, *The Scientific Case for Banning Trans Fats*, SCI. AM. (Mar. 2014), <https://www.scientificamerican.com/article/scientific-case-for-banning-trans-fats>.

428 *Id.*

429 *See* Leah S. Rosenfeld et al., *Regulatory Status of Caffeine in the United States*, 72 NUTRITION REVS. 23, 26 (2014). Technically, the GRAS listing applies only to caffeine used in cola-type beverages at a maximum concentration of 0.02%. *Id.*; 21 C.F.R. § 182.1180. But in practice, FDA does not require caffeine-containing foods to be reviewed before marketing, as companies are permitted to self-determine GRAS status (without FDA awareness) and are incentivized to do so “in almost all cases.” Faustman et al., *supra* note 4, at 1261; *see also* Rosenfeld, *supra* (describing a caffeine concentration of 0.02% as allowed but noting that the legal status of higher concentrations is indeterminate).

430 Faustman et al., *supra* note 4, at 1262.

431 Ricardo Lopez, *Legal Settlement Restricts Marketing of Four Loko Alcoholic Drinks*, L.A. TIMES (Mar. 25, 2014), <https://www.latimes.com/business/la-fi-mo-four-loko-settlement->

drunk” that allows people to drink more before passing out and inhibits self-recognition of being drunk.<sup>432</sup> FDA notified the seven manufacturers in 2010 that caffeine is not GRAS when mixed with alcohol, which led them to pull the products from the market.<sup>433</sup> While FDA took postmarket action on caffeinated alcohol drinks, caffeinated energy drinks (and other caffeinated foods) continue to cause public health concerns sans premarket review.<sup>434</sup> FDA officials have admitted caffeine’s proliferation in the food supply is of growing concern.<sup>435</sup>

The most dangerous GRAS substance of all is probably sugar, which has fueled epidemics of obesity, diabetes, and heart disease.<sup>436</sup> Recent research has found sugar can cause addiction—hardly a characteristic of a known safe chemical.<sup>437</sup> Salt, too, is considered GRAS by FDA, despite being responsible for more than 50,000 American deaths each year,<sup>438</sup> and the American Medical Association has urged FDA to revoke salt’s GRAS status.<sup>439</sup> This is not to say salt and sugar should be banned. Rather, FDA could assess the safety of a particular quantity of salt and sugar; as noted, GRAS status is supposed to be connected to an “intended use.”<sup>440</sup>

The food additive story is largely about resources. FDA’s regulation of food has been almost entirely supported by appropriations, while drug regulation has been supported by user fees since 1992.<sup>441</sup> As Peter Barton Hutt has noted, non-user-fee-funded programs play second fiddle, as Congress must increase appropriations for user fees proportionately to what industry pays.<sup>442</sup> Without increases to FDA funding, user-fee-funded programs can indirectly drain

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20140325-story.html#axzz2x9Uqhhvp.

432 Jenna Johnson & Kevin Sieff, *Four Loko Ban Fuels Buying Binge*, WASH. POST (Nov. 18, 2010), <https://www.washingtonpost.com/wp-dyn/content/article/2010/11/18/AR2010111806114.html>.

433 *Alcohol and Caffeine*, CTRS. FOR DISEASE CONTROL & PREVENTION (Apr. 14, 2022), <https://www.cdc.gov/alcohol/fact-sheets/caffeine-and-alcohol.htm>.

434 See Laila Al-Shaar, *Health Effects and Public Health Concerns of Energy Drink Consumption in the United States: A Mini-Review*, FRONTIERS IN PUB. HEALTH (2017), at 1, 1.

435 Antonia Mattia, *Regulatory Status of Caffeine*, FDA: CFSAN (Aug. 15-16, 2013), <https://ods.od.nih.gov/pubs/energydrinks2013/Mattia.pdf>.

436 See Beyranevand, *supra* note 4, at 916.

437 David A. Wiss, Nicole Avena & Pedro Rada, *Sugar Addiction: From Evolution to Revolution*, FRONTIERS IN PSYCHIATRY (Nov. 8, 2018), at 1, 10, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6234835/pdf/fpsy-09-00545.pdf>; see generally MICHAEL MOSS, SUGAR SALT FAT: HOW THE FOOD GIANTS HOOKED US (2013) (describing addictive power of sugar, salt, and fat).

438 Mozaffarian et al., *supra* note 18.

439 Melanie Warner, *The War Over Salt*, N.Y. TIMES (Sept. 13, 2006), <https://www.nytimes.com/2006/09/13/business/the-war-over-salt.html>.

440 FDCA § 201(s).

441 See *supra* Section II.B.1 (discussing user fees for drugs); Hutt, *supra* note 4, at 452–54.

442 Peter Barton Hutt, *Historical Themes*, *supra* note 56, at 26.

resources from food regulation.<sup>443</sup> Nor was FDA's food center's budget increased commensurate with its vast responsibilities, including food safety, nutrition, dietary supplements, cosmetics, and food additives. Between 1992 and 2007, the Center for Food Safety and Applied Nutrition lost 15% of its staff while accumulating multiple new statutory obligations.<sup>444</sup> A full two-thirds of the \$1.1 billion food budget goes to inspections,<sup>445</sup> leaving \$400 million for everything else. Further, were FDA to promulgate a splashy policy, including revoking GRAS status for sugar or salt at certain quantities, litigation would quickly ensue, thereby further draining regulatory resources.

Case law was mostly a bystander to these regulatory developments. In 2017, several public health organizations challenged FDA's GRAS regulatory regime as arbitrary and capricious and not in accordance with the FDCA.<sup>446</sup> They also alleged that FDA has essentially delegated the core duties of food additive regulation to private parties, despite Congress's intent in the Food Additives Amendment that FDA vet food additives.<sup>447</sup> However, they were rebuffed by the United States District Court for the Southern District of New York, which, in a strikingly formalistic opinion, remarked that GRAS substances are exempted from premarket review.<sup>448</sup> Therefore, FDA has no premarket responsibility to delegate or violate.<sup>449</sup> The court missed the point that companies are self-certifying food additives as GRAS to dodge the premarket process, which FDA has nullified. On formalistic grounds, the court left the GRAS regime in place.

It is hard to think of a system more favorable to industry than self-affirmed GRAS, at least in the short-term. Companies have the flexibility to experiment with new food additives and self-certify them as GRAS, thus allowing a tremendous amount of flexibility in food design. Flexibility in food production has arguably allowed for the design of more addicting food products.<sup>450</sup> Further, companies are likely to be more concerned with short-term harms rather than long-term concerns such as cancer or cardiovascular disease, which are harder to trace back to a product and less likely to cause uproar. Under today's GRAS regime, companies may freely decide how many resources to devote to vetting

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443 Hutt, *supra* note 4.

444 *Id.* at 459.

445 Helena Bottemiller Evich, *The FDA's Food Failure*, POLITICO (Apr. 8, 2022), <https://www.politico.com/interactives/2022/fda-fails-regulate-food-health-safety-hazards>.

446 *Ctr. for Food Safety v. Becerra* at 12, No. 1:17-cv-03833-VSB (S.D.N.Y. Sept. 30, 2021), ECF No. 100.

447 *Id.* at 13.

448 *Id.* at 15.

449 *Id.* at 15.

450 See Michael Moss, *The Extraordinary Science of Addictive Junk Food*, N.Y. TIMES MAG. (Feb. 20, 2013), <https://www.nytimes.com/2013/02/24/magazine/the-extraordinary-science-of-junk-food.html> ("In the process of product optimization, food engineers alter a litany of variables with the sole intent of finding the most perfect version (or versions) of a product.").

additives and avoiding safety scandals. Such a regime should give us pause, given many products have brought industry enormous wealth despite safety concerns and public rebuke, such as e-cigarettes, opioids, sugary foods, and many drugs and devices.

The proposed Ensuring Safe and Toxic-Free Foods Act of 2022<sup>451</sup> would create some measurable changes to improve premarket review, including setting a final date after which no food additive brought to market may be considered GRAS.<sup>452</sup> However, it does not provide the resources to revitalize a starved program, and it appears to focus on food chemicals rather than long-used harmful substances like sugar and salt. Today, food additive premarket review is little more than a dead letter, arguably due to long-term underfunding of this core FDA function.

### E. Medical Devices

A growing chorus of voices has critiqued FDA's premarket review of medical devices.<sup>453</sup> As Matthew Herder and Nathan Cortez have noted, "the vast majority of medical devices escape formal scrutiny of safety and efficacy."<sup>454</sup> Examples of serious harm and lack of effectiveness abound. A 2018 investigation by the International Consortium of Investigative Journalists (ICIJ) found that between 2008 and 2017, more than 5.4 million device adverse event reports were sent to FDA.<sup>455</sup> The ICIJ investigation also found 83,000 deaths and 1.7 million injuries in this time frame were linked to medical device malfunctions in the U.S.<sup>456</sup>

One day after the ICIJ issued its report, FDA announced a plan to repair the

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451 Ensuring Safe and Toxic-Free Foods Act of 2022, S. 4316, 117th Cong. (2021–2022).

452 *Id.* § 2(b)(2)(E).

453 *E.g.*, Darrow et al., *supra* note 4; Martinez, *supra* note 4; Rome et al., *supra* note 4; Kushal T. Kadakia et al., *Renewing the Call for Reforms to Medical Device Safety—The Case of Penumbra*, 182 JAMA INTERNAL MED. 59, 61 (2022); NAT'L ACADS. OF SCIS., MEDICAL DEVICES AND THE PUBLIC'S HEALTH: THE FDA 510(K) CLEARANCE PROCESS AT 35 YEARS (2011); JEANNE LENZER, DANGER WITHIN US: AMERICA'S UNTESTED, UNREGULATED MEDICAL DEVICE INDUSTRY AND ONE MAN'S BATTLE TO SURVIVE IT (2017); Jonathan R. Dubin et al., *Risk of Recall Among Medical Devices Undergoing US Food and Drug Administration 510(k) Clearance and Premarket Approval, 2008-2017*, JAMA NETWORK OPEN (May 6, 2021); Ari J. Gartenberg, Sanket S. Shruva & Rita F. Redberg, *Presumed Safe No More: Lessons from the Wingspan Saga on Regulation of Devices*, BMJ (Jan. 22, 2014); Matthew Herder & Nathan Cortez, *A "DESI" for Devices?*, in THE FUTURE OF MEDICAL DEVICE REGULATION (I. Glenn Cohen et al., eds., 2022); Sanket S. Dhruva et al., *Ensuring Patient Safety and Benefit in Use of Medical Devices Granted Expedited Approval*, in *id.*

454 Herder & Cortez, *supra* note 453, at 132.

455 INT'L CONSORTIUM OF INVESTIGATIVE JOURNALISTS, *supra* note 19.

456 *Id.*



medical device review system.<sup>457</sup> Therefore, it is clear even to FDA that something is amiss—or perhaps the political pressure is so strong that FDA must act. In its plan, FDA stressed the value of a “market-based approach” involving providing information to the public about the basis for some device approvals.<sup>458</sup> Many reforms have been discussed, but few of the fundamentals have changed in response to wide critiques of FDA’s device program. Ultimately, according to former FDA Commissioner David Kessler, “The problem we have is that, when it comes to medical devices, we built a system that doesn’t work.”<sup>459</sup>

### 1. *Statutory Defects: The 510(k) Process and Beyond*

FDA first obtained jurisdiction over medical devices in 1938, but without the power to conduct premarket review.<sup>460</sup> The years after World War II saw numerous “quack” devices using “colored lights, dangerous gases such as ozone and chlorine, radio waves, heat, and vibration with claims of treatment and cure for virtually every disease known to man.”<sup>461</sup> Other devices, including the Dalkon shield contraceptive, cardiac pacemakers, and implantable intraocular lenses, caused severe safety issues warranting greater oversight.<sup>462</sup>

The Medical Device Amendments of 1976<sup>463</sup> allowed FDA to conduct premarket review of medical devices. The framework provided for device classifications under Classes I through III representing escalating levels of risk.<sup>464</sup> Although FDA initially sought to retain many product types in Class III, generally subject to the Premarket Approval (“PMA”) pathway, it was subject to

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457 Matthew Perrone, *FDA Pledges to Modernize How It Approves Medical Devices*, PBS (Nov. 26, 2018, 3:03 P.M.), <https://www.pbs.org/newshour/health/fda-pledges-to-modernize-how-it-approves-medical-devices>.

458 *Statement from FDA Commissioner Scott Gottlieb, M.D. and Jeff Shuren, M.D.*, U.S. FOOD & DRUG ADMIN. (Nov. 26, 2018), <http://web.archive.org/web/20211204100932/www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-jeff-shuren-md-director-center-devices-and>.

459 THE BLEEDING EDGE (Netflix 2018).

460 See HUTT ET AL., *supra* note 37, at 1205.

461 *Id.* at 1195.

462 *Id.* at 1202.

463 The Medical Device Regulation Act, Pub. L. No. 94-295, 90 Stat. 539 (1976).

464 HUTT ET AL., *supra* note 37, at 1204. The classification depends on the use of the product and its risk level. *Classify Your Medical Device*, U.S. FOOD & DRUG ADMIN. (Feb. 7, 2020), <https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device>.

Class I devices include a toothbrush, 21 C.F.R. §§ 872.6855, 872.6865; an elastic bandage, *id.* § 880.5075; and an electrode to measure the pH of the esophagus or stomach, *id.* § 876.1400. Class II devices include a pediatric medical crib, *id.* § 880.5140, an endoscope for visualizing gastrointestinal or urinary tracts, *id.* § 876.1500, and an ultrasound device, *id.* § 892.1540–70. Class III devices include a brain stimulator implant, *id.* § 882.5820, a testicular prosthesis (a round device meant to resemble a testicle), *id.* § 876.3750, and bovine bone tissue grafted into the human spine, *id.* § 888.3015.

resource constraints and corporate and congressional pressure.<sup>465</sup> Enter the 510(k), or Substantial Equivalence, pathway for devices. It was originally designed to identify devices that were substantially equivalent to products on the market as of 1976 (i.e., predicates), and thus to identify exceptions to a baseline requirement of premarket review.<sup>466</sup> Products without a predicate were presumptively placed into Class III.<sup>467</sup> To enter the market, such a device would either need premarket approval or down-classification to Class I or Class II.<sup>468</sup>

However, 510(k) became the exception that swallowed the rule, with even high-risk devices often allowed to use the pathway and enter the market without evidence of safety and effectiveness. Over 2008–2017, FDA cleared 28,246 510(k) submissions but approved only 310 PMA applications.<sup>469</sup> By all standards, the 510(k) process is incredibly lenient; therefore, as long as a predicate is available, clearance is the norm. Between 1976 and 2009, FDA made non-substantially-equivalent determinations for just 1–4% of 510(k) notifications.<sup>470</sup> Industry greatly favors the 510(k) process and has developed sophisticated ways of avoiding PMA. According to one industry consultant, companies introducing a new device will search a database of predicates to find the most similar product for a 510(k) submission.<sup>471</sup> Only something truly novel would be barred from 510(k), and newly cleared devices then contribute to a growing pool of predicates, facilitating avoidance of the PMA process. And even for a truly novel product, the “de novo” review process allows FDA to reject a 510(k) submission but down-classify the product to Class I or Class II (from the automatic Class III designation).<sup>472</sup> With these compelling alternatives, it is no wonder so few devices undergo premarket review.

Numerous safety issues have emerged from 510(k)-cleared devices. A full 13% of them are recalled.<sup>473</sup> Metal-on-metal total hip replacement devices, for example—which FDA cleared under the 510(k) process based on “equivalence” to prior devices<sup>474</sup>—had been tested as early as the 1960s but were generally abandoned after patients suffered leaching of metal particles into their blood and

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465 HUTT ET AL., *supra* note 37, at 1216, 1241.

466 NAT'L ACADS. OF SCIS., *supra* note 453, at 32–33.

467 HUTT ET AL., *supra* note 37, at 1204.

468 *Id.*

469 Dubin et al., *supra* note 453, at 4.

470 NAT'L ACADS. OF SCIS., *supra* note 453, at 33.

471 *Demystifying the De Novo Process*, GLOB. MED. DEVICE PODCAST (May 12, 2022), <https://www.greenlight.guru/blog/demystifying-the-de-novo-process>.

472 *De Novo Classification Request*, U.S. FOOD & DRUG ADMIN. (Jan. 7, 2022), <https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/de-novo-classification-request>.

473 Kadakia, *supra* note 453, at 61.

474 Ardaugh, Graves & Redberg, *supra* note 3, at 97–99.

organs.<sup>475</sup> FDA began allowing them in 1998.<sup>476</sup> Eventually clearing more than 175 submissions,<sup>477</sup> FDA was known to use “split predicates,” in which it would compare hip devices’ characteristics with prior devices’ characteristics without comparing the devices as a whole.<sup>478</sup> Metal-on-metal devices became increasingly used in the 2000s; by the end of the decade, they were used in a full third of U.S. hip replacements<sup>479</sup> and were inserted into more than 500,000 Americans. As one doctor noted, he started implanting them “because they had passed FDA muster.”<sup>480</sup> Yet the devices were found to leach dangerous level of cobalt and chromium ions into the blood, release painful and destructive debris around the joint, and have high failure rates requiring replacement.<sup>481</sup> Some patients suffered cognitive symptoms, sometimes mimicking dementia, from metal ions impairing their brains.<sup>482</sup> In 2016, FDA issued an order requiring PMA for metal-on-metal total hip replacements,<sup>483</sup> which ended their sale.

Similarly, the Penumbra JET7 catheter for extraction of clots from the brain, cleared on thin evidence through the 510(k) process, was found to fracture inside patients’ cerebral blood vessels.<sup>484</sup> The JET7 was part of a daisy chain of a dozen iterations of Penumbra catheters, only one of which had clinical evidence.<sup>485</sup> In addition, the predicate for the original product was authorized on low-quality data.<sup>486</sup> In 2021, FDA announced an urgent recall.<sup>487</sup> The transvaginal mesh is another 510(k)-related saga. The meshes have been implanted in the vaginal wall to treat pelvic organ prolapse. As of 2017, FDA cleared sixty-one vaginal mesh devices that relied on equivalence to the ProteGen Sling from 1996, a recalled device.<sup>488</sup> Transvaginal mesh for pelvic organ prolapse “has not ever generally

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475 Barry Meier, *In Medicine, New Isn’t Always Improved*, N.Y. TIMES (June 25, 2011), <https://www.nytimes.com/2011/06/26/health/26innovate.html?ref=business>.

476 Deborah Cohen, *How Safe Are Metal-On-Metal Hip Implants?*, BMJ (Feb. 28, 2012), at 1, 4.

477 Heneghan et al., *supra* note 1, at 2.

478 Ardaugh, Graves & Redberg, *supra* note 3, at 98.

479 Barry Meier, *Concerns Over ‘Metal on Metal’ Hip Implants*, N.Y. TIMES (Mar. 3, 2010), <https://www.nytimes.com/2010/03/04/health/04metalhip.html>.

480 Meier, *supra* note 475.

481 Heneghan et al., *supra* note 1, at 1; Linda Roth, *Metal-on-Metal Hip Implant Risks*, ARTHRITIS FOUNDATION, <https://www.arthritis.org/health-wellness/treatment/joint-surgery/safety-and-risks/metal-on-metal-hip-implant-risks>; Ardaugh, Graves & Redberg, *supra* note 3, at 98; Cohen, *supra* note 476, at 1–3.

482 THE BLEEDING EDGE (Netflix 2018).

483 81 Fed. Reg. 8146 (Feb. 18, 2016).

484 Kadakia et al., *supra* note 453, at 60.

485 *Id.*

486 *Id.*

487 *Id.*

488 Carl J. Haneghan et al., *Trials of Transvaginal Mesh Devices for Pelvic Organ Prolapse: A Systematic Database Review of the US FDA Approval Process*, BMJ OPEN (2017), at 1, 2–3.

been subjected to adequate clinical studies at any phase of its development.”<sup>489</sup> These meshes have caused pain, bleeding, and infections, as the mesh can perforate and protrude through the vaginal wall.<sup>490</sup> A devastating 2016 Cochrane review found “limited utility” of the mesh given association with a number of worse outcomes compared with simple tissue repair.<sup>491</sup> Although some manufacturers voluntarily left the market, in 2019, FDA ordered the remaining companies to stop all sale and distribution of mesh for pelvic organ prolapse in the United States.<sup>492</sup> More than 100,000 women have sued mesh manufacturers for their injuries, leading to protracted litigation.<sup>493</sup>

Neither the JET7 nor transvaginal meshes should have been allowed on the market without clinical evidence—the foundation of premarket review. The 510(k) pathway has been considered so problematic that, in 2011, the Institute of Medicine (now the National Academy of Medicine) issued a report stating that 510(k) cannot be considered premarket review because it is predicated on equivalence, not safety and effectiveness, and recommending that the entire program be replaced<sup>494</sup>—a shocking recommendation. Yet FDA has doubled down. Since the 2011 report, the agency has embraced 510(k) “lite,” stating it is willing to use postmarket controls coupled with less evidence in 510(k) submissions.<sup>495</sup> It also will tolerate more uncertainty when it deems a technology innovative.<sup>496</sup> And there has been a shift toward third-party 510(k) review, in which private corporations, rather than FDA, review 510(k) submissions.<sup>497</sup> These shifts likely reflect an under-resourced FDA that believes speedier access to devices is warranted and has increasingly accepted corporations policing themselves.

The 510(k) process amounts to a statutory loophole around premarket review but is not the only cause of statutory erosion of device review. In 1997, congressional Republicans passed the Food and Drug Administration

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489 *Id.* at 7.

490 Sheila Kaplan & Matthew Goldstein, *F.D.A. Halts U.S. Sales of Pelvic Mesh, Citing Safety Concerns for Women*, N.Y. TIMES (Apr. 16, 2019), <https://www.nytimes.com/2019/04/16/health/vaginal-pelvic-mesh-fda.html>.

491 Christopher Maher et al., *Transvaginal Mesh or Grafts Compared with Native Tissue Repair for Vaginal Prolapse*, 9 COCHRANE DATABASE OF SYSTEMATIC REVIEWS, at 25 (2016).

492 Kaplan & Goldstein, *supra* note 490.

493 INT’L CONSORTIUM OF INVESTIGATIVE JOURNALISTS, *supra* note 19.

494 NAT’L ACADS. OF SCIS., *supra* note 453, at 5–8.

495 U.S. FOOD & DRUG ADMIN., BENEFIT-RISK FACTORS TO CONSIDER WHEN DETERMINING SUBSTANTIAL EQUIVALENCE IN PREMARKET NOTIFICATIONS (510(K)) WITH DIFFERENT TECHNOLOGICAL CHARACTERISTICS 18 (2018).

496 *Id.* at 16.

497 *510(k) Third Party Review Program*, U.S. FOOD & DRUG ADMIN. (Aug. 18, 2020), <https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/510k-third-party-review-program>.

Modernization Act,<sup>498</sup> which stated FDA “shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.”<sup>499</sup> In other words, Congress instructed FDA to tailor the methods to minimize burden and *increase* the odds of approval, rather than aim for accurate determinations of safety and effectiveness.

The 21st Century Cures Act of 2016<sup>500</sup> weakened device regulation even further; it has an entire subtitle called “Medical Device Innovations.”<sup>501</sup> It requires FDA to include in device decisions “a brief statement regarding how the least burdensome requirements were considered and applied.”<sup>502</sup> If the submission lacks sufficient information, FDA may only request information “necessary” to the determination, and must consider the “least burdensome means” for the applicant to demonstrate substantial equivalence when requesting such information.<sup>503</sup> The statute also (1) created the breakthrough device pathway;<sup>504</sup> (2) requires FDA to review Class I and II devices to determine if they are exempt from 510(k) (an exemption from an exemption);<sup>505</sup> (3) requires FDA to ensure its device employees have training on least burdensome device review;<sup>506</sup> and (4) expanded the use of real-world evidence,<sup>507</sup> which, as discussed, is a work-around for clinical trials.<sup>508</sup>

## 2. Ideological Capture

FDA has appeared to embrace this “pro-innovation” bent advanced by Congress and corporate lobbying. Investigative journalists in 2015 revealed that Jeffrey Shuren, head of FDA’s device center, held secret meetings with a device trade association in advance of the 21st Century Cures Act, and FDA and the association jointly wrote legislative text.<sup>509</sup> Indeed, FDA actually helped craft the

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498 HUTT ET AL., *supra* note 37; Pub. L. No. 105-115, 111 Stat. 2295 (1997).

499 FDCA § 513(a)(3)(D)(ii).

500 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016). Industry heavily lobbied this law. *See supra* note 315.

501 *See* 21st Century Cures Act, Subtitle F.

502 FDCA § 517A(a)(3).

503 FDCA § 513(i)(1)(D)(i). A parallel provision exists for PMA submissions. *See* FDCA § 515(c)(5)(A). The least burdensome provisions originated in the FDA Modernization Act, but the 21st Century Cures Act expanded them. U.S. FOOD & DRUG ADMIN., THE LEAST BURDENSOME PROVISIONS: CONCEPT AND PRINCIPLES 5 (Feb. 5, 2019), <https://www.fda.gov/media/73188/download>.

504 21st Century Cures Act § 3051.

505 *Id.* § 3054.

506 *Id.* § 3058.

507 *Id.* § 3022.

508 *See supra* Section II.B.5.

509 LENZER, *supra* note 453, at 144.

least burdensome provisions in consultation with industry.<sup>510</sup> Meanwhile, Dr. Shuren has acted punitively toward employees concerned about the devices FDA is allowing to market. He famously attempted to prosecute “the FDA Nine,” a group of FDA scientists writing letters to Congress and President Obama about extremely concerning devices about which scientists were overruled by agency leadership.<sup>511</sup> According to a former official who headed device review for four years, after 2012, following congressional and industry pressure, the device center assumed a new attitude: “We need to find ways to get products on the market quicker, faster and we need to figure out how to reduce the premarket data requirements.”<sup>512</sup>

The medical device industry spent \$20 million each year from 2014–2018 lobbying the federal government.<sup>513</sup> Between 2010 and 2017, warning letters to device manufacturers dropped 80%, while new device approvals climbed three-fold.<sup>514</sup> FDA in 2018 announced a new process for applicants to assert the agency has violated the least burdensome provisions,<sup>515</sup> thus hampering its own ability to request evidence.<sup>516</sup> This change occurred during the Trump Administration, one year after the GAO, perhaps under presidential influence, issued a report finding that FDA needed to expend more resources ensuring it complied with the least burdensome requirements.<sup>517</sup> In its 2019 least burdensome guidance, FDA is clear about its stance on premarket review: “FDA intends to, and industry should, consider the use of postmarket data collection to reduce premarket data collection whenever appropriate and feasible.”<sup>518</sup> It is surprising that FDA would seek to reduce premarket data for the devices it regulates—indeed, that is the information on which it must base its decisions.

What is more, when the Institute of Medicine prepared its 2011 report on

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510 Perrone, *supra* note 457.

511 LENZER, *supra* note 453, at 141–42.

512 Matthew Perrone, *At FDA, a New Goal, Then a Push for Speedy Device Reviews*, AP NEWS (Nov. 27, 2018), <https://apnews.com/article/health-north-america-us-news-ap-top-news-implant-files-9f8ea03a4d324d1ba5585680d280804b>.

513 Adiel Kaplan et al., *Medical Device Makers Spend Millions Lobbying to Loosen Regulations in D.C.*, NBC NEWS (Dec. 3, 2018), <https://www.nbcnews.com/health/health-care/medical-device-makers-spend-millions-lobbying-loosen-regs-d-c-n940351>.

514 *Id.*

515 *The Least Burdensome Provisions: Concept and Principles*, U.S. FOOD & DRUG ADMIN. (Mar. 14, 2019), at 21–23, <https://www.fda.gov/media/121002/download>; Nick Tippmann, *When to Throw the Least Burdensome Flag on FDA*, GLOB. MED. DEVICE PODCAST (Oct. 6, 2021), <https://www.greenlight.guru/blog/when-to-throw-the-least-burdensome-flag-on-fda>.

516 It is possible FDA created this process to deflect other methods of contesting FDA’s compliance with the least burdensome provisions.

517 U.S. GOV’T ACCOUNTABILITY OFF., *FDA DEVICE MEDICAL REVIEWS: EVALUATION IS NEEDED TO ASSURE REQUESTS FOR ADDITIONAL INFORMATION FOLLOW A LEAST BURDENSOME APPROACH 28–29* (Dec. 2017), <https://www.gao.gov/assets/gao-18-140.pdf>.

518 U.S. FOOD & DRUG ADMIN., *supra* note 503, at 8.

medical devices, FDA informed it that the goals of the 510(k) program are to “make available to consumers devices that are safe and effective” and to “promote innovation in the medical device industry.”<sup>519</sup> That the function of this review process would be “availability” and “innovation” highlights FDA’s internalization of the goal of being a device approver rather than a consumer protection agency, at least with respect to device review.

### 3. *Other Device Problems*

It should be no surprise that device review pathways other than 510(k) have assumed a neoliberal character. The supplemental PMA pathway, for instance, created by FDA regulations in 1986,<sup>520</sup> allows manufacturers to modify a PMA-approved medical device in ways that affect the device’s safety or effectiveness, or for other significant changes.<sup>521</sup> PMAs undergo a median 50 supplements over 15 years, and supplements are not limited to low-risk devices; in fact, most electronic heart implants are approved via PMA supplement.<sup>522</sup> FDA usually does not require new clinical data.<sup>523</sup> Supplements are generally piecemeal changes, but as they accumulate can make it difficult to evaluate the larger changes occurring to a product over time, rendering the practice of medicine more difficult since the new device is different from the original product that had clinical data.<sup>524</sup>

Consider heart implants. For these devices, between 1979 and 2012, FDA approved 77 PMA applications but 5829 supplemental applications.<sup>525</sup> FDA approved the Sprint Fidelis defibrillator lead in 2004 as a supplement—without clinical trials—based on a PMA approved in 1993 that was supplemented at least 91 times.<sup>526</sup> The Sprint Fidelis was recalled in 2007 after it failed more than 600 times.<sup>527</sup> The device is prone to fracture, estimated to occur in 2.3% of patients,

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519 NAT’L ACADS. OF SCIS., *supra* note 453, at xii.

520 Rome et al., *supra* note 4, at 385. However, it was codified by Congress in the Food and Drug Modernization Act.

521 *PMA Supplements and Amendments*, U.S. FOOD & DRUG ADMIN. (Dec 12, 2019), <https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments>.

522 Rome et al., *supra* note 4, at 387, 390.

523 Benjamin N. Rome, Daniel B. Kramer & Aaron S. Kesselheim, *Approval of High-Risk Medical Devices in the US: Implications for Clinical Cardiology*, 16 CURRENT CARDIOLOGY REPS., at 1, 2, 4 (2014); *PMA Supplements and Amendments*, *supra* note 521; Sarah Y. Zheng & Rita F. Redberg, *Premarket Approval Supplement Pathway: Do We Know What We Are Getting?*, 160 ANNALS INTERNAL MED. 798, 798 (2014).

524 Zheng & Redberg, *supra* note 523; Oluwatobi R. Olaiya et al., *Postmarket Modifications of High-Risk Plastic Surgery Devices*, 8 PLASTIC RECONSTRUCTIVE SURGERY GLOB. OPEN (2020), at 1, 1.

525 Rome et al., *supra* note 4, at 387.

526 *Id.* at 387–88; Zheng & Redberg, *supra* note 523.

527 Zheng & Redberg, *supra* note 523.

yet it is difficult to remove.<sup>528</sup> Caring for these patients remains a challenge.<sup>529</sup> Similarly, the Riata family of defibrillator leads, approved through PMA supplements between 2002 and 2006, was recalled after the failure rate was discovered to be 32%.<sup>530</sup>

Even for the PMA process, FDA does not necessarily require high-quality evidence.<sup>531</sup> Essure, a Class III permanent sterilization device, was implanted into about 750,000 U.S. women.<sup>532</sup> It consisted of two thin coiled wires inserted into the fallopian tubes via the cervix and uterus.<sup>533</sup> The device causes inflammation and scarring of the tubes, thereby blocking egg migration.<sup>534</sup> FDA approved Essure in 2002 under expedited review based on a claimed success rate of 99.8% (after one year).<sup>535</sup> But the company did not rigorously measure outcomes after one year (despite the device being intended to be permanent), and there was no control group.<sup>536</sup> After approval, the number of complaints steadily grew as women suffered tubal perforation, severe pain, bleeds, unintended pregnancies, and even deaths.<sup>537</sup> Women implanted with Essure were ten times as likely to undergo reoperation as women who underwent other sterilization procedures.<sup>538</sup> Bayer pulled Essure from the market in 2018.<sup>539</sup> Essure is emblematic of the low evidence bar FDA has sometimes accepted for new medical devices undergoing premarket review.

The humanitarian device exemption is another pathway illustrating FDA's push for new products with less evidence. To use the pathway, the "probable benefit to health" must outweigh the "risk of injury or illness," and the device must be intended for a condition affecting not more than 8,000 Americans.<sup>540</sup>

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528 Barnaby J. Feder, *Patients Warned as Maker Halts Sale of Heart Implant Part*, N.Y. TIMES (Oct. 15, 2007), <https://www.nytimes.com/2007/10/15/business/15device.html>.

529 Zheng & Redberg, *supra* note 523.

530 *Id.*

531 Sankey S. Dhruva, Joseph S. Ross & Aileen M. Gariepy, *Revisiting Essure — Toward Safe and Effective Sterilization*, 373 NEW ENG. J. MED. e17(1), e17(3) (2015).

532 Darrow et al., *supra* note 4, at 428–29.

533 LENZER, *supra* note 453, at 110–11.

534 *Id.*

535 THE BLEEDING EDGE (Netflix 2018); LENZER, *supra* note 453, at 110–11.

536 Jennifer Block, *The Battle over Essure*, WASH. POST (July 26, 2017), <https://www.washingtonpost.com/sf/style/2017/07/26/essure>. FDA says it accepted the lack of a control group because outcome data for tubal ligations—a very different procedure—was available. *Id.*

537 Dhruva, Ross & Gariepy, *supra* note 531, at e17(1).

538 LENZER, *supra* note 453, at 111.

539 Laurie McGinley, *Sales of Essure Birth Control Implant to Be Halted by Bayer; U.S. last to Sell Controversial Device*, WASH. POST (July 20, 2018, 4:35 P.M.), <https://www.washingtonpost.com/news/to-your-health/wp/2018/07/20/sales-of-essure-birth-control-implant-halted-by-bayer-u-s-was-last-to-sell-controversial-device>.

540 FDCA § 520(m).



Off-label use occurs and is not tracked.<sup>541</sup> For example, FDA approved the Wingspan brain stent system under this exemption based on a study of 45 patients with no active control group.<sup>542</sup> Because this data did not show efficacy or safety, the National Institutes of Health funded its own trial using government dollars.<sup>543</sup> NIH terminated the trial early because 15% of the Wingspan group had a death or stroke, compared with 6% of the medical therapy group.<sup>544</sup> Rather than pull the product, FDA narrowed the indications.<sup>545</sup>

#### 4. *The Fall of Device Review*

Over time, without stronger checks, the device pathways will likely grow more lenient because of statutory erosion and the Center's leadership. For devices, then, the priority is not safety and effectiveness, but faster access ("innovation"). As Dr. Jeffrey Shuren, the head of FDA's device program, has explained, the benefits of "innovative" devices coming to market is worth the risks.<sup>546</sup>

#### F. *Conclusion: Premarket Review, Corporate Power, and Neoliberalism*

FDA was born in an era of broad public awakening about corporations selling fraudulent and unsafe foods and drugs.<sup>547</sup> Crisis after crisis in public health led Congress to steadily entrust FDA with increasing power over products intimately connected with human welfare. FDA received its latest significant premarket authority, over tobacco products, as recently as 2009. However, I, and many others, have documented a serious loss of life in the United States associated with dysfunction in FDA's premarket review systems.<sup>548</sup> Premarket review is a prized symbol of independent scientific inquiry. Review decisions, most agree, belong to FDA<sup>549</sup>—not to HHS, Congress, courts, or the President. This is, in part, why review decisions usually are not reviewed by the Office of

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<sup>541</sup> Gartenberg et al., *supra* note 453, at 2.

<sup>542</sup> *Id.* at 1.

<sup>543</sup> *Id.* at 2.

<sup>544</sup> *Id.*

<sup>545</sup> *Id.*

<sup>546</sup> *Editorial: 80,000 Deaths. 2 Million Injuries. It's Time for a Reckoning on Medical Devices.*, N.Y. TIMES (May 4, 2019), <https://www.nytimes.com/2019/05/04/opinion/sunday/medical-devices.html>.

<sup>547</sup> See Kapczynski, *supra* note 26, at 183.

<sup>548</sup> See *supra* Table 1.

<sup>549</sup> See, e.g., *Muchmore*, *supra* note 10, at 540–41 ("The FDA's highest profile activity is its marketing authorization role. In many industries—such as drugs, medical devices, and biological products—the FDA is the primary agency charged with determining which of those products may be sold in the United States." (footnotes omitted)).

Management and Budget or the White House,<sup>550</sup> even if they might significantly affect the economy or public health. Yet my analysis suggests the day-to-day operation of premarket review has been under assault by corporate power.

Corporate power operated through multiple institutional mechanisms to erode premarket review in five regulatory areas.<sup>551</sup> For laboratory-developed tests (LDTs), corporations lobbied to maintain an “enforcement discretion” policy involving no premarket review at all. Although FDA began to make headway during the Obama Administration, the slow pace (amid corporate lobbying and litigation threats) led to little substantive progress before the election of President Trump, who was protective of the industry. During FDA’s pandemic push to stop fraudulent COVID-19 LDTs, Trump’s HHS used executive power to make premarket review optional, which compromised its public health benefits but retained the financial benefits for industry.

For drugs, Congress has eroded the evidentiary requirements for new drugs both directly (e.g., allowing a single clinical trial in some instances) and through a suite of special pathways, such as accelerated approval. Meanwhile, it has reshaped the funding structure of FDA’s drug center to rely largely on industry money. These “user fees” grant industry tremendous negotiating power over FDA prerogatives and review timelines. With industry-focused commissioners, FDA has seemingly embraced its “innovation” role and partially forgotten its consumer protection moorings, leading to surprising approvals like aducanumab, Makena, and OxyContin. Caselaw was largely a bystander, but it helped tear open the hole of off-label promotion, actively threatens access to mifepristone, and helped lay the groundwork for weakening federal administrative agencies generally.

As to tobacco, in compromise legislation with the tobacco industry, Congress managed to exempt both old and new tobacco products from premarket review. Therefore, premarket review of tobacco products was largely a nullity until 2016, when FDA gained jurisdiction over new types of tobacco products like e-cigarettes. However, under Trump, the industry-friendly Dr. Scott Gottlieb deferred premarket review of e-cigarettes in the name of innovation. When litigation forced FDA to initiate premarket review of e-cigarettes, FDA began scientific review but minimally enforced premarket review as a matter of law. Largely, this decision stemmed from DOJ, which interfered with FDA’s enforcement wishes due to the threat of industry litigation. Despite DOJ’s strategy for FDA to make scientific decisions and minimally enforce the law, industry still sued over tobacco scientific assessments, which has further stalled

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550 See Exec. Order 12866, 58 Fed. Reg. 51735 (1993) (requiring review by the Office of Management and Budget for “significant” regulatory actions and defining “regulatory action” as substantive action expected to lead to a final rule—i.e., not premarket review decisions).

551 See *supra* Sections II.A–E for a full exposition and citations.

enforcement. Although the law clearly requires new tobacco products to undergo premarket review, FDA non-enforcement has built serious distance between the statute and its reality. The most popular e-cigarette products among youth remain unreviewed: while 85% of youth e-cigarette users use flavored e-cigarettes, FDA has not authorized a single flavored e-cigarette product (other than tobacco flavor).

Food additives deregulation reflects the financial starvation of a core FDA responsibility. FDA has allowed industry to ignore the premarket pathway and self-certify their food additives through the loophole of “generally recognized as safe.” The neglect of FDA’s food responsibilities also reflects a prioritization of biomedical “innovation”—by infusion of industry funds into the drug and device centers—over public health and social responsibilities.

Last, the device regime reflects the statutory loophole of 510(k) as a superhighway that manufacturers can use to avoid formal scrutiny of their devices. Ideological capture has led FDA leadership to co-draft legislation that weakened device review, including with “least burdensome” requirements (which FDA strengthened under the Trump Administration) that limit the evidence before FDA in making a device approval decision. As with drugs, FDA has at times embraced new, “exciting” devices with serious holes in their evidentiary basis.

Distilling the arcs of these five regulatory regimes, one can see the forces impacting FDA premarket review (Figure 1, reproduction). Not all these forces were impactful in every example, but together, they have increasingly undermined premarket review over the last four decades. And they share one common feature: as I argue, these efforts have reproduced neoliberal outcomes across all Centers—a striking erosion of the quintessential consumer protection agency. This transformation of FDA is not complete, but it remains ongoing and frequently frustrates public health and legal experts cited throughout this Article.

Some might argue that the forces identified in this Article target the law and policy milieu of premarket review, rather than scientific decisions themselves.<sup>552</sup> However, individual decisions and the law and policy scaffolding of premarket review are intertwined as a current political reality. For example, that FDA must avoid burdening device manufacturers through requests for more data<sup>553</sup> means that each scientific decision will be grounded in less data. The compromise of FDA’s core scientific purpose, whether by influence over individual decisions or the larger policy milieu, raises serious concerns.

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<sup>552</sup> Cf. Holly Fernandez Lynch, Steven Joffe & Matthew S. McCoy, *The Limits of Acceptable Political Influence over the FDA*, 27 NATURE MED. 188, 190 (2021).

<sup>553</sup> See *supra* Section II.E.2.

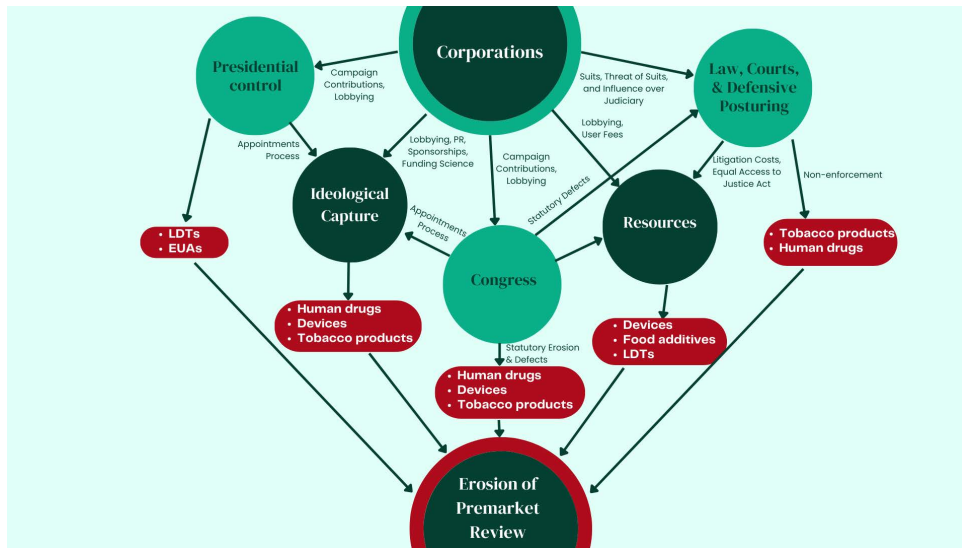


Figure 1 (again): Corporate contributions to the erosion of premarket review.

The decades-long story of premarket review is peppered with courageous employees who risked their careers to challenge the fall of FDA review. Included among them are the FDA Nine, who risked prosecution to draw public attention to problems with device reviews.<sup>554</sup> Unfortunately, FDA appears to have been on the opposing team from this sort of employee who treasures consumer protection. And that is largely because the most effective way to disarm premarket review has been the appointment of pro-business Commissioners laden with conflicts of interest and ideological biases. In 1988, the Commissioner position transitioned from an apolitical career role into one subject to presidential nomination and Senate confirmation,<sup>555</sup> which arguably worsened corporate influence over FDA.

Consider the latest commissioners. Dr. Margaret Hamburg was on the board of a large medical supplies distributor before starting at FDA, was one of the wealthiest Obama appointees, and, together with her husband, held hundreds of thousands of dollars in stock in FDA-regulated companies.<sup>556</sup> She attempted to loosen conflict-of-interest rules for advisory panels, “push[ed] through rules allowing faster drug approvals,”<sup>557</sup> and oversaw FDA during its attempted

554 LENZER, *supra* note 453, at 141–42.

555 Eli Y. Adashi, Rohit S. Rajan & I. Glenn Cohen, *When Science and Politics Collide: Enhancing the FDA*, 364 *SCIENCE* 628, 629 (2019).

556 Alicia Mundy, *New FDA Chief Must Divest Several Stock, Fund Holdings*, *WALL ST. J.* (May 26, 2009), <https://www.wsj.com/articles/SB124328188115551961>.

557 LENZER, *supra* note 321, at 135–36; Toni Clarke, *U.S. FDA Commissioner Margaret Hamburg to Step Down*, *REUTERS* (Feb. 5, 2015, 1:26 A.M.), <https://www.reuters.com/article/us-fda-hamburg-resignation-exclusive/u-s-fda-commissioner-margaret-hamburg-to-step-down-idUKKBN0L90GT20150205> (“Under Hamburg, the agency introduced multiple measures to speed

retaliations against employee whistleblowers bringing attention to dangerous products.<sup>558</sup> Commissioner Andrew von Eschenbach participated in the corrupt ReGen scandal,<sup>559</sup> admitted to wanting drugs to come to market “as quickly as possible,”<sup>560</sup> and decried FDA’s conflict-of-interest rules.<sup>561</sup> Commissioner Scott Gottlieb had connections with more than twenty pharmaceutical companies; according to Daniel Carpenter, he was the “most interest-conflicted commissioner in American history, by far.”<sup>562</sup> Dr. Gottlieb has framed FDA’s search for “extreme certainty” about drugs’ effectiveness to be too burdensome, and has sought to move decisions from the FDA level to the physician level—implying more lenient review.<sup>563</sup> Commissioner Robert Califf accepted millions from life sciences companies<sup>564</sup> and believes the American public craves faster access to drugs despite the risks. Dr. Califf prevailed over the other candidate for commissioner likely because of pharmaceutical industry support.<sup>565</sup> Nine of the last ten commissioners wound up working for the pharmaceutical industry.<sup>566</sup>

Corporations, through their power over Congress and the President, have influenced the appointments process and pushed for pro-industry FDA Commissioners. The last truly public-health-oriented Commissioner was Dr. David Kessler. His tobacco efforts throughout the 1990s helped shift the tide of smoking by expanding public knowledge and highlighting the moral questions about tobacco production and promotion.<sup>567</sup> These efforts bolstered the massive tobacco litigation in the 1990s.<sup>568</sup> And while FDA loosened regulations during the Reagan Administration in the early 1980s, leading many to view FDA as

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new products to the market.”).

558 Ellen Nakashima & Lisa Rein, *FDA Staffers Sue Agency over Surveillance of Personal E-Mail*, WASH. POST (Jan. 29, 2012), [https://www.washingtonpost.com/world/national-security/fda-staffers-sue-agency-over-surveillance-of-personal-e-mail/2012/01/23/gIQAj34DbQ\\_story.html](https://www.washingtonpost.com/world/national-security/fda-staffers-sue-agency-over-surveillance-of-personal-e-mail/2012/01/23/gIQAj34DbQ_story.html).

559 LENZER, *supra* note 453, at 139.

560 Meredith Wadman, *Many Issues in Store for New FDA Commissioner*, 4 NATURE REV.: DRUG DISCOVERY 871, 872 (2005).

561 Andrew von Eschenbach, *Toward a 21st-Century FDA*, WALL ST. J. (Apr. 15, 2012), <https://www.wsj.com/articles/SB10001424052702303815404577331673917964962>.

562 Julia Belluz, *Scott Gottlieb, the New FDA Chief, Explained*, VOX (May 10, 2017), <https://www.vox.com/2017/3/10/14887290/scott-gottlieb-fda-trump>.

563 *Id.*

564 Owerhohle & Cancryn, *supra* note 316.

565 See Matthew Perrone, *New FDA Chief Can’t Come Soon Enough for Beleaguered Agency*, AP NEWS (Oct. 8, 2021), <https://apnews.com/article/coronavirus-pandemic-joe-biden-science-business-health-62291dd94de2ec922bd9a76cbf389d66>; *supra* Section II.B.6.

566 Katherine Ellen Foley, *Trust Issues Deepen as Yet Another FDA Commissioner Joins the Pharmaceutical Industry*, QUARTZ (July 1, 2019), <https://qz.com/1656529/yet-another-fda-commissioner-joins-the-pharmaceutical-industry>.

567 ALLAN M. BRANDT, *THE CIGARETTE CENTURY: THE RISE, FALL, AND DEADLY PERSISTENCE OF THE PRODUCT THAT DEFINED AMERICA* 397 (2007).

568 *Id.*; *Former FDA Chief David Kessler Discusses Tobacco Battle in Book*, CNN (Jan. 17, 2001, 2:47 P.M. E.S.T.), <https://www.cnn.com/2001/books/news/01/17/david.kessler/index.html>.

“bumbling” and “a target under constant attack,” Dr. Kessler asserted his will to restore the credibility of FDA—“and the only way to do that is to focus on strong enforcement. We are going to enforce the law.”<sup>569</sup> Dr. Kessler’s revitalizing spirit—aimed at turning FDA “into a truly effective regulatory agency”<sup>570</sup>—was an outlier. And while the forces on FDA are many, as described above, FDA’s capitulation to a neoliberal perspective on “innovation” might not have occurred without industry influence over FDA leadership.

### III. CONSEQUENCES OF ERODED FDA REVIEW

This Part will examine the public losses stemming from eroded premarket review. It will also review the counterargument that premarket review’s erosion is actually beneficial.

#### A. *Public Health Failures*

Public health failures from the fall of FDA review include the marketing of dangerous products, undermining FDA’s information production function, damaging the reputation and effectiveness of American health care business, and creating a font of legitimacy that discourages other efforts to address product harms.

Most pressingly, numerous lives could have been saved if premarket review successfully performed its gatekeeping role to protect Americans from dangerous and ineffective products. Table 1 describes the lives lost that could be attributed to faltering premarket review, which easily number in the millions.<sup>571</sup> It is possible that American products explain at least part of the country’s larger morbidity and mortality burden compared with peer countries. As the National Academies of Sciences concluded in a 2013 report, “The United States spends much more money on health care than any other country. Yet Americans die sooner and experience more illness than residents in many other countries.”<sup>572</sup> A 2018 study looking at mortality trends found that, in many states, probability of death has recently increased for some age groups, largely due to substance use (e.g., opioids) and dietary risk factors.<sup>573</sup> In addition, the study found that the biggest risk factors for deaths and disability-adjusted life years in the U.S. were tobacco use, dietary risk factors, high blood sugar, high blood pressure, and

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<sup>569</sup> Burkholz, *supra* note 75.

<sup>570</sup> *Id.*

<sup>571</sup> See *supra* Table 1.

<sup>572</sup> NAT’L ACADS. OF SCIS., U.S. HEALTH IN INTERNATIONAL PERSPECTIVE: SHORTER LIVES, POORER HEALTH ix (2013).

<sup>573</sup> *The State of US Health, 1990–2016*, 319 JAMA 1444, 1458 (2018).

alcohol/drug use,<sup>574</sup> all of which are related to the continued use and propagation of tobacco, ultraprocessed foods high in salt and sugar, and opioid use. The scales today are tipped in favor of more products with less evidentiary support and less oversight. Public health suffers when we fail to take seriously the harms resulting from FDA-regulated products, emphasizing only the benefits. Likewise, there is insufficient attention to compounding downstream harms. Patients may need surgery to remove faulty devices (e.g., my mother’s faulty hip);<sup>575</sup> or medical care to recover from addiction, obesity, or other diseases caused by FDA-regulated products. Financially speaking, the U.S. government and other governments and payors pay billions, even trillions, for these products<sup>576</sup>—some of which could be used to restore FDA to better assess these products in the first instance.

Faltering premarket review not only endangers Americans’ health, but also, by failing to produce reliable evidence about product efficacy, undermines the evidence base on which medicine depends. The inevitable downside of rushing products to market is growing uncertainty about these very products. Per Wendy Netter Epstein, a simple “dud” product with no safety issues can nevertheless cause significant harm: harm to government finances, public trust, and future innovation.<sup>577</sup> Every time a person uses a “quack” product, they are deprived of the opportunity to consume effective products and treatments. As Amy Kapczynski has noted, FDA exists largely to solve the “enormous challenges associated with producing and validating high-quality information” about FDA-regulated products.<sup>578</sup> Faltering premarket review jeopardizes this core information-production function. Health law scholars such as Christopher Robertson have argued we have been “shopping in the dark” for medical products for years.<sup>579</sup> The reason is that we “generally failed to invest in a reliable and systematic approach to the production of knowledge about the efficacy of health care we consume.”<sup>580</sup> Further, it is impossible for the average

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<sup>574</sup> *Id.* at 1451.

<sup>575</sup> See *supra* Introduction.

<sup>576</sup> In the single year of 2021, U.S. health care spending on prescription drugs was \$603 billion. *Trends in Prescription Drug Spending, 2016-2021*, ASS’T SEC’Y FOR PLAN. & EVALUATION (Sept. 2022), <https://aspe.hhs.gov/sites/default/files/documents/88c547c976e915fc31fe2c6903ac0bc9/sdp-trends-prescription-drug-spending.pdf>. That figure does not include non-prescription drugs, devices, other product areas, or costs incurred to remedy harms from FDA-regulated products.

<sup>577</sup> Wendy Netter Epstein, *Disrupting the Market for Ineffective Medical Devices*, in COHEN ET AL., *supra* note 453, 179, 187–88.

<sup>578</sup> Amy Kapczynski, *Dangerous Times: The FDA’s Role in Information Production, Past and Future*, 102 MINN. L. REV. 2357, 2359 (2018); Eisenberg, *supra* note 58.

<sup>579</sup> CHRISTOPHER T. ROBERTSON, EXPOSED: WHY OUR HEALTH INSURANCE IS INCOMPLETE AND WHAT CAN BE DONE ABOUT IT 178 (2019).

<sup>580</sup> *Id.* at 183.

American to evaluate whether a product works and is safe.<sup>581</sup> While the efficacy issue seems mainly applicable to medical products, e-cigarette manufacturers frequently claim or imply people can use their products for smoking cessation.<sup>582</sup> Likewise, other types of manufacturers engage in healthwashing,<sup>583</sup> i.e., making unverified health claims on the packaging of foods, dietary supplements, and cosmetics. One can imagine a more robust FDA that provides more certainty about the safety and effectiveness of the products we consume on a daily basis.

What's more, the fall of premarket review causes long-term damage to American business. Products that prove harmful or non-useful can draw increased public scrutiny of a sector, reduce trust in agency review, and cause public health harms that damage product legitimacy. With regard to LDTs, FDA policies helped protect the integrity of the COVID-19 testing market—until the Trump Administration interfered.<sup>584</sup> In the case of e-cigarettes, some companies marketed to youth and drove an arms race of increasing nicotine concentrations and youth marketing, which de-legitimized the entire industry.<sup>585</sup> For metal-on-metal hips, new devices stole market share from the tried-and-true ceramic hips, yet were often recalled and removed from patients due to severe health harms.<sup>586</sup> These cases suggest that faltering premarket review can undermine trust in a market sector and drain market share from responsible manufacturers. And generally, a new product for a particular purpose reduces the benefit businesses will receive for further innovating in that space.<sup>587</sup> While subverting premarket review can have immediate economic gains for some manufacturers, it works damage on U.S. industry and long-term innovation.

But there is more: even where premarket review is in tatters, the legal regime's very existence generates a patina of safety and legitimacy that discourages other measures. FDA continues to praise itself as the guardian of public health, promising that it ensures the safety of drugs, foods, devices, medical tests, tobacco products, and more.<sup>588</sup> Courts have taken these proclamations to heart. In *Riegel v. Medtronic*,<sup>589</sup> the Supreme Court justified preemption of state tort law on the grounds that the device premarket approval

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581 See Kapczynski, *supra* note 578, at 2358.

582 Catherine L. Jo et al., *Effects of E-cigarette Advertising Messages and Cues on Cessation Outcomes*, 4 TOBACCO REG. SCI. 562, 569 (2018).

583 See Raffael Heiss, Brigitte Naderer & Jörg Matthes, *Healthwashing in High-Sugar Food Advertising: The Effect of Prior Information on Healthwashing Perceptions in Austria*, 36 HEALTH PROMOTION INT'L 1029, 1030 (2020).

584 See *supra* Section II.A.

585 Aaron, *supra* note 4, at 887–88.

586 See *supra* Section II.E.1.

587 DiMagno et al., *supra* note 71, at 923.

588 *What We Do*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), <https://www.fda.gov/about-fda/what-we-do>.

589 552 U.S. 312 (2008).



process is rigorous; but consider that the dangerous Essure device passed through this pathway with only short-term data.<sup>590</sup> In the opioid litigation, defendants often claimed that, because FDA approved a drug as safe and effective, a company could not be held accountable for resulting harms.<sup>591</sup> This argument has had some success, including when the Oklahoma Supreme Court reversed a \$465 million judgment against Johnson & Johnson,<sup>592</sup> previously touted as a public health win. The court noted opioids are a “highly regulated industry” that FDA has blessed as safe and effective.<sup>593</sup> Similarly, a California judge has issued a tentative ruling that opioid manufacturers could not have acted unreasonably given federal approval of opioids.<sup>594</sup> Premarket review, then, remains a card to play for defendants in litigation even when it falls short.

### B. *Erosion as Pro-Public-Health?*

For years, legal writers have described benefits to the erosion of premarket review.<sup>595</sup> U.S. life expectancy fell by nearly 2 years between 2018 and 2020, with deeper falls for Black and Hispanic Americans,<sup>596</sup> and the prospect of helping patients increasingly saddled by obesity, diabetes, autoimmune disease, addiction, Alzheimer’s disease, and other conditions by lowering the evidentiary threshold for new therapies is tempting. This argument has two flavors.

The first is a simple get-drugs-to-patients argument. It has been argued that FDA is a “paternalistic bureaucracy interposing costly barriers between patients who demand new products and firms that are eager to supply them.”<sup>597</sup> Ralph Hall and former FDA Commissioner Andrew Von Eschenbach, for example, have pointed to the earlier availability of devices in Europe compared to the United States in the early 2010s.<sup>598</sup>

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<sup>590</sup> See *supra* Section I.E.3.

<sup>591</sup> Aaron, *Opioid Accountability*, *supra* note 256, at 632.

<sup>592</sup> State ex rel. Hunter v. Johnson & Johnson, 2021 OK 54, 499 P.3d 719.

<sup>593</sup> *Id.* at 721, 728.

<sup>594</sup> Tentative Decision at 10, *California v. Purdue Pharma, L.P.* (Cal. Super. Ct. 2021), [https://fingfx.thomsonreuters.com/gfx/legaldocs/znpnezybbvl/11012021california\\_opioid.pdf](https://fingfx.thomsonreuters.com/gfx/legaldocs/znpnezybbvl/11012021california_opioid.pdf).

<sup>595</sup> See, e.g., *supra* notes 52–56 and accompanying text.

<sup>596</sup> Steven H. Woolf, Ryan K. Masters & Laudan Y. Aron, *Effect of the Covid-19 Pandemic in 2020 on Life Expectancy Across Populations in the USA and Other High Income Countries: Simulations of Provisional Mortality Data*, 373 *BMJ* (2021), at 1, 3.

<sup>597</sup> Eisenberg, *supra* note 58, at 367.

<sup>598</sup> Andrew Von Eschenbach & Ralph Hall, *FDA Approvals Are a Matter of Life and Death*, 110 *MO. MED.* 110, 111 (2013). In the EU, as of 2012, devices were assessed for safety and technical performance, not benefit to patients, and limited evidence was needed. U.S. FOOD & DRUG ADMIN., *UNSAFE AND INEFFECTIVE DEVICES APPROVED IN THE EU THAT WERE NOT APPROVED IN THE US* 3 (2012). However, the EU has since issued a new Medical Device Regulation. See Dana A. Elfin, *Device Makers Could Face Approval Lags Under New EU Rule*, *BLOOMBERG LAW* (Dec. 11, 2018), <https://news.bloomberglaw.com/pharma-and-life->

The canonical example of drugs-into-bodies arguments is the story of HIV/AIDS. HIV was a public health and health equity emergency. It spread rapidly through the United States in the 1980s and peaked in the 1990s; by 2001, it killed a cumulative 448,060 Americans.<sup>599</sup> ACT UP, and other LGBTQ advocacy organizations, are credited with pressuring FDA to expand access to unapproved HIV medications and speed up approvals.<sup>600</sup> However, AIDS activists themselves generally sought to preserve FDA's drug review regime,<sup>601</sup> and they successfully pushed FDA to provide drug access in ways that preserved clinical research and therefore premarket review.<sup>602</sup> Specifically, FDA policy preserved trials, but added a "parallel track" providing drugs for people with HIV/AIDS who were ineligible to join a trial.<sup>603</sup> Unfortunately, AIDS activism was *partially* coopted by industry and libertarian activists to justify a "getting drugs into bodies" approach that aligned with corporate interest in earlier revenue within the drug lifecycle.<sup>604</sup> But the drugs that have saved many lives from HIV show the power of premarket review's presence, not its absence. After all, we would not know which drugs work today if we did not invest in evidence generation, which is difficult when drug access is freely provided. In the words of Congressman Henry Waxman, we must have "limited distribution today, so that we will have adequate information for tomorrow."<sup>605</sup>

The second flavor of argument advancing the benefits of premarket review's erosion involves reorientation toward the postmarket setting, the idea being that postmarket studies allow for patient access contemporaneous with evidence generation. For example, Shannon Gibson and Trudo Lemmens have framed the

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sciences/device-makers-could-face-approval-lags-under-new-eu-rule. Therefore, Hall and Eschenbach's longing for the EU's fast approach holds some irony.

<sup>599</sup> *HIV and AIDS — United States, 1981–2000*, 50 MORBIDITY & MORTALITY WKLY. REP. 430, 430 (2001).

<sup>600</sup> Lewis A. Grossman, *FDA and the Rise of the Empowered Patient*, in LYNCH & COHEN, 59, 65–67, *supra* note 23; *A Timeline of HIV/AIDS*, AIDS.GOV, at 1, 3–5, <https://files.hiv.gov/s3fs-public/aidsgov-timeline.pdf>.

<sup>601</sup> Grossman, *supra* note 178, at 715.

<sup>602</sup> *Id.* at 721.

<sup>603</sup> *Id.* at 725.

<sup>604</sup> *Id.* at 706, 740 (explaining the long-term impact of some activists' embrace of "libertarian and industry allies" on the arc of FDA's regulatory regime, which some activists fear has "created a monster they can no longer control"); Michael Specter, *How ACT UP Changed America*, NEW YORKER (June 7, 2021), <https://www.newyorker.com/magazine/2021/06/14/how-act-up-changed-america> (according to one prior activist, "I don't think that we realized at the time that this was part of the broader gutting of the FDA that we've seen since . . . [T]here's a really strong pharmaceutical lobby against the FDA as well that I don't think we were aware of.").

<sup>605</sup> Grossman, *supra* note 178, at 721 (quoting *AIDS Issues: Parallel Track Proposal for Clinical Drug Development: Hearing Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 101st Cong. 1 (1989) (statement of Henry A. Waxman, Chairman, Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce)).

“fixation” with premarket regulatory activity as “premarket syndrome” and argued that there is an “artificial dichotomy” between pre- and postmarket regulation.<sup>606</sup> H-G Eichler and colleagues argue for “adaptive licensing,” in which data is gathered iteratively rather than for a single review process, which could speed drug access for patients.<sup>607</sup> Many patient groups have pushed for such access—of course, usually with substantial industry sponsorship.<sup>608</sup>

These arguments about innovation, to a degree, would benefit from further exposition on what innovation *is*. If innovation is “anything new,” then premarket review probably obstructs innovation. Indeed, this is the popular conception of innovation. For example, the Congressional Budget Office assesses new pharmaceutical legislation for how many fewer new drugs will be marketed in the future,<sup>609</sup> regardless of their safety or effectiveness. Fortune lists the most innovative pharmaceutical companies based on number of approvals and sales.<sup>610</sup> The likely reason that approvals carry such meaning is there is a baseline level of trust in the significance of an FDA approval.

But FDA scholars have been chipping away at the idea that new products, even with an FDA blessing, are necessarily innovative. Zeke Emanuel points out that a minority of new drugs have significant benefits over existing therapies.<sup>611</sup> Former FDA Commissioner Dr. Scott Gottlieb famously postponed premarket review for all e-cigarettes to facilitate tobacco product innovation<sup>612</sup>—to encourage “different technologies to deliver nicotine . . . that doesn’t bring with it the deadly consequences of burning tobacco.”<sup>613</sup> A year later, he made the startling admission that neither he nor FDA foresaw that this decision would

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606 See Shannon Gibson & Trudo Lemmens, *Overcoming “Premarket Syndrome”: Promoting Better Postmarket Surveillance in an Evolving Drug-Development Context*, in LYNCH & COHEN, *supra* note 23, at 268–69.

607 H-G Eichler et al., *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 426, 428 (2012).

608 Alice Fabbri et al., *Industry Funding of Patient and Health Consumer Organisations: Systematic Review with Meta-Analysis*, BMJ (Jan. 22, 2020), at 1, 11; Susannah L. Rose et al., *Patient Advocacy Organizations, Industry Funding, and Conflicts of Interest*, 177 JAMA INTERNAL MED. 344, 347 (2017).

609 See, e.g., John LaMattina, *CBO Report Shows Enacting Drug Pricing Legislation Will Result in Fewer New Drugs*, FORBES (Apr. 12, 2021, 3:02 PM EDT), <https://www.forbes.com/sites/johnlamattina/2021/04/12/cbo-report-shows-enacting-drug-pricing-legislation-will-result-in-fewer-new-drugs/?sh=2baaf77c415b>.

610 Sy Mukherjee & IDEA Pharma, *The Most Innovative and Inventive Drug Companies of 2022 Set the Foundation for Success Before the Pandemic*, FORTUNE (Apr. 20, 2022, 5:30 AM EDT), <https://fortune.com/2022/04/20/top-pharmaceutical-companies-innovation-invention-2022>.

611 Ezekiel Emanuel, *Opinion: Why We Can Have Both Innovative Drugs and Lower Drug Prices*, POLITICO (Oct. 13, 2021, 4:30 AM EDT), <https://www.politico.com/news/agenda/2021/10/13/drug-companies-innovation-prices-false-choice-515844>.

612 Aaron, *supra* note 4, at 847.

613 Gottlieb, *supra* note 349.

accelerate a youth e-cigarette crisis.<sup>614</sup> Daniel Hemel and Lisa Ouellette have chipped away at simplistic notions of innovation, arguing that current innovation institutions helped generate the opioid crisis.<sup>615</sup> They note that Purdue Pharma's OxyContin, which arguably incited the opioid crisis, was probably neither safe nor effective despite receiving FDA approval.<sup>616</sup> As I discuss above, FDA has made haste to speed development of new opioid drugs,<sup>617</sup> arguably favoring "innovation" over a more evidence-based approach. Altogether, FDA-approved opioids have killed more than 263,000 Americans,<sup>618</sup> not including those who started with prescription opioids but migrated to illicit drugs. These "innovation failures," and many others discussed throughout this Article, suggest speeding new products to market carries the risk of seriously injuring, even killing, patients.

Some might still favor postmarket surveillance to premarket review because it couples earlier access with evidence generation. However, postmarket efforts cannot make up for damaged premarket review. To begin with, evidence is difficult to gather in the postmarket setting because patients can obtain drugs through their physicians and have little reason to join a clinical trial, where they might receive the placebo.<sup>619</sup> Even if evidence could be easily gathered during marketing, preventing harms offers more public good than mitigating them, particularly when the harm is potentially severe (e.g., for a product that can cause addiction). Moreover, removing a product from the market is considerably harder than denying it in the first place.<sup>620</sup> There may arise a property interest in the trademark and associated goodwill, leading to litigation over takings or due process.<sup>621</sup> Other types of claims may lead courts to block efforts to remove products from the market.<sup>622</sup> Current users may push for continued access for themselves even if the drug carries net harms.<sup>623</sup> And companies can use the resources gained from sales to contest FDA action. Were FDA to proceed with

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614 U.S. FOOD & DRUG ADMIN., *supra* note 358.

615 Hemel & Ouellette, *supra* note 47.

616 *Id.* at 16–17.

617 *See supra* Section II.B.3.

618 CTRS. FOR DISEASE CONTROL & PREVENTION, *supra* note 11.

619 Aaron et al., *supra* note 235, at 2395.

620 *Id.*; Herder, *supra* note 4, at 841.

621 *See* 65 Fed. Reg. 1000, 1041–42 (2000).

622 *See, e.g.,* Matt Richtel, Lauren Hirsch & Andrew Jacobs, *Juul Gets Temporary Reprieve to Keep Selling Its E-Cigarettes*, N.Y. TIMES (June 24, 2022), <https://www.nytimes.com/2022/06/24/health/juul-ecigarettes-ban.html>.

623 LEWIS A. GROSSMAN, CHOOSE YOUR MEDICINE: FREEDOM OF THERAPEUTIC CHOICE IN AMERICA 257–61 (2021) (describing patient resistance to withdrawing bevacizumab's breast cancer indication despite a "lack of 'credible, objective evidence that the drug is safe and effective'" (quoting Commissioner Margaret Hamburg)).

withdrawal, it stands in the position of discrediting its prior approvals.<sup>624</sup> Further, FDA does not have the resources to surveil the more than 20% of the economy that it regulates.<sup>625</sup> Postmarket surveillance remains underresourced and arguably ineffective.<sup>626</sup>

I would advance that real innovation does not happen through deregulating FDA. Without robust premarket review, new “innovations” coming to market may actually be anti-innovation. For one, they may damage public trust in FDA and the products it regulates. For two, without the information generated by robust premarket review, it is difficult to identify true innovations. The United States has a crisis of not knowing which medical products are effective, given a lack of clinical evidence at the time of approval.<sup>627</sup> In the words of Dr. Rita Redberg, “True innovations are welcomed, but cannot be recognized as such without clinical trial evidence to show that new technologies are beneficial for patients.”<sup>628</sup> The trial evidence required for new products continues to decline, the latest and most severe example being real-world evidence.<sup>629</sup> For three, new “true” innovations may be harder to bring to market if there are unproven products already on the market—a phenomenon some have called “crowding out.”<sup>630</sup> Pharmaceutical companies are well aware that being first-to-market carries the most financial returns.<sup>631</sup> Daniel Carpenter calls this invisible asset “market space.”<sup>632</sup> In these ways, the fall of premarket review may paradoxically be anti-innovation. To the extent actual innovation does arise from premarket review’s erosion, it would have to be weighed against the immense public health cost of allowing life-threatening products on the market, the subversion of evidence-based medicine,<sup>633</sup> and other public health failures that premarket

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624 Dhruva, *supra* note 453, at 224.

625 Aaron, *Opioid Accountability*, *supra* note 256, at 649 (describing FDA’s budget as “shoestring”); *Executive Summary: Strategic Plan for Regulatory Science*, U.S. FOOD & DRUG ADMIN. (Mar. 29, 2018), <https://www.fda.gov/science-research/advancing-regulatory-science/executive-summary-strategic-plan-regulatory-science> (asserting FDA regulates 25 cents of every dollar spent by U.S. consumers).

626 LENZER, *supra* note 453, at 114 (comparing FDA’s device surveillance to using a Ouija board); Curt D. Furberg et al., *The FDA and Drug Safety: A Proposal for Sweeping Changes*, 166 ARCHIVES OF INTERNAL MED. 1938, 1938 (2006).

627 ROBERTSON, *supra* note 579, at 174, 178–83.

628 *FDA Medical Device Approval: Is There a Better Way?: Hearing Before the Subcomm. on Health Care, D.C., Census and the Nat’l Archives of the H. Oversight and Gov’t Reform Comm.*, 112th Cong. 200 (2011) (testimony of Dr. Rita Redberg).

629 See *supra* Sections I.C.6, I.D.

630 DiMagno et al., *supra* note 71, at 923.

631 See Tracy Staton, *First-to-Market Launch? Bonus--But Double Bonus If You’re Big Pharma*, FIERCE PHARMA (Sept. 17, 2014), <https://www.fiercepharma.com/sales-and-marketing/first-to-market-launch-bonus-but-double-bonus-if-you-re-big-pharma>.

632 Carpenter et al., *supra* note 59, at 316.

633 See Eisenberg, *supra* note 58, at 347 (noting FDA processes produce significant value

review's fall engenders.<sup>634</sup>

Nor can it be argued that the examples throughout this Article are outliers in an otherwise functioning regime. There are many cases of devastating harm for all discussed product types. Further, for some product areas, such as for food additives, lab-developed tests, and many tobacco products, premarket review is largely defunct. The claim that a process is working well after it has been nearly eliminated is untenable. Ultimately, many premarket review decisions appear to be driven not by FDA, but by reactivity to politics, lawsuits, and resource issues. These problems are not the hallmark of a well-functioning system, but one that has been torn apart by constant attack.

#### IV. SOLUTIONS

I offer two proposals to reinvigorate premarket review today. The first is statutory reform of premarket review across all product areas—the FDA Premarket Review Restoration Act (FDAPRRA). I am not the first to propose strengthening premarket review. Lawmakers have introduced bills to improve premarket review of food additives,<sup>635</sup> laboratory-developed tests,<sup>636</sup> drugs,<sup>637</sup>

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through evidence generation).

<sup>634</sup> See *supra* Section II.A.

<sup>635</sup> Ensuring Safe and Toxic-Free Foods Act of 2022, S.4316, 117th Cong. (2021–2022). This bill accepts the GRAS regime but makes a series of adjustments, including requiring FDA to make a determination that it has received “sufficient notice” of a manufacturer’s self-determination of GRAS, § 2(b)(2)(A)(i); requiring notice-and-comment before marketing of a GRAS product, *id.* § 2(b)(2)(B)(ii); barring likely carcinogens from being GRAS, § 2(b)(2)(C); mandating at least ten reviews of old GRAS substances every three years (a slow pace), *id.* § 3(c); and tweaking the criteria for being “unsafe”, *id.* § 3(d)–(e). The bill does not provide extra funding, provide FDA additional independence from outside influence, require FDA to spend certain appropriations only on food additive review, or place FDA in a greater role of reviewing food additives than simply determining it has received “sufficient notice.”

<sup>636</sup> VALID Act of 2021, S.2209, 117th Cong. (2021–2022). This lengthy and complex bill for the regulation of in vitro clinical tests adopts problematic provisions such as least burdensome requirements, *id.* § 587B(j); “efficient and flexible approaches to expedite” breakthrough products, *id.* § 587C(a); user fee funding, *id.* § 9(b); privatized premarket review, *id.* § 587P; and numerous exceptions to premarket review, *id.* § 587A(a)(4)(A).

<sup>637</sup> Accelerated Approval Integrity Act of 2022, H.R.6963, 117th Cong. (2021–2022). A modified version of this statute was passed as part of the Food and Drug Omnibus Reform Act of 2022 (FDORA), within the Consolidated Appropriations Act, 2023, Pub. L. No. 117–328, 136 Stat. 4459 (2022). While these provisions reduce delays in confirmatory studies and slightly reduce the cumbersome withdrawal procedures, the withdrawal procedures are still excessive, and FDA retains discretion to go far beyond safety and effectiveness within the accelerated approval program. Jeff Craven, *FDA Withdraws Pre-Term Birth Drug Makena*, REGUL. FOCUS (Apr. 5, 2023), <https://www.raps.org/news-and-articles/news-articles/2023/4/fda-withdraws-pre-term-birth-drug-makena>. Nor did this reform infuse FDA with needed funding or transition its funding source from industry user fees to appropriations.

opioids,<sup>638</sup> and more. These bills generally create half-measures for specific product areas and are arguably band-aids for long-term problems. That is because the real problem facing FDA is financial power (largely corporations'), not simple statutory problems.<sup>639</sup> Even my suggested statute, FDAPRRA, despite being cross-product-area, may suffer from some of the same problems, although it is much more ambitious, cross-disciplinary, and structural than the above bills. The second proposal is a deeper reckoning with corporate influence and changes in the law that undermine agencies' core functions.

#### A. *FDA Premarket Review Restoration Act (FDAPRRA)*

Congress represents the most direct route for reform. Although passing pro-regulatory statutes is not easy, Congress has proven uniquely willing to do so throughout FDA's history.<sup>640</sup> And given statutes can adjust most of the forces undermining premarket review (e.g., statutory defects, court decisions, funding, etc.), they are a powerful tool. Agencies are creatures of statute, after all.

A commonly advanced solution is to refashion FDA as an independent agency, as seven former FDA Commissioners have urged.<sup>641</sup> Certainly, protecting FDA's Commissioner from termination would insulate the agency from presidential and HHS control, which have damaged certain areas of premarket review (e.g., laboratory-developed tests). However, I believe this solution alone fails to grapple with the reasons for premarket review's fall that I have described. Figure 1 indicates that all three branches of government, as well as ideological capture and resource deprivation, contribute to premarket review's erosion, so insulating FDA from presidential control is a mere half-measure. Further, it may even be counterproductive. Under current law,<sup>642</sup> an independent FDA would have multiple heads, which could politicize FDA leadership and create standstills, as it has for the Federal Election Commission.<sup>643</sup>

Instead, FDAPRRA would grant FDA independent litigating authority. According to former FDA Commissioner Margaret Hamburg, "[A] strong FDA enforces the law."<sup>644</sup> Yet FDA enforcement actions appear to have declined over

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638 FDA Accountability for Public Safety Act, S.1439, 117th Cong. (2021–2022).

639 Of course, the exercise of corporate power can lead to statutory problems.

640 See *supra* Section I.A.

641 Califf et al., *supra* note 44, at 84.

642 *Seila Law, LLC v. CFPB*, 140 S. Ct. 2183, 2211 (2020) (holding that a single individual wielding "significant executive power" in leading an agency must be removable at will). Therefore, the only way for FDA to be independent is for it to have multiple heads.

643 See Brian Naylor, *The Federal Election Commission Can Finally Meet Again. And It Has a Big Backlog*, NPR (Dec. 24, 2020), <https://text.npr.org/949672803> (describing structural issues in multi-headed Federal Election Commission, including lack of quorum, internal disagreement, and partisan deadlocks).

644 HUTT ET AL., *supra* note 37, at 166 (emphasis removed).

the last fifteen years.<sup>645</sup> Currently, FDA relies on DOJ to prosecute firms that bring products to market without authorization. Kirti Dalta and Richard Revesz have argued that DOJ control over litigation leads to less enforcement and, because DOJ conducts its affairs in secret with significant financial independence, reduces accountability to Congress.<sup>646</sup> Therefore, DOJ control increases the probability of nullifying congressional premarket review requirements. A legal agency with minimal experience or interest in public health<sup>647</sup> should not have authority to create de facto *postmarket* review by vetoing FDA enforcement, as it appeared to do for tobacco products.<sup>648</sup> To fulfill science-based premarket review, FDA needs independent litigating authority, more than agency independence, to prosecute violators. This litigating authority could be limited to enforcing against unreviewed products—essentially cookie-cutter cases that hardly require the litigation expertise of DOJ. Other agencies, which often have much broader litigation authorities, could serve as a model. For example, the Consumer Finance Protection Bureau has authority to “seek all appropriate legal and equitable relief” for consumer protection violations and “may act in its own name and through its own attorneys.”<sup>649</sup>

Another persistent problem is FDA’s consistent use of enforcement discretion to vitiate statutory mandates. FDAPRRA would declare with clarity that premarket review for a listed set of product categories is mandatory, and products must pass through at least one pathway involving FDA review to enter the market. Then, the Act could assign mandatory action from FDA for illegally marketed products. Courts have recognized that mandatory language in statutes can impose affirmative obligations on FDA.<sup>650</sup> For example, the D.C. Circuit held in 2013 that FDA must follow FDCA’s importation provisions, which *require* FDA to take certain actions when a manufacturer attempts to import violative drugs.<sup>651</sup>

Mandatory action, applied to premarket review, could foreclose FDA laying down enforcement discretion or other lenient policies over entire categories of products, as it did with laboratory-developed tests, e-cigarettes, and food

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645 *See id.* at 165; Charles Piller, *Exclusive: FDA Enforcement Actions Plummet Under Trump*, SCIENCE (Jul. 2, 2019), <https://www.science.org/content/article/exclusive-fda-enforcement-actions-plummet-under-trump>. It is true some types of FDA actions increased in number at various points over the last fifteen years, HUTT ET AL., *supra* note 37, at 165, but FDA also gained authority over tobacco products, *supra* Section II.C.1.

646 Kirti Dalta & Richard L. Revesz, *Deconstructing Independent Agencies (and Executive Agencies)*, 98 CORNELL L. REV. 769, 801–02 (2013).

647 Daval, *supra* note 378, at 8.

648 *See supra* Section II.C.

649 12 U.S.C. § 5564(a)–(b).

650 *See, e.g.*, Am. Acad. of Pediatrics v. FDA, 379 F. Supp. 3d 461 (D. Md. 2019); Cook v. FDA, 733 F.3d 1, 12 (D.C. Cir. 2013).

651 Cook, 733 F.3d at 12.



additives. In addition, it would help prevent HHS, DOJ, and the President from interfering with premarket review. Naturally, such mandatory action could require significant resources, but Congress could require smaller steps needing fewer resources. For example, a statute could say that, where FDA is informed of violative products, it “shall issue” a notice to such manufacturer of the violation and it “shall refuse” imports. Given manufacturing often occurs abroad, importation restrictions could significantly reduce the marketing of unauthorized products, while leveraging existing processes within Customs and Border Protection. In addition, manufacturers subject to premarket review should be required to submit notices to FDA to sell products, which would trigger these clauses. Likewise, statutorily mandated action would empower public health organizations to submit notices to FDA that trigger the action. Together, these measures pare back the discretion that FDA, HHS, and DOJ have leveraged to spare manufacturers from statutory premarket review requirements.

FDAPRR must reduce the impact of industry litigation on premarket review. Mandatory action would forestall some industry litigation, as it is difficult to argue that FDA has acted not in accordance with law when it has followed statutory commands. In addition, Congress, having the power to shape federal courts, could remove industry causes of action to challenge premarket review.<sup>652</sup> Courts do not have the expertise to supervise FDA’s scientific decisions, and many industry cases serve to deter, or defer, FDA enforcement rather than to win on the merits. Appeals of denials should operate exclusively through the administrative process, which could involve another scientific agency to improve objectivity. Congress must also stipulate that companies may not market products during appeals of an FDA denial and forbid federal courts from enjoining enforcement of premarket review requirements.<sup>653</sup> One limitation of this solution is Congress may have limited power to remove constitutional claims related to premarket review,<sup>654</sup> but this aspect may be a feature rather than a bug.

In addition, the statute could patch loopholes and design problems that have hollowed out premarket review. These fixes would include ending the arguable loopholes for devices and food additives (i.e., the 510(k) and GRAS pathways<sup>655</sup>); restricting the use of expedited programs such as accelerated approval; vesting premarket review authority in FDA leadership, rather than

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<sup>652</sup> For further discussion of Congress limiting federal jurisdiction or relief, see *Federal Jurisdiction: Patchak v. Zinke*, 132 HARV. L. REV. 297 (2018).

<sup>653</sup> See, e.g., *Wages & White Lion Invs. v. FDA*, 16 F.4th 1130 (5th Cir. 2021) (enjoining FDA market denial order pending review); *Wages & White Lion Invs. v. FDA*, 41 F.4th 427 (5th Cir. 2022) (changing course and denying manufacturer’s petition for review), *rehearing en banc granted*, 58 F.4th 233 (5th Cir. 2023).

<sup>654</sup> John F. Preis, *In Defense of Implied Injunction Relief in Constitutional Cases*, WM. & MARY BILL OF RTS. J. 1, 51–53 (2013).

<sup>655</sup> See *supra* Sections II.D–E.

HHS, to prevent “un-delegation”;<sup>656</sup> requiring two clinical trials for new products sold for specific health purposes; requiring surrogate endpoints to have clearly established links to clinical outcomes; and ending the user-fee legislative cycle that repeatedly weakens premarket review. These changes would empower FDA to hold new products to appropriate standards while erecting barriers to countervailing corporate influence.

Some of these measures would require an already resource-starved FDA to spend more money. As discussed, for food additives,<sup>657</sup> laboratory-developed tests,<sup>658</sup> and devices,<sup>659</sup> resource deprivation by Congress (and, by extension, its lobbyists) has made it difficult to support robust premarket review programs. Similarly, the drugs program historically faced backlogs.<sup>660</sup> Recently, tobacco premarket review, the newest variety, appears to be struggling. Not only is FDA managing a morass of tobacco applications, but it also has stayed some of its own marketing denial orders, including Juul’s, citing “scientific issues.”<sup>661</sup> Juul had alleged that FDA overlooked more than 6,000 pages of safety data,<sup>662</sup> and it is possible FDA was concerned the allegation was true.

There is no way around a strong infusion of resources into the agency to support its core premarket review function. User fees provide too much control by industry over the legislative process and bestow too much negotiating leverage on the companies FDA regulates. The money must come from direct appropriation.

One serious issue in transitioning to a truly mandatory premarket review regime is a phase-in protocol—i.e., how to handle existing products on which people might depend. Congress has historically had trouble handling products that were already on the market. Every FDA regime handles the phase-in process differently.<sup>663</sup> Moreover, a mandatory review regime could immediately lead to

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656 The FDCA gives authority to the Secretary of HHS, which HHS delegates to FDA.

657 *See supra* Section II.D.

658 *See supra* Section II.A.

659 *See supra* Section II.E.

660 CONG. BUDGET OFF., HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 17 (1998), <https://www.cbo.gov/sites/default/files/105th-congress-1997-1998/reports/pharm.pdf>.

661 *FDA Denies Authorization to Market JUUL Products*, U.S. FOOD & DRUG ADMIN. (June 23, 2022), <https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products>.

662 Ian Krietzberg, *Juul Seeks to Extend Stay on FDA Ban, Saying Agency Did Not Evaluate All Its Evidence*, CNBC (June 28, 2022), <https://www.cnbc.com/2022/06/28/juul-seeks-to-extend-stay-on-fda-ban-saying-agency-did-not-evaluate-all-its-evidence.html>.

663 *Compare* Hutt et al., *supra* note 37, at 1215 (exempting preexisting Class III devices from premarket review, and any substantially equivalent devices), *with* Carpenter, Greene & Moffitt, *supra* note 59, at 312–14 (conducting rigorous panel reviews for preexisting drugs followed by withdrawal orders for those deemed ineffective), *and with supra* Section II.C.1 (exempting preexisting tobacco products and substantially equivalent products from premarket review).

the submission of millions of applications to FDA and unpredictable product shortages.

The answer to the phase-in problem is not to “grandfather” millions of products, but to invest billions of dollars in studying the technologies we have allowed onto the market without review. A historical model is the Drug Efficacy Study Initiative (DESI), which took place after Congress updated the FDCA to require efficacy data for new drugs.<sup>664</sup> Similar to DESI, panels of experts could evaluate products and submit reports, or tentative decisions, to FDA scientists. The study should prioritize the highest-risk products, including those mentioned in this Article. DESI appears to have been successful: it likely reduced U.S. mortality by removing ineffective therapies and creating “market space” for better ones.<sup>665</sup> However, it was retrospective—products remained on the market during review. This aspect is unwanted given the severe risks posed by many products that I have discussed in this Article. High-risk products, including those creating substantial public health harms, should be removed from the market indefinitely during the review phase. For some products in common use, such as sugar and salt, particular *uses* of the product should be restricted until review is complete (e.g., sugar over a certain quantity). Congress should define high-risk products and specifically list the most prominent examples, while FDA can gap-fill. Congress could also impose absolute tort liability for high-risk products as an additional incentive for manufacturers to pull them from the market. This type of regime would infuse us with knowledge about the products we use every day that may be harming our health.

### B. Addressing Root Causes: Neoliberalism and FDA

These bold changes to premarket review, though worthwhile, are not enough to insulate FDA from neoliberal influence. To begin with, a massive infusion of resources into FDA through appropriations and a strengthening of premarket review would be opposed tooth-and-nail by regulated industry. The bills Congress passes are largely determined by corporations and corporate-funded lobbying organizations.<sup>666</sup> Even if statutory changes were readily possible,

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<sup>664</sup> Carpenter, Greene & Moffitt, *supra* note 59, at 307–08.

<sup>665</sup> *Id.* at 316.

<sup>666</sup> See MARTIN GILENS, AFFLUENCE AND INFLUENCE: ECONOMIC INEQUALITY AND POLITICAL POWER IN AMERICA 1–2 (2012) (“[U]nder most circumstances, the preferences of the vast majority of Americans appear to have essentially no impact on which policies the government does or doesn’t adopt.”); Martin Gilens & Benjamin I. Page, *Testing Theories of American Politics: Elites, Interest Groups, and Average Citizens*, 12 PERSPS. ON POL. 564, 577 (2014) (“[P]olicy-making is dominated by powerful business organizations and a small number of affluent Americans . . .”); Lee Drutman, *How Corporate Lobbyists Conquered American Democracy*, THE ATLANTIC (Apr. 20, 2015), <https://www.theatlantic.com/business/archive/2015/04/how-corporate-lobbyists-conquered-american-democracy/390822> (“Corporations now spend about \$2.6 billion a year on

political actors, the President, and DOJ can still seek avenues to control (or eliminate) premarket review. Nor would FDAPPRA fully insulate premarket review from federal courts, which have become increasingly aggressive toward administrative agencies.<sup>667</sup> Even the most clever statutory overhaul could suffer from congressional disappropriation or serious litigation challenges. And with the President and Senate co-deciding FDA's leadership, it is likely future FDA Commissioners will continue to favor faster and lighter review at the expense of public health.

When FDA's tools are compromised, it can rely on communication—at least when it is not ideologically captured. If enforcement is impossible, it can issue press releases highlighting the corporate determinants of health.<sup>668</sup> One example of strong communication was FDA's holding e-cigarette companies to the fire for causing surging youth e-cigarette use.<sup>669</sup> This communication strategy helped cement public support for raising the legal age for tobacco products from 18 to 21.<sup>670</sup> Emphasizing the corporate determinants of health can challenge exercises of corporate power and build public support for change. Health movements have historically been powerful tools of social change.<sup>671</sup> FDA could cement these movements by stepping up as a voice of consumer protection.

FDA can also bring more attention to outside attacks on the agency. To do so, it must transition from a “timid,” docile, and secretive<sup>672</sup> agency to one that is open with the issues facing it. Again and again, public crises arise and FDA suffers enormous criticism. Instead of engaging, FDA generally spins the facts to

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reported lobbying expenditures—more than the \$2 billion we spend to fund the House (\$1.18 billion) and Senate (\$860 million) . . . . For every dollar spent on lobbying by labor unions and public-interest groups together, large corporations and their associations now spend \$34.”)

<sup>667</sup> See *infra* notes 691–699 and accompanying text.

<sup>668</sup> For a discussion of the corporate determinants of health, see Ilona Kickbusch, Luke Allen & Christian Franz, *The Commercial Determinants of Health*, 4 LANCET GLOB. HEALTH e895 (2016); John S. Millar, *The Corporate Determinants of Health: How Big Business Affects Our Health, and the Need for Government Action!*, 104 CANADIAN J. PUB. HEALTH e327 (2013); Aaron, *supra* note 11, at 65.

<sup>669</sup> See, e.g., *FDA Takes New Steps to Address Epidemic of Youth E-cigarette Use, Including a Historic Action Against More Than 1,300 Retailers and 5 Major Manufacturers for Their Roles Perpetuating Youth Access*, U.S. FOOD & DRUG ADMIN. (SEPT. 11, 2018), <https://www.fda.gov/news-events/press-announcements/fda-takes-new-steps-address-epidemic-youth-e-cigarette-use-including-historic-action-against-more>.

<sup>670</sup> Aaron, *supra* note 4, at 852–53.

<sup>671</sup> Phil Brown et al., *Embodied Health Movements: New Approaches to Social Movements in Health*, 26 SOCIO. OF HEALTH & ILLNESS 50, 51 (2004).

<sup>672</sup> See Herder, *supra* note 4, at 849. The reasons for FDA's timidity deserve an entire article. Possibilities include: (1) the siloed nature of FDA's centers impairing a broader understanding of premarket review's fall; (2) continued control over FDA leadership through the appointment process, see *supra* Section I.F; (3) a strong corporate push for FDA fostering innovation across all sectors; (4) internal siloing of legislative advocacy and budgeting; (5) FDA attorneys discouraging frank discussion of the agency's weaknesses; and (6) agency rules restricting employee speech.

defend itself despite serious public criticism, which makes the agency look even worse.<sup>673</sup> FDA cannot continue to paint itself as the public guardian for all the products it regulates, while suffering neoliberal influence and public rebuke. It must try to maximize public health, and when it cannot, it should attempt to explain why. For example, after the recent court decision staying approval of the abortion drug mifepristone,<sup>674</sup> FDA could have amplified public anger by highlighting the court's botching of the science and co-opting of FDA's regulatory power.<sup>675</sup> Both HHS and the White House issued (short) statements,<sup>676</sup> while FDA remained silent.<sup>677</sup>

If FDA is considering terminating a review program because of resources (e.g., food additives), it should publicly explain that Congress has not appropriated enough funds. When HHS purports to remove FDA's authority to conduct premarket review (e.g., laboratory-developed tests), FDA should clarify it had no role in the decision and criticize the industry lobbying leading to that outcome.

When the Supreme Court facilitates corporate spending in congressional

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<sup>673</sup> See, e.g., *supra* notes 369–371 and accompanying text (denying tobacco regulatory failures). After a 2019 Science article concluding that “FDA’s compliance and enforcement actions have plummeted since President Donald Trump took office,” FDA and Commissioner Dr. Scott Gottlieb were openly defensive. Charles Piller, *Exclusive: FDA Enforcement Actions Plummet Under Trump*, SCIENCE (July 2, 2019), <https://www.science.org/content/article/exclusive-fda-enforcement-actions-plummet-under-trump>. Despite pressure from the Trump administration to authorize the COVID-19 vaccine, FDA Commissioner Dr. Stephen Hahn denied any pressure and claimed the decision was based on science and evidence. Emily Shapiro, *FDA Commissioner Hahn Denies Reports He Was Threatened with Firing*, ABC NEWS (Dec. 12, 2020, 12:03 P.M.), <https://abcnews.go.com/Politics/fda-commissioner-denies-reports-threatened-firing/story?id=74689216>. After a 2021 scandal about McKinsey consulting for FDA’s drug policy while simultaneously consulting with opioid manufacturers to fend off FDA regulation, FDA asserted, “The agency takes our role awarding contracts seriously and we work to ensure the agency maintains high standards of integrity . . . .” Ian MacDougall, *McKinsey Never Told the FDA It Was Working for Opioid Makers While Also Working for the Agency*, PROPUBLICA (Oct. 4, 2021), <https://www.propublica.org/article/mckinsey-never-told-the-fda-it-was-working-for-opioid-makers-while-also-working-for-the-agency>.

<sup>674</sup> Memorandum Opinion and Order at 67, *All. for Hippocratic Med. v. FDA*, No. 2:22-CV-223-Z (N.D. Tex. Apr. 7, 2023).

<sup>675</sup> See Aaron, Brown & Sinha, *supra* note 312 (critiquing judges who felt empowered to reevaluate FDA’s scientific judgment in the case challenging the approval of mifepristone).

<sup>676</sup> *HHS Secretary Xavier Becerra Statement on Court Rulings on Mifepristone*, DEP’T OF HEALTH & HUM. SERVS. (Apr. 7, 2023), <https://www.hhs.gov/about/news/2023/04/07/hhs-secretary-xavier-becerra-statement-court-rulings-mifepristone.html>; *Statement from President Joe Biden on the Supreme Court’s Decision in Alliance for Hippocratic Medicine v. FDA*, WHITE HOUSE (Apr. 21, 2023), <https://www.whitehouse.gov/briefing-room/statements-releases/2023/04/21/statement-from-president-joe-biden-on-the-supreme-courts-decision-in-alliance-for-hippocratic-medicine-v-fda>.

<sup>677</sup> For example, a search of FDA’s official Twitter account reveals zero tweets containing the words “mifepristone” or “Mifeprex” up through July 7, 2023.

elections and undermines checks on such spending<sup>678</sup>—which subjects FDA to further corporate influence—FDA should help the public understand why this makes its job harder. For an agency with more than 18,000 employees,<sup>679</sup> there is no doubt the agency has much on its tongue. It, and its staff, should say more. FDA (as well as HHS) could amend its ethics regulations to facilitate employee speech on important public health issues; traditionally, the agency requires supervisory approval for employee speech on FDA matters.<sup>680</sup>

Public health communication efforts would help combat the rise of corporate media. Today, six companies control most of American media,<sup>681</sup> and many corporate-funded organizations seek to undermine premarket review. For example, *Filter* magazine, a self-proclaimed harm reduction website, released an article titled “The FDA’s Unconscionable Campaign to Destroy Juul” lobbying allegations that FDA, in denying Juul marketing authorization, lied, undermined harm reduction, and triggered a “death sentence for smokers.”<sup>682</sup> *Filter* takes funding from Juul.<sup>683</sup> In addition, more than 90% of patient “voices” in PDUFA discussions have historically been funded by pharmaceutical companies.<sup>684</sup> According to Ray Moynihan and Lisa Bero, “The very way we all think about disease—and the best ways to research, define, prevent, and treat it—is being subtly distorted because so many of the ostensibly independent players, including patient advocacy groups, are largely singing tunes acceptable to companies seeking to maximize markets for drugs and devices.”<sup>685</sup> FDA could participate more actively in this discourse as a representative of public health.

Of course, what FDA says aloud merits some caution. For example, it would not be wise to publicly state that the agency does not have enough funding to

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678 *Buckley v. Valeo*, 424 U.S. 1 (1976); *Citizens United v. Federal Election Commission*, 558 U.S. 310 (2010); *Ams. for Prosperity Found. v. Bonta*, 141 S. Ct. 2373 (2021).

679 U.S. FOOD & DRUG ADMIN., FISCAL YEAR 2023: JUSTIFICATION OF ESTIMATES FOR APPROPRIATIONS COMMITTEES 380 (Mar. 9, 2023), <https://www.fda.gov/media/157192/download>.

680 *Outside Activity*, U.S. FOOD & DRUG ADMIN. (Mar. 24, 2022), <https://www.fda.gov/about-fda/ethics/outside-activity>.

681 Ashley Lutz, *These 6 Corporations Control 90% of the Media in America*, BUSINESS INSIDER (June 14, 2012, 9:49 AM EDT), <https://www.businessinsider.com/these-6-corporations-control-90-of-the-media-in-america-2012-6>; Nicolas Rapp & Aric Jenkins, *Chart: These 6 Companies Control Much of U.S. Media*, FORTUNE (July 24, 2018, 8:00 AM EDT), <https://fortune.com/longform/media-company-ownership-consolidation>.

682 Helen Redmond, *The FDA’s Unconscionable Campaign to Destroy Juul*, FILTER (July 11, 2022), <https://filtermag.org/fda-destroy-juul>.

683 *Our Supporters*, FILTER (Accessed July 12, 2022), <https://filtermag.org/about-the-influence-foundation>.

684 David S. Hilzenrath, *Drug Money: In FDA Meetings, “Voice” of the Patient Often Funded by Drug Companies*, POGO (Dec. 1, 2016), <https://www.pogo.org/investigation/2016/12/in-fda-meetings-voice-of-patient-often-funded-by-drug-companies>.

685 Ray Moynihan & Lisa Bero, *Toward a Healthier Patient Voice: More Independence, Less Industry Funding*, 177 JAMA INTERNAL MED. 350, 351 (2017).

enforce a statutory requirement. Such a statement could elicit illegal activity and potentially create legal risk if the agency is abdicating a responsibility. However, FDA can communicate the same problem in softer terms (e.g., “FDA cannot sufficiently enforce due to resource constraints, and we strongly encourage more funding as soon as possible”). Similarly, FDA might practice some caution in criticizing judges, as it will likely be before those judges in the future. However, it is well within FDA’s prerogative to criticize a legal decision on the merits and be part of the public forum engaging with these decisions. In fact, to the extent modern law is especially harmful to agencies, their views ought to be heard.

While FDA should be louder in representing its own interests, it cannot solve the problem on its own. This is so because the forces that have eroded premarket review are larger than the agency: the dominant neoliberal logic that FDA review is fundamentally anti-innovation,<sup>686</sup> increasing corporate ownership and consolidation of media;<sup>687</sup> Senate and President control over appointments; and political disfavor toward social spending and “big government,”<sup>688</sup> especially with rising inflation.

FDA’s work is not siloed; other agencies are trying to solve pressing problems yet being rebuffed by all three branches of government and aggressive corporate lobbying. Instead of playing the field alone, FDA must forge alliances with other agencies and institutions—something it already has statutory authority to do.<sup>689</sup> FDA has allied with other organizations before,<sup>690</sup> and joint press statements that offer refreshing honesty could garner public support.

Another issue larger than FDA is that the edifice of law itself grows more aggressive toward agencies with each year. Gillian E. Metzger has written of a boiling anti-administrativism in which judges and libertarian legal scholars assault the administrative state.<sup>691</sup> In 2022, the Supreme Court decided an agency statutory interpretation question without mentioning *Chevron* once,<sup>692</sup> leading commentators to suggest the Court had “shun[ned]” a bedrock administrative law rule.<sup>693</sup> Moreover, the Supreme Court granted certiorari to decide a case in its

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686 Eisenberg, *supra* note 58, at 346–47.

687 *See supra* notes 681–685 and accompanying text.

688 NAOMI KLEIN, *THE SHOCK DOCTRINE* 14–15, 57 (2007).

689 FDCA § 1003(c).

690 *FDA, NIH, and 15 Private Organizations Join Forces to Increase Effective Gene Therapies for Rare Diseases*, U.S. FOOD & DRUG ADMIN. (Oct. 27, 2021), <https://www.fda.gov/news-events/press-announcements/fda-nih-and-15-private-organizations-join-forces-increase-effective-gene-therapies-rare-diseases>.

691 *See* Gillian E. Metzger, *Foreword: 1930s Redux: The Administrative State Under Siege*, 131 *HARV. L. REV.* 1, 3 (2017).

692 *Am. Hosp. Ass’n v. Becerra*, 142 S. Ct. 1896 (2022).

693 *See, e.g.*, James Romoser, *In an Opinion That Shuns Chevron, the Court Rejects a Medicare Cut for Hospital Drugs*, SCOTUSBLOG (June 15, 2022, 2:24 P.M.), <https://www.scotusblog.com/2022/06/in-an-opinion-that-shuns-chevron-the-court-rejects-a>

2023 term that asks whether *Chevron* should be overruled.<sup>694</sup> In 2020, the Supreme Court limited agencies' power to seek disgorgement remedies in court,<sup>695</sup> and in 2021, it limited agencies' ability to seek equitable money remedies.<sup>696</sup> Numerous courts, including the Supreme Court, have struck down COVID-19 laws aimed at securing public health, including an eviction moratorium and an employee vaccine-or-test policy.<sup>697</sup> In *West Virginia v. EPA*,<sup>698</sup> the Supreme Court sliced EPA's authority under the major questions doctrine; in the words of Justice Kagan:

Some years ago, I remarked that “[w]e’re all textualists now.” . . . It seems I was wrong. The current Court is textualist only when being so suits it. When that method would frustrate broader goals, special canons like the “major questions doctrine” magically appear as get-out-of-text-free cards. Today, one of those broader goals makes itself clear: Prevent agencies from doing important work, even though that is what Congress directed.<sup>699</sup>

But of course, FDA cannot on its own change the course of law, nor corporate and political systems. We, as a society, must take corporate power seriously and insulate premarket review from its influence. FDAPRA offers some measures to protect FDA, but we must ask deeper questions about the genesis of corporate power in the United States. These sources may include corporate consolidation greenlit by changes in antitrust law, accumulated corporate wealth, weak campaign finance regulation, reduction in countervailing power (e.g., unions), global competition, and trends in U.S. court composition.

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medicare-cut-for-hospital-drugs. The implication is increased judicial invalidation of agency legal interpretations.

<sup>694</sup> Loper Bright Enterprises v. Raimondo, 143 S. Ct. 2429 (2023); Josh Gerstein & Alex Guillén, *Supreme Court Move Could Spell Doom for Power of Federal Regulators*, POLITICO (May 1, 2023, 3:14 P.M. EDT), <https://www.politico.com/news/2023/05/01/supreme-court-chevron-doctrine-climate-change-00094670>.

<sup>695</sup> Liu v. SEC, 140 S. Ct. 1936 (2020).

<sup>696</sup> AMG Capital Mgmt., LLC v. FTC, 141 S. Ct. 1341 (2021).

<sup>697</sup> Lance Gable, *Distancing, Movement and Gathering Restrictions, and Business and Activity Control Measures*, in COVID-19 POLICY PLAYBOOK: LEGAL RECOMMENDATIONS FOR A SAFER, MORE EQUITABLE FUTURE 33, 36 (Scott Burris et al. eds., 2d. ed., 2021) (“[A]s the pandemic stretched on, courts — including the newly reconstituted and more conservative U.S. Supreme Court — have increasingly given less deference to state orders imposing social distancing and community mitigation measures.”); Alabama Ass’n of Realtors v. HHS, 141 S. Ct. 2485 (2021) (eviction moratorium); Nat’l Fed’n Indep. Bus. v. Dep’t of Lab., 142 S. Ct. 661 (2022) (vaccine-or-test rule).

<sup>698</sup> 142 S. Ct. 2587 (2022).

<sup>699</sup> *Id.* at 2641 (Kagan, J. dissenting) (citation and footnote omitted).



Much of these forces are beyond FDA's control. Greater public involvement, perhaps even a social movement, may be necessary to reverse these trends. Still, FDA can judiciously participate in these conversations instead of appearing to be a bystander.

As a final note, this Article advises caution in the creation of new premarket review regimes. No doubt, premarket review has tremendous power as a regulatory tool. However, across product areas, FDA's premarket review has been undermined and disconnected from public health, leaving, in many cases, only the illusion of regulation—which could ward off public concern and impetus for change.

## V. CONCLUSION

When many people think of the paragon of regulation—an agency whose mission is so essential that it must not be disturbed—they point to FDA. It goes without saying that products intimately connected with human life, like drugs and foods, should only be allowed on the market if they are safe and appropriate for public use. However, this Article uses a birds-eye view of five FDA product areas to examine how corporate power and neoliberalism have impacted FDA's core mission. The result is a disconnection of premarket review from its original moorings in public health. Today, a large fraction of death and disease in the United States stems from products that premarket review should have caught.

This Article urges a reconnection between FDA review and public health. Statutory repairs could insulate premarket review from corporate and political influence, provide robust resources, and restore the agency's position to maximize public health. But we must also engage with the root cause of agency dysfunction: the rise of corporate power. FDA cannot fight that battle alone, but it can boldly enter the public discourse—with the spirit of honesty, not defensiveness. From Amanda Gorman:

When day comes we step out of the shade,  
 aflame and unafraid.  
 The new dawn blooms as we free it.  
 For there is always light,  
 if only we're brave enough to see it,  
 if only we're brave enough to be it.<sup>700</sup>

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<sup>700</sup> Lian Parsons, 'History Has Its Eyes on Us', HARVARD GAZETTE (Jan. 20, 2021), <https://news.harvard.edu/gazette/story/2021/01/amanda-gormans-inauguration-poem-the-hill-we-climb>.