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Erika Lietzan

University of Missouri School of Law, lietzane@missouri.edu

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ACCESS BEFORE EVIDENCE AND THE PRICE OF THE FDA'S NEW DRUG AUTHORITIES

Erika Lietzan *

ABSTRACT

Sometimes drug innovation seems to happen in reverse. Patients enjoy a treatment for years even though the treatment has not been approved by the FDA or proven safe and effective to the FDA's standards. (Sometimes this happens because the FDA has declined to take enforcement action.) The agency encourages companies to perform the work necessary to satisfy the United States "gold standard" for new drug approval, however, by promising exclusivity in the marketplace. When a company does this work, at considerable expense, the results are predictable. The new drug is expensive, and patients and payers (and sometimes policymakers) are outraged. To them, it seems like nothing more than a sudden and significant price increase in a drug that was already widely available.

This reverse sequence happens regularly. Doctors all over the country prescribe medicines for a variety of ailments, not realizing the medicines are supposed to be approved by the FDA—but have not been. Every time a company finally does the research that the FDA requires and enjoys the reward of exclusivity in the marketplace, the public cries foul. Today doctors administer fecal microbiota therapy, using an unapproved stool preparation that has been shipped by a

* Associate Professor of Law, University of Missouri School of Law. In June 2015, Diane Hoffmann and coinvestigators from the University of Maryland Baltimore received a grant from the National Institute for Allergy and Infectious Diseases to study legal and regulatory aspects of microbiota transplantation. The author served on an expert working group convened to advise the investigators from December 2015 through February 2018. This project was supported by the Joe Covington Faculty Research Fellowship and the William F. Sutter Faculty Research Fellowship Fund. The author is grateful for feedback from audience members at the sixth annual fall conference of Scalia Law School's Center for the Protection of Intellectual Property (IP for the Next Generation of Technology, in October 2018) and for the opportunity to discuss this project at a symposium hosted by Mizzou Law's Center for Intellectual Property & Entrepreneurship (Protecting the Public While Fostering Innovation and Entrepreneurship: First Principles for Optimal Regulation in February 2019). Krista Carver, Joseph Gabriel, Brook Gotberg, Thomas Lambert, and Patricia Zettler provided helpful comments. Henry Adams (University of Missouri School of Law Class of 2020) and Alec Larsen (Class of 2019) provided research assistance.

company in Massachusetts. But companies are studying new drugs based on the principle. A recent New York Times article described the looming controversy, quoting doctors and patients who seem to question whether the new drug approval process will be worth its cost.

These scenarios force us to confront basic questions about the cost and the benefit of the new drug framework. This article examines the new drug authorities with fresh eyes, with the added benefit of these unusual scenarios where in a sense the gatekeeping mechanism has failed. Its principal insights are that, in addition to ensuring the production of high quality evidence about treatments in the marketplace, the new drug authorities: (1) ensure the disclosure—and provide a mechanism for close regulation of the disclosure—of that information, and (2) give federal regulators a leash on new drugs, and the companies who market them, through the life cycle of those drugs. It explores the costs of error and delay associated with new drug approval and alternatives that some scholars and policymakers have proposed, ultimately arguing that—though aspects may need tweaking—the new drug approval paradigm is worthwhile.

But these access-before-evidence scenarios bring home the point that the new drug approval standard does not, itself, ensure high quality innovation is performed. Something else must provide the encouragement. It concludes that those who object to temporary exclusivity for new medicines that complete the approval process (and the high prices they make possible for a while) must ask themselves whether they value the new drug framework (including good evidence) as much as they thought.

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INTRODUCTION

Clostridium difficile (“*C difficile*”) infections kill perhaps 100,000 people every year in the United States.¹ The bacteria release toxins that destroy the lining of the intestine, triggering diarrhea and eventually a progressive systemic inflammatory response.² Although antibiotics may vanquish the bacterium, *C difficile* has a high recurrence rate.³ Abrupt and severe cases have a 50% mortality rate, even with surgical removal of the colon.⁴ Over the last decade, however, a promising new therapy has emerged. Gastroenterologists have been transferring feces from healthy people into the intestines of patients suffering from *C difficile* infections, sometimes reporting cure rates as high as 100%.⁵ This procedure seems to restore a healthy balance of bacteria to the patient’s gut.

Now, drug companies are developing pharmaceuticals based on this “fecal microbiota” technology.⁶ Any resulting approved drugs would be rigorously tested and heavily regulated, but also expensive. But patients are already receiving treatment, cheaply, through the transfer procedure. This raises the question whether the regulatory framework is *worth it*. The answer to this question depends, of course, on what the framework offers us and what it costs us.

New drug development usually follows a well-worn path.⁷ Researchers identify or synthesize a promising molecule in the laboratory. Tests in the laboratory (with human and animal tissues, and eventually live animals) identify promising medical uses. The next

1. Elaine O. Petrof & Alexander Khoruts, *From Stool Transplants to Next-Generation Microbiota Therapeutics*, 146 GASTROENTEROLOGY 1573, 1574 (2014).

2. *Id.*; see also Ramsey M. Dallal et al., *Fulminant Clostridium difficile: An Underappreciated and Increasing Cause of Death and Complications*, 235 ANNALS SURGERY 363, 363 (2002).

3. David W. Eyre et al., *Predictors of First Recurrence of Clostridium difficile Infection: Implications for Initial Management*, 55 CLINICAL INFECTIOUS DISEASES S77, S77 (2012) (reporting average recurrence rate of 20%).

4. Petrof & Koruts, *supra* note 1, at 1574; Baddr Shakhsheer & John Alverdy, *Surgery for Fulminant Clostridium difficile Infection*, 25 SEMINARS COLON & RECTAL SURGERY 150, 151 (2014) (“Total abdominal colectomy with end ileostomy confers a modest survival advantage but historical mortality rates range from 35% to 80% in small series.”).

5. Colleen R. Kelly et al., *Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook*, 149 GASTROENTEROLOGY 223, 223 (2015).

6. See *infra* Part I.A.

7. See generally Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 39, 46–56, 77–82 (2018).

step is to formulate a product—the active ingredient formulated with inactive ingredients, in a particular dosage form for a particular route of administration (for instance, a capsule for oral delivery)—and begin testing the product in humans. Several phases of human (“clinical”) trials assess the drug’s safety and effectiveness, sorting out the right dosage, the right disease or disease state, and the clinical outcome possible. With the right results in these trials, the United States Food and Drug Administration (“FDA”) may approve the drug, allowing the company to market it to patients. By this point, the company may have spent hundreds of millions of dollars, or more, on its research.⁸ For a while, it has the market to itself—perhaps because of patents, but always because the FDA’s statute temporarily prevents the agency from approving copies.⁹ During this time, the company can price the drug advantageously, recovering its investment and maybe making a profit.¹⁰ Although prices are high during this period, the company’s exclusivity in the market will end. Even in the near term, other companies may introduce drugs based on the same principle, creating price competition.¹¹ Eventually, the patents will expire, and federal law will permit the FDA to approve copies made by companies that did not do their own research.¹²

In short, in the usual sequence, a new medicine is expensive when first available to patients, but it may soon face price compe-

8. Estimates of the cost of new drug research and development vary. *E.g.*, Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really \$802 Million?*, 25 HEALTH AFF. 420, 427 (2006) (finding costs vary from around \$500 million to more than \$2 billion, depending on the therapy and the company); Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 26 (2016) (finding that pretax capitalized per approval costs were \$2.5 billion in 2013 dollars); see also Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 SAN DIEGO L. REV. 419, 448–57 (2014) (arguing that cognitive biases pervade discussion of drug development costs).

9. See *infra* Part I.D.2.

10. See *infra* note 43.

11. *E.g.*, John Carroll, *Merck Goes Toe-to-Toe with Gilead’s Hep C Goliath, Flags Discount with Blockbuster OK*, FIERCE BIOTECH (Jan. 28, 2016, 5:16 PM), <https://www.fiercebiotech.com/regulatory/merck-goes-toe-to-toe-gilead-s-hep-c-goliath-flags-discount-blockbuster-ok> [<https://perma.cc/J64G-B925>] (noting price competition among protease inhibitors and polymerase inhibitors that for the first time permitted cure of hepatitis C); see Derrick Ginyery, *Real-World Evidence Could Speed Development of Drugs Offering Incremental Improvements*, PINK SHEET (Oct. 29, 2018), <https://pink.pharmaintelligence.informa.com/PS124157/RealWorld-Evidence-Could-Speed-Development-Of-Drugs-Offering-Incremental-Improvements> [<https://perma.cc/3H7E-N9UY>] (quoting Commissioner Gottlieb on the importance of having more drugs in each class, for clinical and pricing reasons).

12. See *infra* Part I.D.2.

tition, and eventually cheap copies become available. The development of fecal microbiota has not followed the usual sequence. Doctors have administered fecal microbiota for nearly a decade in their offices.¹³ For a half-dozen years, organizations have been collecting stool from donors, filtering and freezing the stool, and—in at least one case—selling it to doctors around the country treating patients.

The companies developing products based on the same principle are in a tough spot. They must invest hundreds of millions of dollars to prove the safety and effectiveness of their products, but then they may have to compete for patients with stool banks that are basically unregulated. The FDA, too, is in a tough spot. Its statute is clear; stool banks cannot ship products to treat *C difficile* without premarket approval.¹⁴ If the agency acts against stool banks after approving products from companies, though, patients will have *only* the approved products to choose among. These will have been proven safe and effective, and every aspect of these products—from the manufacturing to the labeling—will be heavily regulated by the FDA.¹⁵ They will also be expensive until the law permits the FDA to approve cheaper copies.¹⁶ The sequence seems backwards: patients enjoy an inexpensive therapy for nearly a decade, *then* research occurs and the FDA approves an application, and *then* the therapy is expensive.

The reversed sequence is not unique to fecal microbiota. There are thousands of prescription drugs on the market today without FDA approval.¹⁷ They are marketed unlawfully, but many have been on the market for a half century or longer, and most are cheap.¹⁸ The FDA does not have the resources to take enforcement action against every drug, even though all are marketed unlawfully, so it focuses on the subset that present health problems. And if a company does the research needed for approval, the agency will remove illegal versions from the market. This has the same result: patients enjoy an inexpensive therapy for decades, *then* research

13. See *infra* Part I.A.

14. Shipment triggers the premarket approval requirement; whether the manufacturer operates for profit, and whether a commercial sale occurred, are beside the point. See *infra* Part I.B.

15. See *infra* Part III.A.

16. See *infra* Part I.D.2.

17. See *infra* Part II.A.

18. See *infra* Part II.A.

occurs and the FDA approves an application, and *then* the therapy is expensive.

In these reversed sequences, sales of a new medical treatment precede the development of clinical evidence supporting the treatment and precede government approval of the treatment. But consumers mainly perceive a surge in the price of an already available treatment. The intervening research and development may be mostly invisible, *especially* if the form of the treatment has not changed, as when an unapproved prescription drug is replaced by an approved prescription drug in a similar dosage form. The perception of a price hike leads scholars and others participating in policymaking discussions to criticize the newcomer's exclusivity in the marketplace.¹⁹ This article argues that the criticism is misplaced.

The centerpiece of the FDA's authority over new drugs is the preapproval requirement; the agency acts as a gatekeeper to the market.²⁰ Gatekeeping is meant to protect the public health by precluding the market entry of medicines that are not safe and effective, at least as those concepts are interpreted by the agency.²¹ This suggests the new drug paradigm has no role to play when patients already enjoy, and seem to benefit from, an unapproved medicine. But, as this article explains, the FDA *can* still apply its safety and effectiveness standards in these reversed scenarios—by approving the first application that satisfies the standards and then holding the other companies to the standard, forcing them to meet the standards or remove their products from the market.

And there is more to the FDA's gatekeeping role. Recently scholars have focused on the agency's information-mediating role, pointing out that gatekeeping ensures the generation of valuable information about medicines and, in some cases, arguing that it also

19. *E.g.*, Aaron S. Kesselheim & Daniel H. Solomon, *Incentives for Drug Development—the Curious Case of Colchicine*, 362 *NEW ENG. J. MED.* 2045, 2046 (2010) (arguing that Colchicine, the first approved formulation of colchicine, should not have enjoyed exclusivity); James P. Reichmann, Letter to the Editor, *Makena or Compounded 17P?*, 37 *P&T* 487, 487 (2012) (suggesting doctors should use illegal pharmacy compounded alternative to Makena); Inbar Fried & Andrew Beam, *Pricing and the Orphan Drug Act: The Curious Case of 17P*, *HARV. MED. SCH.* (Oct. 2, 2017, 15:00), <https://dbmi.hms.harvard.edu/content/pricing-and-orphan-drug-act-curious-case-17p> [<https://perma.cc/P6FZ-GFR8>] (suggesting Makena should not have approved orphan exclusivity).

20. See *infra* Part III.A.2.

21. Richard Merrill, *The Architecture of Government Regulation of Medical Products*, 82 *VA. L. REV.* 1753, 1782 (1996); see *infra* Part III.B.

encourages information production.²² This article adds the insight that the leverage of the gatekeeping mechanism ensures the disclosure—and creates a mechanism for close regulation of the disclosure—of that information.²³ But it disputes the claim that the gatekeeping mechanism *motivates* companies to generate this information, suggesting instead that if the barrier is too high, a firm might turn to other investments.²⁴

This article also adds the insight that the new drug authorities give federal regulators a leash on any company marketing an approved product. The statute uses the approval authority to give the FDA permanent regulatory oversight, and even if some of this oversight could be imposed without the approval hook, the hook provides the government with efficient enforcement options. The new drug authorities give the FDA a continuing flow of clinical information, penalty-backed mechanisms to require labeling changes and new trials, and enhanced supervision of the company's manufacturing practices. Placing a medicine under the FDA's new drug authorities thus mean much more than installing a gatekeeper that imposes a one-time safety and effectiveness standard. It means more rigorous oversight for the life of the drug.

This article considers whether the new drug authorities are *worth it* in these reversed innovation sequences and, necessarily, also whether they are *worth it* in general. To frame this discussion, it identifies the problems in the market to which the new drug authorities respond, explores the costs associated with applying those authorities, and considers the alternatives available to policymakers for new drugs in general and access-before-evidence treatments in particular.²⁵ It assumes also that policymakers should select the least costly approach to addressing the problems identified, meaning the remedy that minimizes Type 1 errors (false positives: regulating behavior that does not need regulation), Type 2 errors (false negatives: failing to regulate behavior that does need regulation), and decision costs.²⁶ This article uses "Type 1 error" to refer

22. *E.g.*, Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 370–71 (2007); Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past and Future*, 102 MINN. L. REV. 2357 *passim* (2018).

23. *See infra* Part III.A.2.

24. *See infra* Part III.A.2.

25. *See infra* Parts III.B, III.C. *See generally* THOMAS LAMBERT, HOW TO REGULATE: A GUIDE FOR POLICYMAKERS 14–15 (2017).

26. LAMBERT, *supra* note 25, at 13.

to rejection of a drug that is safe and effective and “Type 2 error” to refer to approval of a drug that is not safe and effective.²⁷ Type 2 errors include not only approval of drugs that are directly harmful—causing significant adverse side effects—but approval of drugs that are indirectly harmful by being ineffective. Ineffective drugs can lead to harm from the delay in use of an effective treatment.²⁸

The FDA’s new drug authorities respond to the fact that companies might introduce medicines without performing enough testing to know their benefits on average exceed their risks.²⁹ They respond to the fact that companies might not fully and accurately describe for consumers the testing they *have* done.³⁰ But there is no way to solve these problems fully, because we can never know *everything* about a new drug. The choice to impose a gatekeeper to address these problems therefore also requires policymakers to decide how much certainty they want about a drug’s benefits and risks before making the decision whether to approve the drug. Asking for more certainty creates delay, which is costly but minimizes both Type 2 errors (approval of drugs that are not safe and effective) and Type 1 errors (failure to approve drugs that are safe and effective). Accepting less certainty before the decision reduces the cost of delay but increases the risk of both types of error.³¹

Although there is lively debate on the issue, this article takes no position on whether policymakers have struck the right balance between evidence development, on the one hand, and access without costly delay, on the other hand. Instead, it notes that policymakers can vary the balance (choose differing levels of certainty) by context—for example, prioritizing speed over elimination of Type 2 errors for drugs that might save a patient from imminent

27. Scholars writing about the FDA vary in their use of these terms. Compare Michael I. Krauss, *Loosening the FDA’s Drug Certification Monopoly: Implications for Tort Law and Consumer Welfare*, 4 GEO. MASON L. REV. 457, 467 (1996) (using “Type 1” to refer to mistaken approvals and “Type 2” to refer to mistaken rejections), with HENRY G. GRABOWSKI & JOHN M. VERNON, *THE REGULATION OF PHARMACEUTICALS: BALANCING THE BENEFITS AND RISKS* 10 (1983) (using “Type 2” to refer to mistaken approvals and “Type 1” to refer to mistaken rejections).

28. See U.S. FOOD & DRUG ADMIN., PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS 6 (2017) [hereinafter FDA MEMO].

29. See *infra* Part III.B.2.

30. See *infra* Part III.B.2.

31. See *infra* Part III.B.2.

death—*within* a gatekeeping framework.³² This article does, however, generally embrace the new drug approval requirement.³³ The FDA requires a rigorous type of testing that establishes causation—that drugs *cause* the benefits their sellers claim.³⁴ And it requires that *all* reasonably relevant safety tests be done.³⁵ Our experience with unapproved prescription drugs casts doubt on suggestions that competitive pressures and tort liability will ensure this sort of testing is completed.³⁶ It is unclear whether other policy options could adequately address the problems that the new drug authorities address, let alone for lower overall cost.³⁷ And the gatekeeping mechanism and post-approval leash on regulated drugs provide enormous efficiency benefits that might not be easily replicated without the leverage of the approval requirement.³⁸

This article turns a corner, however, by pointing out that for all their advantages the new drug authorities standing alone do not ensure that valuable research will be done.³⁹ Policymakers need to encourage new drug research: not the discovery of biologically useful substances, but the development of finished approvable drug products manufactured using current good manufacturing practices, and the generation of safety and effectiveness data sufficient to justify commercial approval.⁴⁰ This problem is the same whether the substance is newly discovered (the usual sequence) or already available to patients because of academic experiments and agency enforcement discretion (the reversed sequence). Whether a company will do new drug research depends on whether the company expects to recover its investment and earn a profit.⁴¹

32. See *infra* Part III.B.2.

33. See *infra* Part III.B.2.

34. See *infra* Part III.A.

35. See *infra* Part III.A.

36. See *infra* Part III.B.

37. See *infra* Part III.B.

38. See *infra* Part III.B.

39. See *infra* Part III.A.1.

40. See Janet Woodcock, *The PCAST Report on Pharmaceutical Innovation: Implications for the FDA*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 297, 299 (2013) (discussing report from the President's Council of Advisors on Science and Technology that called for doubling the current annual output of innovative new medicines). This is not to say that all new drug research or all new drugs have equal social value. The point is simply that policymakers must figure out how to encourage the *development* of the new drugs of value, because the new drug approval requirement will not do that work.

41. Dana P. Goldman et al., *The Benefits from Giving Makers of Conventional 'Small Molecule' Drugs Longer Exclusivity over Clinical Trial Data*, 30 HEALTH AFF. 84, 85 (2011) ("Although some have questioned whether profits drive innovation, empirical evidence

Our legal system assures companies this will be possible by promising exclusivity in the marketplace.⁴² Exclusivity encourages the steps needed to create a medicine that the FDA can approve: refinement of a product (formulation of active and inactive ingredients, route of administration, dosage form, and strength) and its manufacturing process, and testing of *that* product to the FDA's standards. It encourages these steps because it allows higher prices to recoup investment in the work.⁴³ Those who object to exclusivity for a medicine that completes the approval process—including exclusivity in these reversed innovation scenarios—must ask themselves whether they value this work, and the benefits of the new drug authorities, as much as they thought.

This article proceeds as follows. Part I describes the emergence and evolution of fecal microbiota transplantation and arguments that either the new drug authorities or at least exclusivity should not apply. Part II explains that the issue is really innovation that proceeds in reverse, where access precedes evidence and approval. It describes two other scenarios in which this has occurred: the illegal marketing of thousands of unapproved prescription drugs today, and the illegal manufacturing—by pharmacies—of copies of an approved drug to prevent premature birth. Part III considers the problem from the policymaker's perspective, considering the nature and purpose of the FDA's new drug authorities and the price we pay for those authorities. Part IV concludes, explaining that if we value the new drug authorities, as Part III suggests is warranted, policymakers should ensure that firms enjoy meaningful exclusivity in the marketplace. It offers several concrete recommendations for reversed innovation scenarios and reaches a final

strongly supports this relationship.”); Henry Grabowski, *Are the Economics of Pharmaceutical Research and Development Changing?: Productivity, Patents, and Political Pressures*, 22 PHARMACOECONOMICS (SUPPLEMENT) 15, 22 (2004) (“Pharmaceutical R&D is a lengthy, risky process and is based on the expectations that future market environments will reward successful drug innovation with premium returns.”).

42. See *infra* Part III.A.2.

43. Goldman et al., *supra* note 41, at 85 (“A longer period [of exclusivity] delays competition from generic drug companies . . . [and] [t]he prospect of higher profits gives drug companies a stronger incentive to innovate”); John A. Vernon et al., *Exploration of Potential Economics of Follow-On Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B.U. J. SCI. & TECH. L. 55, 68 (2010) (“In a series of recent papers we have identified a robust empirical link between R&D investment and real drug prices, firm pharmaceutical profit margins, R&D project risk, and the length of a product's market exclusivity period.”).

point relevant to all innovation scenarios: if we value the new drug framework, we must pay the price for it. Research is not free.

I. THE POLICY DEBATE ABOUT FECAL MICROBIOTA TRANSFERS

Over the last decade, researchers have been exploring the possibility that microorganisms in the human body can play a role in the treatment and prevention of serious illness. The healthy human body hosts between 10 and 100 trillion of these microbes.⁴⁴ A distinct community of microorganisms (“microbiota”) resides in the intestinal tract, and there are distinct microbiota on the skin, and in the mouth, nose, and vagina.⁴⁵ Intestinal microbiota helps with digestion of food and produces vitamins for their human host.⁴⁶ It also stimulates the immune system and plays a role in preventing the growth of dangerous pathogens.⁴⁷ Conversely, a microbial community in “dysbiosis”—imbalanced, with normally dominating microbial species underrepresented and normally repressed species filling the gap—may be linked to poor health conditions. For instance, scientists have linked disruption of the intestinal microbiota to inflammatory bowel disease and diabetes.⁴⁸

These realizations led to the hypothesis that transferring microbiota from healthy humans to patients could treat disease and poor health associated with microbial dysbiosis.⁴⁹ Stool from healthy donors has emerged as a meaningful therapeutic option in the treatment of a dangerous bacterial infection of the large intestine, recurrent *C difficile* infection.⁵⁰ Recurrent *C difficile* infection may

44. Luke K. Ursell et al., *Defining the Human Microbiome*, 70 NUTRITION REVIEWS (SUPPLEMENT 1) S38, S38 (2012).

45. *Id.*

46. Gail A. Hecht et al., *What Is the Value of a Food and Drug Administration Investigational New Drug Application for Fecal Microbiota Transplantation to Treat Clostridium difficile Infection?*, 12 CLINICAL GASTROENTEROLOGY & HEPATOLOGY 289, 289 (2014) (noting that some bacteria in the gut help with digestion of complex carbohydrates); *ACOG Opinion # 175: Vaginal Seeding*, 130 OBSTETRICS & GYNECOLOGY e274, e274 (2017) [hereinafter *ACOG Opinion # 175*] (noting that bacteria in the gut “ferment unused energy substrates” and “produce vitamins for the host”).

47. *ACOG Opinion # 175*, *supra* note 46, at e274; Hecht et al., *supra* note 46, at 289 (“We rely on the microbiota for protection against proliferation and invasion by enteropathogens.”).

48. See Hecht et al., *supra* note 46, at 289; Colleen R. Kelly et al., *Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook*, 149 GASTROENTEROLOGY 223, 229 (2015).

49. Ursell et al., *supra* note 44, at 543.

50. Alexander Khoruts, *Developing Human Gut Microbiota as a Class of Therapeutics*,

stem from dysbiosis following the administration of antibiotics.⁵¹ Doctors usually treat a patient's initial *C difficile* infection with antibiotics, which reduce the prevalence of *C difficile* and seem to restore the patient to health.⁵² The antibiotics may also reduce bacterial diversity in the intestine, however, making it possible for the vanquished *C difficile* bacteria—which other species would normally contain—to bounce back.⁵³ The hypothesis behind fecal microbiota transfer is that transferring a healthy microbial community to the patient's intestinal tract can reestablish healthy ratios of the various species in the patient's intestine, permanently checking the infection.

A. *Emergence and Evolution of Fecal Microbiota Therapy*

Although the use of human stool for therapeutic purposes may date back thousands of years,⁵⁴ the modern era of fecal transfer dates to an academic publication in 2010 describing the procedure.⁵⁵ Generally, a doctor administers filtered stool from a healthy donor during a colonoscopy or through an enema or nasogastric tube.⁵⁶ Often, either the patient or the doctor knows the donor, and typically the doctor assumes responsibility for ensuring the donor

11 NATURE REVIEWS GASTROENTEROLOGY & HEPATOLOGY 79, 79–80 (2014). *C difficile* infections affect more than 600,000 patients annually in the United States and have both a high mortality rate (more than 100,000 deaths a year) and a high recurrence rate (as many as 15,000 relapses every year). Fulminant infections have a mortality rate approaching 50% even with surgery. Diane Hoffmann et al., *Improving Regulation of Microbiota Transplants*, 358 SCIENCE 1390, 1390 (2017); Petrof & Khoruts, *supra* note 1, at 1574.

51. See Alison Laufer Halpin & L. Clifford McDonald, Editorial Commentary, *The Dawning of Microbiome Remediation for Addressing Antibiotic Resistance*, 62 CLINICAL INFECTIOUS DISEASES 1487, 1487 (2016); Janis C. Kelly, *Fecal Transplants Bring Hope to Patients, Challenge the FDA*, MEDSCAPE (Dec. 15, 2014), <https://www.medscape.com/viewarticle/836225> [<https://perma.cc/5JAD-Y48V>].

52. Kelly, *supra* note 51.

53. *Id.*; see also Halpin & McDonald, *supra* note 51, at 1487 (“Treatment with antibiotics eliminates not only pathogenic but also beneficial bacteria . . . [and] loss of diversity in the intestinal microbial composition places individuals at increased risk for . . . colonization by pathogens, such as *C. difficile*.”).

54. F. Zhang, Letter to the Editor, *Should We Standardize the 1700-Year-Old Fecal Microbiota Transplantation?*, 107 AM. J. GASTROENTEROLOGY 1755, 1755 (2012).

55. Michael S. Silverman et al., *Success of Self-Administered Home Fecal Transplantation for Chronic Clostridium difficile Infection*, 8 CLINICAL GASTROENTEROLOGY & HEPATOLOGY 471 (2010) (describing seven patients with chronic relapsing refractory *C difficile* infection who successfully self-administered fecal material at home and had no further infection after the procedure, also describing the procedure).

56. Mark B. Smith et al., Comment, *How to Regulate Faecal Transplants*, 506 NATURE 290, 290 (2014).

is healthy and for screening the donor, the stool, or both, for infectious disease.⁵⁷ After early studies in 2012 and 2013 reported astonishingly high cure rates—91% in one study⁵⁸—use of the procedure spread rapidly.⁵⁹ Academic doctors continued to enroll patients in studies, generating evidence of safety and effectiveness, but the procedure spread as a treatment for patients at the same time.⁶⁰

The high cure rate reported in 2012 heralded a paradigm shift in treatment of *C. difficile*. Almost immediately, the first “stool bank”—a nonprofit organization, OpenBiome—emerged.⁶¹ A stool bank assesses the health of prospective donors, collects stool from the qualified donors, screens the stool for infectious diseases, processes the acceptable stool (for instance, by filtering and freezing it), and ships the stool to doctors.⁶² OpenBiome ships frozen stool nationally, but some university-affiliated hospitals also maintain their own stool banks.⁶³

The news about fecal microbiota transfers also attracted the interest of conventional drug developers. In 2012, several companies began developing microbiota treatments in more traditional oral dosage forms.⁶⁴ Rebiotix, for instance, is harvesting live microbes from stool and encapsulating the full spectrum naturally occurring microbial mix.⁶⁵ Seres Therapeutics is designing and constructing

57. Petrof & Khoruts, *supra* note 1, at 1575–76, 1579.

58. Lawrence J. Brandt et al., *Long-Term Follow-Up of Colonoscopic Fecal Microbiota Transplant for Recurrent Clostridium difficile Infection*, 107 AM. J. GASTROENTEROLOGY 1079, 1082 tbl.3 (2012) (reporting a cure rate of 91% in a multicenter follow-up study of seventy-seven patients who had colonoscopic fecal microbiota transfers for recurrent *C. difficile* infection); Els van Nood et al., *Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile*, 368 NEW ENG. J. MED. 407, 411 (2013) (report of first randomized controlled clinical trial, in which interim analysis showed that fecal transfer plus vancomycin was three times more effective than vancomycin alone).

59. Kelly, *supra* note 51, at 4 (“In the wake of such encouraging studies, patients with recurrent *C. difficile* began to approach gastroenterologists and infectious disease specialists, seeking FMT; the specialists in turn began to offer the procedure.”).

60. Colleen R. Kelly et al., Commentary, *The AGA’s Fecal Microbiota Transplantation National Registry: An Important Step Toward Understanding Risks and Benefits of Microbiota Therapeutics*, 152 GASTROENTEROLOGY 681, 681 (2017) (“The availability of the therapeutic substrate (i.e., stool), together with its ease of administration, has advanced the practice of gut microbiota manipulation in patients more rapidly than our scientific understanding.”).

61. Mark Zipkin, *Microbiotal Reverse-Engineering*, BIOCENTURY, July 31, 2017, at 9. A for-profit venture could perform the same functions.

62. Smith et al., *supra* note 56, at 291.

63. *Id.*

64. Zipkin, *supra* note 61, at 9.

65. Lee Jones, *The Human Microbiome: A New Frontier in Drug Discovery*, DRUG

an artificial community of microbes using a library of individual microbial strains isolated from the stool of healthy donors.⁶⁶ Other companies may be pursuing products that contain metabolites produced by microbes.⁶⁷

B. *The Governing Regulatory Framework*

The fecal microbiota therapies just described fall under the FDA's regulatory authority, because they are "drugs" and also "biological products." Any "article" (item) intended for use in the treatment or cure of a disease is a drug.⁶⁸ If this item is a virus, blood, protein, or analogous product, it is also a biological product.⁶⁹ Any article (other than food) intended to affect the structure or function of the body is a drug.⁷⁰ Applying these definitions, the FDA has told doctors performing fecal transfers and companies developing related products that fecal microbiota intended to treat *C difficile* is both a drug and biological product.⁷¹ In addition to being

DISCOVERY WORLD, Summer 2016, at 73, 77. OpenBiome recently spun off a commercial firm, and the two are partnering to develop an approvable product, presumably an encapsulated version for oral delivery. See Press Release, Finch Therapeutics Announces Strategic Collaboration with OpenBiome to Develop Microbiome Therapies for FDA Approval (Feb. 23, 2017), <https://finchtherapeutics.com/news/openbiome-collaboration-fin403> [<https://perma.cc/R6S6-GVZ8>].

66. Elaine O. Petrof et al., *Microbial Ecosystem Therapeutics: A New Paradigm in Medicine?*, 4 BENEFICIAL MICROBES 53 (2013); see SERES THERAPEUTICS, *Microbiome Therapeutics Platform*, <https://www.serestherapeutics.com/our-science/microbiome-therapeutics-platform> [<https://perma.cc/T4VW-ASQ5>].

67. Jones, *supra* note 65, at 77.

68. 21 U.S.C. § 321(g)(1)(B) (2012). There is one exception. It would be a device, instead, if it: (1) were an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article"; (2) did not achieve its primary intended purpose through chemical action in the body; and (3) were not dependent on being metabolized to achieve this purpose. *Id.* § 321(h) (2012 & Supp. V 2018). Fecal microbiota do not satisfy this definition.

69. 42 U.S.C. § 262(i) (2012).

70. 21 U.S.C. § 321(g)(1)(C) (2012). Again, such an article could instead be a device, but fecal microbiota is not. See *supra* note 68.

71. Lee Jones, Chief Exec. Officer, Rebiotix, Remarks at Fecal Microbiota for Transplantation: Scientific and Regulatory Issues (May 3, 2013) (noting that FDA told Rebiotix in 2012 that the company's product was a drug); Letter from Karen Midthun, Dir., Ctr. for Biologics Evaluation & Research, to C. Richard Boland, Am. Gastroenterological Ass'n (Apr. 13, 2013) [hereinafter FDA Letter to AGA], <https://www.naspgghan.org/files/documents/FDA%20response%20letter%20to%20FMT%20Inquiry.pdf> [<https://perma.cc/XP48-A8NP>] ("Fecal microbiota when used to prevent, treat, or cure a disease or condition would fall within the definition of biological product . . . and the definition of drug Fecal microbiota would also fall within the definition of a drug if it is intended to affect the structure or any function of the body of man."). Fecal microbiota is a biological product as well as a drug because it comprises mainly bacteria. Federal law defines "biological product" to include items "analogous" to viruses. FDA regulations and 42 U.S.C. § 351(i) provide that for this

a drug, this microbiota is a “new drug”—another statutorily defined category—because it is not generally recognized as safe and effective for this use.⁷²

Because it is a new drug and biological product, fecal microbiota intended for treatment of *C difficile* cannot be shipped in interstate commerce without an approved marketing application or permission from the FDA to conduct human testing.⁷³ That is, shipment must be covered by either an effective “investigational new drug application” (“IND”) or an approved “biologics license application” (“BLA”).⁷⁴ The FDA also claims that it has new drug authority over a compound administered in a doctor’s office that contains both fecal microbiota obtained from a donor on the premises and a component (such as saline) that has crossed state lines.⁷⁵

As use of fecal microbiota for treatment of recurrent *C difficile* spread, doctors and patients objected to the FDA’s position that fecal microbiota must be covered by an approved marketing application or effective IND.⁷⁶ Completing the process necessary to submit a marketing application is time-consuming and expensive; estimates vary, but one study states that it takes more than a decade and more than \$2 billion for a new molecular entity.⁷⁷ But even an application to perform trials takes time to prepare, because it must

purpose bacteria are analogous to viruses. 21 C.F.R. § 600.3(h)(1) (2018) (“A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.”).

72. 21 U.S.C. § 321(p).

73. *Id.* § 355(a); 42 U.S.C. § 262(a)(1).

74. 21 U.S.C. § 355(a); 42 U.S.C. § 262(a)(1). Ordinarily a new drug needs an NDA. If it is also a biological product, it needs a BLA instead. 42 U.S.C. § 262(j).

75. A component of a drug is also a drug, so its own shipment must be covered by an IND or approved marketing application. 21 U.S.C. § 321(g)(1) (defining “drug” to include any article “intended for use as a component of” another drug). The FDA has used this theory to assert jurisdiction over stem cell preparations assembled *within* doctor offices for administration to patients on site, when those preparations contained ingredients that had traveled in interstate commerce. *E.g.*, *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1320–21, 1326 (D.C. Cir. 2014) (affirming summary judgment for the FDA). In its communications with doctors performing fecal microbiota transfers, the agency has gone further—failing to mention the interstate commerce requirement and asserting that “for any use of FMT in a clinical investigation or for treatment of *C. diff.*, an IND would be needed.” FDA Letter to AGA, *supra* note 71. This is incorrect, and the agency’s lawyers would probably not defend this position in court. Either the article or a component of the article must have traveled in interstate commerce.

76. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF FECAL MICROBIOTA FOR TRANSPLANTATION TO TREAT CLOSTRIDIUM DIFFICILE INFECTION NOT RESPONSIVE TO STANDARD THERAPIES 2 (2013) [hereinafter JULY 2013 GUIDANCE].

77. DiMasi et al., *supra* note 8.

assure the FDA that the safety and rights of subjects will be adequately protected.⁷⁸ One researcher has described spending “hundreds of hours” preparing an IND for a fecal microbiota study.⁷⁹

C. Widespread Access Through Enforcement Discretion

In 2013, the FDA responded to these objections by announcing an enforcement discretion policy.⁸⁰ Although the policy has since evolved, the agency still exercises enforcement discretion when a doctor transfers stool from a person known to the patient or the doctor for the treatment of refractory *C difficile*.⁸¹ Enforcement discretion means the doctor will not face enforcement action for administering fecal microbiota without an effective IND.⁸² But the FDA no longer exercises enforcement discretion when a stool bank ships fecal microbiota across state lines.⁸³ In March 2014, the agency concluded that centralized manufacturing—the one-to-many distribution model of stool banks—presents safety concerns

78. 21 C.F.R. § 312.22 (2018). The IND describes the composition and manufacturing of the test treatment and its active ingredient, with enough detail to ensure not only proper identification of both but also their quality, purity, and strength. *Id.* § 312.23(7). It contains the results of laboratory and animal testing showing it is reasonably safe to conduct tests in humans, and it describes the proposed trial, including the number of patients and how investigators will select and treat those patients. *See id.* § 312.23; *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: Q&A, CONTENT AND FORMAT OF INDs FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS (2000).

79. Colleen R. Kelly, Brown Univ. & Women’s Med. Collaborative, Remarks at Fecal Microbiota for Transplantation: Scientific and Regulatory Issues (May 3, 2013).

80. JULY 2013 GUIDANCE, *supra* note 76, at 2.

81. U.S. FOOD & DRUG ADMIN., DRAFT ENFORCEMENT POLICY REGARDING INVESTIGATION NEW DRUG REQUIREMENTS FOR USE OF FECAL MICROBIOTA TO TREAT CLOSTRIDIUM DIFFICILE INFECTION NOT RESPONSIVE TO STANDARD THERAPIES 4 (2016) [hereinafter MARCH 2016 DRAFT GUIDANCE], <https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm488223.pdf> [https://perma.cc/G8BW-JKSL]. The FDA will exercise this discretion if: (1) the donor and stool have been screened and tested for this purpose and (2) the patient has provided informed consent. *Id.* at 1.

82. If the fecal material did not cross state lines and was not mixed with a component that *did* cross state lines, though, the FDA could not take enforcement action in the first instance. *See United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1320 (D.C. Cir. 2014).

83. Compare JULY 2013 GUIDANCE, *supra* note 76, at 2 (stating that agency would exercise enforcement discretion for stool banks), with U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY, ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF FECAL MICROBIOTA FOR TRANSPLANTATION TO TREAT CLOSTRIDIUM DIFFICILE INFECTION NOT RESPONSIVE TO STANDARD THERAPIES 3 (2014) [hereinafter MARCH 2014 DRAFT GUIDANCE] (stating the opposite), and MARCH 2016 DRAFT GUIDANCE, *supra* note 81, at 4 (no enforcement discretion for stool banks).

that should be addressed through centralized oversight.⁸⁴ According to the FDA, centralized oversight will ensure consistent screening and testing practices, as well as consistent manufacturing conditions.⁸⁵ Shipment of frozen stool from a stool bank across state lines therefore must be covered by an approved marketing application or permission from the FDA to conduct clinical trials (an effective IND).⁸⁶

Permission to conduct a trial can be secured by either the manufacturer *or* the recipient. FDA regulations permit a manufacturer to maintain a “master file” at the agency, with information about the composition of its product and its manufacturing process and controls.⁸⁷ This allows recipients (here, doctors) to submit clinical trial applications cross-referencing the file for the necessary information about the substance they plan to administer.⁸⁸ OpenBiome took this approach; it holds a master file, which doctors using its frozen stool reference.⁸⁹

The arrangement here is curious, however. To be sure, none of these doctors is developing a product for the market. But this is not unusual; academic doctors perform clinical trials of unapproved new drugs all the time with no plan to develop a commercial product.⁹⁰ Here, though, they often administer the processed stool for treatment purposes, with data collection being—at most—a subsidiary objective.⁹¹ Such an arrangement does not easily square

84. MARCH 2014 DRAFT GUIDANCE, *supra* note 83, at 3.

85. 81 Fed. Reg. 10,632, 10,633 (Mar. 1, 2016) (describing agency’s “intent to mitigate risk, based on the number of patients exposed to a particular donor or manufacturing practice”).

86. MARCH 2014 DRAFT GUIDANCE, *supra* note 83, at 3.

87. 21 C.F.R. § 314.420(a) (2018) (“A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used [among other reasons] to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person.”).

88. *Id.* § 314.420.

89. OPENBIOME, FDA REGULATION OF FECAL MICROBIOTA FOR TRANSPLANTATION 3 (2018) (“OpenBiome’s Biologics Master File (BB-MF 15543), registered with the FDA, provides regulators with comprehensive insight into OpenBiome’s processes. Physicians who wish to conduct FMT under IND may also reference the OpenBiome BB-MF. By doing so, physicians may use our robust quality and manufacturing protocols rather than needing to develop these components internally to support their IND applications.”).

90. Sometimes academic researchers perform early safety testing (or even early effectiveness testing) of molecules they have discovered or invented, to show the promise of the molecule and attract an industry purchaser or partner. But sometimes they are simply pursuing a topic of professional interest or trying to advance medical knowledge.

91. *E.g.*, *Fecal Microbiota Transplantation (FMT) & You*, OPENBIOME, <https://www.op>

with the FDA's current regulations and policy. The closest analogy is a regulatory mechanism known as the "Treatment IND," which allows widespread treatment use of an investigational product for a serious or life-threatening condition.⁹² But the FDA permits a company to open a Treatment IND only if the company is actively pursuing marketing approval *and* the drug is part of a controlled trial designed to support approval (or those trials have finished).⁹³ The agency does not ordinarily permit indefinite treatment use under the IND mechanism.⁹⁴

enbiome.org/patients [<https://perma.cc/QGU6-DMMY>] (last visited Apr. 1, 2019) ("FMT is a new therapy that is still under investigation, and your doctor should help you determine whether it is the right choice for your treatment If you and your doctor have determined that a fecal transplant is the best treatment option for your *C. difficile* infection, you can find information here about how to prepare for your procedure and how to protect yourself against reinfection with *C. difficile* after your procedure."). Bioethicists have for decades expressed concern about the boundary between treatment and research and, in particular, the risk that research subjects sometimes do not appreciate the distinction and inaccurately attribute therapeutic intent to research procedures—a phenomenon known as "therapeutic misconception." Gail Henderson et al., *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*, 4 PLOS MED. 1735, 1735 (2007); Charles Lidz, *The Therapeutic Misconception: Problems and Solutions*, 40 MED. CARE (SUPPLEMENT) V55, V57 (2002). With fecal microbiota, however, the concern is the *opposite*: that an investigational substance is used *as treatment*, when research has not finished.

92. 21 C.F.R. § 312.320; *see also* U.S. FOOD & DRUG ADMIN., EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR TREATMENT USE—QUESTIONS AND ANSWERS: GUIDANCE FOR INDUSTRY 6–8 (2017), <https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf> [<http://perma.cc/YZ9K-AT7B>].

93. 21 C.F.R. § 312.20(a)(1). These same regulations also permit an "intermediate-size population" to have access to an unapproved drug that is "not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial." *Id.* § 312.315(a). This mechanism would not apply here, because it is tied to unusual indications—indications for which drugs are not usually developed in the United States. When issuing the regulation, the FDA explained that this category of expanded access responds to situations in which there is "no alternative" way to make a treatment available to a "small number of patients who could benefit from it." 74 Fed. Reg. 40,900, 40,927 (Aug. 13, 2009). It gave the example of antivenoms and drugs for tropical diseases, which are not marketed commercially in the United States but are nevertheless "needed on occasion." *Id.* And it explained that drugs are "rarely developed (at least not in the United States) for the types of indications for which drugs are made available under this category." *Id.*

94. There is precedent. The FDA permitted INDs for use of cannabis to treat glaucoma and various other conditions in the 1980s, even though no one was pursuing a marketing application. *See* Sean O'Connor & Erika Lietzan, *The Surprising Reach of FDA Regulation of Cannabis, Even After Descheduling*, 68 AM. U. L. REV. 823, 864–65 (2019). These INDs are no longer in effect. *Id.* at 65. In addition, there is lore that before the 1962 drug amendments, the agency may have permitted drugs for rare diseases to remain permanently in investigational status. Merrill, *supra* note 21, at 1791 n.119.

D. *Objections to Application of the FDA's New Drug Authorities*

1. Calls for Enforcement Discretion

Just as doctors objected to the FDA's application of the new drug approval requirements to fecal material intended for treatment of *C difficile*, stool bank representatives and some scholars have argued that the new drug authorities do not—or should not—apply. They argue that fecal microbiota falls at least some of the time within a product category known as “human cell and tissue based products” or that, if it does not fall in this category, it should be regulated the same way.⁹⁵

Tissue products contain or consist of human tissue and are intended for implantation, transplantation, infusion, or transfer into a human.⁹⁶ Tissue transplantation emerged and evolved much like fecal microbiota transfers.⁹⁷ In the early years doctors performed transplants without FDA oversight, and later a tissue banking industry emerged.⁹⁸ Like fecal microbiota, tissue intended to treat a disease or affect the structure or function of the body is usually a “drug” and “new drug.”⁹⁹ Its shipment in interstate commerce triggers a premarket approval requirement.¹⁰⁰ When banks began shipping tissue over state lines, the FDA's lawyers thus advised its leadership that the tissues satisfied the statutory definition of drug.¹⁰¹ The agency stayed its hand for a while, concerned that tissue banks lacked the resources to fund clinical trials and perhaps

95. Diane Hoffmann et al., *Improving Regulation of Microbiota Transplants*, 358 SCIENCE 1390, 1390–91 (2017); Margaret F. Riley & Bernat Olle, *FDA's Pathway for Regulation of FMT: Not So Fraught*, 26 J.L. & BIOSCIENCES 742, 744–45 (2015); Rachel E. Sachs & Carolyn A. Edelstein, *Ensuring the Safe and Effective FDA Regulation of Fecal Microbiota Transplantation*, 2 J.L. & BIOSCIENCES 396, 398, 408–09 (2015); Smith et al., *supra* note 56, at 290.

96. 21 C.F.R. § 1271.3(d).

97. See generally Richard A. Merrill, *Human Tissue and Reproductive Cloning: New Technologies Challenge FDA*, 3 HOUS. J. HEALTH L. & POL'Y 1, 8 (2002). Tissue transplantation emerged in the first half of the twentieth century. *Id.* at 9–14.

98. Marc O. Williams, *The Regulation of Human Tissue in the United States: A Regulatory and Legislative Analysis*, 52 FOOD & DRUG L.J. 409, 410–11 (1997).

99. 21 U.S.C. § 321(g) (2012); 42 U.S.C. § 262(i) (2012). It could in theory be a device instead. See *supra* note 68.

100. 21 U.S.C. §§ 321(p), 355(a) (2012); 42 U.S.C. § 262(a) (2012 & Supp. V 2018).

101. Stuart L. Nightingale, *The Regulation of Human Tissue and Organs*, 46 FOOD DRUG COSM. L.J. (SPECIAL ISSUE) 4, 5 (1991) (noting that a chief counsel, Peter Hutt, concluded that tissues “might” be biologics because they are analogous to blood, and “[i]n any event . . . they clearly are drugs when used for therapeutic purposes or to affect any bodily function”); *id.* (quoting another chief counsel, Richard Cooper, that “any residual doubt about

believing that it should not prevent doctors from performing medical procedures they wanted to perform.¹⁰² At the same time, though, the risk of infectious disease transmission was clear, as when a thirty-seven-year-old woman died of rabies after receiving a corneal transplant.¹⁰³

The AIDS crisis in the 1980s forced a solution.¹⁰⁴ The FDA invoked a rarely used provision of law allowing it to draft regulations to prevent the introduction, transmission, or spread of communicable diseases from one state into another.¹⁰⁵ The agency used this authority to write regulations that require donor screening and testing, labeling, inspections, and adverse event reporting for tissue products.¹⁰⁶ In the same regulations, the agency also exempted *some* tissue products from the statutory premarket approval requirement, if certain conditions were met.¹⁰⁷

Some scholars argue that fecal microbiota should be regulated only as a tissue product, meaning that it should enjoy the exemp-

(the FDA's) authority can be put aside").

102. *Id.* at 7. As Professor Zettler has pointed out, concerns that the regulatory barrier to entry for new drugs "is tantamount to regulation of medical practice" have been raised "throughout the FDA's history." Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 461 (2015). These are policy concerns, not legal arguments. The *entire* drug framework interferes substantially with the freedom of doctors to treat patients as they see fit. If an item satisfies the definition of "new drug" or the definition of "biological product," the item may not be shipped in interstate commerce (to doctors for use) without the FDA's permission. The scheme *always* limits the treatments available to a doctor. That this effectively precludes a doctor from performing a medical procedure—a procedure that the doctor believes is in the patient's best interest—does not change the legal analysis.

103. Nightingale, *supra* note 101, at 5.

104. Merrill, *supra* note 97, at 16–34; see Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514 (Dec. 14, 1993) (to be codified at 21 C.F.R. pts. 16, 1270) (issuing interim rule to require infectious disease testing, donor screening, and recordkeeping to help prevent the transmission of AIDS and hepatitis through human tissue used in transplantation).

105. 42 U.S.C. § 264 (2012 & Supp. V 2018).

106. See generally 21 C.F.R. pt. 1271 (2018). The regulations in part 1271 apply only to human cell and tissue products recovered on or after May 25, 2005. Part 1270 applies to earlier-recovered tissues. 69 Fed. Reg. 68,612, 68,680 (Nov. 24, 2004) (to be codified at 24 C.F.R. pts. 16, 1270, 1271).

107. For a tissue product to qualify for the exemption, four things must be true. 21 C.F.R. § 1271.10. First, the tissue must be minimally manipulated. Second, it must be intended for homologous use; for example, a cadaver's Achilles tendon must be intended for use *as* an Achilles tendon in the recipient patient. Third, manufacturing the tissue product cannot involve combining the tissue with any other article, except for water, crystalloids, or a sterilizing, preserving, or storage agent. And fourth, either (1) the tissue cannot have systemic effect and cannot depend on metabolic activity of living cells for its primary function, or (2) the tissue must be intended for autologous use (in the person from whom it was taken), use in the person's first-degree or second-degree blood relative, or reproductive use. *Id.*

tion from premarket approval that the FDA created in these regulations.¹⁰⁸ That is, fecal microbiota shipped by stool banks to treat *C difficile* infections should be regulated as a tissue.¹⁰⁹ But the tissue regulations are best understood as enforcement discretion. Tissue products intended to treat disease are new drugs and biological products (unless they are devices).¹¹⁰ Their shipment in interstate commerce requires an effective application.¹¹¹ Tissue products intended to affect the structure or function of the body are also new drugs (unless they are devices), and their shipment in interstate commerce similarly requires an effective application.¹¹² The tissue regulations simply describe the circumstances under which the FDA will permit interstate shipment of new drugs without the effective application that federal law requires. The argument that the FDA should apply only its tissue authority to fecal microbiota is thus an argument that the agency should decline to enforce the premarket approval requirement.¹¹³

108. See *supra* note 95 and accompanying text. Most argue that the FDA should regulate fecal microbiota the same way as it regulates tissue, but an executive from OpenBiome has argued that the gut microbiome is analogous to an organ of the body and thus *is* a tissue. Smith et al., *supra* note 56, at 290; see also Sachs & Edelstein, *supra* note 95, at 411 n.104 (“[M]any scientists have begun to refer to the microbiome as a human organ.”). Professor Megerlin and colleagues respond, pointing out that although human stool contains some human cells, the stool is simply a “substrate in which the gut microbiota prospers.” Francis Megerlin et al., *Faecal Microbiota Transplantation: A Sui Generis Biological Drug, Not a Tissue*, 72 ANNALES PHARMACEUTIQUES FRANCAISES 217, 219 (2014). In any case, there is no “organ” category in the FDA regulatory framework. If an item is intended to treat disease and is not a device, it is a drug. See 21 U.S.C. § 321(g) (2012). And, as an agency official pointed out in the 1980s, a whole organ intended for transplantation also satisfies the definition of “drug” in the FDCA. *Organ Transplants: Hearings Before the Subcomm. on Investigations & Oversight of the H. Comm. on Sci. & Tech.*, 98th Cong. (1983). The agency has simply declined to regulate whole vascularized organs. *Id.*

109. Shipment for other purposes would fall under the FDA’s new drug authorities. See Sachs & Edelstein, *supra* note 95, at 415; Riley & Olle, *supra* note 95, at 745; Hoffmann et al., *supra* note 95, at 1390. Some argue that fecal microbiota transferred in a doctor’s office for treatment of *C difficile* should be regulated as a tissue product, while others call this the practice of medicine and say that the states should regulate it. Compare Riley & Olle, *supra* note 95, at 745 (suggesting that all FMT products be regulated under tissue-type regulations), with Hoffmann et al., *supra* note 95, at 1390 (suggesting that all FMT products be regulated as the practice of medicine).

110. 21 U.S.C. § 321(g) (2012) (drug); *id.* § 355 (2012 & Supp. V 2018) (new drugs); 42 U.S.C. § 262(i) (2012) (biological product). Some tissues could be devices. See *supra* note 68.

111. 21 U.S.C. § 355(a) (2012); 42 U.S.C. § 262(a) (2012).

112. 21 U.S.C. § 321(g) (2012); *id.* § 355 (2012 & Supp. V 2018); 42 U.S.C. § 262(i) (2012).

113. These scholars have been somewhat equivocal in their writing about whether the new drug provisions apply. *E.g.*, Hoffmann et al., *supra* note 95, at 1391 (“FDA would need to change its position and determine that microbiota derived from stool is . . . not a drug or biological product.”); Sachs & Edelstein, *supra* note 95, at 408 (“[W]hile FMT may fall within the broad statutory definition of ‘drug.’”). More recently, Professor Sachs has stated that regulation as a drug “was not obviously required by existing statutes and regulations,” a

2. The Nature and Cost of Applying the New Drug Authorities

Those arguing against application of the FDA's new drug authorities make two arguments—that the new drug approval requirements do not really fit fecal microbiota and that applying the new drug provisions would have harmful economic consequences. There are easy answers to the “fit” arguments, however, suggesting that the key objection is economic.

They argue that the new drug approval paradigm is not “appropriate” and that applying it would be “problematic.”¹¹⁴ For instance, they point out that microbiota are dynamic and metabolically active, and fecal material complex and inconsistent, varying from donor to donor.¹¹⁵ It cannot be reproduced exactly, even by the same donor.¹¹⁶ They suggest that fecal microbiota therefore cannot be characterized adequately to satisfy FDA approval standards.¹¹⁷ One adds that it would be hard to conduct preliminary effectiveness testing of fecal microbiota in animals.¹¹⁸ But the FDA has decades of experience regulating complex biological products and even some nonbiological drugs that are not well-characterized and not well understood.¹¹⁹ Historically, rather than relying on complete characterization of the active ingredients of their proposed products, biological product applicants described the manufacturing process used to make the products. The FDA defined the product

claim with which this author disagrees. Rachel E. Sachs, *The Uneasy Case for Patent Law*, 117 MICH. L. REV. 499, 518 (2018).

114. Hoffmann et al., *supra* note 95, at 1390 (“The transplanted material is not a ‘typical’ drug and thus may not be appropriate for the drug regulatory pathway.”); Riley & Olle, *supra* note 95, at 744 (“It is debatable whether the full process of regulatory approval for a new biological drug is appropriate for [fecal microbiota transfers]”); Sachs & Edelstein, *supra* note 95, at 414 (“[T]rying to shoehorn FMT into the traditional drug regulatory paradigm is problematic”).

115. *E.g.*, Hoffmann et al., *supra* note 95, at 1390 (stating that fecal material “consists of a community of highly dynamic, metabolically active organisms” and “each batch of ‘product’ is different”); Sachs & Edelstein, *supra* note 95, at 402 (“[T]he regulation of stool as a drug is complicated by the material’s complexity and inconsistency across samples.”).

116. Riley & Olle, *supra* note 95, at 743 (arguing that “each lot obtained from a different donor has a different composition, and even different lots obtained from the same donor on different days will have different compositions”).

117. Hoffmann et al., *supra* note 95, at 1390 (arguing that characterization of fecal microbiota is “difficult”); Sachs & Edelstein, *supra* note 95, at 398 (arguing that “stool [defies] the typical scientific characterization that the FDA has long applied to small molecule and biologic drugs”); Smith et al., *supra* note 56, at 291 (stating that stool “cannot be characterized to the rigorous standards applied to conventional drugs”).

118. Hoffmann et al., *supra* note 95, at 1390.

119. Janet Woodcock et al., Opinion, *The FDA’s Assessment of Follow-On Protein Products: A Historical Perspective*, 6 NATURE REVIEWS DRUG DISCOVERY 437, 438 (2007).

as the composition resulting from the process.¹²⁰ And it has already said that it can focus on characterization and control of the manufacturing process to assure the consistency and quality of fecal microbiota products.¹²¹ Moreover, it need not ask for animal efficacy data, if those data are not relevant. Consider, for instance, its approach to premarket approval of blood.¹²² The natural constituents of blood—red blood cells, white blood cells, platelets, and plasma—do not vary from human to human.¹²³ Although there are many types of blood, within each type it is essentially generic.¹²⁴ That is, O negative blood is O negative blood. As a result, there is no need for the approval process to focus on whether the product proposed for shipment has the right composition or whether it will function as blood in a recipient's body.¹²⁵ It does, and it will.¹²⁶ For the same

120. *Frequently Asked Questions About Therapeutic Biologic Products*, FDA, <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm> [https://perma.cc/YK97-9CJD] (last visited Apr. 1, 2019) (“Because, in many cases, there is limited ability to identify the identity of the clinically active component(s) of a complex biological product, such products are often defined by their manufacturing processes.”). The agency takes a similar approach today with botanically derived new drugs. O’Connor & Lietzan, *supra* note 94, at 149–151.

121. Jay Slater, Dir., Div. of Bacterial, Parasitic & Allergenic Products, U.S. Food & Drug Admin., Remarks at Fecal Microbiota for Transplantation: Scientific and Regulatory Issues (May 3, 2013) (explaining that “chemistry, manufacturing, and controls” section of the IND submission “focuses on the manufacturing process, what’s the process for donation and storage, for instance, if it’s fresh or frozen, method of preparation, the addition of saline or stabilizers, the quality of the ingredients that are used, tests to characterize the materials, and the storage conditions”); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EARLY CLINICAL TRIALS WITH LIFE BIOTHERAPEUTIC PRODUCTS: CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION (2016). Although the “process” may include “the complex and very specific life history of the individual donors,” Sachs & Edelstein, *supra* note 95, at 402, the FDA could require donor screening and stool testing as part of the chemistry, manufacturing, and controls portion of an application. It could also require compliance with its tissue regulations as well as submission of a marketing application, as it does for blood. *See infra* note 127.

122. If intended to treat disease, blood is a biological product. 42 U.S.C. § 262(i) (2012) (defining “biological product” to include “blood” or a “blood component or derivative” that is “applicable to the prevention, treatment, or cure of a disease or condition of human beings”); 21 U.S.C. § 321(g) (2012). Shipment of blood in interstate commerce thus requires an effective application. 42 U.S.C. § 262(a)(1) (2012).

123. LAURA DEAN, BLOOD GROUPS AND RED CELL ANTIGENS 1 (2005).

124. Blood is sorted by the antigens expressed on the red blood cell surface—generally into one of four types (A, B, AB, and O) and then by whether the red cells have or lack a Rhesus (Rh) factor on their surface, leading to eight primary categories (A positive, A negative, and so on). *Id.* at 12.

125. An application identifies the *type* of product the manufacturer ships. *See Alphabetical List of Licensed Products Information Updated Through 30 Nov. 2018*, FDA, <https://www.fda.gov/downloads/BiologicsBloodVaccines/UCM149970.pdf> [https://perma.cc/T3N4-3ZK4] (last visited Apr. 1, 2019).

126. A transfusion requires that the donated blood be compatible with the recipient’s

reason, there is usually no need to submit the full suite of animal and human safety and effectiveness data.¹²⁷ Requiring these data would make no sense. The FDA could be similarly flexible, if appropriate, with fecal microbiota applications.

Those arguing for permanent enforcement discretion also point to the cost of applying the new drug authorities. For instance, they argue that regulation of fecal microbiota as a new drug and biological product places a heavy burden on doctors, who lack the expertise and resources to complete INDs.¹²⁸ They also argue that applying the new drug authorities will stifle innovation, or at least innovation by individuals and entities with limited resources.¹²⁹ Academic doctors, working independently from commercial firms, did the earliest fecal microbiota transfers and the first trials in humans. This is not unusual; even in the traditional drug development model, academic researchers may discover or invent a molecule and perform tests, before a firm develops a commercial product for FDA approval. But here, doctors used stool bank material that was outside the FDA framework, until the agency ended enforcement discretion in 2014, and some doctors continue to oper-

blood, which must be determined at the time of treatment. DEAN, *supra* note 123, at 19. Thus the ABO antigens and Rh antigens must be matched. *Id.* Because there are additional antigens not captured in the ABO and Rh sorting system, the donor's blood and recipient's blood are usually mixed *in vitro* before transfusion to confirm compatibility. *Id.*

127. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: FOR THE SUBMISSION OF CHEMISTRY, MANUFACTURING, AND CONTROLS AND ESTABLISHMENT DESCRIPTION INFORMATION FOR HUMAN BLOOD AND BLOOD COMPONENTS INTENDED FOR TRANSFUSION OR FOR FURTHER MANUFACTURE AND FOR THE COMPLETION OF THE FORM FDA 356H "APPLICATION TO MARKET A NEW DRUG, BIOLOGIC OR AN ANTIBIOTIC DRUG FOR HUMAN USE" 13 (1999), <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm080803.pdf> [<https://perma.cc/BN47-JN4X>]. The FDA focuses on quality standards for blood manufacturing. *See generally* 21 C.F.R. § 606 (2018) (current good manufacturing practice requirements for blood); *id.* § 607 (establishment registration and product listing requirements for manufacturers of blood); U.S. FOOD & DRUG ADMIN., *supra*, at 13. And because blood is a powerful vector for the transmission of infectious diseases, the FDA also invokes its authority under 42 U.S.C. § 264 to impose testing and recordkeeping requirements aimed at protecting the blood supply. 80 Fed. Reg. 29,842, 29,842 (May 22, 2015) (issuing final rule intended to assure the safety, purity, and potency of blood products used for transmission, issued "under the authority of sections 351 and 361 of the Public Health Service Act"); *see* 21 C.F.R. §§ 610.40, 640.3, 640.5.

128. *E.g.*, Hoffmann et al., *supra* note 95, at 1390–91 (noting criticism of the FDA decision to require INDs because it will create "barriers to access" and offering a proposal that "improves" on the FDA proposal, "as it allows stool banks to continue to provide stool"); Smith et al., *supra* note 56, at 291 (calling the IND requirement "a hurdle that will dissuade some physician-investigators").

129. Smith et al., *supra* note 56, at 291 (arguing that development of naturally derived encapsulated products would "restrict" fecal microbiota therapy "mainly to companies with the resources to fund large clinical trials").

ate outside the FDA framework using stool from in-person donors.¹³⁰ Some believe that this lack of regulation was critical to the innovation.¹³¹

Nor is it unusual that drug companies—rather than individuals—are testing embodiments of the principle in trials intended to satisfy the FDA’s standards. A substantial investment is needed to take a product through the years of product development and clinical trials needed to meet the agency’s standard.¹³² One scholar who objects to application of the new drug framework is concerned that effectively limiting research to large companies with resources has implications for patient access,¹³³ but another scholar (writing with an executive from OpenBiome) puts her fingers on the real significance of shifting research to firms capable of completing pre-market applications.¹³⁴ Applying the new drug authorities means statutory exclusivity, with an attendant increase in cost.

This point bears explaining. New drugs and biological products are supported by extensive and expensive applications containing safety and effectiveness data from laboratory, animal, and human testing.¹³⁵ Federal law provides that after a fixed period, the FDA may accept (or approve, depending on the provision) “abbreviated”

130. Each doctor was subject to a state medical practice act, which might have imposed standards relating to education and competence and even requirements relating to medical procedures. *See generally* Zettler, *supra* note 102, at 450–53. The doctors were also subject to state laws relating to negligence and (if separate) medical malpractice. *Id.* The Federal Policy for the Protection of Human Subjects might have applied, as well, if they performed their research at an institution receiving federal funding. *See* 45 C.F.R. § 46.101.

131. *E.g.*, Megerlin et al., *supra* note 108, at 217 (describing a “fecund research and business ecosystem that has grown up in the current, relatively unrestricted climate”).

132. *See* DiMasi et al., *supra* note 8, at 20–21. A marketing application must show that the product is safe and effective, that it can be manufactured in compliance with current good manufacturing practices, and that it is labeled truthfully and completely. 21 U.S.C. § 355(d) (Supp. V 2018). For ethical and scientific reasons, generating the safety and effectiveness data is an iterative process that starts with laboratory and animal testing and proceeds through several phases of progressively larger and larger human trials. 21 C.F.R. § 312.21. The final phase of trials may involve hundreds or thousands of patients at locations around the globe. *See id.*; INST. OF MED., TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES 24–26 (2010).

133. *See* Hoffmann et al., *supra* note 95, at 1391. She suggests that application of the conventional drug paradigm means that access will be limited to patients enrolled in clinical trials under an IND. *Id.* Some patients, she writes, might not be eligible for the trials, and others might choose not to participate because they do not want to risk receiving placebo. *Id.* at 1391. To some extent these concerns are overblown, because the FDA has always permitted compassionate use for patients who cannot qualify for clinical trials. *E.g.*, 21 C.F.R. § 300. But the essence of her concern is valid, and it is inherent in application of the conventional drug paradigm to *any* new medicine.

134. Sachs & Edelstein, *supra* note 95, at 403–06.

135. *See* DiMasi et al., *supra* note 8, at 22.

applications for copies.¹³⁶ Until this point, any company seeking to market a copy must perform trials of its own.¹³⁷ But when this period—known as “data exclusivity”—ends, these other companies may rely on the research performed by the first company, to support approval of their own products.¹³⁸ This scholar and collaborator also express concern about the potential for “orphan exclusivity,” a different type of statutory exclusivity awarded to drugs approved for treatment of rare diseases, also known as “orphan” diseases.¹³⁹ If a drug has received orphan exclusivity, the FDA may not approve any application for the same drug for the same disease for seven years.¹⁴⁰ This blocks not only abbreviated applications but also applications supported by research of their own.¹⁴¹

They argue that there is no normative justification for exclusivity in the setting of fecal microbiota transfers. Exclusivity, they contend, is meant to “provide innovative drug manufacturers with sufficient incentive to carry new products” through the expensive and risky new drug approval process.¹⁴² It reflects a “bargain” made with these firms.¹⁴³ The “bargain breaks down,” these scholars argue, “when that very same drug was already widely, cheaply available on the market.”¹⁴⁴

136. 21 U.S.C. § 355(j) (2012 & Supp. V 2018). A company may submit an abbreviated application for a generic copy of a new chemical entity five years after the FDA approves the first company’s full application (the application supported by data) for the new chemical entity. *Id.* § 355(j)(5)(F)(ii) (2012). This drops to four years if the generic company challenges a patent claiming the innovator’s drug or a method of using the drug. *Id.* If the innovator’s drug is not a new chemical entity but is still supported by clinical data (other than bioavailability data), the agency must wait three years before it can approve any abbreviated application. *Id.* § 355(j)(5)(F)(iii). A biosimilar company may not submit an abbreviated application for a biosimilar copy of a biological product until four years after the FDA approves the full application, and the FDA cannot approve that biosimilar copy until twelve years after it approved the full application. 42 U.S.C. § 262(k)(7) (2012).

137. See Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 105 (2016) (explaining that during the data exclusivity period, “[a]nyone may apply for a license . . . seeking approval of the same thing on the same terms” and “all face the same scientific burden—preclinical and clinical research in a full application, showing the finished product is safe and effective”).

138. *Id.* at 106 (explaining that, as both a scientific matter and a regulatory matter, a later applicant who files an abbreviated application relies on the first entrant’s research once it performs comparative testing sufficient to justify inferring that the results of testing the first entrant’s product apply equally to its own product).

139. Sachs & Edelstein, *supra* note 95, at 403–05.

140. 21 U.S.C. § 360cc(a) (2012 & Supp. V 2018).

141. *Id.*

142. Sachs & Edelstein, *supra* note 95, at 403.

143. *Id.* at 403–04.

144. *Id.* at 404.

The effect of orphan exclusivity in this setting is uncertain,¹⁴⁵ but there is no disputing the applicability or impact of data exclusivity. If the FDA approved an encapsulated microbiota product, that product would enjoy twelve years of data exclusivity—blocking copies from companies that did not perform their own research.¹⁴⁶ This would provide the company an opportunity to charge higher prices, allowing it to recover its investment and enjoy a profit. Regulating stool bank products as tissue products alone—as other scholars have suggested—would provide patients with an inexpensive alternative to the expensive approved products. Requiring the stool bank to secure premarket approval or stop shipping to doctors whose primary objective is treatment, in contrast, would mean that future patients with *C. difficile* would (for a time) pay more than today's patients do.¹⁴⁷ They are essentially arguing that the FDA should not invoke applicable statutory authority, because the resulting exclusivity would have undesirable economic consequences.¹⁴⁸

145. The FDA has designated three investigational fecal microbiota products as orphan drugs, but the designations vary. MaaT Pharma holds an orphan designation for allogenic fecal microbiota for the treatment of graft-versus-host-disease. *MaaT Pharma Presents Positive Phase 1b/2a Study Results in Acute Myeloid Leukemia Patients at the ASH 2018 Annual Meeting*, PR NEWS USA (Dec. 2, 2018), <http://www.prnewsusa.com/maat-pharma-presents-positive-phase-1b-2a-study-results-in-acute-myeloid-leukemia-patients-at-the-ash-2018-annual-meeting/> [https://perma.cc/6S36-ACL6]. Seres Therapeutics holds an orphan designation for encapsulated spores from fecal microbiota for treatment of recurrent *Clostridium difficile* infection. *Seres Therapeutics, Inc. Announces FDA Orphan Drug Designation for SER-109 for the Prevention of Recurrent Clostridium Difficile Infection in Adults*, WUXI APP TEC (Aug. 21, 2015), <http://wxpress.wuxiapptec.com/seres-therapeutics-inc-announces-fda-orphan-drug-designation-ser-109-prevention-recurrent-clostridium-difficile-infection-adults/> [https://perma.cc/W8DS-GYCD]. And Rebiotix holds an orphan designation for fecal microbiota for prevention of recurrent *Clostridium difficile* infection in individuals with recurrent *Clostridium difficile* infection. *Rebiotix Clinical, Microbiome Data from First-In-Class Microbiota Restoration Therapy to Be Presented at IDWeek 2018*, REBIOTIX (Oct. 1, 2018), <https://www.rebiotix.com/news-media/press-releases/rebiotix-clinical-microbiome-data-from-first-in-class-microbiota-restoration-therapy-to-be-presented-at-idweek-2018/> [https://perma.cc/XXH8-USVE]. It is conceivable that none of these will block any of the others, because they are different drugs, or for different diseases, or both.

146. 42 U.S.C. § 262(k)(7)(A) (2012).

147. How much more remains to be seen; data exclusivity blocks only abbreviated applications, so (depending on the FDA's application of the orphan exclusivity provisions) the various encapsulated products under development could compete in the market, lowering prices. And today's treatments are not always cheap; there are reports of fecal microbiota procedures costing as much as \$10,000 per patient. Kelly, *supra* note 79.

148. Megerlin et al., *supra* note 108, at 218 (noting that the tissue thesis is "based on the possible undesirable economic consequences of [the drug designation]—not on its scientific and conceptual basis").

II. WIDESPREAD ACCESS BEFORE EVIDENCE AND APPROVAL

Policymakers face a dilemma. Firms developing encapsulated filtered feces and microbial communities for treatment of *C difficile* are approaching the end of their premarket research and development programs. On the one hand, if the FDA permits stool banks to ship frozen filtered feces for *C difficile* indefinitely without approved applications, these firms may never recoup their investments. Data exclusivity, protection from competing copies approved based on their research, will not assure an exclusive position in the market. Nor will orphan exclusivity, even if it blocks other innovative products supported by research. Other innovative products are not the problem. The problem is the availability of a competing new drug *from stool banks* marketed to the same customers without approval and thus without the need to recover research and development costs.¹⁴⁹ The concern for policymakers is that no rational firm would invest in the work needed to develop a product to the FDA's new drug standards if the marketplace would include unlawfully marketed products that consumers might perceive as substitutes.¹⁵⁰ On the other hand, if the FDA takes steps to ensure the newly approved products enjoy exclusivity in the marketplace, for a time the nearly 15,000 patients who suffer relapsing *C difficile* each year may pay much more for a cure than similarly situated patients currently pay. The public will perceive this as an unjustified price hike, leading to intense political pressure on the agency.

This part explains that this reversed sequencing is not unique to fecal microbiota. Policymakers face this dilemma with other

149. The availability of unregulated in-office and at-home procedures creates the same problem, but the FDA has less authority here. See *supra* note 75 and accompanying text.

150. One might ask why the firms developing microbiota-based conventional drugs began research and development programs under the circumstances. Several answers come to mind. *First*, the FDA rescinded its policy of enforcement discretion for stool banks in 2014, which may have given the companies confidence that it would remove unapproved products from the market once they completed the approval process. See Sachs, *supra* note 113, at 519 (showing that companies investing in microbiota-based products focus on the prospect of data exclusivity after approval). *Second*, for any company developing synthetic microbial communities, the fecal microbiome may be low-hanging fruit and the first of several planned therapies using the same proprietary platform. *Third*, some may believe that the imprimatur of FDA approval will make a difference in the market, and producers of artificial microbial communities may believe that their products will appeal to patients uncomfortable with the notion of a stranger's feces as medicine.

product types as well, with predictable result: patients and payers express outrage about a perceived price hike.

A. *Unapproved New Drugs*

The FDA faces the same dilemma with thousands of older prescription drugs marketed today without approved applications. These products contain old active ingredients, typically dating to the first half of the twentieth century but in some cases to even earlier.¹⁵¹ Examples include many phenobarbital preparations, morphine sulfate preparations, and belladonna preparations; various products containing nitroglycerin, atropine sulfate, or epinephrine; as well as drugs containing phenazopyridine hydrochloride (labeled for relief of pain, burning, urgency frequency, and other discomfort arising from irritation of the mucosa of the lower respiratory tract), tetrofosmin (labeled for use as a diagnostic agent to assess areas of reversible myocardial ischemia), and hycosamine sulfate (labeled for use in the treatment of peptic ulcer, irritable bowel syndrome, and acute enterocolitis).¹⁵² These unapproved prescription drugs are new drugs that require premarket approval, but they lack approval.¹⁵³ Their lack of approval is an artifact of history—exemptions and exclusions that changed over time.

A brief explanation may be helpful. Before 1938, drugs reached the market without applications.¹⁵⁴ Between 1938 and 1962, new

151. *E.g.*, Kesselheim & Solomon, *supra* note 19, at 2045 (noting that colchicine in tablet form was widely available in the United States in the nineteenth century).

152. One can generate a list of marketed unapproved prescription drugs from the FDA's website. Section 510 of the FDCA, 21 U.S.C. § 360, requires every person engaged in the manufacture of drugs—whether subject to the approval requirement or not—to file a list of all drugs manufactured for commercial distribution. Drug products are identified and reported using a unique three-segment number known as the National Drug Code. The resulting database can be downloaded. When this article was prepared, the database contained nearly 3000 unapproved prescription drug products.

153. This discussion refers only to unapproved *prescription* drugs. The FDA has concluded that many nonprescription drugs are exempt from the premarket approval requirement because they are not new drugs. *See* Over-the-Counter Drug Monograph System—Past, Present, and Future; Public Hearing, 79 Fed. Reg. 10,168, 10,169 (Feb. 24, 2014) (“If a drug meets each of the conditions contained in part 330, as well as each of the conditions contained in any applicable [nonprescription] drug monograph, and other applicable regulations, it is considered GRAS/GRAE and not misbranded, and is not required by FDA to obtain approval of a new drug application (NDA) under section 505 of the FD&C Act (21 U.S.C. 355).”).

154. Pure Food Act of 1906, Pub. L. No. 59-384, §§ 2–5, 34 Stat. 768, 768–69 (1906). This statute prohibited adulteration and misbranding but did not require safety or premarket

drugs had to be shown safe in new drug applications.¹⁵⁵ Drugs could reach the market without these applications, if they were grandfathered (the same as a pre-1938 drug) or if they were generally recognized as safe.¹⁵⁶ In 1962, Congress amended the law to require that new drugs be proven effective.¹⁵⁷ This rule applied retroactively, so the FDA reviewed the pre-1962 drugs with safety-only applications.¹⁵⁸ If the agency found a drug effective for its labeled uses, each company marketing the drug under an application had to file a conforming supplement to its application.¹⁵⁹ If the FDA found the drug ineffective, the companies had to withdraw their drugs from the market.¹⁶⁰ A similar rule applied to generic copies, which had been marketed without applications. If the agency found the drug with the application effective, the generic companies had to submit conforming applications (though abbreviated) for their copies.¹⁶¹ If the FDA found the drug ineffective, the generic companies had to withdraw their copies from the market.¹⁶²

Some illegally marketed prescription drugs are pre-1962 drugs that the FDA found effective but for which no conforming supplement (or application) was ever filed.¹⁶³ Some are pre-1962 drugs that are ineffective but were never removed from the market.¹⁶⁴ And some companies market prescription drugs without approval on the theory—almost certainly wrong—that an exemption under current law applies.¹⁶⁵

review. *Id.*

155. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052–53 (1938).

156. *Id.* § 201(p), 52 Stat. at 1041–42.

157. Drug Amendments of 1962, Pub. L. No. 87-781, § 104, 76 Stat. 780, 784 (1962) (amending section 505 of the Food, Drug, and Cosmetic Act).

158. *Id.* § 107, 76 Stat. at 788–89. Some drugs with pre-1962 applications may still be under review. FDA policy permits these drugs (and any copies) to remain on the market until the proceeding finishes. U.S. FOOD & DRUG ADMIN., MARKETED UNAPPROVED DRUGS COMPLIANCE POLICY GUIDE 10 (2011) [hereinafter UNAPPROVED DRUGS GUIDANCE].

159. 80 Fed. Reg. 70,822, 70,824 (Nov. 16, 2015); see also UNAPPROVED DRUGS GUIDANCE, *supra* note 158, at 9.

160. 80 Fed. Reg. at 70,822–23.

161. *Id.* at 70,824.

162. *Id.* at 70,823.

163. UNAPPROVED DRUGS GUIDANCE, *supra* note 158, at 11.

164. *Id.*

165. There are two possibilities. First, if a drug was lawfully marketed without an application before 1962, it can remain on the market as long as the drug and its labeling have not changed. Drug Amendments Act of 1962, Pub. L. No. 87-781, § 107(c), 76 Stat. 789. Second, an application is not required if the drug is “generally recognized as safe and effective” under the conditions of use in its labeling. 21 U.S.C. § 321(p) (2012). The FDA believes

The FDA faces a dilemma with unlawfully marketed prescription drugs. No reasonable firm with a medicine marketed for decades will invest hundreds of millions of dollars to support an application unless it is either forced or motivated to do so. The FDA cannot force these companies to perform this research without threatening enforcement action. The threats would be effective only if backed by actual enforcement action, which would involve fact-intensive disputes over whether an exemption was warranted. The FDA does not have the resources to engage in this kind of dispute over every unapproved prescription drug on the market. And doing so would deprive patients of medicines on which they have relied for years—medicines which might, in fact, prove safe and effective under the new drug standard. The agency therefore focuses its energy on drugs that present public health concerns.¹⁶⁶

But unapproved prescription drugs are marketed illegally, and some might not be safe and effective as labeled. No one has performed the safety and effectiveness research needed to determine whether they meet the FDA approval standard. Prescribers and patients may not even realize they are using medicines that have not been through the approval process.¹⁶⁷ So the FDA encourages companies to complete the research necessary for approval.¹⁶⁸ The agency does this by promising that once a company completes the approval process, it will take enforcement action against other companies marketing the same drug illegally.¹⁶⁹

that no marketed drugs satisfy either test. See UNAPPROVED DRUGS GUIDANCE, *supra* note 158, at 12.

166. For example, the agency acted against an unapproved high potency Vitamin E intravenous injection that “was associated with adverse reactions in about 100 premature infants, 40 of whom died.” UNAPPROVED DRUGS GUIDANCE, *supra* note 158, at 11.

167. Independence Blue Cross, *Coverage of Non-FDA-Approved Drugs* (Dec. 1, 2015), <http://provcomm.ibx.com/ProvComm/ProvComm.nsf/07edde68453f923d8525792c00554102/403cb2df9960d64f85257f08005df92e!OpenDocument> [<https://perma.cc/8V46-UCD2>] (“Many health care providers continue to unknowingly prescribe unapproved drugs, usually because they are unaware of the non-FDA-approved status of the drugs.”); ACAD. OF MANAGED CARE PHARMACY, PRACTICE ADVISORY ON UNAPPROVED MEDICATIONS (2009), <http://amcp.org/WorkArea/DownloadAsset.aspx?id=10095> [<https://perma.cc/8FTY-LKPM>] (“Few health care professionals, patients, and organizations involved in the distribution, sales, or payment for medications are aware of this issue.”).

168. A strategy of encouragement, in the agency’s view, “benefits the public health by increasing the assurance that marketed drug products are safe and effective” and “reduces the resources that FDA must expend on enforcement.” UNAPPROVED DRUGS GUIDANCE, *supra* note 158, at 7.

169. *Id.*

The agency sees two benefits to doing this.¹⁷⁰ First, it ensures patients use only the version that has been tested and brought under the new drug authorities. And second, it motivates companies to do this testing and bring their drugs under these authorities. It motivates a company to invest in the research, because enforcement action means the company's drug could be alone in the market for three or even seven years, because of statutory exclusivity.¹⁷¹ Removal of competing products, combined with a period before generic competition, may enable the company to recover its investment and some profit. This may entice companies to do the work. From the perspective of patients, however, the price of a long available drug has skyrocketed.¹⁷²

The FDA faces essentially the same dilemma with unapproved new drugs as it does with fecal microbiota. On the one hand, if firms know the agency will permit the continued unlawful marketing of unregulated competing drugs, they may not invest in the research needed to assess whether their drugs satisfy today's new drug standard. On the other hand, if the agency removes the unlawful alternatives from the market, the steep price increase for a well-known therapy is upsetting to stakeholders.¹⁷³

170. *Id.*

171. See *supra* Part I.D.2 (explaining the different types of exclusivity). Sometimes statutory exclusivity may not be available. The applications for Adrenalin (epinephrine), Akovax (ephedrine sulfate injection), Bloxiverz (neostigmine methylsulfate), and Colcris (colchicine) were supported by literature reviews and bioequivalence studies, rather than clinical evidence. Aaron Hakim et al., *High Costs of FDA Approval for Formerly Unapproved Marketed Drugs*, 318 JAMA 2181, 2181 (2017). These applications did not lead to three-year exclusivity, because this exclusivity applies only if an application contained clinical data essential to its approval. 21 U.S.C. § 355(j)(5)(F)(iii) (2012). Colcris, however, benefitted from orphan exclusivity. The exclusivity awarded at approval can be determined from the relevant annual edition of the FDA's publication, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS.

172. Hakim et al., *supra* note 171, at 2181 ("A recent examination of all prescription drugs targeted by the [FDA unapproved drugs initiative] between 2006 and 2015 demonstrated that the price of these drugs increased by a median of 37% after . . . regulatory action or approval.")

173. Eric Palmer, *Study Says No Good Has Come from FDA's Action on Gout Drug Colchicine*, FIERCE PHARMA (Apr. 10, 2015), <https://www.fiercepharma.com/regulatory/study-says-no-good-has-come-from-fda-s-action-on-gout-drug-colchicine> [<https://perma.cc/72Y4-4G4F>] ("A stink was raised a few years back when the FDA asked for a safety study of colchicine, an inexpensive drug that had been prescribed for decades for gout, then granted exclusive approval to one company who stepped up. As soon as the approval was in place, the price of the drug went up from pennies per pill to \$5 and patients and doctors screamed foul."). The outrage is ironic because the effect of the FDA's policy—removing competing versions from the market so that the firm's statutory exclusivity is meaningful—ensures that patients receive *only* the version tested, manufactured, and labeled in accordance with FDA regulations. Scholars who complain that colchicine had been marketed safely since the

B. *Compounded Copies of Approved Drugs*

Several years ago, the FDA faced the same dilemma when pharmacies compounded illegal copies of a recently approved drug. Compounding means making a drug to order, in a pharmacy, in response to a doctor's prescription.¹⁷⁴ Usually the pharmacist prepares an alternative to an approved product to satisfy a patient's special needs—for instance, omitting an inactive ingredient to which the patient is allergic, or preparing a flavored liquid for a child.¹⁷⁵ A compounded drug is a “new drug,” but federal law exempts it from premarket approval if certain conditions are met; among other things, the compounded drug cannot be a copy of an approved drug.¹⁷⁶ In this case, the FDA approved an application for Makena (hydroxyprogesterone caproate), but pharmacies had been compounding drugs with the same active ingredient for years.¹⁷⁷ Faced with stakeholder outrage about the price of Makena, the agency exercised enforcement discretion—effectively permitting pharmacies to keep making what were now copies of an approved drug, even though doing so was illegal.¹⁷⁸

The back story was unusual, making it especially difficult for the public to accept the price increase. Hydroxyprogesterone caproate had been marketed before the 1962 amendments, by Bristol Myers-Squibb (“BMS”).¹⁷⁹ BMS labeled its drug for several conditions including habitual and threatened abortion (miscarriage).¹⁸⁰ When

19th century, for example, Kesselheim & Solomon, *supra* note 19, may have forgotten that the FDA took enforcement action against injectable colchicine products in 2008 after twenty-three deaths were reported to the agency. Drug Products Containing Colchicine for Injection; Enforcement Action Dates, 73 Fed. Reg. 7565 (Feb. 8, 2008).

174. U.S. FOOD & DRUG ADMIN., FDA'S HUMAN DRUG COMPOUNDING PROGRESS REPORT THREE YEARS AFTER ENACTMENT OF THE DRUG QUALITY AND SECURITY ACT 4 (2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM536549.pdf> [<https://perma.cc/UHC4-N924>].

175. Nathan A. Brown & Eli Tomar, *Could State Regulations Be the Next Frontier in Preemption Jurisprudence? Drug Compounding as a Case Study*, 71 FOOD & DRUG L.J. 271, 276 (2016).

176. 21 U.S.C. § 353a (2012 & Supp. V 2018) (providing that § 355 does not apply to compounded drugs covered by the section). Federal law also exempts these compounded drugs from current good manufacturing practices and the need to have labeling for doctors. *Id.* (providing that § 351(a)(2)(B) and § 352(f)(1) also do not apply).

177. Reichmann, *supra* note 19, at 487 (noting that pharmacies began compounding drugs with the active ingredient eight years before the FDA approved Makena).

178. *See infra* note 191.

179. Determination that DELAUTIN Was Not Withdrawn from Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 36,419 (June 25, 2010).

180. *Id.* at 36,419–20.

the FDA reviewed the drug's effectiveness after the 1962 change in the law, it concluded that there was *not* substantial evidence of effectiveness for prevention of miscarriage.¹⁸¹ BMS removed this use from the labeling and eventually stopped marketing the drug, and the FDA withdrew approval in 2000.¹⁸² In 2003, however, the *New England Journal of Medicine* published the results of a government-sponsored clinical trial of hydroxyprogesterone caproate in pregnant women with a documented history of spontaneous preterm delivery.¹⁸³ The results showed that weekly injections lowered the rate of recurrent preterm delivery among high risk women and reduced the likelihood of severe complications in their infants.¹⁸⁴ With this news, doctors began prescribing hydroxyprogesterone caproate to prevent recurrent preterm birth. Because no approved product was available, pharmacies compounded it using raw materials from overseas.¹⁸⁵

The approval of Makena in 2011—to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth¹⁸⁶—changed the marketplace. Doctors and patients had relied for years on the compounded drugs, typically sold by pharmacies at \$10 to \$20 per dose.¹⁸⁷ Makena received seven years of orphan exclusivity, slated to expire in February 2018,¹⁸⁸ and KV Pharmaceuticals (“KV”) priced the drug at \$1500 per dose.¹⁸⁹ Public outrage about the price spilled

181. 38 Fed. Reg. 27,947 (Oct. 10, 1973).

182. 66 Fed. Reg. 55,264, 55,264 (Sept. 13, 2000).

183. P.J. Meis et al., *Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate*, 348 NEW ENG. J. MED. 2379, 2380 (2003).

184. *Id.* at 2385.

185. Brief of Appellants K-V Pharm. Co. & Ther-Rx Corp. at 20, *K-V Pharm. Co. v. FDA*, No. 12-5349 (D.C. Cir. Mar. 11, 2013).

186. Letter from Julie Beitz, Dir., Off. of Drug Evaluation III, to Robb Hesley, Vice President, Hologic, Inc. (Feb. 3, 2011) (on file with the U.S. Federal Food and Drug Administration), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021945s000ltr.pdf [<https://perma.cc/UYQ8-3ACL>].

187. Sumin Kim, *The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity*, 11 NW. J. TECH. & INTELL. PROP. 541, 549 (2013).

188. U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at ADA 102 (33d ed. 2013).

189. *In re K-V Pharm. Co. Secs. Litig.*, No. 4:11-CV-01816, 2014 U.S. Dist. LEXIS 40828, at *6 (E.D. Mo. Mar. 27, 2014).

over into legislative hearings,¹⁹⁰ and the FDA responded by announcing that it would *not* take enforcement action against pharmacies that made and sold illegal copies of the drug.¹⁹¹

The results were predictable. Competitive pressure from the illegal pharmacy copies forced KV to reduce the drug's list price by more than 50%.¹⁹² Although the FDA softened its stance in June 2012, stating that it might take enforcement action "if warranted,"¹⁹³ the company's cease-and-desist letters to pharmacies were ineffectual without a meaningful threat of the FDA enforcement action. The company's lawsuit seeking to compel enforcement action failed in September 2012.¹⁹⁴ By this time, the company had filed for bankruptcy.¹⁹⁵

The story is unusual because KV did not do any research itself. It purchased a pending application to generate a cash flow that would stave off bankruptcy.¹⁹⁶ Also the application relied heavily on the government-funded trial, published before the company's predecessor began pursuing approval.¹⁹⁷ As a result, it was difficult

190. Brief of Appellants, *supra* note 185, at 16 (discussing the congressional budget hearing in which Commissioner was pressured to do "something").

191. FDA Statement on Makena, FDA (Mar. 30, 2011), <http://wayback.archive-it.org/7993/20170113105714/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm249025.htm> [<https://perma.cc/3E86-D4EJ>].

192. *In re K-V Pharm. Co. Secs. Litig.*, 2014 U.S. Dist. LEXIS 40828, at *6, *13.

193. *Questions and Answers on Updated FDA Statement on Compounded Versions of Hydroxyprogesterone Caproate (the Active Ingredient in Makena)*, FDA (June 2012), <http://wayback.archive-it.org/7993/20170113105722/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310215.htm> [<https://perma.cc/4WYE-8Y7T>].

194. *K-V Pharm. Co. v. FDA*, 889 F. Supp. 2d 119 (D.D.C. 2012) (granting motion to dismiss largely part because the plaintiff challenged a discretionary decision not to enforce the law, which was unreviewable). This decision was vacated for reconsideration in light of *Cook v. FDA*, 733 F.3d 1 (D.C. Cir. 2013) and the Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587, but the parties settled before the lower court could reconsider its ruling. *K-V Pharm. Co. v. FDA*, No. 12-5349, 2014 WL 68499 (D.C. Cir. Jan. 7, 2014); Kurt Karst, *KV Lawsuit Involving MAKENA and Compounded 17p Concludes . . . in Sopranos Style*, FDA L. BLOG (July 7, 2014), <http://www.fdalawblog.net/2014/07/kv-lawsuit-involving-makena-and-compounded-17p-concludes-in-sopranos-style/> [<https://perma.cc/Z4LR-AU4D>].

195. Kim, *supra* note 187, at 556.

196. *Id.* Adeza Biomedical Corporation filed the application in 2006, and the pending application changed hands several times before KV acquired it under an \$82 million asset purchase agreement in January 2008. *Id.*, at 549-50; *In re K-V Pharm. Co. Secs. Litig.*, No. 2014 U.S. Dist. LEXIS 40828, at *6.

197. The initial application relied on an active treatment trial terminated in March 1999, the study published in the *New England Journal*, and a follow-up safety study. CTR. FOR DRUG EVALUATION & RESEARCH, MEDICAL REVIEW, NDA 21-945, at 14 (2011) [hereinafter MEDICAL REVIEW], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000MedR.pdf [<https://perma.cc/CEP9-EPWF>]; CTR. FOR DRUG EVALUATION & RESEARCH,

for the public to accept claims that the pricing benefit of orphan exclusivity was necessary to ensure that the drug would be subject to the testing needed for approval. Still the purchase price paid by KV presumably reflected in part the cost of testing to date (as well as the returns anticipated from seven years of orphan exclusivity), and its predecessors had performed several years of work to bring the drug into the modern new drug framework. This was nothing like the work needed to bring a new molecular entity to market, to be sure, but it was not negligible.¹⁹⁸ In any case, the work was necessary to satisfy the FDA's approval standard, and it is hard to imagine why any company would make this kind of investment, if it knew that every doctor could ask the local pharmacy to whip together a knock-off.

III. THE POLICYMAKER'S DILEMMA

In the access-before-evidence scenarios just described, policymakers face a choice. Approving a marketing application for one version of a treatment requires them to decide whether to take steps to remove the unregulated alternatives from the market (to subject them to the same premarket testing and approval requirement)—steps that will lead to higher treatment costs for patients for a time.¹⁹⁹ These scenarios therefore raise two questions at the heart of new drug policy: first, whether the new drug authorities

SUMMARY REVIEW, NDA 21-945, at 7 (2011) [hereinafter SUMMARY REVIEW], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000SumR.pdf [<https://perma.cc/5GXV-Z63F>] (noting that the 2006 submission was a "literature-based application").

198. It included conducting a nonclinical multigenerational reproductive toxicology study in rodents; refining the chemistry, manufacturing, and controls portion of the submission; designing and beginning a second clinical trial to prove effectiveness; and designing a follow-up study of the children born to the mothers in the trial. SUMMARY REVIEW, *supra* note 197, at 18, 22–34.

199. The FDA has clear authority to take enforcement action when a firm introduces an unapproved new drug into interstate commerce and when a pharmacy sells an unapproved new drug that does not fall within the compounding exception. 21 U.S.C. §§ 331(d), 355(a) (2012). The agency could also terminate (or refuse) any IND arrangement—for instance, for fecal microbiota—that it concluded was not genuinely investigational. The statutory language requiring the FDA to exempt drugs for clinical trials from the premarket approval requirement provides broad discretion to the agency. *Id.* § 355(i) (2012 & Supp. V 2018). It directs the agency to draft regulations to govern the exemption, but—apart from a few requirements relating to informed consent, *id.* § 355(i)(4) (Supp. V 2018)—gives the agency complete discretion in the conditions it sets. Also, these regulations are supposed to exempt "drugs intended *solely* for investigational use." *Id.* § 355(i)(1) (2012) (emphasis added). And the FDA's regulations permit it to place an ongoing investigation on hold if the drug has received marketing approval for the same indication in the same patient population, which may provide a basis for acting after approval of an encapsulated naturally derived product. 21 C.F.R. § 314.42(b)(4)(vi) (2018).

are *worth* it, and second, whether they should be applied here in particular. Answering these questions requires understanding the nature and purpose of the new drug authorities, to which this part turns first.

A. *Describing the FDA's New Drug Authorities*

The new drug authorities in current law comprise three strands: (1) the new drug approval standard, (2) the gatekeeping mechanism, and (3) a leash on the drug held by the FDA through the lifecycle of the drug.

1. The New Drug Approval Standard

Holding a medicine to the new drug approval standard means requiring that three things be true: (1) there is substantial evidence of the medicine's effectiveness, (2) adequate safety testing has been performed, and (3) on average the medicine's benefits outweigh the risks.

First, there must be substantial evidence of the medicine's effectiveness.²⁰⁰ The phrase "substantial evidence" has a specialized meaning in the drug approval setting. It means evidence from "adequate and well-controlled investigations, including clinical investigations, by [appropriately qualified experts], on the basis of which it could fairly and responsibly concluded be that . . . the drug will have the effect [in question]."²⁰¹ The FDA has explained the design characteristics of an "adequate and well-controlled" clinical trial in regulations, and decades of guidance documents, agency publications, and approval decisions elaborate the clinical design and statistical methods that it expects.²⁰²

In practice, the substantial evidence standard means at least one—preferably two—randomized, controlled, double-blinded, prospective interventional trials. A prospective interventional trial is one in which investigators administer the test drug to patients and

200. 21 U.S.C. § 355(d) (Supp. V 2018). The biologics statute does not require that biological drugs meet this standard, but the FDA usually applies it. See 37 Fed. Reg. 16,679 (Aug. 18, 1972) (discussing decision to apply the substantial evidence standard to biologics, though more flexibly).

201. 21 U.S.C. § 355(d).

202. 21 C.F.R. § 314.126(b) (describing the design characteristics of an adequate and well-controlled trial); Lietzan, *supra* note 7, at 51–54.

take measurements that reflect safety and effectiveness parameters of interest, including the clinical endpoint, meaning the hoped-for clinical benefit of the drug.²⁰³ Randomization and controls mean that investigators randomly assign patients meeting inclusion and exclusion criteria to either the test drug or a comparator (control).²⁰⁴ Double blinding means neither the patients nor the investigators know the assignments.²⁰⁵ Randomization and double-blinding reduce the potential for bias and confounding, meaning unaccounted-for variables responsible for the outcome.²⁰⁶ By design, if these trials are large enough to permit meaningful conclusions, they can identify casual relationships: that the test drug is effective (causes the therapeutic benefit in question) and, depending on trial design, which of two treatment methods is superior.²⁰⁷ Randomized controlled trials are the “gold standard” for proof of effectiveness.²⁰⁸

203. See Matthew S. Thiese, *Observational and Interventional Study Design Types; an Overview*, 24 *BIOCHEMIA MEDICA* 199, 200, 204–05 (2014).

204. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS 3–4 (2001).

205. *Id.* at 4.

206. Thomas R. Frieden, *Evidence for Health Decision Making: Beyond Randomized Controlled Trials*, 377 *NEW ENG. J. MED.* 465, 465 (2017); see also U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: STATISTICAL PRINCIPLES FOR CLINICAL TRIALS 10–12 (1998).

207. Frieden, *supra* note 206, at 470. Smaller trials are less reliable. They usually have a wide confidence interval around effectiveness—meaning that the true value (actual effectiveness) could be anywhere within a larger range of numbers. Trevor A. Sheldon, *Estimating Treatment Effects: Real or the Result of Chance?*, 3 *EVIDENCE-BASED NURSING* 36, 36 (2000); see also Lee Kennedy-Shaffer, *When the Alpha Is the Omega: P-Values, Substantial Evidence, and the 0.05 Standard at FDA*, 72 *FOOD & DRUG L.J.* 595, 602 (2017) (explaining that a larger trial and larger effect size will lead to a smaller “p-value,” meaning a lower probability that the null hypothesis—no effectiveness—is true). It is, however, a fair criticism that the FDA’s standard does not specify a particular degree of effectiveness that is required, and some approved drugs may be only slightly better than the alternative. *E.g.*, Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 *WASH. & LEE L. REV.* 2073 (2013).

208. Vinay Prasad & Vance Berger, *Hard-Wired Bias: How Even Double-Blind Randomized Controlled Trials Can Be Skewed from the Start*, 90 *MAYO CLINIC PROC.* 1171 (2015) (“Well-designed, adequately-powered randomized controlled trials . . . are rightfully considered the highest form of evidence on which to base treatment and diagnostic decisions, minimizing potential biases, particularly confounding, that plague alternate, lesser forms of evidence.”). Randomized controlled trials do, however, have shortcomings. For example study populations tend to be homogenous, which can make it inappropriate to generalize the results to broader populations. Frieden, *supra* note 206, at 465. They have also limited duration and sample size, which can preclude assessment of a treatment effect’s duration and prevent identification of rare or latent side effects. *Id.*; see also Anna B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 *ALA. L. REV.* 305, 327–331 (2011) (discussing inherent limitations of randomized controlled trials).

Application of the new drug standard also means the applicant must perform “adequate” tests by “all methods reasonably applicable” to assess the safety of the treatment when used as described in the labeling.²⁰⁹ These include laboratory and animal studies looking at the drug’s pharmacological actions (effect on the body) and toxicological effects, and sometimes its effect on reproduction and developing (animal) fetuses.²¹⁰ They include human pharmacokinetic testing (of how the drug is absorbed, distributed, metabolized, and excreted) and bioavailability testing (to see how much of the drug gets to where it needs to go in the body, and how quickly it does so).²¹¹ The application summarizes all available information about the drug’s safety and sometimes data from studies of related drugs.²¹²

A drug meets the new drug standard if, taking all this evidence into account, its expected benefits outweigh its potential risks.²¹³ Potential risks include the known (adverse reactions that happened in the trials) and the unknown (adverse reactions that are more severe or common than observed in the trials, for instance, those arising from long term use, and those not detected given the size of the trials).²¹⁴ The FDA considers risk and benefit at the population level; that is, it relies on population-average statistics when comparing the benefits and the risks.²¹⁵ The benefits may not outweigh the risks for a particular patient for whom the drug is labeled, but on average for the intended population they do.

209. 21 U.S.C. § 355(d)(2) (Supp. V 2018).

210. 21 C.F.R. § 314.50(d)(5)(i) (2018); *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY M4S: THE CTD—SAFETY 8 (2001).

211. 21 C.F.R. § 314.50.

212. *Id.*

213. *E.g.*, U.S. FOOD & DRUG ADMIN., BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING: DRAFT PDUFA VI IMPLEMENTATION PLAN (FY 2018–2022), at 3 (2018) (“Simply put, for a drug to be approved for marketing, FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients.”); U.S. FOOD & DRUG ADMIN., DEVELOPING TARGETED THERAPIES IN LOW-FREQUENCY MOLECULAR SUBSETS OF A DISEASE 4 (2018) (“As with all new drug approvals, the FDA will consider the totality of the evidence in weighing the benefits and risks of the drug.”).

214. NAT’L ACADS. OF SCI, ENG’G & MED., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 106 (2007); *see also* U.S. FOOD & DRUG ADMIN., REVIEWER GUIDANCE: CONDUCTING A CLINICAL SAFETY REVIEW OF A NEW PRODUCT APPLICATION AND PREPARING A REPORT ON THE REVIEW (2005).

215. *See* Anup Malani et al., *Improving the FDA Approval Process* (John M. Olin Law & Econ., Working Paper No. 580 (2d Series), Public Law and Legal Theory, Working Paper No. 367, 2011).

2. The Gatekeeper

Applying the agency's new drug authorities also means that the new drug standard serves as a barrier to entry. Federal law prohibits the commercial distribution of any new drug that lacks an approved application, which in turn must persuade the FDA that the drug satisfies the new drug standard.²¹⁶ In theory patients receive new drugs only if they satisfy this standard.

But the barrier to entry does not mean that every medicine available to patients in the United States has been proven effective in gold standard randomized controlled trials, for two reasons. First, the standard is flexible.²¹⁷ Federal law does not *require* two adequate and well-controlled clinical trials showing effectiveness.²¹⁸ And the gold standard is not always imposed; FDA regulations permit the use of historical controls, even "experience historically derived from the adequately documented natural history of the disease or condition."²¹⁹ Federal law does not even require biologics to meet the substantial evidence test in the first place, so the agency will waive controlled trials if not reasonably applicable or essential to establish effectiveness.²²⁰ The FDA has approved drugs and biologics based on studies without controls, based on effectiveness trials involving as few as six or thirteen patients, and even with no human effectiveness data.²²¹ Second, the barrier to entry is porous. Doctors and patients use medicines that bypass the barrier—for instance, because no components cross state lines, because no manufacturer or seller makes new drug claims, or for

216. 21 U.S.C. § 355(a) (2012); 42 U.S.C. § 262(a) (2012 & Supp. V 2018).

217. 21 C.F.R. § 314.105(c) ("While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus, the FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.").

218. 21 U.S.C. § 355(d) (Supp. V 2018) (permitting approval based on "data from one adequate and well-controlled clinical investigation and confirmatory evidence"); *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS (1998) (describing approval based on one study providing "statistically very persuasive evidence").

219. 21 C.F.R. § 314.126.

220. 38 Fed. Reg. 1318, 4322 (Feb. 13, 1973); *see supra* Part I.D.2 (discussing requirements for blood).

221. Frank Sasinowski et al., *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014*, THERAPEUTIC INNOVATION & REGULATORY SCIENCE 1, 17 (2015); *see also* Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 JAMA 368 (2014) (finding that the quality of clinical trial evidence required for approval varies widely).

other reasons.²²² The scenarios described in this article provide another example. Also patients may receive medicines *before* firms know whether the medicines satisfy the standard, if they enroll in premarket trials or obtain access on a compassionate basis outside those trials.²²³

Even if it enforces the new drug standard imperfectly, the gate-keeping mechanism plays two other important roles. First, by assigning the job of application review to a single entity staffed by scientists, it ensures that the data supporting each new drug face at least one formal structured assessment grounded in science.²²⁴ Whether the effectiveness data amount to substantial evidence, and whether the applicant has conducted all reasonably applicable safety testing, are scientific judgments. Scientists may disagree on the particulars—for instance, whether trial endpoints are too subjective to be reliable, or whether additional measures might reduce the potential for bias from incomplete blinding—but not on the inferences that can and cannot be drawn based on a particular statistical design. Randomized controlled clinical trials are more reliable and thus more persuasive than observational data, and larger trials are better than smaller trials; these are scientific facts, not a public policy position, let alone a matter of opinion.²²⁵ Whether the

222. A state may permit the sale within its borders of an unapproved medical product manufactured within its borders from constituents that never crossed state lines. For instance at one time the states permitted sales of laetrile to treat cancer, even though the FDA never approved the drug. Patricia Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 879 (2017).

223. 21 U.S.C. § 360bbb-0 (Supp. V 2018) (describing expanded access to investigational drugs for treatment use); 21 C.F.R. §§ 312.300–.320 (describing expanded access to investigational drugs for treatment use); Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act, Pub. L. No. 115-176 (codified at 21 U.S.C. § 360bbb-0) (exempting certain investigational drugs from the new drug approval and IND requirements, including expanded access regulations, for treatment use by eligible patients after phase 1 trials are complete).

224. See also Robert M. Temple, *Commentary on “The Architecture of Government Regulation of Medical Products,”* 82 VA. L. REV. 1877, 1898 (1996) (“[A]part from contributing independent review, the existence of the regulator helps maintain the safety assessment enterprise, as public standards, applicable to all parties, assure a level playing field and discourage excessive corner-cutting.”).

225. See *supra* note 208 and accompanying text; see also Hertzler C. Gerstein et al., *Real-world Studies No Substitute for RCTs in Establishing Efficacy*, 393 LANCET 210 (2019) (noting that observational data from the real world “can help to identify associations between drug exposures and outcomes” but that the conclusions can reflect “unaccounted for confounders,” while a carefully designed and implemented randomized controlled trial allows between-group differences in outcome to be “confidently attributed to the intervention being evaluated”); Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 387–88 (2002) (noting that randomized controlled trials “discredit long-accepted medical treatments with disturbing

benefits outweigh the risks at the population level requires consideration of other scientific questions—such as the severity of the condition and how well other therapies address the condition—and may invite some subjectivity, but the FDA is moving toward a more structured approach to this assessment.²²⁶ The low rate of turnover in the FDA’s new drug leadership helps ensure final decisions are based in science and benefit from not only scientific expertise but also experience and institutional memory.²²⁷ This ensures predictability as well as consistency with precedent, both hallmarks of a better decision making process.²²⁸

Second, the gatekeeping function plays an important role mediating information about drugs in the market.²²⁹ Several scholars

regularity, and they also sometimes cast doubts on the conclusions of observational studies”); Jacqueline Zummo, *We Need to Raise the Bar to Improve Cancer Treatments*, HEALTH AFF. BLOG (July 26, 2017), <https://www.healthaffairs.org/doi/10.1377/hblog20170726.061240/full/> [https://perma.cc/U6WZ-Z7PG] (“Large, well-powered trials provide greater certainty that the observed effect is not just a fluke and will be replicable in other studies and in the real world.”). The problem is that large swaths of the public and of the prescribing community itself remain skeptical of the value of randomized controlled trials. Laakman, *supra* note 208, at 312 (“Significant skepticism persists within the medical community regarding the clinical utility of [randomized control trials], particularly among community practitioners unaffiliated with academic medical centers. This resistance to fully embrace [randomized controlled trials] reflects physicians’ traditional reliance on personal experience and anecdotal information to guide treatment decisions.”).

226. U.S. FOOD & DRUG ADMIN., BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING: DRAFT PDUFA VI IMPLEMENTATION PLAN (FY 2018–2022), at 2 (2018), <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf> [https://perma.cc/83TW-UBW7].

227. For example, the Director of the Center for Drug Evaluation and Research, Janet Woodcock, has been with the agency since 1986. *Meet Janet Woodcock, M.D., Director, Drug Evaluation and Research*, FDA, <https://www.fda.gov/AboutFDA/CentersOffices/ucm193984.htm> [https://perma.cc/5ZCH-7HHN] (last visited Apr. 1, 2019). The Deputy Center Director for Clinical Science, Robert Temple, has been with the agency since 1972. *Robert Temple, M.D., Deputy Center Director for Clinical Science*, FDA, <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm374560.htm> [https://perma.cc/57NM-GRHS] (last visited Apr. 1, 2019). Dr. Temple also serves as the Acting Deputy Director of the Office of Drug Evaluation I and has served in this capacity since 1995. *Id.* Dr. Temple has been the agency’s foremost expert and, effectively, final word on matters of clinical trial design and conduct for decades. *Id.* The last director of the Office of New Drugs, John Jenkins, served at FDA for twenty-five years and ran the new drug office for fifteen years. *John K. Jenkins, MD*, GREENLEAF HEALTH, <https://www.greenleafhealth.com/team/john-k-jenkins-md/> [https://perma.cc/4PQ9-A5FJ] (last visited Apr. 1, 2019).

228. See Yoav Dotan, *Making Consistency Consistent*, 57 ADMIN. L. REV. 995, 1000–01 (2005) (arguing that consistency is “fundamental” to the notion of “rationality” in administrative decision making, that it is “congruent with the need to protect reasonable expectations and reliance interests,” and that inconstancy “may signal serious flaws in the administrative process”).

229. Anna B. Laakmann, *A Property Theory of Medical Innovation*, 56 JURIMETRICS 117, 149, 156 (2016) (describing the FDA as “an information intermediary, not simply a market

have noted that the gatekeeping mechanism requires that clinically meaningful information be generated in the first instance.²³⁰ A firm must perform laboratory, animal, and clinical trials to overcome the regulatory barrier to entry.²³¹ The barrier to entry combined with the new drug standard ensures that this information is created. But the mechanism plays another information-mediating role that others may not have fully appreciated. It ensures the disclosure of information and provides leverage for regulation of that disclosure.

When the FDA approves a new drug, it also approves the drug's "labeling" for doctors. This document describes the drug's approved indications (the diseases it treats), its clinical pharmacology and efficacy (as determined from the adequate and well controlled studies), and its safety (from all relevant sources).²³² And physicians use this document when making individualized benefit-risk assessments as part of their medical practice.²³³ The document is long and detailed—as many as thirty pages, single-spaced, and 30,000 words or more—and the FDA must approve every word. The format is standardized, and the FDA regulations and guidance govern what must, may, and may not appear in each section.²³⁴ For example, the Clinical Studies section must describe the clinical studies that will help a doctor understand how to use the drug safely and effectively—their design, the study population, their endpoints, and their results.²³⁵ The Clinical Pharmacology must explain the

gatekeeper").

230. Eisenberg, *supra* note 22, at 370 (pointing out the new drug framework ensures "information production"); Kapczynski, *supra* note 22, at 2365 (explaining that the gatekeeping mechanism ensures the generation of information and, in particular, negative as well as positive information about a proposed new drug).

231. *See supra* note 77.

232. *See* Expert Report of Dr. David W. Feigal, Drake v. Allergan at 2–3, 2014 WL 7877383. Dr. Feigal held leadership positions in both the drug center and the device center at the FDA. *Id.* at 2–3.

233. *Id.* at 13.

234. 21 C.F.R. § 201.57 (2018); e.g., U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY, INDICATIONS AND USAGE SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT 2 (2018); U.S. FOOD & DRUG ADMIN., GUIDANCE, LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—IMPLEMENTING THE PLR CONTENT AND FORMAT REQUIREMENTS 1 (2013); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DOSAGE AND ADMINISTRATION SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT 1–2 (2010); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ADVERSE REACTIONS SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT 9 (2006).

235. 21 C.F.R. § 201.57(c)(15).

drug's mechanism of actions, its biochemical or physiologic effects in the body, and how the drug is absorbed, distributed, metabolized, and excreted.²³⁶ Many sections present the drug's safety data, sorting the most serious from the less serious, and drawing more attention to the former.²³⁷

A firm proposes labeling in its application, but in the end, the FDA holds the pen, and it will not approve a drug until the applicant agrees to labeling that agency scientists believe truthfully and accurately describes the safety concerns associated with the drug and the results of the trials performed.²³⁸ The gatekeeping function thus improves the flow of clinically meaningful information to decision makers—the doctor and, through the doctor, the patient—by ensuring that labeling disclosures meet a particular standard governing the scope, level of detail, substantiation, word choices, and format.²³⁹ Doctors can rely on the fact that risks appearing in the Warnings and Precautions section of any drug's labeling met the same evidentiary and severity threshold, for instance; they can compare the labeling of two drugs in the same class and draw inferences from wording differences; and they can assume that words mean the same thing across drug labeling.²⁴⁰ The FDA's preapproval role promises consistency in judgment calls and uniformity in approach.²⁴¹ In contrast, prescription drugs outside the new drug framework are subject to a different labeling regulation, and the FDA does not review and approve their labeling.²⁴²

The approval process itself generates valuable information for doctors and the public, because agency reviewers prepare detailed

236. *Id.* § 201.57(c)(13).

237. *Id.* § 201.57(c)(1), (5)–(9).

238. 21 U.S.C. § 355(d) (Supp. V 2018).

239. See FDA MEMO, *supra* note 28, at 10–11 (asserting that labeling review and approval is essential to inform safe and effective prescribing practices and use of new drugs and that there is “significant potential for harm to patients” without accurate information about safe and effective use).

240. The current labeling regulation, which dates to 2006, represents the culmination of a fourteen-year administrative process—in which broader public health community and prescribing physicians participated—to modernize and simplify labeling and ensure it “optimally” communicated information to prescribers. 71 Fed. Reg. 3922 (Jan. 24, 2006); 65 Fed. Reg. 81,082, 81,083 (Dec. 22, 2000).

241. *But see* Jonathan Darrow, *Pharmaceutical Gatekeepers*, 47 IND. L. REV. 363, 368 (2014) (complaining that clinical effectiveness information is: (1) “buried in section fourteen,” (2) “often written in such a way that it is difficult for doctors (let alone patients) to understand,” and (3) “not standardized even among drugs within the same category”).

242. 21 C.F.R. § 201.56(b).

memoranda of their findings and conclusions.²⁴³ These include a medical review of the clinical trials and a chemistry review (of the raw materials, manufacturing process, analytical testing, and specifications).²⁴⁴ They also include a review prepared by agency statisticians, who assess the design of the company's clinical trials and the company's interpretation of trial results *and* conduct their own analyses of the raw data.²⁴⁵ When the FDA approves a drug, it posts these memoranda online, with the company's proposed labeling, a summary memo that discusses any disagreements with the company and how they were resolved, and the decision memorandum from the senior agency official with approval authority.²⁴⁶

Although the gatekeeping mechanism ensures that information about the safety and effectiveness of drugs is generated and disclosed, it does not *encourage* the creation of high quality evidence.²⁴⁷ That is, the mechanism does nothing to ensure that a firm will invest its resources in developing a promising new drug for the market rather than investing in a widget without a barrier to entry. If the new drug barrier is too high it could *discourage* the creation of evidence, causing firms to shutter research and development programs.²⁴⁸ The best way to describe the information-mediating aspect of the FDA's gatekeeping function is thus to say it ensures that high quality information about a new drug is generated and disclosed. It does not *encourage* anyone to invest in generating the information or bringing that drug to market. Something else must do that.

Our legal system uses statutory exclusivity for this purpose.²⁴⁹ Data exclusivity is an inherent structural feature of any govern-

243. See U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, 21ST CENTURY REVIEW PROCESS DESK REFERENCE GUIDE 1, 3–4 (2017), <https://www.fda.gov/downloads/aboutfda/centersoffices/cder/manualofpoliciesprocedures/ucm218757.pdf> [<https://perma.cc/H8DR-V73M>].

244. *E.g.*, U.S. FOOD & DRUG ADMIN., DRUG APPROVAL PACKAGE: TYSABRI (NATALIZUMAB) (2004), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/125104s000_natalizumab.cfm [<https://perma.cc/Y34W-AVRR>].

245. *Id.*

246. 21 U.S.C. § 355(l) (2012).

247. *But see* Kapczynski, *supra* note 22, at 2358 (arguing that, “[b]y controlling marketing, the FDA . . . encourages the creation of high-quality evidence about medicines that is not biased toward positive results” (emphasis added)).

248. See Lietzan, *supra* note 7, at 44 n.11 (noting companies that have shut down neuroscience programs).

249. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH.

ment licensing scheme that requires premarket testing and permits later applicants to rely on the work done by earlier applicants.²⁵⁰ The law must say when the competitors may do so. If policymakers allowed a firm's competitors to rely on its research immediately and bring their copies to market with an investment of a few million dollars at most—if they provided no period of data exclusivity—no rational firm would invest in the new drug approval process. Data exclusivity is therefore both an inherent structural feature and, depending on its length, a key way to encourage companies to invest in clinical research.²⁵¹

3. The New Drug Leash

The new drug authorities in current law also provide a mechanism for permanent regulatory oversight, allowing the government to impose—and efficiently enforce—requirements designed to ensure that marketed drugs *remain* safe, effective, and accurately described. For example, they ensure a continuing flow of clinically valuable information to the FDA. Companies with approved applications must file adverse drug experience reports with the agency.²⁵² Every company with an approved application must review adverse drug experience information received from any source and must report serious unexpected events within 15 days.²⁵³ For the first three years after approval, it must also submit quarterly reports summarizing and analyzing the other adverse drug experiences; from that point it files an annual report.²⁵⁴ The

TELECOMM. & TECH. L. REV. 345, 360 (2007) (calling exclusivity “FDA-administered proprietary rights in regulatory data, awarded to encourage particular kinds of innovation”); Henry G. Grabowski et al., *The Roles of Patents and Research and Development Incentives in Biopharmaceutical Innovation*, 34 HEALTH AFF. 302, 302 (2015) (“Patents and other forms of intellectual property protection are generally thought to play essential roles in encouraging innovation in biopharmaceuticals.”); Ben Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 511 (2009) (“Pharmaceutical companies therefore rely on a lengthy period of market exclusivity to recoup their investments in developing new drugs.”).

250. Lietzan, *supra* note 137, at 105–07.

251. *Id.* Orphan exclusivity similarly rewards socially desirable research and development that policymakers concluded would not otherwise be done. See H.R. REP. NO. 97-940, pt. 1, at 6 (1982).

252. 21 C.F.R. § 314.80 (2018). The adverse event reporting requirement stems from the provision of statute that requires a marketing application in the first instance. 21 U.S.C. § 355(k) (2012 & Supp. V 2018). Drugs that are *lawfully* marketed as not-new drugs without approved applications—most nonprescription drugs—are subject to adverse event reporting requirements under another provision of the statute. *Id.* § 379aa (2012).

253. 21 C.F.R. § 314.80(c)(1).

254. See *id.* § 314.80(c)(2). Annual reports summarize new information that might affect

substantial safety database in the marketing application provides the FDA with context for assessing the significance of any safety signals emerging from the marketplace. Failure to submit adverse event reports triggers the FDA's civil and criminal enforcement powers.²⁵⁵

In contrast, although the FDA has issued regulations requiring the sellers of unapproved prescription drugs to file adverse drug experience reports,²⁵⁶ the statutory basis for these regulations is shaky and the agency's enforcement power limited. The agency relies on the statutory provision that governs drugs with approved applications.²⁵⁷ It reasons that these unapproved drugs are subject to this provision because they *should* have approved applications.²⁵⁸ But the FDA must rely on the leverage of enforcement discretion: a company that enjoys "deferred enforcement" may be "immediately subject to action" if it does not submit these adverse event reports.²⁵⁹ In other words if a company marketing an unapproved prescription drug fails to submit adverse event reports, the FDA has only the option to take the enforcement action that it eschewed before: arguing that the drug is really a "new drug" lacking approval.²⁶⁰ This would entail litigating the company's claim of an exemption, which could be fact-intensive and resource-draining.²⁶¹ Current law does not allow the agency to take enforcement action simply for failure to submit the reports. The fact that the FDA has *only* the nuclear option may prevent it from responding to reporting violations that *would* be corrected if the drug fell under its new drug authorities. And even if the agency *did* receive adverse event reports from these sellers, it would lack a premarket safety database to place the signals in context.

the drug's safety, effectiveness, and labeling. *Id.* § 314.81(b)(2). They also include distribution data, copies of any unpublished and published laboratory and animal studies of the drug in the last year, published clinical trials, and summaries of complete unpublished clinical trials. *Id.*

255. 21 U.S.C. § 331(k) (2012) (deeming "failure to . . . make any report . . . required under section . . . 355(k)" a prohibited act under the FDCA).

256. 21 C.F.R. § 310.305(a).

257. 50 Fed. Reg. 11,478, 11,478 (Mar. 21, 1985) (citing 21 U.S.C. § 355(k), which provides that "[i]n the case of any drug for which an approval of an application filed under subsection (b) or (j) is in effect, the applicant shall establish and maintain such records . . . as the Secretary may . . . prescribe").

258. *Id.* at 11,480.

259. *Id.*

260. See 21 U.S.C. § 355(a) (2012).

261. See *supra* note 165–76 and accompanying text.

If a drug falls under the FDA's new drug authorities, the agency also retains control over the drug's labeling for doctors. Any change must be reviewed by the agency, and all but ministerial changes must be approved—often preapproved.²⁶² The FDA may also require changes in the labeling to reflect new safety information, such as information emerging from adverse event reporting.²⁶³ The FDA may also require additional research, including a randomized controlled clinical trial, to explore a safety signal.²⁶⁴ In addition to pursuing criminal sanctions, the agency may impose a fine for refusing these orders, up to \$1 million for every 30-day period while the company refuses.²⁶⁵ Ultimately the new drug authorities give the FDA an efficient mechanism for removing the drug from the market if the new information shows the drug's benefits in fact do not outweigh its risks.²⁶⁶ In contrast, if the FDA became concerned that the labeling of an unapproved prescription drug did not adequately disclose new safety information, it could not order the company to add the information to the labeling. Nor could it remove the drug for lack of safety. It could, in theory, seize the product and seek an injunction (or prosecute) on the theory that the labeling was "false or misleading," *if* it could satisfy that standard on these facts.²⁶⁷ Or it might seek an injunction on the theory that the drug's labeling lacked adequate directions for use, *if* the facts supported this theory.²⁶⁸ Otherwise, it would have to take fact-intensive and

262. 21 C.F.R. § 314.70(a)–(d) (2018).

263. 21 U.S.C. § 355(o)(4)(A) (2012).

264. 21 U.S.C. § 355(o)(3) (2012). The FDA may also impose use and distribution restrictions to manage a safety risk identified after approval. *Id.* § 355-1(a)(1). Failure to comply with a requirement in this risk management plan renders a drug both "misbranded" under section 502 of the FDCA and in violation of section 505 of the FDCA. *Id.* §§ 352(y), 355(p).

265. 21 U.S.C. § 333(f)(4) (2012) (civil money penalties for violating a labeling change order under section 505(o)(4)); *id.* § 331(d) (prohibiting the introduction into interstate commerce of any article in violation of section 505); *id.* § 333(a) (criminal prosecution for violating section 301); *id.* § 352(z) (deeming an approved drug misbranded if the application holder violates a labeling change order).

266. 21 U.S.C. § 355(e) (2012) (permitting withdrawal of approval on safety and effectiveness grounds); *id.* § 355-1 (2012 & Supp. V 2018) (permitting imposition of use and distribution restrictions if necessary to ensure the drug's benefits outweigh its risks).

267. The FDA might argue that the labeling was misleading by omission. 21 U.S.C. § 321(n) (2012).

268. 21 C.F.R. § 201.100(c)(1) (requiring that prescription drug labeling include "any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely" so that the drug may be exempt from section 502(f)(1) of the FDCA, which otherwise would require adequate directions for a lay person's use, something that no prescription drug can satisfy); 21 U.S.C. § 352(f)(1) (2012) (requiring adequate directions for use in all drug labeling); 21 C.F.R. § 201.5 (defining this to mean adequate directions for lay use).

resource-draining enforcement action to remove the drug from the market, on the theory that the drug was really an unapproved new drug.²⁶⁹

If a drug falls under the FDA's new drug authorities, the agency also has a tighter rein on the drug's manufacturing processes. A marketing application describes the composition, manufacture, and specifications of both the active ingredient and finished product.²⁷⁰ It describes how the active ingredient is synthesized (or isolated from a natural source) and purified, and describes how its identity, strength, quality, and purity are ensured.²⁷¹ It provides comparable information about other ingredients and components used in the manufacturing process, and it includes a step-by-step description of the process.²⁷² Premarket review usually includes a preapproval inspection of the manufacturing facility, to (1) determine whether the firm has sufficient control over its commercial manufacturing operations and (2) verify that the manufacturing, processing, and analytical methods in use conform to what appears in the application.²⁷³ The FDA may not approve a marketing application that does not assure compliance with current good manufacturing practices, and it may withhold approval upon a failed inspection.²⁷⁴

Even after a drug's approval, the firm may not make any change to the manufacturing process without assessing the effect of the change and in many cases submitting a supplemental application to the agency.²⁷⁵ Major changes will require preapproval and sometimes even clinical data.²⁷⁶ Firms with approved applications also

269. 21 U.S.C. § 355(a) (2012).

270. 21 U.S.C. § 355(b)(1)(C); 21 C.F.R. §§ 601.2(a), 314.50(d)(1).

271. 21 U.S.C. § 355(b)(1)(C); 21 C.F.R. §§ 601.2(a), 314.50(d)(1).

272. 21 U.S.C. § 355(b)(1)(D); 21 C.F.R. §§ 601.2(a), 314.50(d)(1).

273. U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, PROGRAM 7346.832, at 12 (2010)

274. *Id.* at 2; *see also* 21 U.S.C. § 355(d)(3) (Supp. V 2018).

275. 21 U.S.C. § 356a (2012) (governing manufacturing changes for drugs that are the subject of approved marketing applications); 21 C.F.R. §§ 314.70, 601.12 (requiring approval of any manufacturing change); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA 5–7 (2004) (describing applicant's obligation to assess impact of changes and submit information supporting a change).

276. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA 11–16 (2004); U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: CHEMISTRY, MANUFACTURING, AND CONTROLS CHANGES TO AN APPROVED APPLICATION: CERTAIN BIOLOGICAL PRODUCTS 7–9 (2017) (describing agency assessment of change and need for comparability protocols); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DEMONSTRATION OF COMPARABILITY OF HUMAN BIOLOGICAL PRODUCTS, INCLUDING

have reporting obligations tied to emerging manufacturing issues. For example, the holder of a new drug application has three days to tell the FDA that a batch of distributed product failed to meet a specification in its marketing application.²⁷⁷

In contrast, the FDA has only the basic current good manufacturing practice authorities over unapproved new drugs—and not even this authority over compounded medicines.²⁷⁸ Thus it can inspect the manufacturers and take enforcement action, labeling the drugs adulterated, if it finds a violation.²⁷⁹ The new drug authorities give the FDA more information, more opportunities for enforcement action, and more leverage.

B. *Assessing the FDA's New Drug Authorities*

As a historical matter, the new drug authorities can be understood as responding to problems confronting policymakers.²⁸⁰ For example, Congress enacted the basic licensure statute for biologics in 1902 after the deaths of children in St. Louis and Camden, New Jersey, from smallpox vaccine contaminated with tetanus.²⁸¹ This gave the government an opportunity to evaluate a company's manufacturing before the company released its product. Congress enacted the basic statute for drugs in 1938 on the heels of a tragedy in which an inadequately tested sulfanilamide preparation killed more than one hundred people, including many children.²⁸² The agency's inability to pursue the manufacturer for nothing but "misbranding"—because it had called its drug an "elixir" though it

THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS (1996) (explaining that comparability testing may include clinical pharmacology, safety, and efficacy studies).

277. 21 C.F.R. § 314.81(b)(1); *see also id.* § 600.14 (imposing a similar obligation on the holder of a biologics license).

278. 21 U.S.C. § 353a(a) (2012 & Supp. V 2018) (exempting compounded drugs from § 351(a)(2)(B)).

279. 21 U.S.C. § 374(a)(1) (2012) (authorizing the FDA to inspect any factory, warehouse, or establishment in which drugs are manufactured, processed, packed, or held for introduction into interstate commerce or after this introduction); *id.* § 351(a)(2)(B) (deeming a drug adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice").

280. *See* LAMBERT, *supra* note 25, at 14–15.

281. PAUL OFFIT, *THE CUTTER INCIDENT* 36, 59 (2005); Pub. L. No. 57-244, 32 Stat. 728 (1902).

282. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938); DANIEL CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* 85–92 (2010).

lacked alcohol—made a compelling case for government to act as gatekeeper.²⁸³

The 1962 amendments—adding the preapproval requirement—trace in part to the thalidomide catastrophe; more than 10,000 children in forty-six countries were born with severe deformities after their mothers used thalidomide during pregnancy.²⁸⁴ The 1962 law created the modern framework in which the FDA requires substantial evidence of effectiveness and regulates how the evidence is described in labeling for doctors.²⁸⁵ Imposing the new drug standard as a barrier to entry responded to concerns that physicians were making treatment decisions—and some companies were bringing their medicines to market—based on observational data, anecdote, personal opinion, and poorly run trials.²⁸⁶ Legislators were also concerned about inefficient dissemination of information in the market and the possibility that doctors prescribed medicines before learning the medicines were unsafe or ineffective.²⁸⁷

283. *Letter from the Secretary of Agriculture Transmitting in Response to Senate Resolution No. 194: A Report on Elixir Sulfanilamide-Massengill*, S. DOC. NO. 124 at 1, 9, reprinted in 5 A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND ITS AMENDMENTS 895–96 (1979) (“[T]he only basis of action under the Food and Drugs Act against the interstate distribution of the ‘elixir’ was the allegation that the word implies an alcoholic solution, whereas the product was a diethylene glycol solution . . . [and] [t]o protect the public from drugs which, like the ‘elixir’ are dangerous because of their inherent toxicity, it is the Department’s recommendation that legislation be enacted to provide . . . [l]icense control of new drugs . . .”).

284. CARPENTER, *supra* note 282, at 213–97.

285. See Lietzan, *supra* note 7, at 54–56. Some suggest that the gatekeeping function responds to information asymmetry, which occurs when consumers have less information about a product than sellers have. *E.g.*, Ariel Katz, *Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry*, 14 MICH. TELECOMM. & TECH. L. REV. 1, 8 (2007). But this is not quite right. Without the new drug paradigm in place there would be only a modest amount of information asymmetry when a substance is first discovered and its biological potential identified. The case for government leverage to ensure and regulate disclosure of information is strongest only *after* the barrier to entry and new drug standard have required the generation of this information in the first instance.

286. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 630 (1973) (“The ‘substantial evidence’ requirement reflects the conclusion of Congress, based upon hearings, that clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy.” (footnote omitted)); *id.* at 619 (“The hearings underlying the 1962 Act show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.”); Brief for the Petitioners, *Thompson v. W. States Med. Ctr.*, No. 01-344 (Dec. 13, 2001) (“[B]ecause hundreds of new drugs were introduced each year, and information about their effectiveness took considerable time to develop and (when published at all) was scattered among hundreds of medical journals, physicians were unable to ascertain whether the drugs they were prescribing were effective.”).

287. See S. REP. NO. 87-1744 at 33 (1962) (views of Sens. Kefauver, Carroll, Hart, Dodd, and Long) (“Because of this lack of information and also because of the pressures engendered

Later changes to the FDA's new drug authorities have also responded to challenges facing policymakers. For instance, policymakers created mechanisms for "accelerated approval" in the 1990s in response to pressure placed on approval timelines by the AIDS crisis.²⁸⁸ This allows the FDA to approve a medicine intended for treatment of a serious or life-threatening disease based on a trial showing effectiveness at achieving a "surrogate" endpoint, which predicts but does not prove clinical benefit.²⁸⁹ And Congress gave the FDA the power to require labeling changes and clinical testing after approval after a series heavily prescribed drugs turned out to be less safe than thought at the time of approval.²⁹⁰

1. Data Generation Without a Barrier to Entry

Access-before-evidence scenarios provide a powerful rejoinder to any argument that, without a federal gatekeeper, competitive market pressures and liability exposure would ensure that new medical treatments are subjected to modern rigorous safety and effectiveness trials.²⁹¹ At least for unapproved prescription drugs, compounded drugs, and fecal microbiota, this proposition is manifestly false. The sellers of unapproved prescription drugs have not done the type and amount of testing that would satisfy the new drug standard.²⁹² If a firm had enough data to support approval of

by the [fact that applications took effect automatically unless the agency objected within sixty days], the FDA has released too many drugs for sale only to have to take them off the market later as new information concerning side effects develops.”)

288. See Lietzan, *supra* note 7, at 63 n.116, 68–69; see also Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America's Drug Constitution*, 42 AM. J.L. & MED. 687, 728–29 (2016) (explaining the development of accelerated approval in response to the AIDS crisis).

289. 21 U.S.C. § 356(c)(2)(A) (2012).

290. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (codified as amended in scattered sections of 21 U.S.C.).

291. E.g., Harold E. Glass et al., *Are Phase 3 Clinical Trials Really Becoming More Complex?*, 49 THERAPEUTIC INNOVATION & REG. SCI. 852, 857 (2015) (suggesting that companies extend their premarket testing to make comparative effectiveness and cost effectiveness claims using data that are not required for approval); Krauss, *supra* note 27, at 466 (“Tort and products liability law can and do result in increased information output from manufacturer to consumer precisely in those instances where such output might otherwise be insufficient.”).

292. When the FDA reviewed the data related to the effectiveness of new drugs that had reached the market between 1938 and 1962, it found that 70% of the claimed uses were not supported by substantial evidence, and only 11% of marketed drugs were effective for all claimed uses. Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 621 (1973); see also Temple, *supra* note 224, at 1902 (“Where such trials are not required, however, they are far less often carried out.”). Dr. Temple gives many examples of alternative medicines that are only infrequently the subject of controlled studies. *Id.*

a marketing application, it would submit the data to take advantage of the FDA's offer to clear the competition from the market.²⁹³ Presumably these sellers have a basis for confidence in their merchandise (because it would not otherwise be rational for them to market the merchandise), but there is evidently a gap between the evidence on which they rely and the evidence that federal regulators expect for new drug approval.²⁹⁴ Products liability pressure and competitive market pressure may remove medicines that harm patients because of toxicity (and perhaps those ineffective in the treatment of acute symptoms), but they are less likely to identify and remove medicines that have long-term safety risks or that are ineffective in the treatment of asymptomatic conditions or progressive or chronic conditions.

And use of fecal microbiota spread rapidly in the clinic based on rudimentary clinical evidence. The first randomized placebo-controlled trial of fecal microbiota transfer for recurrent *C difficile* infection was published only in 2016—four years *after* OpenBiome began shipping fecal microbiota around the country.²⁹⁵ The results were curious: placebo was just as effective as treatment at one of the two trial sites.²⁹⁶ Testing by academic researchers has been idiosyncratic; they use their own protocols and often their own materials, pursuing their own hypotheses. Many trials are small and thus less reliable than the larger trials supporting a marketing application would be.²⁹⁷ Some are open-label, meaning that the patients and investigators know which treatment each patient receives, which introduces the potential for bias.²⁹⁸ Some trials have

293. See *supra* Part II.A.

294. But the pharmacies compounding hydroxyprogesterone caproate performed no testing of their products and simply took comfort from a single article in the *New England Journal of Medicine* relating to a formulation with the same active ingredient. See *supra* Part II.B.

295. See Colleen R. Kelly et al., *Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection*, 165 ANNALS INTERNAL MED. 609, 609 (2016); *supra* note 61 and accompanying text.

296. In Rhode Island, the cure rate was 90% with treatment and 42.9% with placebo, but in New York the rates were 91.7% and 90% respectively. Kelly et al., *supra* note 295, at 612. As a placebo, investigators used the patient's own stool (removed and replaced). *Id.* at 615.

297. *E.g.*, *id.* at 609, 615 (reporting a 95% confidence interval of 69.2% to 97.8% effectiveness in a trial of forty-six patients).

298. See, *e.g.*, Dina Kao et al., *Effect of Oral Capsule- vs. Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent Clostridium difficile Infection*, 318 JAMA 1985, 1986, 1992 (2017). This trial also used a noninferiority design and lacked an arm of patients who did not receive fecal microbiota, so it did not produce information on the efficacy of fecal microbiota as compared to other interventions. *Id.* at 1992.

failed.²⁹⁹ And there are serious questions about the method of subject selection in some trials. The startling results in the 2016 trial raised the question whether, as the study authors themselves admitted, “[s]ome of the[] patients could have been cured before enrollment.”³⁰⁰

To be clear, the concern is not that companies would market the modern equivalent of “snake oil”—only that they would not produce the quantity and quality of information that the FDA requires when it applies the new drug provisions. And one may well wonder whether the safety and effectiveness standard applied by the FDA is *too high*—whether the information we have for these treatments (and would have for other medicines without the new drug authorities) is *enough*. That is a philosophical question, rather than a scientific question. It invites the policymaker to consider the purpose and the cost of new drug testing—and the goals that are achievable with a premarket approval requirement.

2. Certainty, Delay, and Error

The most that regulators could ask for is a drug as to which the benefits exceed the risks for most people most of the time. And the notion that the benefits of a medical intervention should generally outweigh its risks is the prevailing sentiment in the scientific, medical, and public health communities. Even those who think that medicines should be available in the market regardless of their overall benefit-risk profile would agree that an individual person, acting rationally, will select a medicine only if the benefits to him exceed the costs. The problem is that we can never know everything there is to know about the clinical effects of a new medicine.³⁰¹ We can never have complete certainty that a drug’s benefits outweigh its risks. And there is always a possibility of mistake.

299. See, e.g., Susy S. Hota et al., *Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent Clostridium difficile Infection: An Open-Label, Randomized Controlled Trial*, 64 *CLINICAL INFECTIOUS DISEASES* 265, 265 (2017) (noting that trial was discontinued because interim analysis showed futility: a single fecal transfer by enema was not significant different from oral vancomycin).

300. Kelly et al., *supra* note 295, at 617.

301. See INST. OF MED. OF THE NAT’L ACADS., *PREVENTING MEDICATION ERRORS* 56 (Philip Aspden et al. eds., 2007) (noting that “only the most profound and overt risks and side effects that occur immediately after taking a drug can be detected” and that “[r]isks that are medically important but delayed . . . may not be revealed prior to marketing”).

The primary concern with the gatekeeping function at the FDA is the risk of what is called a “Type 1 error” in statistics—a false negative—meaning rejection of a medicine that is in fact safe and effective. Many believe that the FDA routinely commits Type 1 errors, that it is conservative because of criticism when it commits Type 2 errors—false positives, approval of drugs that are not safe and effective.³⁰² Although complete certainty about a drug’s effects is impossible, more testing will always provide more certainty. But more testing delays the FDA’s decision on the application. And when delay is followed by approval (that is not erroneous), the delay had a cost; in a sense, there was a kind of Type 1 error—rejection, for a time, of a drug that was safe and effective. Moreover, eventually the cost of delay would become too high: decades of testing might provide an extremely high level of certainty for the decision, but if policymakers required decades of testing many drugs would not be developed, and those developed might be unacceptably expensive.³⁰³ At some point the benefits from more information are unlikely to be worth their cost.³⁰⁴

Assuming a gatekeeper, the primary choice for policymakers is how much testing will be needed before regulators rule on marketing applications. This changes the trade-off among Type 2 errors, Type 1 errors, and costs of delay. Making the decision with fewer data or lower quality data reduces the cost of delay and Type 1 errors (failure to approve safe and effective drugs) but would increase the risk of Type 2 errors (approval of drugs that are not safe

302. Professors Grabowski and Vernon explain that an FDA official who “approves a drug subsequently shown to be not safe or effective stands to bear heavy personal costs” while the “costs of rejecting a good drug are borne largely by outside parties (drug manufacturers and sick patients who might benefit from it).” GRABOWSKI & VERNON, *supra* note 27, at 10; *see also* Laakman, *supra* note 208, at 320 (“FDA conservatism stems from the fact that, while the agency is invariably pilloried when an approved drug is later discovered to possess previously unknown harms, the agency rarely faces public rebuke for failing to timely approve promising new therapies.”); Daniel P. Carpenter, *The Political Economy of FDA Drug Review: Processing, Politics, and Lessons for Policy*, 23 HEALTH AFF. 52, 55 (2004) (“For most of the FDA’s history, Type I errors have been more visible than Type II errors.”). *But see* Temple, *supra* note 224, at 1887 (“This is so much the conventional wisdom that even suggesting that it is an unsupported myth seems almost impertinent. But myth it is and no one has ever even attempted to demonstrate its truth, either through an analysis of FDA decisions or, at least, by a comparison of FDA decisions with decisions by other regulatory authorities.”).

303. *See* GRABOWSKI & VERNON, *supra* note 27, at 12.

304. Carpenter, *supra* note 302, at 55 (“Some uncertainty will always remain in drug review, and the marginal benefit of more trials and more delay tends to decline as the drug review gets longer.”).

and effective).³⁰⁵ Requiring more data before decision, in contrast, increases delay costs but reduces the risk of both Type 1 and Type 2 errors.

Concerns about the cost of and delay from premarket testing, combined with its inability to provide certainty about a drug's benefits and risks, lead some to propose that policymakers render decisions based on much less evidence.³⁰⁶ Consider one proposal: that policymakers require only safety testing before market entry.³⁰⁷ This is simply a recommendation that policymakers agree to a lower level of confidence that a drug's benefits outweigh its risks—for two reasons. First, safety is always relative to something else.³⁰⁸ A debilitating side effect might be acceptable in a medicine for treating metastatic cancer but unacceptable in a medicine for treating indigestion. Second, early trials may provide only basic information about a drug's toxicity and bioavailability at low doses in healthy humans.³⁰⁹ A complete understanding of the drug's safety profile emerges only over many years of testing as well as

305. Many drugs fail in the second and even third phase of clinical testing before approval. Chi Heem Wong et al., *Corrigendum: Estimation of Clinical Trial Success Rates and Related Parameters*, *BIostatistics*, Nov. 14, 2018, at 2 tbl.1 (finding that only 13.8% of all drug development programs lead to approval, that nearly 80% of drugs in phase 2 will not be approved, and that around 40% of drugs in phase 3 will not be approved); Chi Heem Wong et al., *Estimation of Clinical Trial Success Rates and Related Parameters*, *BIostatistics*, Jan. 31, 2018, at 5, 9 tbl.1.

306. R. Alta Charo, *Speed Versus Safety in Drug Development*, *FDA IN THE TWENTY-FIRST CENTURY* 251, 255 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015) (explaining that the “inherent limitations” of traditional premarket testing—“which for reasons of practicality, finance, and diminishing returns will often be neither long enough, nor large enough, nor demographically comprehensive enough” to achieve kind of certainty the public expects—have prompted calls for “far less time in premarket testing” and “enhanced post-market surveillance”).

307. *E.g.*, S. 1956, 109th Cong. (2005); Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBs*, 96 *GEO. L.J.* 559, 579 (2008) (arguing that the agency should apply its new drug standard in an advisory capacity—at least after drugs complete phase 1 testing—but certifying their safety and effectiveness, but not barring any from the market for lack of effectiveness); Andrew von Eschenbach, *Medical Innovation: How the U.S. Can Retain Its Lead*, *WALL STREET J.* (Feb. 14, 2012), <https://www.wsj.com/articles/SB10001424052970203646004577215403399350874> [<https://perma.cc/44PN-2BMN>] (arguing that the FDA should approve drugs “based on safety and leave efficacy testing for post-market studies”).

308. Even the “safety only” applications between 1938 and 1962 contained efficacy data, and the FDA considered benefit when permitting new drugs to market. Robert Temple, *Development of Drug Law, Regulations, and Guidance in the United States*, in *GOVERNMENTAL REGULATION OF DRUGS* 1643, 1644 (Paul L. Munson et al. eds., 1994) (explaining that “the required showing of safety in the 1938 law . . . always had some elements of weighing benefit against risk”).

309. 21 C.F.R. § 312.21 (2018).

commercial marketing.³¹⁰ This proposal, in other words, means making the benefit-risk call with fewer data. Doing so would reduce delay costs and Type 1 errors, but increase Type 2 errors (approval of drugs that are not safe and effective).

Those advancing the proposal have an important insight: that the cost-minimizing solution may depend on the context. The risk of Type 2 error may be less concerning to patients facing imminent death, because delay could be catastrophic.³¹¹ In this context, permitting patient access earlier—with less certainty about the drug's benefit-risk profile—may minimize overall costs. In other contexts, later access might minimize the costs. Our legal system currently addresses this context dependence by modifying access restrictions *within* the new drug framework. The FDA may grant earlier approval of medicines intended to treat serious or life-threatening diseases, based on trials using endpoints that *predict* clinical benefit.³¹² This reduces delay but introduces greater uncertainty about the medicine's ultimate clinical profile—increasing the risk of Type 2 error.³¹³

3. Efficient Information Mediation

The gatekeeping mechanism allows the government to require a particular quality and quantity of clinical testing. Policymakers could dispense with everything but basic safety testing, however, and allow companies to choose what sort of effectiveness testing they wished to perform. The gatekeeping also gives the FDA leverage to review those data, reach conclusions, and dictate how the conclusions are communicated to doctors. Private sector actors could perhaps perform a similar role—reviewing whatever data *are* generated, reaching conclusions, and sharing them with the public.³¹⁴ But a private solution is unlikely to lead to be as efficient or to lead to informed decision-making.

310. Cf. INST. OF MED. OF THE NAT'L ACADS., *supra* note 301, at 56.

311. Epstein, *supra* note 307, at 579.

312. See *supra* note 289 and accompanying text.

313. Lietzan, *supra* note 7, at 66–68.

314. See Richard A. Epstein, *Against Permatitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 23–31 (2009) (calling for professional medical organizations to review marketing application data); Epstein, *supra* note 307, at 574 (“[T]he FDA should get out of the banning business and stay in the warning business.”); see also Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48

Although it is unlikely companies would generate the same amount of data without a mandate to do so,³¹⁵ if they did the volume of work for private reviewers would be staggering. The FDA receives seventy or eighty full applications per year.³¹⁶ The data supporting each new medicine can fill 500,000 or more pages,³¹⁷ and the agency typically assigns a large team of scientific and regulatory experts who can take most of a year to sift through the data, conducting their own statistical analyses, and evaluating the medicine's risks and benefits.³¹⁸ The total cost of reviewing drug applications in a given year—over \$1.2 billion—is profound.³¹⁹ Some of this work is supported by general tax revenues, but a substantial amount—\$905 million out of \$1.2 billion in 2017—is supported by fees paid by applicants themselves.³²⁰ Perhaps private entities could review these data more quickly and cheaply, but the funding mechanism for such an exercise is unclear.

A private reviewer would also lack the decades of experience with marketing applications, expertise assessing differing types and qualities of clinical data, and institutional memory that the FDA can bring to its assessments.³²¹ And the leverage created by

RUTGERS L. REV. 883, 987–1016 (1996) (discussing proposals to shift agency responsibilities to private parties).

315. See *supra* Part III.B.1.

316. Prescription Drug User Fee Rates for Fiscal Year 2019, 83 Fed. Reg. 37,504, 37,506 (Aug. 1, 2018).

317. E.g., Iain S. Bruce, *New Standards Cut Drug Paperwork*, TODAY'S CHEMIST WORK, <https://pubs.acs.org/subscribe/archive/tcaw/09/i11/html/11bruce.html> [<https://perma.cc/KV/C4-ERAN>] (last visited Apr. 1, 2019).

318. The agency reviews applications for priority new drugs within eight months (sixty days to “file” the application plus six months of review) and applications for standard new drugs within twelve months (sixty days plus ten months). See U.S. FOOD & DRUG ADMIN., FY 2017 PERFORMANCE REPORT TO CONGRESS FOR THE PRESCRIPTION DRUG USER FEE ACT 6 (2017).

319. Prescription Drug User Fee Rates for Fiscal Year 2019, 83 Fed. Reg. at 37,504 tbl.2 (showing a total cost of \$1,206,657,269 in 2017).

320. U.S. FOOD & DRUG ADMIN., FY 2017 PDUFA FINANCIAL REPORT REQUIRED BY THE PRESCRIPTION DRUG USER FEE ACT AS AMENDED 13 tbl.8 (2018).

321. See Ralph F. Hall, Response, *Right Question, Wrong Answer: A Response to Professor Epstein and the “Permititis” Challenge*, 94 MINN. L. REV. HEADNOTES 50, 77–80 (2009) (explaining that the FDA has better and faster access to relevant data, superior resources, and access to expertise, that voluntary professional organizations lack); Kapczynski, *supra* note 22, at 2368–71 (describing the advantage that FDA reviewers have, as compared to organizations like the Cochrane Group, which performs meta-analyses of publicly available evidence); Aaron S. Kesselheim et al., *FDA Regulation of Off-Label Drug Promotion Under Attack*, 309 JAMA 445, 446 (2013) (noting that “FDA approval involves numerous highly skilled scientists reviewing a great deal of data for months” and arguing that “[i]t is not possible for individual prescribers to conduct the same rigorous evaluation”); Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERN. MED.

the barrier to entry contributes to the efficiency of this process by ensuring that companies perform the same type of testing, using the same types of clinical trial design and the same statistical methodologies, and then compile their applications into the same predictable modules.³²² In addition, unless a single entity reviewed and summarized the data for every medicine in the market, the private sector solution would not offer prescribing doctors the efficiency that comes from the uniform format of approved labeling, or its consistency in judgments and wording.³²³

4. More Certainty and Better Information Communication over Time

The new drug leash—post-approval oversight—imposes a burden on companies as well as the agency. In the end, the benefits of *some* post-approval requirements may not be worth their added cost. This will depend on the requirement, the benefit, and the cost. The answer might be different for the requirement that application holders submit every page of advertising and promotion at the time of first use so that FDA staff may compare the words with the drug's approved labeling than it is for the requirement that application holders submit prompt adverse event reports.³²⁴ And policy-makers could create mechanisms for some continuing oversight without the leverage of the new drug authorities. For example, they could require every firm selling drugs to file adverse event reports and give the FDA power to require labeling changes or clinical trials based on those adverse event reports. Failure to make the labeling changes or conduct the trials could be the basis for enforcement action.

295 (2016) (arguing that doctors “are not in a position to substitute for regulators” in part because “few have training in research methods”).

322. Cf. FDA MEMO, *supra* note 28, at 9 (“Although some of the assurances from independent review for a particular study can be obtained by review by non-governmental entities (such as peer review coordinated by a scientific or medical journal), the standards governing FDA review provide an assurance of data completeness, scientific rigor, and a thoroughness of evaluation that are not met by the more narrow examination of the peer review process, given the limited data typically available to and reviewed by peer review process, given the limited data typically available to and reviewed by peer reviewers, the more limited number of peer reviewers (and thus more limited areas of expertise), and the scope of a journal article.”).

323. See *supra* Part III.A.2.

324. 21 C.F.R. §§ 314.81(b)(3), 314.80 (2018).

But some aspects of post-approval authority could be hard to duplicate in a model without the leverage of the initial barrier to entry. After market entry, information about the clinical profile of a drug continues to emerge. Continued testing by the company and use by real-world patients produce information that reduces uncertainty about the drug's benefits and risks. Current law requires the company to share this information with the FDA,³²⁵ which—thanks to the approval requirement—has both a deep file on the drug and extensive experience with other drugs to place the new information in context. Although the government could authorize the FDA to consider this information and require labeling changes *without* having preapproved the drug earlier, the agency would be doing so based on less information (if no data had been submitted for market entry) or less robust information (if companies simply submitted whatever they planned to use to support therapeutic claims).

In addition, the FDA must make a new approval decision every time it receives a supplement to the marketing application. Requiring preapproval of labeling changes provides the same leverage and efficiency benefits that requiring approval of labeling provides in the first instance.³²⁶ At the same time, some decisions on supplements present another risk of error. For example, the FDA must decide how much and what type of data to require in support of a manufacturing change, and here too more data will reduce uncertainty and error but impose a cost of delay.³²⁷ The cost of Type 1 error (failure to approve a manufacturing change that would be safe and effective) may be lower in this setting than the premarket setting, because in most cases the firm would be able to keep making and selling the drug using its old process. The cost of delay would similarly be lower. Depending on the change, though, Type 1 error might deny patients access to a *safer* drug, or deny the firm an opportunity to reduce its cost of production. As a result it may make sense for policymakers to focus on minimizing Type 2 error

325. See *supra* Part III.A.3.

326. See *supra* Part III.A.3. Congress focused on this efficiency in 1962. See *Drug Industry Antitrust Act of 1962: Hearings Before the Antitrust Subcomm. of the H. Comm. on the Judiciary*, 87th Cong. 171 (1962) (“It is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse game where a firm can fool the public until the [FDA] finally catches up with him.”).

327. See *supra* Part III.A.3.

(approval of changes that would *not* be safe and effective) and thus require more data.

C. *Applying the New Drug Authorities to Access-Before-Evidence Scenarios*

Determining whether policymakers should apply the new drug authorities to access-before-evidence scenarios requires understanding what it would *mean* to apply the new drug authorities in this context. When access has preceded evidence, policymakers face three options. First, the government could refuse to consider any marketing application for a drug containing an active ingredient already available. Thus, it would not apply the new drug authorities. Second, the government could accept (and if appropriate approve) applications, but do nothing about the competing unregulated drugs containing the same active ingredient. Thus it would not apply the new drug authorities to treatments already on the market; it would turn a blind eye. Third, the government could accept marketing applications *and* apply the new drug authorities to the previously unregulated competitors. Fully applying the new drug authorities here means, in other words, placing unregulated versions of the treatment under the new drug authorities, after approving one version. It means removing them from the market until they complete marketing applications.³²⁸

The first option is not realistically under consideration and should not be, because it would invite firms to market all new medicines unlawfully at first. It is far simpler just to repeal the new drug approval provisions, which would have the same result. This part therefore considers the costs associated with the second and third option.

There is one significant cost associated with the third option—applying the new drug authorities: removing the illegal competition from the market.³²⁹ The products might be safe and effective under the FDA's new drug standard. Removing them from the

328. A fourth option would be to remove the unapproved treatments from the market proactively, before any firm has achieved new drug approval. Although the FDA lacks the resources to do this, policymakers could provide the funds if they were indifferent to the firestorm this would create. This action presents a higher risk of Type 1 error than any other option mentioned, because some unapproved prescription drugs probably *would be* found safe and effective if someone performed the testing needed.

329. Although the FDA might make a Type 2 error in approving the first company's application, the drug was already on the market, so the error imposes no (new) cost.

market does not deny patients access to treatment, however, because there is an approved version on the market. Removing them from the market means, instead, that the company with the approved application may charge supracompetitive prices for its approved drug for a time.³³⁰ Removing them imposes a barrier to entry, which these companies might choose to overcome at some risk and cost. They would not face the same risk and cost as the first applicant, because they could submit abbreviated applications showing that their products were sufficiently similar to the approved product to rely on the first applicant's research.³³¹ But they would face some risk and cost, which would be reflected in the price of their products once they rejoined the market.

But there are significant costs associated with the second option, turning a blind eye. First, policymakers should be concerned about the information available for doctors and patients considering a treatment. Consumers would have two choices: expensive approved versions of the drug for a disease, and cheap unapproved versions of the drug for the same disease. The gulf between the evidence supporting the unapproved treatments and the evidence supporting the approved drugs might be substantial.³³² And the difference between the drugs might not be clear to prescribers, who often do not realize when they have prescribed an unapproved drug in the first instance.³³³ Even if policymakers required sellers to call attention to the lack of gold standard evidence supporting their medicines, many prescribers are unjustifiably skeptical of the value of randomized controlled trials.³³⁴ And even if all prescribers were scientifically literate, they might not appreciate the gap without a close review and comparison of the studies and data supporting both treatments, which would delay treatment and increase transaction costs. In any case, implementation of the disclosure alternative would be problematic. If companies were told to disclose what they have, subject to enforcement action for (a) failure to disclose everything, or (b) failure to disclose truthfully and accurately, enforcement actions would be just as laborious and fact-intensive

330. In most cases involving drugs, the period of monopoly prices could not exceed three years. *See supra* note 136. In some cases, there would be no statutory exclusivity, and the period of monopoly would last as long as it took another company to perform the comparisons needed to justify relying on the first applicant's data. *See supra* note 171.

331. 21 U.S.C. §§ 355(b)(2), 355(j); 42 U.S.C. § 262(k).

332. *See supra* Part III.B.2.

333. *See supra* Part II.A.

334. *See supra* note 225 and accompanying text.

for the government as the enforcement actions (for marketing unapproved new drugs) that the FDA currently declines on resource grounds. If the FDA's failure to enforce the approval requirement has led companies to market despite the requirement, there is no particular reason to think companies would comply with a new labeling requirement that would be similarly inefficient to enforce.

The second cost is more concerning. It is likely firms would not complete the new drug approval process if they expected a marketplace that included cheaper and comparatively unregulated versions of the same active ingredient. Developing a new drug to the new drug standard is expensive work.³³⁵ If the FDA does not remove the unapproved competition from the market, there is a meaningful risk that no firms will complete the research needed for marketing applications because they would have no assurance of meaningful exclusivity in the market to recover their investments. The Makena experience suggests that price competition from unregulated near-substitutes can be fatal to a company that invested hundreds of millions in the regulated alternative. Meaningful exclusivity in the marketplace may be essential to persuade companies to perform new drug research, and it is possible only if the FDA takes enforcement action against the unregulated and unlawful competing products. Put another way, *if* policymakers want the new drug authorities to apply to these treatments—if they want anyone to perform gold standard safety and effectiveness testing of these drugs—they must make exclusivity meaningful by removing the illegal competition from the market.

Complaints that the exclusivity is unwarranted because the treatment is already available therefore miss the point. First, the treatment was not available. If the FDA has approved a new drug, the consumer does not simply purchase an active ingredient for medical use. Instead, the consumer purchases a specific physical product that has been the subject of rigorous hypothesis-testing clinical trials. The consumer pays for the research that supported approval and the labeling that synthesizes the research to better inform decisions. The consumer also pays for the greater confidence in product safety and effectiveness that comes from the FDA's review of the company's manufacturing process through its marketing application, the agency's supervision of the company's

335. See *supra* note 77 and accompanying text.

adverse event monitoring, and the assurance that the FDA can order labeling changes, more testing, and distribution restrictions if problems emerge.³³⁶ And second, the exclusivity is the price that must be paid, if policymakers want the gold standard research done and want medicines in the market under the new drug leash. Without it, companies will keep marketing in violation of the law. They have no reason to do the research.

The alternative actions available to policymakers effectively abandon the new drug paradigm altogether. Carving the active ingredients in question out of the new drug authorities would create a mechanism for regulatory arbitrage; firms developing new treatments—at least those for serious or life-threatening conditions—might be able to circumvent the new drug paradigm by ignoring the law (inviting enforcement discretion) or by encouraging pharmacy compounding. This solution amounts to jettisoning the new drug paradigm altogether. Accepting applications but continuing to exercise enforcement discretion for the unapproved treatments is not meaningfully different from carving the active ingredients in question out of the new drug authorities; it invites the same arbitrage *and* runs the risk of eliminating any incentive to develop the drugs anyway. This cannot be squared with the view that the new drug paradigm has value.

CONCLUSION

The new drug paradigm offers more benefits than simply the traditional gatekeeping mechanism. It ensures the creation of a specific quantity and quality of safety and effectiveness information about drugs. It ensures this information is thoughtfully synthesized, summarized, and disclosed to prescribing doctors. And it ensures that a single scientific institution reviews every word of those disclosures to achieve consistency in judgment calls, substantiation of claims, and wording choice and format. This makes prescribing decisions more efficient. The new drug authorities also give federal regulators a leash on the drug and company

336. We do not know that consumers (on average, because they are heterogenous) *value* these things. These aspects of the purchase are mostly invisible to consumers. This is why consumers and politicians balk at the apparent price hike; they do not realize that they are purchasing something different. That said, we do know that in some contexts consumers do not value them; for instance, many would agree to less certainty about risk and benefit, when choosing a medicine for a serious disease. But these preferences can be accommodated within a framework that includes new drug approval. *See supra* Part III.B.2.

after approval, ensuring they receive more information about the drug's safety and effectiveness, and giving them leverage and efficient enforcement options that they would lack without the mechanism of the preapproval requirement.

The gatekeeping mechanism presents a risk of Type 1 and Type 2 errors, to be sure, as well as the cost of delay and regulation. But these costs can be adjusted by choosing to render the decision with more—or less—certainty, as appropriate. This article does not claim that policymakers currently require the right amount of certainty before ruling on marketing applications. Nor does it claim that every post-approval new drug authority is worth the costs it imposes. But ability to contextualize the amount of certainty needed to render a decision, combined with the guarantee that each drug's benefits have been causally established with “gold standard” clinical trials and each drug's risks have been assessed through “all methods reasonably applicable” to assess its safety, combined with the profound efficiency benefits made possible by government oversight of labeling and continuing government oversight after market entry, make a compelling case for much of the new drug paradigm.

The true cost of the new drug paradigm is a period of monopoly pricing. A new drug paradigm *without* this period of monopoly pricing is impossible—as a structural matter and probably also as a practical matter. That is, if the government plans to permit companies to copy new drugs by relying on a first applicant's data, it must specify a date on which those companies may do so. And if it decides they may do so immediately, it is unlikely any company will invest the hundreds of millions (or billions) of dollars needed to bring the first product to market. The new drug paradigm, in other words, comes with exclusivity. The primary policy issue left open is the *length* of that exclusivity period, which this Article does not address, except to note that if the period is too short, companies similarly might not make the investment necessary. This could be especially true if the companies expect profound pressure about their pricing during the exclusivity period.

If policymakers value the new drug authorities, then firms *should* seek premarket approval of new medical treatments—and policymakers *should* use available policy levers to ensure that they do. This leads to several conclusions for policymakers. First, they should focus on ways of making the new drug research and development process more efficient and thus less expensive while still

robust from an evidentiary standpoint.³³⁷ Second, they should accept the price differential between newly approved products and previously available unapproved products, understanding that the products are not the same and that many valued benefits of the new drug authorities are invisible to patients and doctors.³³⁸ Third, once a firm has completed the approval process, policymakers should revoke enforcement discretion and remove illegal competition from the market.³³⁹ Finally, because stakeholders have a hard time stomaching the reversed sequence, regulators should avoid enforcement discretion in the first instance if exercising discretion will make it politically impossible to ensure meaningful exclusivity for an eventual marketing application. This counsels against enforcement discretion when other important uses of microbiota emerge from academic experiments.³⁴⁰

The ultimate cost of the new drug authorities is the price that society must pay for it through exclusivity. The gatekeeping mechanism does not ensure that valuable research is done or that, in these reversed scenarios, companies will bring marketed treatments into the new drug fold. The challenge of encouraging this work is the same whether the substance is newly discovered and unavailable to patients, or available to patients because of academic experimentation and enforcement discretion. In the end, if policymakers are not willing to pay the price for gold standard research and the new drug authorities, then they must rethink imposing a barrier to entry in the first instance. Research is not free.

337. For example, they should keep searching for suitable biomarkers to shorten clinical trial durations and considering novel trial designs that will reduce cost and time to market. Policymakers should also consider public funding for research when there may still be insufficient incentive to perform the research desired. This might be the case if competing products will remain on the market because the agency lacks the authority to remove them or prevent their use.

338. See *supra* Part III.C.

339. Policymakers could look for ways to reduce the effect of this action when the medicine in question is intended for chronic use and patients have been stabilized on the unapproved versions. They might encourage the first applicant to offer patient assistance, for example, or they might consider continued enforcement discretion only for these patients. It would also be reasonable for FDA to stay its hand where its jurisdiction is unclear or where there are strong practice of medicine concerns.

340. See, e.g., Courtney Humphries, *Detecting Diversity*, 550 NATURE S12 (2017) (discussing ongoing research relating to connection between vaginal dysbiosis—depletion of *Lactobacillus*—and health outcomes, specifically premature delivery).
