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Article

## Dangerous Times: The FDA's Role in Information Production, Past and Future

Amy Kapczynski<sup>†</sup>

### INTRODUCTION

These are challenging times for the Food and Drug Administration. Congress passed a so-called right-to-try law in May 2018, sharply limiting the Agency's oversight of the use of experimental drugs.<sup>1</sup> Nearly the only thing the lame duck Congress could agree upon in 2016 was that the FDA should lower its regulatory standards to speed drugs to market.<sup>2</sup> The resulting 21st Century Cures Act urges the Agency to approve drugs with less evidence, but gives the Agency no significant new tools to ensure that companies produce adequate data after a drug enters the market.<sup>3</sup> The Agency also faces profound challenges in the courts. Drug companies have successfully leveraged recent developments in commercial free speech doctrine to call into question the constitutionality of the Agency's restrictions on drug marketing, particularly regarding unapproved (off-label) uses of approved drugs.<sup>4</sup>

Proponents argue that these developments will yield better, faster access to cures. For the most part, these proposed changes

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1. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Belina Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372 (2018).

2. See 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016).

3. See Aaron S. Kesselheim & Jerry Avorn, *New "21st Century Cures" Legislation: Speed and Ease vs. Science*, 317 JAMA 581, 581 (2017).

4. *United States v. Caronia*, 703 F.3d 149, 169 (2d Cir. 2012) (holding that the government cannot, consistent with the First Amendment, construe the misbranding provision of the Food, Drug, and Cosmetic Act to criminalize off-label speech itself); *Amarin Pharma v. FDA*, 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015) (holding that drug companies have a commercial speech right to make off-label claims that are not false or misleading and barring the FDA from using such speech as evidence of misbranding).

are instead likely to put patients in danger and lead to wasteful spending. To understand why, we first need a shared understanding of the central purpose of the FDA's regulation of drug marketing. That mission is commonly described as paternalistic in nature: via pre-market review, the FDA protects us from unsafe medicines. Another prominent view asserts that the justification for the FDA's regulatory power comes from information asymmetries between consumers and companies: by certifying the quality of medicines, the FDA helps consumers make good choices. Both of these arguments have come under sustained attack recently, the first from certain patients' groups and conservative advocacy groups that object to the paternalism it implies, and the second from scholars and advocates who believe that decentralized certification would be more efficient.

Neither of these two visions provides the best justification for the FDA's regulatory power over the marketing of medicines. As Rebecca Eisenberg has suggested, the FDA in its modern form aims primarily to address a problem of *information production*.<sup>5</sup> The core function of the FDA as a drug regulator, as I will elaborate below, is not to make choices for the public, or to certify the truth, but to generate and validate information about medicines.

We need the FDA to play this role because it is, quite simply, extraordinarily hard to know whether something is or is not a cure. By controlling marketing, the FDA targets a distortion inherent to systems that rely on the profit motive and patents to generate clinical trial data: it encourages the creation of high-quality evidence about medicines that is not biased toward positive results. (By "positive" I mean results that appear to favor the safety or efficacy of the drug.) Critically, the Agency also validates evidence about medicines—an activity that is more intensive than what is implied by the term certification. Evaluating the qualities of drugs, as I will describe, has very little in common with rating hotel rooms or warranting used cars. A typical FDA new drug review involves hundreds of thousands of pages of data, and may require reviewers to rerun data analyses, to query companies for more information, and to closely scrutinize individual trial records. Validation of the results of drug trials requires significant expertise, significant resources, and access to all of the relevant clinical trial data. While markets sometimes

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5. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 370 (2007).

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produce viable third-party certifiers, they cannot produce adequate third-party *validators*, absent major interventions that effectively turn third parties into smaller, independent versions of regulatory agencies.

In the pages that follow, I first aim briefly to explain these claims in more detail and show that the most persuasive justification for the FDA's modern regulatory approach stems from the enormous challenges associated with producing and validating high-quality information about medicines. The point is underappreciated both in the academic literature and in policy debates, and is critical to understanding the problems with the recent challenges to the FDA's drug regulatory authority that are sketched above. Such changes might bring compounds more quickly to patients. But they also plausibly could bring about a world where we know less and less about the medicines we put in our bodies.

Understanding the FDA's information production role, I'll show, allows us to see more clearly the danger of immensely popular right-to-try laws. It also helps highlight the grave dangers of emerging First Amendment law that asks judges rather than regulators to determine what is true about a drug. Finally, the information production lens also clarifies the stakes of the FDA's implementation of the 21st Century Cures Act. In particular, it makes plain that the implementation of that Act must be preceded by a much more complete account of the reliability of regulatory decisions made on accelerated timelines and with less evidence. Any move to lower regulatory standards should also be avoided until we have a better understanding of why postmarketing study requirements are so rarely fulfilled in a timely fashion, and until FDA has the resources and authority needed to alter this fact.

## I. THE FDA'S INFORMATION PRODUCTION FUNCTION

Since the 1960s, the FDA has exerted profound regulatory power over new medicines.<sup>6</sup> The Agency exercises that power primarily by controlling drug marketing. No company may promote any new drug—or any existing drug for a new use—without first providing “substantial evidence” of the safety and efficacy

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6. For a description of the unusual power of the FDA as a U.S. regulatory body, and a sweeping history of the development of the Agency's powers, see DANIEL CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* (2010).

of that medicine for a specific use.<sup>7</sup> This premarket review system was refined over many decades, and has had a profound global influence.<sup>8</sup>

Key developments in the drug regulatory process typically have followed from highly publicized tragedies. The most salient was the thalidomide disaster.<sup>9</sup> Used to prevent morning sickness in pregnancy, the drug caused thousands of children in Europe and Australia to be born without limbs, or to suffer other forms of organ damage or even death.<sup>10</sup> The United States was largely spared because of the stubborn—now legendary—refusal of FDA reviewer Dr. Frances Kelsey to approve the marketing of the drug in this country.<sup>11</sup> The event deeply shaped the public's perception of the Agency, and helped justify significant expansions in its regulatory authority.<sup>12</sup> It is therefore not surprising that the FDA's purpose is commonly described first and foremost in paternalistic terms, as a project of protecting consumers from dangerous products.<sup>13</sup>

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7. 21 U.S.C. § 355(a) (2001) (prohibiting the marketing of a new drug prior to FDA approval); *id.* § 355(d) (requiring drug sponsors to provide “substantial evidence” of a drug's safety and effectiveness with respect to the specific use in the proposed labeling and defining “substantial evidence” as “evidence consisting of adequate and well-controlled investigations, including clinical investigations”). Accordingly, if a drug sponsor wishes to add a new use to an existing drug's label, the sponsor must conduct studies that demonstrate the drug's safety and efficacy for the proposed new use.

8. CARPENTER, *supra* note 6, at 687 (noting that “the FDA influence[s] . . . international politics and [the] political economy of pharmaceuticals more than any other regulatory Agency,” and “has become a setter of standards for technological, scientific, economic, and cultural development in medicine”). The Agency also has had profound influence over modern practices of evidence-based drug development. For example, it was FDA regulators that invented the familiar stages of clinical trial development. *Id.* at 278–80, 292–95; *see also* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1777–82 (1996) (describing the FDA's oversight of clinical trial design for pharmaceutical research and its development of requirements and guidelines for clinical trials).

9. CARPENTER, *supra* note 6.

10. *Id.* at 119.

11. *Id.* at 242–48.

12. *See id.* at 238–45 (describing the public impact of the thalidomide example); *id.* at 230 (describing the link between the tragedy and the 1962 Kefauver-Harris Amendments as well as the 1963 Investigational New Drug Amendments). Advocates for reform used the averted tragedy to argue that the system could not over the long term rely on the heroism of individual reviewers but needed structural changes—for example, to remove the default rule that a drug was approved after sixty days absent objections. *Id.* at 254.

13. Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 8 (2007) (describing

This paternalistic justification has been sharply criticized in recent years. Patients with grave diseases, libertarian critics, and conservative think tanks have all argued that the government has no business protecting people from risks that they wish to take.<sup>14</sup> The power of this critique is exemplified by the recent wave of so-called right-to-try laws, which passed in forty states,<sup>15</sup> and very recently into federal law. These laws seek to make it easier for patients to access unapproved drugs.<sup>16</sup> Though they differ in their details, the state laws typically purport to permit manufacturers to market unapproved drugs to terminally ill patients, and immunize companies from liability for any adverse effects.<sup>17</sup> They had little practical effect, because their main provisions were preempted by federal FDA law.<sup>18</sup> Now, however, Congress has adopted a similar law at the federal level,

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the conventional account that “drug regulation is essentially paternalistic because it seeks to protect the misinformed consumer from better-informed sellers”); *see also* Merrill, *supra* note 8, at 1776 (describing one perception of the FDA’s post-1962 role as a gatekeeper that prevents harmful or ineffective drugs from entering the market); *What We Do*, FDA, <https://www.fda.gov/AboutFDA/WhatWeDo> (last visited June 18, 2018) (“The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices . . .”).

14. *See* Eisenberg, *supra* note 5, at 367–68 (describing the objection that “patients may be harmed by disease as well as by drugs,” and the role of patient advocates in criticizing this justification); *see also* Richard A. Epstein, *Against Permittitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 11–13 (2009) (providing a libertarian critique); Karlyn Bowman & Joseph Kosten, *From the Archives: Pharmaceuticals, the FDA, and the Drug Lag*, AM. ENTERPRISE INST. (Nov. 2, 2017), <https://www.aei.org/publication/from-the-archives-pharmaceuticals-the-fda-and-the-drug-lag> (criticizing the FDA for delaying access to new drugs purportedly being used to effectively treat patients in other countries).

15. According to the Goldwater Institute, the main proponent of the right-to-try movement, forty states had right-to-try laws, as of June 2018. Goldwater Inst., *Right to Try in Your State*, RIGHT TO TRY, <http://www.righttotry.org/in-your-state> (last visited June 18, 2018); *see generally* DARCY OLSEN, THE RIGHT TO TRY: HOW THE FEDERAL GOVERNMENT PREVENTS AMERICANS FROM GETTING THE LIFESAVING TREATMENTS THEY NEED (2015) (describing the Goldwater Institute’s role in promoting these laws).

16. Goldwater Inst., *About Right to Try*, RIGHT TO TRY, <http://www.righttotry.org/about-right-to-try> (last visited June 18, 2018) (advocating for right-to-try laws on these grounds).

17. Lisa Kearns & Alison Bateman-House, *Who Stands to Benefit? Right to Try Law Provisions and Implications*, 51 THERAPEUTIC INNOVATION & REG. SCI. 170, 170–71, 174 (2017) (noting variations and commonalities among state right-to-try laws).

18. David Farber, et al., *How Right to Try State Laws Create False Expectations*, HEALTH AFFAIRS BLOG, <https://www.healthaffairs.org/doi/10.1377/hblog20150522.047884/full> (May 22, 2015).

with very significant potential implications for our regulatory system.<sup>19</sup>

Some people who see government paternalism as problematic nonetheless see a legitimate role for the FDA in addressing a particular kind of market failure rooted in information asymmetries.<sup>20</sup> On this account, because consumers know far less than companies about the safety and efficacy of drugs, “in the absence of mechanisms to signal and commit to the quality of drugs, the market for drugs may become a ‘market for lemons’: a smaller market in which only low quality drugs are sold, by non-trustworthy sellers.”<sup>21</sup> Here, the FDA’s purpose is less to protect the public from dangerous drugs than to provide the public with accurate signals about drug quality.<sup>22</sup>

This view, too has been criticized. Richard Epstein, for example, has argued that the need for certification cannot justify the breadth of the FDA’s powers, and particularly the power that the Agency has to ban products from the market.<sup>23</sup> Epstein contends that this power should be removed, and that the FDA should compete as a certifier with private-sector entities, such as trade associations or nonprofits.<sup>24</sup> If the central aim of the Agency is simply to evaluate evidence that already exists, he argues, this work could be done by many entities.<sup>25</sup>

The market-for-lemons justification has difficulty accounting for much of the power that the FDA has long wielded over drug companies. The paternalism justification seems difficult to square with what many people believe government respect for autonomy requires, particularly as regards the very ill. There is, however, a third and more powerful justification for the FDA’s power over drug marketing.

As Rebecca Eisenberg has suggested, the FDA’s modern approach to drug regulation can best be understood through the

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19. See *infra* Part II.

20. See, e.g., HENRY G. GRABOWSKI & JOHN M. VERNON, *THE REGULATION OF PHARMACEUTICALS* 7 (1983).

21. Katz, *supra* note 13, at 11.

22. *Id.* at 35.

23. Epstein, *supra* note 14, at 3-4.

24. *Id.* at 4, 6-8. For responses to Epstein’s points, see Katz, *supra* note 13, at 34-36; and Ralph F. Hall, *Right Question, Wrong Answer: A Response to Professor Epstein and the “Permititis” Challenge*, 94 MINN. L. REV. HEADNOTES 50 (2010).

25. Epstein, *supra* note 14, at 4, 6-8.

lens of innovation policy.<sup>26</sup> The account begins with the economics of information production. Pharmaceuticals are very complex products, whose effects can be understood only through sophisticated and costly empirical studies. These studies often enroll hundreds or thousands of patients, and typically take many years and many millions of dollars to complete.<sup>27</sup> Clinical trial results are also classic public goods: they are nonrivalrous and nonexcludable.<sup>28</sup> Unregulated markets are therefore likely to produce them in inadequate supply.<sup>29</sup> Patents are one means of providing market incentives to produce trial data, but they provide asymmetric incentives. (Data and marketing exclusivities operate similarly to patents for these purposes.)<sup>30</sup> An originator company holding a patent on a compound has reason to invest in positive evidence about a drug, because it can exclude others from recouping the benefits of the information by monopolizing the drug.<sup>31</sup> But it also has high-powered incentives to avoid or hide negative information about the drug.<sup>32</sup>

Competitors can profit by producing negative information about the originator's drug but not to the same degree.<sup>33</sup> They may sell a competing product, but there will often also be other competitors, meaning that there is a free rider concern: many

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26. Eisenberg, *supra* note 5, at 348.

27. AYLIN SERTKAYA ET AL., E. RESEARCH GRP., EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT 4-1 to 4-2 (2014), [https://aspe.hhs.gov/system/files/pdf/77166/rpt\\_erg.pdf](https://aspe.hhs.gov/system/files/pdf/77166/rpt_erg.pdf) (analyzing costs of clinical trials for drug development).

28. Clinical trial results can be kept secret, but like many other information goods, their value cannot be realized without sharing them.

29. See generally Kenneth J. Arrow, *Economic Welfare and the Allocation of Resources for Invention*, in THE RATE AND DIRECTION OF INVENTIVE ACTIVITY: ECONOMIC AND SOCIAL FACTORS 609, 623 (Nat'l Bureau of Econ. Research ed., 1962) (“[F]or optimal allocation to invention[,] it would be necessary for the government or some other Agency not governed by profit-and-loss criteria to finance research and invention.”).

30. Marketing and data protection generate a term of exclusivity because they prevent registration of a generic unless the competing company conducts its own costly trials. Because they also reward invention via the market, they create a bias toward positive information.

31. Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limit of Patents*, 122 YALE L.J. 1900, 1924 (2013).

32. See Eisenberg, *supra* note 5, at 370 (“[F]rom the perspective of the manufacturer, rigorous clinical trials of off-label uses may be as likely to diminish the value of a particular product as to enhance it.”); see also Kapczynski & Syed, *supra* note 31, at 1923–28 (2013) (discussing these incentives, and the general problem that markets conditioned by exclusive rights have producing adequate negative information about products).

33. Kapczynski & Syed, *supra* note 31, at 1927.



competitors can benefit if one of them invests in negative information about a patented drug, but only one company benefits from positive information. And patents cannot solve the free rider problem here, because negative information about a drug is difficult to exclude even in the presence of patents.<sup>34</sup>

The problem is not just theoretical. We now know of prominent examples where companies have designed trials to avoid learning about potentially deadly side effects of their drugs. (As this reveals, the FDA has also not always been able to adequately police the problem in practice.) Consider the history of rofecoxib (Vioxx), a pain-killer developed by Merck that became popular because it reportedly had fewer side effects than alternatives like aspirin.<sup>35</sup> Early in the development process, Merck scientists raised concerns that the drug might have unintended cardiovascular side effects.<sup>36</sup> Despite this, none of the studies Merck conducted for FDA approval “were designed to evaluate cardiovascular risk.”<sup>37</sup> Merck also manipulated the presentation of its data in published studies to obscure evidence of increased cardiovascular risk.<sup>38</sup> The drug stayed on the market from 1999 to 2004, when it was “voluntarily” withdrawn.<sup>39</sup> By that time, nearly 30,000 people had brought legal claims against the company for cardiac events that occurred while taking the drug.<sup>40</sup>

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34. As Talha Syed and I describe:

Positive information is easier to render excludable than negative information, because of its closer nexus to a tangible, physical product. A company that sought to profit from a patent on negative information about a drug would need to track either thoughts or abstention from purchasing. Even if monitoring such intangibles across a large number of individuals were technically feasible, it is doubtful that such monitoring would be economically viable and, in any event, it would bump up against deeply entrenched privacy norms against invasive mental surveillance.

*Id.* at 1926. Excludability, as we show,

is highly variable across information goods, and is affected not only by formal legal entitlements, but also by existing technologies for detecting or tracing such uses (and their costs); existing social norms regarding “acceptable” or “reasonable” enforcement efforts (in light of concerns about privacy, freedom of thought and speech, and so forth); and the existing institutions—or social roles, relations, and organizational forms—within which the predominant uses of the good will be made.

*Id.* at 1903.

35. Harlan Krumholz et al., *What Have We Learnt from Vioxx?*, 334 BRIT. MED. J. 120, 120 (2007).

36. *Id.*

37. *Id.*

38. *Id.* at 121.

39. *Id.* at 122.

40. *Id.* at 120.

Such suits may create incentives to disclose negative information earlier. But they operate *ex post*, and are contingent themselves on balanced information production—for how can plaintiffs show harm without evidence of such harm in the first place?<sup>41</sup> In the Vioxx case, the key evidence was belatedly developed only through FDA oversight. Merck had to conduct new studies when it sought a new indication for the drug, and it was in this process that the company was pushed to study serious cardiovascular events.<sup>42</sup>

Notice that the issue here is *not* that it is difficult to interpret information about drugs without expertise. That is the point of the certification justification: there is a lot of information out there, and someone has to understand or translate it. Rather, the problem here is an information production problem. It is hard to generate that information in the first place, and in *balanced fashion, negative as well as positive*. Marketing restrictions are the stick that complements the carrot provided by patents and data exclusivity.<sup>43</sup>

There are many aspects of the FDA's modern approach to drug regulation that become more intelligible when understood through the lens of information production.<sup>44</sup> For example, the FDA restricts off-label marketing, but not off-label prescribing.<sup>45</sup> Drugs are approved for particular uses. Those uses are described on the drug label, which in turn defines the limits of a company's legitimate marketing—but not a doctor's legitimate prescribing. If a cholesterol drug is approved for use in individuals with a history of heart attacks, doctors may prescribe it to individuals who have no such history, and are at lower risk of cardiovascular events (for example, based on blood lipid levels). The company,

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41. See Eisenberg, *supra* note 5, at 387 (“[G]iven that tort law places the burden of proof upon plaintiffs, drug manufacturers might minimize their liability exposure by remaining ignorant and keeping consumers ignorant of the effects of their products.”).

42. See Krumholz, *supra* note 35, at 121 & n.9 (noting that a clear safety signal was identified in the process of a supplemental new drug application, and that this led the safety board to “recommended that an analysis plan be developed to examine serious cardiovascular events”); see also Eisenberg, *supra* note 5, at 378 (noting the role of the FDA).

43. Ian Ayres & Amy Kapczynski, *Innovation Sticks: The Limited Case for Penalizing Failures to Innovate*, 81 U. CHI. L. REV. 1781, 1785 (2015).

44. Eisenberg, *supra* note 5, at 349.

45. See, e.g., *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012) (“Once FDA-approved, prescription drugs can be prescribed by doctors for both FDA-approved and -unapproved uses; the FDA generally does not regulate how physicians use approved drugs.”).

however, may not market it for those purposes unless it proves to the FDA that its benefits outweigh the risks in that population.

From a paternalistic standpoint, this seems odd, or even discriminatory. Off-label uses are demonstrably riskier than on-label uses.<sup>46</sup> Drugs that are effective for one indication can be ineffective or even harmful when used for another indication.<sup>47</sup> The risk-benefit ratio of a drug is also not the same for different populations: counterintuitively, when people have less severe disease, drugs often are more relatively risky, because the benefits associated with the drug are smaller, but the side effects the same.<sup>48</sup> This is one reason evidence of the benefits and risks of a drug must be considered anew for each indication. But as Eisenberg put it:

If off-label uses of drugs threaten patient safety, then why permit them? On the other hand, if off-label uses do not threaten patient safety enough to prohibit them, then why not promote, rather than prohibit, the dissemination of any information about these uses that will help physicians make better choices for their patients?<sup>49</sup>

The restriction on off-label marketing is puzzling if the purpose of drug regulation is primarily paternalistic. But it makes sense from an information production standpoint. Restricting off-label marketing gives companies incentives to invest in developing evidence about new uses.<sup>50</sup> Companies, unlike doctors, are in a good position to develop that data. They have expertise in trial design. They also typically hold patents or enjoy other

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46. Jennifer R. Bellis et al., *Adverse Drug Reactions and Off-Label and Unlicensed Medicines in Children: A Nested Case-Control Study of Inpatients in a Pediatric Hospital*, 11 *BMC MED.* 238, 238 (2013) (showing drugs prescribed off-label for pediatric populations pose a 2.25 times higher risk of adverse effects than do drugs approved for use in children).

47. For example, tiagabine (Gabitril), approved to reduce the risk of seizures in people diagnosed with epilepsy, in fact caused seizures in patients who were administered the drug for other disorders. See Charlene M. Flowers et al., *Seizure Activity and Off-Label Use of Tiagabine*, 354 *NEW ENG. J. MED.* 773, 773 (2006).

48. The benefits of potent opioids, for example, may outweigh the risks for certain kinds of severe pain. But for those suffering chronic mild pain, the benefits are smaller, and the risks—for example of addiction—relatively more significant. See William B. Schultz, *Trump's New FDA Commissioner Has a Huge Decision to Make*, *WASH. POST* (May 16, 2017), [https://www.washingtonpost.com/opinions/trumps-new-fda-commissioner-has-a-huge-decision-to-make/2017/05/16/4ee187f8-3667-11e7-b412-62beef8121f7\\_story.html](https://www.washingtonpost.com/opinions/trumps-new-fda-commissioner-has-a-huge-decision-to-make/2017/05/16/4ee187f8-3667-11e7-b412-62beef8121f7_story.html).

49. Eisenberg, *supra* note 5, at 370.

50. *Id.*

kinds of exclusivity that can help them to recoup the costs of such research.

Eisenberg points to several other aspects of the FDA's approach to drug regulation that are also easier to understand from the perspective of information production. The FDA requires companies to produce much more extensive information about medicines than about dietary supplements before each can be marketed.<sup>51</sup> Supplements can also be dangerous, so she argues that the difference makes sense less as an expression of paternalistic values than as an expression of differing dynamics of information production. Dietary supplements are natural products, and so less amenable to patents.<sup>52</sup> Using marketing restrictions to encourage evidence production about supplements via the private market could plausibly push supplements out of the market rather than produce good evidence about supplements.<sup>53</sup>

Similarly, the FDA's regime governing the use of experimental drugs makes little sense from a paternalistic standpoint, but much more sense viewed through the lens of information production. For example, in general, it is illegal for individuals to import medical products that are not approved in the United States,<sup>54</sup> but the FDA provides a discretionary exemption for personal use in certain situations, such as when the product is for the treatment of a serious condition.<sup>55</sup> It also allows individuals who are seriously ill to choose to take experimental drugs via its compassionate-use program, and it approves nearly all

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51. *Id.* at 379.

52. *See* *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 66 (“Laws of nature, natural phenomena, and abstract ideas are not patentable.”).

53. Eisenberg, *supra* note 5, at 379–80.

54. 21 U.S.C. § 355(a) (2012) (“No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.”).

55. *Id.* § 384(j)(1)(B) (allowing FDA to “exercise discretion to permit individuals to make such importations in circumstances in which—(i) the importation is clearly for personal use . . . and (ii) the prescription drug or device imported does not appear to present an unreasonable risk to the individual”); *Personal Importation*, FDA, <https://www.fda.gov/ForIndustry/ImportProgram/ImportBasics/ucm432661.htm> (last visited June 18, 2018) (describing criteria for personal importation of unapproved drugs).

such requests.<sup>56</sup> But the FDA has historically not allowed companies to market to patients in these same circumstances.<sup>57</sup> This reflects less a commitment to protect patients from risk than it does a commitment to protect a system of evidence production. Drug companies are well situated to respond to marketing restrictions by producing evidence, but individual patients are not.

Finally, notice one additional puzzle that the information production perspective can help resolve. If the FDA is needed merely to inform consumers, then it is hard to see—as Epstein argues—why it can go beyond certifying the effects of a drug, to ban a drug from the market altogether. But from an information production standpoint, power over marketing is essential. The ability to ban marketing is a stick that the FDA requires to ensure that companies produce balanced information about drugs and submit it to regulators for review.

Shifting our focus to the domain of information production also allows us to see another market failure that the FDA seeks to solve, here related not to the production of evidence but to its validation. Unregulated markets can neither produce balanced information about drugs nor rigorously evaluate evidence produced about drugs. The notion that the FDA can serve as merely one certifier among many neglects two problems. One relates to *secrecy* and the other to *financing*.

First, accurately evaluating clinical trial evidence requires access to all of the associated clinical trial data. But no entity other than the FDA has the right to demand access to all of the data associated with a drug, and no third party can expect routinely to receive it. Epstein seems to envision that third-parties will be able to consult the literature to make informed judgments

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56. 21 U.S.C. § 360bbb (providing for expanded access to unapproved therapies and diagnostics). According to a 2017 report by the U.S. Government Accountability Office, of the nearly 5800 expanded access requests received by the FDA from 2012 to 2015, the FDA allowed ninety-nine percent to proceed, and for emergency single-patient requests, the Agency typically responds within hours. GAO, GAO-17-564, FOOD AND DRUG ADMINISTRATION: INVESTIGATIONAL NEW DRUGS: FDA HAS TAKEN STEPS TO IMPROVE EXPANDED ACCESS PROGRAM BUT SHOULD FURTHER CLARIFY HOW ADVERSE EVENTS DATA ARE USED 17, 19 (2017), <http://www.gao.gov/assets/690/685729.pdf>.

57. Ashley Ochs, *A Study in Futility: Abigail Alliance for Better Access to Developmental Drugs Will Not Expand Access to Experimental Drugs for the Terminally Ill*, 39 SETON HALL L. REV. 559, 570 (2009) (discussing the need for testing completion before marketing will be approved). For possible implications of the new federal right-to-try law on this restriction, see *infra* Part II.

about the value of medicines.<sup>58</sup> About half of all completed clinical trials, however, are not published.<sup>59</sup> Recent evidence also suggests that the published literature is biased toward positive studies. In a 2008 paper, for example, researchers compared FDA reviews of antidepressant drugs with the published literature.<sup>60</sup> Only one study that the FDA considered positive was not published.<sup>61</sup> In all but three cases, however, studies that the FDA considered negative were not published at all or were published and described as positive.<sup>62</sup> With full access to the study results, a reviewer would have seen that around half of the studies were negative, while with access to only the published results, a reviewer would have believed that ninety-four percent of the trials conducted were positive.<sup>63</sup> Reviewers relying on published evidence will systematically overestimate the effectiveness of medicines, if, as it appears, the literature is systematically skewed.

The problem goes beyond publication bias. There are excellent nonprofit groups, the Cochrane Group for example, that seek to generate neutral, expert evidence about the effects of drugs by conducting metastudies of all of the available trials.<sup>64</sup> Those studies are often considered the gold standard in meta-research, and have had a significant influence on prescribing guidelines.<sup>65</sup> But they are typically based on incomplete data.

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58. See Epstein, *supra* note 14.

59. Carolina Riveros et al., *Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals*, 10 PLOS MED. e1001566 (2013); Joseph S. Ross et al., *Publication of NIH Funded Trials Registered in Clinicaltrials.gov: Cross Sectional Analysis*, 344 BRIT. MED. J. 1, 3 (2012).

60. Erick H. Turner et al., *Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy*, 358 NEW ENG. J. MED. 252 (2008).

61. *Id.* at 256 (table showing one (3%) unpublished positive study and 37 (97%) published positive studies).

62. *Id.* (table showing sixteen (67%) unpublished negative studies, five (21%) published negative studies that conflict with FDA decision, and three (12%) published negative studies that agree with FDA decision).

63. *Id.* at 255 (“Overall, 48 of the 51 published studies were reported to have positive results (94%). According to the FDA, 38 of the 74 registered studies had positive results (51%).”).

64. See *About Us*, COCHRANE, <http://www.cochrane.org/about-us> (last visited June 18, 2018).

65. Marie Baudard et al., *Impact of Searching Clinical Trial Registries in Systematic Reviews of Pharmaceutical Treatments: Methodological Systematic Review and Reanalysis of Meta-Analyses*, 356 BRIT. MED. J. 1, 1 (2017). (“Systematic reviews are considered to provide the highest level of evidence . . . [and form the basis] of clinical practice guidelines . . . .”); Richard Smith, *The Cochrane Collaboration at 20*, 347 BRIT. MED. J. 1, 1 (2013) (“Many see

The depth of the problem has only recently begun to be understood. For example, several years after the approval of oseltamivir (Tamiflu), a drug used to treat influenza, concerns were raised about the efficacy of the drug.<sup>66</sup> The Cochrane Group published a metastudy of the evidence that was largely positive,<sup>67</sup> but an outside researcher pointed out potential problems with some of the unpublished studies, and the Cochrane reviewers decided to undertake further investigation.<sup>68</sup> The company, Roche, was unwilling to turn over the data underlying the unpublished trials that the reviewers requested.<sup>69</sup> Eventually, after four years of work that included a public campaign for release of the data by a prominent medical journal, the researchers were able to access all published and unpublished data, and conducted an updated review.<sup>70</sup> They reversed their earlier findings, and concluded that the drug could not be affirmatively recommended to reduce symptoms.<sup>71</sup> The group also recommended further study—but unlike the FDA, had no tools to press the company to comply.

The example shows the issue in stark relief: we now know that the gold standard for clinical meta-research is often based on incomplete information—information that may also be systematically biased, because it too must typically rely substantially on publicly available data. Groups like Cochrane have no entitlement to access data held by companies, and they obtain secret data only rarely and with great effort. The FDA, in contrast, does have that entitlement.<sup>72</sup> It receives enormous quantities of data that companies do not make public. These include

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Cochrane reviews as the gold standard, and the collaboration has played a major role in promoting evidence based practice.”).

66. Tom Jefferson et al., *Neuraminidase Inhibitors for Preventing and Treating Influenza in Healthy Adults: Systematic Review and Meta-Analysis*, 339 BRIT. MED. J. 1, 5–7 (2009).

67. *Id.* at 2 (noting that the review “found positive evidence” with regard to the ability of neuraminidase inhibitors to prevent or ameliorate influenza, to interrupt transmission of the virus, and to reduce influenza related complications).

68. *Id.* at 2.

69. Peter Doshi, *Neuraminidase inhibitors—the story behind the Cochrane review*, 339 BMJ 5164, 5194 (2009).

70. TOM JEFFERSON ET AL., COCHRANE DATABASE SYST. REV. NEURAMINIDASE INHIBITORS FOR PREVENTING AND TREATING INFLUENZA IN ADULTS AND CHILDREN (REVIEW) (2014) (reviewing all the clinical study reports of published and unpublished clinical trials).

71. *Id.* at 2–6.

72. Amy Kapczynski & Jeanie Kim, *Clinical Trial Transparency: The FDA Should and Can Do More*, 45 J. LAW MED. ETHICS 33, 33 (2018).

trial protocols (necessary to interpret data produced in trials), summaries of trial results (such as the clinical study reports that companies prepare for the Agency), and the underlying analyzable datasets—none of which are routinely available to researchers.<sup>73</sup>

FDA reviewers may also query applicants for more data and dig deeper into the record to validate and—if needed—correct data. For example, after postmarket safety concerns emerged in association with the diabetes medicine rosiglitazone (Avandia), the FDA conducted a manual review of adverse event forms submitted to the Agency, collected additional data for hundreds of trial participants, and found a number of deaths that had not previously been recorded.<sup>74</sup> This is a good example of the extraordinary complexity of trial evaluation. Just a few missed deaths in a trial—stemming from inadequate follow-up, or misreporting that is either accidental or deliberate—can translate into hundreds or even thousands of deaths in a population, once a drug is widely prescribed.

One solution to this problem is simple transparency.<sup>75</sup> In practice, transparency has been anything but simple. Companies resist turning over protocols, summary data, and especially analyzable datasets to researchers, citing concerns about commercial confidentiality as well as patient privacy.<sup>76</sup> The FDA has long repeated these concerns and released most such data only after protracted litigation via FOIA—and some not even then.<sup>77</sup> The FDA and drug companies are likely wrong that clinical trial data relevant to the assessment of the safety or efficacy of a drug categorically should be considered commercially confidential and kept secret.<sup>78</sup> Where manufacturers' concerns are genuine and

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73. *Id.* at 34

74. FDA, Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Comm. and the Drug Safety and Risk Mgmt. Advisory Comm., Readjudication of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes Trial (RECORD) (June 5–6, 2013); Kenneth W. Mahaffey et al., *Results of a Reevaluation of Cardiovascular Outcomes in the RECORD Trial*, 166 *AMERICAN HEART J.* 240, 242 (2013).

75. Eisenberg suggests this, for example. *See* Eisenberg, *supra* note 5, at 383.

76. Kapczynski & Kim, *supra* note 72, at 34.

77. *Id.*

78. *See* Aaron S. Kesselheim & Michelle M. Mello, *Confidentiality Laws and Secrecy In Medical Research: Improving Public Access To Data on Drug Safety*, 26 *HEALTH AFF.* 483, 487–88 (2007); *see also* *Corn Prods. Refining Co. v. Eddy*, 249 U.S. 427, 431–32 (1919) (“[I]t is too plain for argument that a manufacturer or vendor has no constitutional right to sell goods without giving to



not contrary to the public's interest in understanding the quality of a product—where, for example, companies wish to protect information about manufacturing processes—the information in question can readily be redacted.<sup>79</sup> (There are also accepted protocols for sharing data while protecting patient privacy.)<sup>80</sup> But there is undoubtedly an awkward fit between a profit-motivated system for clinical data development and the call for radical transparency. Moreover, even if all data routinely given to the FDA were made available to outside researchers, those researchers would not have the right that FDA reviewers have to demand a response, and more data, from companies. Even the most ambitious transparency agenda cannot give private entities the powers possessed by the FDA without turning them, in effect, into decentralized and smaller versions of a regulatory Agency.

Even if the access-to-data problem were solved, the financing of validation efforts would still be an issue. The expense associated with rigorous validation of study results is substantial. The FDA's Office of New Drugs, for example, has a staff of more than 1000.<sup>81</sup> New drug approval packages submitted to the FDA routinely run in the hundreds of thousands of pages, and analysis of this data demands a great deal of expertise and time.<sup>82</sup> While groups like Cochrane or formulary committees may have the capacity to consult the published literature and, in rare cases, seek some additional underlying summary data, this is the very tip of the clinical data iceberg. The FDA reviews not only clinical data from all trial phases, in primary as well as

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the purchaser fair information of what it is that is being sold. The right of a manufacturer to maintain secrecy as to his compounds and processes must be held subject to the right of the State, in the exercise of its police power and in promotion of fair dealing, to require that the nature of the product be fairly set forth.”); Epstein, *supra* note 14, at 34 n.135 (declaring support for “the publication of trade secret information needed to evaluate serious health risks”).

79. Kapczynski & Kim, *supra* note 72, at 34.

80. *Id.* at 33.

81. Zachary Brennan, *FDA's Office of New Drugs Director to Retire*, RAPS (Dec. 5, 2016), <http://www.raps.org/Regulatory-Focus/News/2016/12/05/26301/FDA%E2%80%99s-Office-of-New-Drugs-Director-to-Retire>.

82. *Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 108th Cong. 36–37 (2004) (statement of Janet Woodcock, Deputy Comm'r for Operations, FDA), <https://www.gpo.gov/fdsys/pkg/CHRG-108hrg96094/pdf/CHRG-108hrg96094.pdf> (noting that raw data from drug submissions runs in the “hundreds or thousands of volumes” and that “there are very few individuals who are capable of going through all that at that level”); see also *id.* at 179 (Statement of John R. Hayes, Product Team Leader, Eli Lilly Company) (“We recently had a new drug application that was 417,000 hard copy pages for a single indication.”).

summary form, but also evaluates animal studies, pharmacokinetic information, and postmarket adverse events.<sup>83</sup> Given their limited capacity, third-party groups like Cochrane focus on a limited set of drugs and primarily consult secondary sources rather than the voluminous primary data. Academics have little reason to do reanalysis of this sort, because it is unlikely that any particular study will generate new knowledge, and replication studies are difficult to publish if they indeed validate the initial results.<sup>84</sup>

Might insurance companies take on a larger role in validating studies, because it would serve their interest in “controlling drug costs,” as Eisenberg wonders?<sup>85</sup> Not likely, and certainly not at the scale undertaken by the FDA. First, there is a classical principal-agent problem: insurers have reason to focus only on clinical evidence associated with high cost drugs, and have incentive to find fault with them in order to deny coverage. Collective action issues present another problem: if insurers were to invest in hiring hundreds of staff members to undertake the same work that the FDA undertakes and share the results publicly, other insurers could free ride. If they kept the results a secret—perhaps difficult, given patients’ need to understand the basis for coverage decisions—then their work could not serve the role of public validation of the quality and safety of drug products.

The FDA, in sum, plays a critical role in the production and validation of information about medicines—one that is essential to the production of balanced evidence about the harms and benefits of medicines, and to the intensive work needed to evaluate the studies that companies conduct. The reason that we apply this regime to medicines and not to all products has to do with the substantial risks and benefits associated with drugs, and in this way the Agency’s role is fundamentally about protecting the public. But the Agency protects the public not by *making choices for it* or by *certifying the truth* but by *generating and validating information* about medicines. These aims, moreover, are inter-

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83. Lee et al., *Publication of Clinical Trials Supporting Successful New Drug Applications: A Literature Analysis*, 5 PLOS MED 191, 191 (2008).

84. YALE COLLABORATION FOR RESEARCH INTEGRITY & TRANSPARENCY, PROMOTING TRANSPARENCY IN CLINICAL RESEARCH: WHY AND HOW 9–10 (2017), [https://law.yale.edu/system/files/area/center/crit/crit\\_white\\_paper\\_november\\_2017\\_best\\_promoting\\_transparency\\_in\\_clinical\\_research\\_why\\_and\\_how.pdf](https://law.yale.edu/system/files/area/center/crit/crit_white_paper_november_2017_best_promoting_transparency_in_clinical_research_why_and_how.pdf).

85. Eisenberg, *supra* note 5, at 374.

twined: if no entity had the resources to closely monitor the conduct and results of trials, it would be trivially easy for companies to slant the data or summaries in favor of their products. *Both* tasks are critical, and neither can be performed adequately by an unregulated market.

## II. WHY RECENT REFORMS THREATEN THE FDA'S INFORMATION PRODUCTION AND VALIDATION FUNCTION

From this perspective, we can see better why so-called right-to-try laws and recent First Amendment cases are so troubling. We can also see the enormous stakes of how the FDA implements its new authority under the 21st Century Cures Act.<sup>86</sup> Changes that reduce the power of the FDA's stick, as these do, threaten our system for producing and validating evidence about medicines.

Prior to the new right-to-try law, federal statutes and regulations already provided a pathway for patients to access unapproved compounds.<sup>87</sup> Under that approach, patients with a serious or life-threatening disease can request permission from the FDA to use an unproven therapy if they cannot access other satisfactory approved treatments or a clinical trial.<sup>88</sup> The FDA grants ninety-nine percent of all such requests.<sup>89</sup> Companies, however, routinely refuse to supply investigational drugs to patients, leaving many who are seriously ill without the ability to access compounds that they wish to try.<sup>90</sup> Experts commonly have cited two reasons that companies do not more frequently grant patient requests. By regulation, companies may not profit from expanded access uses.<sup>91</sup> Providing drugs to patients who are often sicker than the typical intended population also risks

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86. 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016).

87. 21 C.F.R. § 312.305(a) (2017).

88. See 21 C.F.R. § 312.305(a); *Expanded Access: Information for Patients*, FDA (Jan. 4, 2018), <https://www.fda.gov/ForPatients/Other/ExpandedAccess/ucm20041768.htm>.

89. Jonathan P. Jarow et al., *Ten-Year Experience for the Center for Drug Evaluation and Research, Part 2: FDA's Role in Ensuring Patient Safety*, 51(2) THERAPEUTIC INNOVATION & REG. SCI. 246, 246 (2017). In eleven percent of the cases, the FDA also requested changes to protect patients, suggesting that the Agency's review provides important input to patients and companies. *Id.* at 248.

90. See Alison Bateman-House et al., *"Right to Try" Won't Give Patients Access to Experimental Drugs. Here's What Will*, HEALTH AFFAIRS: BLOG (May 3, 2017), <https://www.healthaffairs.org/doi/10.1377/hblog20170503.059926/full>.

91. 21 C.F.R. § 312.8(d)(1) (limiting a company's recoverable costs to "direct costs").

additional adverse events that may mar the record of an unproven therapy and make approval more complex.<sup>92</sup>

State and federal right-to-try laws were promoted—most prominently by the Goldwater Institute—as a way to increase access to experimental therapies.<sup>93</sup> The recently passed federal version allows patients with life-threatening diseases or conditions to bypass the existing expanded access process.<sup>94</sup> It forbids the FDA to use any data arising from uses under the new pathway to negatively impact drug approval decisions, with certain narrow exceptions.<sup>95</sup> The law also limits liability for companies and prescribers “unless the relevant conduct constitutes reckless or willful misconduct, gross negligence, or an intentional tort under any applicable State law.”<sup>96</sup> Because it does not explicitly restrict what companies can charge, some argue that the law “open[s] the door for companies to profit from selling unproven drugs.”<sup>97</sup> The law does refer to existing FDA regulations that permit companies only to charge “direct costs,” but these regulations might be changed.<sup>98</sup>

The law’s provisions mainly target the FDA, despite the fact that the Agency has not been the main barrier to access.<sup>99</sup> The

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92. See Bateman-House et al., *supra* note 90.

93. See *id.*; see also Goldwater Inst., *supra* note 15.

94. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Belina Right to Try Act of 2017, Pub. L. No. 115-176, sec. 2(a), § 561B(a)(1)(A); see also Alison Bateman-House & Christopher T. Robinson, *The Federal Right to Try Act of 2017—A Wrong Turn for Access to Investigational Drugs and the Path Forward*, 178 JAMA Internal Med. 321, 321 (2018) (summarizing the Senate Bill, S 204, that was the basis for the adopted law). The law applies to medicines that are in development and have completed only the most minimal (phase I) tests. Pub. L. No. 115-176, sec. 2(a), § 561B(a)(2)(A). Phase I trials give no information about efficacy and provide only preliminary information on safety, typically drawn from tests on healthy volunteers rather than in persons with the disease. See *The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA (Nov. 24, 2017), <https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>.

95. Pub. L. No. 115-176, sec. 2(a), § 561B(c)(1) (“[T]he Secretary may not use a clinical outcome associated with the use of an eligible investigational drug pursuant to this section to delay or adversely affect the review or approval of such drug [unless the sponsor requests it or the Secretary finds it] is critical to determining the safety of the eligible investigational drug.”).

96. *Id.* at sec. 2(b)(1)(B).

97. Bateman-House & Robertson, *supra* note 94, at 321.

98. Pub. L. No. 115-176, sec. 2(a), § 561B(b) (citing 21 C.F.R. § 312.8(d)(1)).

99. Bateman-House & Robertson, *supra* note 94, at 321. In addition to the FDA’s rapid review and approval of almost all requests, when the FDA receives reports of adverse events in the expanded access program, it considers them in context and gives them very little weight in the approval process. U.S. DEPT OF HEALTH & HUMAN SERVS., EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR

law also explicitly states that companies have no obligation to provide patients with access to experimental therapies.<sup>100</sup> It will therefore likely do little to help patients.<sup>101</sup> But by further limiting the FDA's role in the process, it may mean that patients end up with less information about medicines. If new regulations permitted companies to profit from unapproved uses, the results would be more troubling still. Companies would have less incentive to quickly complete trials to gain approval.

Once we appreciate the importance of marketing restrictions in our system of producing information about drugs, it becomes clear that the push to deregulate access to experimental therapies comes along with grave risks. More targeted approaches that seek to reduce the administrative burden of the existing expanded access program, and to improve patients' and companies' understanding of the process, would better serve patients' need for treatment, while also protecting their need for answers.<sup>102</sup>

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TREATMENT USE: QUESTIONS AND ANSWERS 18–19 (2017), <https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf>. (“In a very small number of cases, [FDA has used] adverse event information from expanded access [in the safety assessment of a drug] . . . FDA reviewers of these adverse event data understand the context in which the expanded access use was permitted [(e.g., use in patients with serious or immediately life-threatening diseases or administered in a clinical setting (not clinical trial)] and will evaluate any adverse event data obtained from an expanded access submission within that context . . . Expanded access INDs (Investigational New Drugs) and protocols are generally not designed to determine the efficacy of a drug; however, the expanded access regulations do not prohibit the collection of such data. Because expanded access INDs or protocols typically involve uncontrolled exposures (with limited data collection), it is unlikely that an expanded access IND or protocol would yield efficacy information that would be useful to FDA in considering a drug's effectiveness.”).

100. Pub. L. No. 115-176, sec. 2(b)(2).

101. See, e.g., Bateman-House & Robinson, *supra* note 94; see also Vibhav Rangarajan, *The “Cruel Joke” of Compassionate Use and Right to Try: Pharma Companies Don't Have to Comply*, STAT NEWS (June 5, 2018), <https://www.statnews.com/2018/06/05/right-to-try-compassionate-use-pharma-compliance>. Even if companies were eventually allowed to charge for such medicines, if insurance coverage is not mandated for such uses, patients will likely have difficulty covering the costs on their own. Most state laws explicitly say that insurance plans are not required to cover experimental uses. Kearns & Bateman-House, *supra* note 17, at 171.

102. Bateman-House et al., *supra* note 90 (recommending a series of changes of this sort, including improved communication, and eliminating the requirement for an institutional review board to review requests for individual patients).

The recent First Amendment cases are similarly troubling once we have in view the role that the FDA's restrictions on marketing play in information production and validation. Commercial speech has long received only limited constitutional protection, but recent Supreme Court cases have begun to blur the lines between commercial speech and more protected public or political speech.<sup>103</sup> In response to these cases, lower courts have begun to call into question the constitutionality of the FDA's longstanding approach to evidence production as applied to off-label uses.

As described above, under current law, to be permitted to market a drug for a particular use, a company must first produce data that the drug is safe and efficacious for that use and submit such data to regulators. A recent Second Circuit case, *United States v. Caronia*, suggested that this longstanding approach may today be unconstitutional.<sup>104</sup> The majority viewed the primary aim of the Agency's restriction on off-label promotion as protecting patients from unsafe medicines.<sup>105</sup> It concluded that marketing restrictions did not "directly advance" an interest in patient safety because if this is the government's aim, it makes little sense to permit off-label prescribing but forbid off-label promotion.<sup>106</sup> It concluded that the FDA could restrict marketing that it could show to be false or misleading, but that it could not constitutionally restrict marketing merely because it is off-label.<sup>107</sup>

The Second Circuit left open additional arguments that the Agency may make in its defense,<sup>108</sup> though these were rejected in a subsequent district court case, *Amarin Pharma, Inc. v. FDA*.<sup>109</sup> In that case, a company that made a pharmaceutical derived from fish oil wished to market it broadly for an unapproved

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103. See *Sorrell v. IMS*, 564 U.S. 552, 566 (2011).

104. *United States v. Caronia*, 703 F.3d 149, 162–69 (2d Cir. 2012).

105. *Id.* at 153.

106. *Id.* at 166–67 ("Prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions.").

107. *Id.* at 168–69.

108. See *id.* at 162 n.9 (noting that the government might have argued, but had not in this case, that off-label promotion was merely being used as evidence of mislabeling).

109. *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 227–28 (S.D.N.Y. 2015).

use, despite the FDA's conclusion that there was no reason to think that the product provided any clinical benefit for the use in question.<sup>110</sup> The court interpreted *Caronia* to imply that restrictions on off-label marketing were flatly unconstitutional, and issued an order—on a preliminary injunction motion, with neither a full record nor expert testimony—effectively adjudicating the merits of the company's marketing claims.<sup>111</sup> The court concluded, for example, that the drug could be promoted to reduce the risk of coronary artery disease, despite the FDA's objection that there was inadequate evidence to support such a use.<sup>112</sup> The FDA's contrary conclusion drew on its expert review of a substantial body of evidence, including recent clinical studies of other drugs that operated in a similar fashion that showed no clinical benefit.<sup>113</sup>

*Amarin's* approach replaces expert FDA reviewers with federal judges who may have no training in science, and who have access to almost none of the data and evidence that drug reviewers enjoy. Judges have neither the skills nor the data needed to adequately validate claims about medicines. And because the FDA's validation role is intertwined with its evidence production role, *Amarin's* logic also threatens to undermine the production of evidence about new uses. As I have described elsewhere, *Amarin* has implications for drug-approval strategy in the future:

Once a drug is approved for any indication, it can be promoted to physicians for any use as long as a judge, not the FDA, views the marketing to be truthful and nonmisleading . . . . The *Amarin* decision invites a world where companies no longer pursue broad clinical indications for new drugs but instead seek the narrowest possible indication for approval and then market the drug for any new use for which there is *some* evidence, no matter how weak. Companies would no longer have to conduct rigorous trials and submit, to the FDA, data demonstrating the safety and efficacy of new uses. Such an approach would compromise the future evidence base for medicines, expose patients to a greater risk of adverse events, and increase pharmaceutical spending without evidence that the expenditures would help improve patients' health.<sup>114</sup>

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110. *Id.* at 198.

111. *Id.*

112. *Id.* at 214, 234–35.

113. Letter from Janet Woodcock, Director, Ctr. Drug Eval. & Research, FDA, to Steven Ketchum, President, Research & Dev., Amarin Pharma, Inc. 3 (June 5, 2015) (on file with author).

114. Jeanie Kim & Amy Kapczynski, *Promotion of Drugs for Off-Label Uses: The US Food and Drug Administration at a Crossroads*, 177 JAMA INTERNAL MED. 157, 157 (2017).

Fortunately, *Amarin* is only a district court opinion. The Second Circuit might resolve differently the argument left open in *Caronia*, and other theories remain that might convince other appellate courts.<sup>115</sup> But there is now significant pressure on the Agency to voluntarily relinquish its power over off-label uses, and there are some indications that it may be considering this approach.<sup>116</sup>

The risks of this to the Agency's information production and validation function, again, are substantial. If companies continue to press this line of cases, and courts agree, what might be done in response? It is worth noting that private industry is not the only entity that can fund clinical research. If substantial public funding were directed to study off-label uses, then additional marketing of such uses might be compatible with continued evidence production.<sup>117</sup>

Finally, the impact of the 21st Century Cures Act is also clarified by an appreciation for the FDA's information production role. Broadly summarizing, the Act encourages the FDA to approve drugs more quickly and with less evidence.<sup>118</sup> For example, it urges the Agency to increase its reliance on "biomarkers and surrogate measures" in the drug approval process, along with "real world evidence"—observational data arising from routine clinical use, rather than prospectively collected data from randomized controlled trials."<sup>119</sup>

In theory, it may be possible to approve drugs with less evidence, and gather more evidence after approval, when the drug is in use in the wider population. In part with this in mind, the FDA has already begun to employ forms of accelerated approval, and has increasingly relied on nonclinical endpoints as markers

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115. *Id.* at 158 (noting that the FDA has a strong argument that its approach is one that does not penalize speech as such but that merely uses speech for evidentiary purposes); see also Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERNAL MED. 295, 296 (describing why the correct application of the *Central Hudson* test would also favor the FDA).

116. Kim & Kapczynski, *supra* note 114, at 157.

117. The point must be taken with caution, though, since it might be harder to enroll trials if patients have widespread access to drugs for off-label uses and if drugs are being widely marketed for those uses.

118. Betty Lengyel-Gomez, *21st Century Cures Act—A Summary*, HIMSS NEWS, <http://www.himss.org/news/21st-century-cures-act-summary> (last updated Feb. 20, 2017).

119. Kesselheim & Avorn, *supra* note 3, at 581–82.



of success.<sup>120</sup> But there are costs as well as benefits of approving drugs on the basis of more preliminary trials, and neither has been well-characterized. For example, we know of many cases where early and small clinical trials suggested benefits but larger and more definitive trials revealed that drugs did not work or even caused harm.<sup>121</sup> We do not yet know how representative these examples are. Recent evidence also shows that drugs that are approved through accelerated pathways are more likely to be subject to serious postmarket safety warnings, indicating that when the FDA accelerates its review this comes at some cost to patient safety.<sup>122</sup> But again, we have little sense of how substantial these risks are on the whole, nor how large the associated benefits of faster review may be.

The FDA has also already begun to use surrogate markers extensively.<sup>123</sup> Surrogate markers can make trials faster and cheaper because they may be assessed more quickly or easily than clinical benefits. For example, a trial might measure cholesterol levels instead of cardiovascular deaths, or tumor shrinkage instead of survival time. But if these markers turn out not to correlate with clinical outcomes, approving drugs on this basis increases risks to patients (because drugs almost always have associated risks) and wastes scarce resources.

Are scientists and regulators good at selecting surrogate markers? Existing studies give cause for concern.<sup>124</sup> For example, a recent systematic review of drugs approved by the FDA over a twelve-year period showed that for those approved on the basis of surrogate markers, “less than one-tenth . . . had a published peer-reviewed post-market study establishing that the

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120. Suzanne White Junod, FDA, *FDA and Clinical Trials: A Short History*, <https://www.fda.gov/aboutfda/whatwedo/history/FOrgsHistory/evolvingpowers/ucm304485.htm> (last updated Feb. 1, 2018).

121. See generally Zachary Brennan, Twenty-Two Case Studies Where Phase Two and Phase Three Trials Had Divergent Results, *STATE NEWS SERV.*, Jan. 19, 2017 Gale, Doc. No. A4778165802.

122. Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 *JAMA* 1854, 1860–61 (2017); see also Daniel Carpenter et al., *Drug-Review Deadlines and Safety Problems*, 358 *NEW ENG. J. MED.* 1354, 1357 (2008) (showing increased safety issues in the postmarket phase for drugs benefiting from expedited approval and faster review times).

123. Nicholas S. Downing, et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 *JAMA* 368, 377 (2014).

124. Yale Collaboration for Research Integrity & Transparency, *What’s in Your Medicine Cabinet? Ensuring the Safety and Efficacy of Prescription Drugs, Biologics and Medical Devices in the United States*, 14, 14–15 (2017).

drug was effective based on clinical evidence.”<sup>125</sup> In other words, it is likely that many drugs currently approved on the basis of surrogate markers are *never* shown to be effective in clinical terms. In another study, the authors gathered twenty years of cardiovascular trials involving medicines and other interventions that had been published in the most prominent medical journals.<sup>126</sup> They selected those that used surrogate markers, and then searched the literature for follow on studies. Less than one-third all of the trials that showed a positive result for a surrogate were even studied for clinical endpoints.<sup>127</sup> More worryingly still, when they *were* tested, half of the time surrogate markers that were thought to correlate with clinical benefit in fact did not.<sup>128</sup>

If we are to expedite the FDA’s review process and employ more surrogate markers without compromising the FDA’s evidence production and validation function, we must shift the regulatory system to require rigorous follow-on studies that can confirm or disprove early results. Companies are already required to conduct such studies in many cases, but here too, the early evidence suggests that the system isn’t working well. Post-marketing studies are rarely completed on time.<sup>129</sup> For example, in one study of twenty-two drugs that were subject to fast-track approval by the FDA from 2009 to 2013, only half of required follow-up studies were completed within three years.<sup>130</sup> More troublingly still, these follow-on studies often also used surrogate or biomarkers, rather than clinically meaningful endpoints such as the alleviation of symptoms or improvements in morbidity or mortality.<sup>131</sup> This suggests that currently the FDA is unable to require studies to be done in a timely fashion, or to require that

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125. *Id.* at 14 (citing Alison M. Pease et al., *Postapproval Studies of Drugs Initially Approved by the FDA on the Basis of Limited Evidence: Systematic Review*, 357 BRIT. MED. J. 1680 (2017)).

126. Behnood Bikdeli et al., *Two Decades of Cardiovascular Trials with Primary Surrogate Endpoints: 1990–2011*, 6 JAMA 1, 4 (2017).

127. *Id.*

128. *Id.*; see also Chul Kim & Vinay Prasad, *Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals*, 175 JAMA INTERNAL MED. 1992, 1993–94 (2015) (showing similar results in oncology).

129. GAO, GAO-16-192: FDA EXPEDITES MANY APPLICATIONS, BUT DATA FOR POSTAPPROVAL OVERSIGHT NEED IMPROVEMENT 22–28 (2015).

130. Huseyin Naci et al., *Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration*, 318 JAMA 626, 626 (2017).

131. *Id.*

studies are done on the right outcomes. Whether this is the result of inadequate legal frameworks, insufficient resources with the Agency, or a more fundamental political economy problem with postmarketing requirements is not yet known.

Patients, providers, and policymakers all want better medicines, and want them faster. But clinical evidence production is complex and takes time. When implementing the 21st Century Cures Act, the FDA should exercise caution, and ensure that its approach is consistent with the Agency's critical role in producing and validating high quality information about medicines. Moving forward to reduce the evidence required prior to approval without identifying why postmarketing studies are so often not completed in a timely fashion, and without assurances that the Agency has the tools and resources to address the problem going forward, seems ill-advised.

#### CONCLUSION

The most persuasive justification for the FDA's modern regulatory approach to drug marketing relates to the enormous challenges associated with producing and validating high-quality information about medicines. Unregulated markets cannot adequately perform either function, and modern FDA law is shaped substantially by this fact. Recent challenges to the Agency's regulatory structure have not adequately addressed these issues. Facing them head on allows us to see that some of these reforms are plainly ill-advised, and that others should be stayed until we know better how to make them compatible with the FDA's critical information production and validation functions.