
ARTICLE

RETHINKING INNOVATION AT FDA

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ABSTRACT

In several controversial drug approval decisions in recent years, the Food & Drug Administration (“FDA”) has publicly justified its decision partly on the ground that approving the drugs in question would support innovation in those fields going forward. To some observers, these arguments were surprising, as the Agency’s determination whether a drug is “safe” and “effective” does not seem to depend on whether its approval also supports innovation. But FDA’s

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use of these innovation arguments in drug approval decisions is just one example of the ways in which the Agency has come to make many innovation-related judgments as part of its regulation of drugs. In this Article, we investigate the broad set of innovation-related judgments that FDA has been making and argue that there are serious concerns with the major innovation role FDA has been playing, at least as the Agency is currently constituted. We conclude that FDA should not separately weigh innovation in decisions about a product's safety and effectiveness. In other areas, health policymakers could reasonably decide that FDA should have either a larger or a smaller role than it currently does in shaping the development of novel drugs. But policymakers should do so while thoughtfully considering both the opportunities and challenges of FDA actively considering innovation incentives in its decisions; those challenges have been rarely considered in the literature and policy discourse. Further, we argue that whether policymakers aim to bolster or limit the ways that FDA considers innovation in its regulatory decisions, changes are needed to the Agency's structure to support its ability to make reasoned judgments based on relevant expertise.

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INTRODUCTION

From its inception more than a century ago,¹ the U.S. Food & Drug Administration (“FDA”) has been a public health agency.² A core part of the Agency’s public health mission is “ensuring that . . . drugs are safe and effective.”³ This mission may not, at first glance, suggest that FDA’s regulatory decisions involve judgments about how best to promote and shape biomedical innovation writ large, rather than just considering the product in front of it.⁴ But, during its more than 115 years of existence, the Agency has made, and continues to make, just these kinds of innovation judgments.

Two relatively recent and highly controversial drug⁵ approval decisions provide instructive examples. The first is the Agency’s June 2021 decision to approve Aduhelm (aducanumab) for Alzheimer’s disease based on the drug’s reduction of amyloid plaques in the brain, rather than on evidence that the drug improves clinical outcomes for patients.⁶ Although FDA has express statutory authority to approve drugs based on biomarkers⁷ that are “reasonably likely” to predict clinical benefit,⁸ in this instance, many in the scientific community—including the Agency’s own advisory committee—argued that an effect on amyloid plaques is not likely to predict clinical benefit (and also that the product raised safety concerns).⁹ The Agency’s approval decision was met with unusual

¹ *When and Why Was FDA Formed?*, FOOD & DRUG ADMIN. (Mar. 28, 2018), <https://www.fda.gov/about-fda/fda-basics/when-and-why-was-fda-formed> [<https://perma.cc/HK38-TXA6>].

² See Margaret A. Hamburg & Joshua M. Sharfstein, *The FDA as a Public Health Agency*, 360 NEW ENG. J. MED. 2493, 2493 (2009); 21 U.S.C. § 393(b) (declaring FDA’s “mission” includes “protect[ing] the public health by ensuring that . . . drugs are safe and effective” and “promot[ing] the public health by . . . taking appropriate action on the marketing of regulated products in a timely manner”); *United States v. An Article of Drug Bacto-Unidisk*, 394 U.S. 784, 798 (1969) (acknowledging that the Federal Food, Drug, and Cosmetic Act’s “overriding purpose [is] to protect the public health”).

³ 21 U.S.C. § 393(b)(2).

⁴ As explained *infra* Part I. See Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 388 (2007) (“[S]ome otherwise puzzling features of the FDA’s current regulatory authorities make more sense from the perspective of promoting provision of information than from the perspective of protecting patients.”).

⁵ This Article generally uses the term “drug” to include both traditional small-molecule drugs and biologics that undergo similar approval processes, such as vaccines.

⁶ Patrizia Cavazzoni, *FDA’s Decision to Approve New Treatment for Alzheimer’s Disease*, FOOD & DRUG ADMIN. (June 7, 2021), <https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease> [<https://perma.cc/P25T-8FUD>].

⁷ Biomarkers are readily measurable biological characteristics that may correlate—if not always reliably—with a clinical outcome that is harder, or takes longer, to observe; for instance, cholesterol levels are a biomarker for heart disease.

⁸ 21 U.S.C. § 356(c).

⁹ See, e.g., G. Caleb Alexander, Scott Emerson & Aaron S. Kesselheim, *Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility*, 325 JAMA 1717, 1717-18 (2021) (noting that “as many as 0.9% of participants with [amyloid-related imaging abnormalities] experienced severe symptoms”).

uproar, to put it mildly. Three members of the advisory committee resigned in protest.¹⁰ In April 2022, Medicare announced that it would strictly limit coverage for the drug, as there was not yet sufficient evidence that it was “reasonable and necessary” for patients.¹¹ Some hospital systems refused to administer the drug.¹² Some private insurers refused to pay for the drug.¹³ The Department of Health and Human Services (“HHS”) Office of Inspector General launched a review of FDA’s implementation of the statutory authority used to approve aducanumab, and in one report raised concerns about Medicare “paying billions of dollars for treatments that are not verified to have clinical benefit.”¹⁴ And the House Oversight and Reform and Energy and Commerce Committees issued a report in December 2022 that found troubling irregularities in FDA’s processes regarding communications between the Agency and Aduhelm’s manufacturer.¹⁵

Notwithstanding this controversy, FDA has stood by its decision to approve Aduhelm.¹⁶ It has asserted there was sufficient evidence of the drug’s safety and

¹⁰ See, e.g., Rachel Sachs, *Prescription Drug Policy, 2021 and 2022: The Year in Review, and the Year Ahead*, HEALTH AFFS. FOREFRONT (Jan. 7, 2022) [hereinafter Sachs, *Prescription Drug Policy, 2021 and 2022*], <https://www.healthaffairs.org/content/forefront/prescription-drug-policy-2021-and-2022-year-review-and-year-ahead>.

¹¹ Tamara Syrek Jensen et al., *Decision Memo for National Coverage Determination for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Apr. 7, 2022), <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=305> [<https://perma.cc/ZS5W-XQWB>].

¹² Sachs, *Prescription Drug Policy, 2021 and 2022*, *supra* note 10.

¹³ *Id.*

¹⁴ DEP’T OF HEALTH & HUM. SERVS. OFF. OF INSPECTOR GEN., DELAYS IN CONFIRMATORY TRIALS FOR DRUG APPLICATIONS GRANTED FDA’S ACCELERATED APPROVAL RAISE CONCERNS 7 (2022). Although some statutory changes to FDA’s accelerated approval authority were included in the 2022 year-end omnibus spending bill, Food and Drug Omnibus Reform Act of 2022, Pub. L. No. 117-328 § 3210, 135 Stat. 5822, 5822-25 (2022), there continues to be substantial interest in accelerated approval reform. See, e.g., Jill Wechsler, *Pressure Mounts for FDA to Reform Accelerated Approval Program*, PHARMTECH (Oct. 26, 2022), <https://www.pharmtech.com/view/pressure-mounts-for-fda-to-reform-accelerated-approval-program> [<https://perma.cc/G79A-JFA9>]; Rachel Sachs, *FDA User Fee Reauthorization Bills Emerge in Both Chambers*, HEALTH AFFS. FOREFRONT (June 2, 2022), <https://www.healthaffairs.org/content/forefront/fda-user-fee-reauthorization-bills-emerge-both-chambers> (discussing pressure to include such reforms in the 2022 user-fee legislation).

¹⁵ STAFF OF COMM. ON OVERSIGHT & REFORM & COMM. ON ENERGY & COM., THE HIGH PRICE OF ADUHELM’S APPROVAL: AN INVESTIGATION INTO FDA’S ATYPICAL REVIEW PROCESS AND BIOGEN’S AGGRESSIVE LAUNCH PLANS 15-24 (2022) (finding that the extent of collaboration between FDA and Biogen was inappropriate, FDA did not follow documentation protocol, and FDA pivoted unusually quickly to using the accelerated approval pathway for Aduhelm).

¹⁶ See, e.g., Billy Dunn, Peter Stein & Patricia Cavazzoni, *Approval of Aducanumab for Alzheimer Disease—The FDA’s Perspective*, 181 JAMA INTERNAL MED. 1276, 1278 (2021). FDA did, however, alter the labeled indication for the drug after approval, noting that

effectiveness to merit approval.¹⁷ Less predictable to some observers, however, were the Agency's references to innovation, including explaining in its announcement of the initial approval that the accelerated pathway used for the approval could "spur[] more research and innovation."¹⁸

Such references to innovation were arguably surprising for several reasons. Other agencies, like the Patent and Trademark Office ("PTO"), may be more clearly tasked with promoting innovation than FDA is.¹⁹ The Federal Food, Drug, and Cosmetic Act ("FDCA") frames the drug approval standard in terms of "safety" and "effectiveness"²⁰ and not in terms of innovation. And it was not at all clear that the Aduhelm approval would in fact spur innovation. Commentators outside the Agency instead argued the decision could *harm* innovation in Alzheimer's disease by incentivizing the development of drugs that, like Aduhelm, demonstrate an effect on biomarkers instead of a direct clinical benefit or otherwise are not supported by robust evidence of effectiveness.²¹

treatment "should be initiated in patients with mild" Alzheimer's rather than all patients with Alzheimer's. FDA, ADUHELM LABELING 1 (2021), https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s003lbl.pdf [<https://perma.cc/ZP5N-TGPH>].

¹⁷ *E.g.*, Dunn et al., *supra* note 16, at 1277-78.

¹⁸ News Release, FDA, FDA Grants Accelerated Approval for Alzheimer's Drug (June 7, 2021), <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug> [<https://perma.cc/ESP4-5XXM>]; *see also* Patrizia Cavazzoni, Billy Dunn & Peter Stein, *Here's Why We Approved the First New Alzheimer's Drug in Two Decades*, WASH. POST (June 23, 2021, 11:37 AM), <https://www.washingtonpost.com/opinions/2021/06/23/fda-alzheimers-drug-approval-aducanumab/> (likening the aducanumab approval to accelerated approvals of cancer drugs that "have propelled progress forward" in cancer treatment).

¹⁹ *See, e.g., Inclusive Innovation*, U.S. PAT. & TRADEMARK OFF., <https://www.uspto.gov/initiatives/equity> [<https://perma.cc/8GQZ-55V6>] (last visited Feb. 3, 2024); Press Release, U.S. Pat. & Trademark Off., USPTO Launches National Council for Expanding American Innovation (NCEAI) (Sept. 14, 2020), <https://www.uspto.gov/about-us/news-updates/uspto-launches-national-council-expanding-american-innovation-nceai> [<https://perma.cc/Z8P6-7S LN>]. To be fair, FDA's mission, as described in its enabling statute, includes "promot[ing] the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner," 21 U.S.C. § 393(b)(1), which arguably may involve aspects of innovation.

²⁰ 21 U.S.C. § 355(d) (standard approval); § 356(c) (accelerated approval).

²¹ *See, e.g.*, Meeting Report, Peter Whitehouse et al., *Making the Case for Accelerated Withdrawal of Aducanumab*, 87 J. ALZHEIMER'S DISEASE 1003, 1005 (2022); Dylan Scott, *The New Alzheimer's Drug Is the First of Its Kind. Will It Be the Last?*, VOX (June 24, 2021, 12:00 PM), <https://www.vox.com/policy-and-politics/22547044/new-alzheimers-disease-drug-aducanumab-research-science> [<https://perma.cc/C76W-4PGY>]. *But see* Dana Goldman & Darius Lakdawalla, *FDA's Approval of Aducanumab Paves the Way for 'More Momentous' Alzheimer's Breakthroughs*, UNIV. S. CAL. LEONARD D. SCHAEFFER CTR. FOR HEALTH POL'Y & ECON. (June 11, 2021), <https://healthpolicy.usc.edu/article/fdas-approval-of-aducanumab-paves-the-way-for-more-momentous-alzheimers-breakthroughs/> [<https://perma.cc/66M5-R ACA>] (quoting a scientific advisor and consultant to Biogen, Aduhelm's manufacturer,

Moreover, the Aduhelm decision came several years after another controversial approval in which the Agency even more explicitly invoked innovation-related reasoning—FDA’s 2016 approval of Exondys 51 (eteplirsen) for Duchenne muscular dystrophy,²² a rare genetic disorder in which patients progressively lose their muscle function, typically passing away in their twenties or thirties. As with Aduhelm, FDA approved Exondys 51 through the accelerated approval pathway, based on the drug’s effect on a biomarker—dystrophin, a protein²³—and against the recommendation of the Agency’s advisory committee.²⁴ Although using dystrophin as a biomarker was not particularly controversial in itself, the pivotal clinical trial supporting approval included only twelve patients, was uncontrolled, and showed, at best, only a very small effect on dystrophin levels.²⁵ Further, the Exondys 51 approval came after heated internal debate among FDA officials about whether there was sufficient safety and effectiveness evidence to support approval.²⁶

Alongside this debate about the scientific evidence, there was substantial internal disagreement within FDA about the approval’s impact on innovation. Dr. Janet Woodcock, then the Director of FDA’s Center for Drug Evaluation and Research (“CDER”) and the career official who ultimately made the

arguing that “[w]ith its approval of aducanumab, the FDA is fueling the chances of even more breakthroughs”).

²² See, e.g., Matthew Herper, *Approving a Muscular Dystrophy Drug Ignites a Civil War at the FDA*, FORBES (Sept. 20, 2016, 9:17 AM), <https://www.forbes.com/sites/matthewherper/2016/09/20/approving-a-muscular-dystrophy-drug-ignites-civil-war-at-the-fda>.

²³ FDA, Exondys 51 Labeling (Jan. 2022), https://www.accessdata.fda.gov/drugs_atfda_docs/label/2022/206488s027s028s029lbl.pdf [<https://perma.cc/562G-BZW3>].

²⁴ See, e.g., FDA Ctr. for Drug Evaluation & Rsch., Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting 7-8 (Apr. 25, 2016) [hereinafter Exondys 51 Summary Minutes], <https://fda.report/media/99235/Minutes-for-the-April-25-2016-Meeting-of-the-Peripheral-and-Central-Nervous-System-%28PCNS%29-Drugs-Advisory-Committee.pdf> [<https://perma.cc/S29W-CQ94>].

²⁵ FDA, Exondys 51 Labeling, *supra* note 23 (noting that a study found only a 0.28% increase in dystrophin compared to placebo control); see also Aaron S. Kesselheim & Jerry Avorn, *Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy*, 318 JAMA 2357, 2357-58 (2016) (observing that clinical studies of Exondys 51 did not include “true control”).

²⁶ In short, the FDA Center for Drug Evaluation and Research (“CDER”) Director approved the drug against the recommendation of other high-ranking career staff. After an internal dispute process, the Commissioner ultimately affirmed the CDER Director’s approval decision, explaining that experts could disagree about whether the drug’s effect on dystrophin is reasonably likely to predict clinical benefit and deferring to the CDER Director, as the career official to whom approval decisions are delegated. Memorandum from Robert M. Califf, Comm’r, FDA, to Janet Woodcock, Dir., Ctr. For Drug Evaluation & Rsch., FDA et al. 5 (Sept. 16, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_redacted.pdf [<https://perma.cc/7A7M-XLHE>]; see also Patricia J. Zettler, *The FDA’s Power over Non-Therapeutic Uses of Drugs and Devices*, 78 WASH. & LEE L. REV. 379, 418 n.157 (2021) (noting that one reason for the Commissioner’s decision was the Agency’s norm that career, rather than political, staff typically make approval decisions).

approval decision, argued that the approval would help ensure “some path forward for such innovative products” for Duchenne muscular dystrophy, and noted that the manufacturer of Exondys 51, specifically, “would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline” without the approval.²⁷ Others within the Agency, however, asserted that the decision would undermine innovation and expressed concern about the idea of considering a specific company’s finances during the approval process.²⁸ For example, FDA’s Acting Chief Scientist, Dr. Luciana Borio explained:

Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies—both by discouraging others from developing effective therapies for [Duchenne muscular dystrophy] and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit.²⁹

The Agency hedged against these outcomes by expressly stating that the Exondys 51 approval decision should not serve as a precedent for future approvals.³⁰ Nevertheless, some of Dr. Borio’s concerns, arguably, have come to pass. In 2019, for example, FDA approved a second drug for muscular dystrophy from Exondys 51’s manufacturer, again based on the drug’s effect on dystrophin production and amid recommendations against approval.³¹

²⁷ Memorandum from Luciana Borio, Acting Chief Scientist, FDA, to Robert M. Califf, Comm’r, FDA 16 (Aug. 8, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_redacted.pdf [<https://perma.cc/7A7M-XLHE>].

²⁸ See, e.g., Memorandum from Robert M. Califf, *supra* note 26, at 8 n.23, 9 n.25 (acknowledging criticism that the decision to approve could discourage development of effective therapies for Duchenne muscular dystrophy).

²⁹ Memorandum from Luciana Borio, *supra* note 27, at 26.

³⁰ Memorandum from Robert M. Califf, *supra* note 26, at 11 (“I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information.”).

³¹ Jordan Paradise, *Three Framings of “Faster” at the FDA and the Federal Right to Try*, 11 WAKE FOREST J.L. & POL’Y 53, 81 (2020) [hereinafter Paradise, *Federal Right to Try*]. In 2021, FDA approved a third Duchenne muscular dystrophy drug from this manufacturer based on its effect on dystrophin levels. See, e.g., News Release, FDA, FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation (Feb. 25, 2021), <https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation-0> [<https://perma.cc/P2MM-CHMP>]. In 2023, the Agency approved a fourth Duchenne muscular dystrophy product from this manufacturer. But this most recent approval is for a different kind of product—a single-dose gene therapy designed to deliver a gene that leads to production of dystrophin. See, e.g., News Release, FDA, FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy (June 22, 2023), <https://www.fda.gov/news-events/press->

Additionally, years later, it is still unknown whether Exondys 51 has a clinical benefit: although FDA had initially requested that Sarepta complete and submit confirmatory trials designed to show such a benefit by 2020, these trials did not even begin until 2020 and are not expected to be completed until late 2024.³²

Taken together, the Aduhelm and Exondys 51 approvals demonstrate that—for better or for worse—FDA is, at least sometimes, making innovation-related judgments as part of its regulatory decisions. And these judgments come in various forms. With the Aduhelm and Exondys 51 approvals, the Agency made substantive judgments about how to best drive innovation on its own initiative, seeming to consider the future development of *other* products not presently before the Agency, and without express statutory language directing it to do so. In other instances, Congress has expressly created a role for FDA in drug innovation policy programs. These congressionally created roles can be relatively ministerial, as is the case with certain FDA-administered exclusivity periods for approved drugs, for which the Agency arguably simply implements Congress's judgments about how exclusivity periods should be used to promote innovation.³³ Other congressionally created innovation roles involve FDA actively administering an innovation program and considering what is needed to promote innovation, as is the case with the priority review voucher program for drugs for certain neglected diseases, for which Congress has expressly empowered FDA to add new eligible diseases on innovation-related grounds.³⁴

To be clear, it is inevitable that, by overseeing the safety and effectiveness of drugs and extensively regulating the biopharmaceutical market, FDA's regulatory regime will affect drug innovation.³⁵ This unavoidable impact on innovation can be viewed as an important component of the Agency's public health mission. Its drug regulatory regime requires manufacturers to develop extensive information about the safety and effectiveness of their products—information that otherwise likely would not be produced—and helps ensure that companies develop novel drugs that actually work.³⁶

announcements/fda-approves-first-gene-therapy-treatment-certain-patients-duchenne-muscular-dystrophy [https://perma.cc/Q96Q-F52M].

³² See *A Study to Compare Safety and Efficacy of a High Dose of Eteplirsen in Participants with Duchenne Muscular Dystrophy (DMD) (MISSION)*, NAT'L LIBR. OF MED., <https://clinicaltrials.gov/ct2/show/NCT03992430> (last updated Nov. 29, 2023). Such timelines are not uncommon, and one study found the majority of confirmatory trials were late. Anjali D. Deshmukh, Aaron S. Kesselheim & Benjamin N. Rome, *Timing of Confirmatory Trials for Drugs Granted Accelerated Approval Based on Surrogate Measures from 2012 to 2021*, JAMA HEALTH F., Mar. 2023, at 1, 1 <https://jamanetwork.com/journals/jama-health-forum/fullarticle/2803074> [https://perma.cc/KW9T-QQEW].

³³ See *infra* Section I.B.

³⁴ See *infra* Section I.C.

³⁵ See *infra* Section I.A.

³⁶ See Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 348; Memorandum from FDA Regarding Public Health Interests and First Amendment

Likewise, FDA has long sought to develop and adopt innovative regulatory approaches to best protect and promote public health. In 1973, then FDA Chief Counsel Peter Barton Hutt explained, “Except where expressly prohibited, I believe the Food and Drug Administration is obligated to develop whatever innovative and creative regulatory programs are reasonable and are most appropriate to achieve the fundamental objectives laid down by Congress.”³⁷ It is, perhaps, inevitable that FDA will continue this kind of regulatory process innovation.

This Article, however, does not focus either on innovation effects that inevitably result from FDA’s core public health functions or on the Agency’s efforts to improve its own implementation of its authorities. Instead, it aims to investigate the broad set of innovation-related *judgments* that FDA has been making about drugs and the costs and benefits of the Agency doing so. After examining the various ways that FDA has been incorporating innovation into its regulatory decisions regarding individual drugs—from more ministerial to more substantive judgments, including both congressionally directed judgments and ones the Agency appears to undertake on its own initiative—we argue that, as currently constituted, FDA is an awkward fit for making these innovation-related judgments. The Agency, for example, has not publicly articulated a strategy for promoting drug innovation across its different regulatory decisions, nor does it obviously have the expertise to empirically assess whether its decisions, like the Aduhelm and Exondys 51 approvals, do in fact promote future innovation in the relevant disease areas. By examining a broad set of innovation-related judgments that FDA has been making regarding individual drugs, and considering the normative implications of those judgments, we aim to add to the existing literature, which largely works to uncover ways that FDA’s core public health functions drive innovation or to investigate ways to improve congressionally created innovation programs that FDA administers, without examining the first-order question of whether FDA ought to be in its role.³⁸

Ultimately, we argue that when the Agency is evaluating a particular product’s safety and effectiveness, innovation considerations regarding the future development of other products not presently before the Agency should not separately come into play.³⁹ In other areas, health policymakers could

Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products 4 (Jan. 2017) [hereinafter FDA Off-Label Use Memo], https://downloads.regulations.gov/FDA-2016-N-1149-0040/attachment_1.pdf [<https://perma.cc/9N6Y-C6P6>].

³⁷ Peter Barton Hutt, *Philosophy of Regulation Under the Federal Food, Drug and Cosmetic Act*, 28 FOOD DRUG COSM. L.J. 177, 179 (1973). Cf. Marie C. Boyd, *Cricket Soup: A Critical Examination of the Regulation of Insects as Food*, 36 YALE L. & POL’Y REV. 17, 66 (2017) (criticizing FDA for its “inaction” on adopting an approach that would regulate insects as food).

³⁸ For an in-depth discussion of the literature, see *infra* Part I.

³⁹ This is not to say that FDA cannot consider the availability, or lack thereof, of other approved products to treat a condition in assessing the benefits and risks of a drug.

reasonably decide that FDA should have either a larger or a smaller role than it currently does in making judgments about how to shape the development of novel drugs. But policymakers should do so thoughtfully, weighing both the opportunities and challenges of FDA actively considering innovation in its decisions. Those challenges in particular have gone largely unexamined in the literature and policy discourse. Some may have relatively obvious fixes—such as providing the Agency additional resources to build expertise in assessing the innovation effects of its decisions—but others may be less easily solved. Nevertheless, whether policymakers aim to bolster or limit the ways that FDA considers innovation in its regulatory decisions, changes may be needed to the Agency's structure to assist its ability to make judgments based on relevant expertise, or, alternately, to limit the ways that innovation creeps into Agency decision making.

Finally, two caveats on scope. First, FDA, as the name suggests, regulates more than just drugs; for example, it also regulates food, devices, and tobacco products.⁴⁰ We focus here almost exclusively on drugs (including certain biologics). Although many of the arguments in this Article may apply to other products within FDA jurisdiction, each product category comes with its own specific set of requirements, including different pathways to premarket authorization for drugs, devices, and tobacco products. As described below, Congress has taken an active role in enabling FDA's management of drug innovation, while it has been less active with respect to certain other product areas.⁴¹ We also set aside questions about an innovation focus on physical products like drugs as opposed to other types of health interventions.⁴² Second,

⁴⁰ 21 U.S.C. ch. 4-9. *See generally* PETER BARTON HUTT ET AL., *FOOD AND DRUG LAW: CASES AND MATERIALS* (5th ed. 2022). The line between drugs and medical devices is a contested space. *See, e.g.*, *Genus Med. Techs. LLC v. FDA*, 994 F.3d 631, 644 (D.C. Cir. 2021); Patricia J. Zettler, Eli Y. Adashi & I. Glenn Cohen, *A Divisive Ruling on Devices* — *Genus Medical Technologies v. FDA*, 385 *NEW ENG. J. MED.* 2409, 2409-10 (2021).

⁴¹ *See, e.g.*, W. Nicholson Price II, *Regulating Black-Box Medicine*, 116 *MICH. L. REV.* 421, 442 (2017) (noting the lack of exclusivity for medical devices); Patricia J. Zettler & Erika Lietzan, *Regulating Medical Devices in the United States*, in *THE OXFORD HANDBOOK OF COMPARATIVE HEALTH LAW* 755, 763 (David Orentlicher & Tamara K. Hervey eds., 2022) (noting the lack of data exclusivity for devices authorized for marketing via de novo classification). *But see* Sara Gerke, *Health AI for Good Rather Than Evil? The Need for a New Regulatory Framework for AI-Based Medical Devices*, 20 *YALE J. HEALTH POL'Y L. & ETHICS* 433, 475, 483, 494-95 (2021) (considering FDA's role in promoting innovation for AI-based devices); Catherine M. Sharkey, *Direct-to-Consumer Genetic Testing: The FDA's Dual Role as Safety and Health Information Regulator*, 68 *DEPAUL L. REV.* 343, 375-83 (2019) (considering FDA's role in information-related innovation for medical devices).

⁴² FDA is likely to prioritize physical *things*—drugs and other health care technologies—over other interventions or treatments. FDA's jurisdictional tools, including approvals, vouchers, and exclusivity periods, work best for such innovations. For some products like drugs, FDA administers regulatory exclusivity that allows the developer to readily exclude others from using the information. *See* Rebecca S. Eisenberg, *The Problem of New Uses*, 5 *YALE J. HEALTH POL'Y L. & ETHICS* 717, 725-30 (2005). But if FDA exclusivity tools are like

this Article is focused on questions about whether FDA *should* make innovation judgments as part of regulating drugs, and related implications for the Agency's design, rather than focusing on surprisingly complex questions about whether and when FDA is statutorily authorized to do so.⁴³

Part I examines the existing literature on FDA's role in innovation policy and the inevitable innovation impacts of FDA's drug regulation. It then examines the range of innovation-related judgments that the Agency has been making, from ministerial to substantive, and from congressionally directed to those seemingly undertaken on the Agency's own initiative. Part II considers the case both for and against FDA actively considering innovation in its regulatory decisions, examining the Agency's expertise advantages and disadvantages as well as competing policy considerations that might counsel against FDA incorporating innovation into its decisions, even if equipped with sufficient resources and expertise. Drawing on Part II, Part III then argues that when FDA is evaluating a product's safety and effectiveness as part of its approval decisions, it should not consider innovation promotion in answering that question. For other kinds of decisions, however, health policymakers could reasonably decide either to limit or to bolster the Agency's role. Part IV appraises how FDA would be restructured should policymakers decide the Agency should be innovation-agnostic, while Part V offers a vision for restructuring the Agency to be intentionally innovation-focused and equipped with the necessary expertise for that focus.

I. THE SCOPE OF FDA'S INNOVATION ACTIVITIES

Put simply, FDA should be understood as, among other things, an innovation agency.⁴⁴ It is inevitable that FDA regulation will play a substantial role in

patents, they are also likely to incorporate patent pathologies. As Amy Kapczynski and Talha Syed point out, exclusivity does little to drive innovation in nonexcludable advances, such as basic understanding of a disease, knowledge of what development paths don't work, or positive information about effective nonpharmaceutical interventions like diet, exercise, or cognitive training. Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 YALE L.J. 1900, 1942-50 (2013).

⁴³ FDA is explicitly authorized to administer certain innovation programs, *see infra* Section I.B, and to make certain innovation judgments. The question of how and when it may take innovation into account in other circumstances is complicated in statutory, political economy, and practical terms, and is a subject of some scholarly debate. *Cf.* Craig J. Konnoth, *Drugs' Other Side-Effects*, 105 IOWA L. REV. 171, 197-216 (2019) (arguing that FDA should consider a broad range of drugs' "collateral effects" in its regulatory decisions); Patricia J. Zettler, Margaret Foster Riley & Aaron S. Kesselheim, *Implementing A Public Health Perspective in FDA Drug Regulation*, 73 FOOD & DRUG L.J. 221, 224, 235-47 (2018) (arguing that the FDCA authorizes FDA to take a "broad approach in its drug approval and withdrawal decisions").

⁴⁴ *See, e.g.*, Daniel J. Hemel & Lisa Larrimore Ouellette, *Innovation Institutions and the Opioid Crisis*, 7 J.L. & BIOSCIENCES 1, 4 (2020). Although we focus on drug innovation, FDA can also be characterized as an innovation agency with respect to other products within its

shaping biopharmaceutical innovation through the Agency's extensive regulation of drugs across their lifecycles, from early research to approval to manufacturing to monitoring marketed drugs' safety and effectiveness.⁴⁵ But over time, Congress has given FDA jobs that expand its innovation-shaping role beyond the unavoidable effects of the Agency's core public health functions. For example, FDA administers exclusivity periods that serve as patent-like monopolies, often in parallel with the patent system. Congress has also charged FDA with administering other drug innovation incentives, such as priority review vouchers and orphan drug designations, in ways that require FDA to make judgments on innovation-related grounds. Moreover, as the Aduhelm and Exondys 51 approvals show, the Agency often has significant discretion in its regulatory decisions, and innovation-related reasoning seemingly has crept into certain FDA decisions, even when Congress has not expressly directed FDA to consider innovation.⁴⁶

This Part begins by describing the unavoidable innovation impacts of FDA's core functions because it is important to recognize that innovation is and will remain influenced by FDA's central public health mission. But we then bracket these unavoidable impacts for much of the rest of the Article, because our focus is on how much FDA should make innovation-related *judgments*, rather than on how FDA regulation inescapably shapes innovation.⁴⁷ Consistent with this focus, this Part goes on to examine the range of innovation-related judgments that the Agency has been making, from ministerial to substantive judgments, and

jurisdiction. For example, FDA must authorize certain devices as safe and effective, and generally must authorize new tobacco products as "appropriate for the protection of the public health," 21 U.S.C. § 387f(d)(1), before they may be marketed. Just as with drug premarket approval processes, FDA's gatekeeping role for devices and tobacco products can shape innovation and help ensure that scientifically sound information about products is produced. *See, e.g.*, Sharkey, *supra* note 41, at 344-45 (describing how FDA's regulatory role influences innovation in genetic testing products); Patricia J. Zettler, Natalie Hemmerich & Micah L. Berman, *Closing the Regulatory Gap for Synthetic Nicotine Products*, 59 B.C. L. REV. 1933, 1976-79 (2018) (arguing that one reason FDA should regulate synthetic nicotine products is to incentivize research on the products' effects).

⁴⁵ *See, e.g.*, Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 347-350.

⁴⁶ *But cf.* Memorandum from Robert M. Califf, *supra* note 26, at 7 (describing "the emergence of patient-centered drug development and the extensive interactions with the patient community as part of the overall environment" in which the Exondys 51 approval decision was made); Paradise, *supra* note 31, at 66-73 (describing increased opportunity for patient input on FDA's drug and device regulatory decisions, partly as a result of changes to the Federal Food, Drug, and Cosmetic Act made in the 21st Century Cures Act); Jordan Paradise, *21st Century Citizen Pharma: The FDA & Patient-Focused Product Development*, 44 AM. J.L. & MED. 309, 314 (2018) [hereinafter Paradise, *Citizen Pharma*] (quoting an FDA report explaining "[p]atients are committed to contributing their views, data, and resources to increase patient-centric medical product innovation, assessment, and regulatory decision-making").

⁴⁷ We recognize that these two issues may have fuzzy boundaries.

from congressionally directed to those seemingly undertaken on the Agency's own initiative.

A. *Inevitable Innovation Impacts*

FDA is typically viewed as a consumer protection agency, protecting people by requiring that drugs be demonstrated safe and effective for their intended use before they may be marketed.⁴⁸ Even in this role, FDA's actions have effects on innovation—effects which, whether or not FDA actively considers innovation, are essentially inescapable. For example, in 1983, FDA's Chief Counsel explained that the drug “approval system has, intentionally or not, entered into the investment-backed decisions of research-oriented drug companies and has operated to create incentives for them to develop new drug therapies.”⁴⁹

Rebecca Eisenberg offers one vitally important example of such an innovation impact. As Eisenberg has persuasively argued, even “FDA's core function of reviewing data from clinical trials to determine the safety and efficacy of drugs prior to market approval may be understood as a means of promoting costly investments in a particular form of [research and development] rather than simply as a means of protecting patients from untoward risks of harm.”⁵⁰ Eisenberg notes that the key feature of drugs, as distinct from “poisons,” dietary supplements, or otherwise less regulated chemicals, is the extensive information demonstrating that drugs are safe and effective to treat a particular ailment.⁵¹ But that information remains difficult, expensive, and time-consuming to generate.⁵² FDA requirements for the production of clinical trial data before allowing drugs on the market, then, are best understood as a mandate for firms to engage in a

⁴⁸ See, e.g., Zettler et al., *supra* note 43, at 230.

⁴⁹ *Drug Labeling and Advertising and New Drug Application: Hearing on H.R. 1554 and H.R. 3605 Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Com.*, 98th Cong. 20 (1983); see also Peter Barton Hutt, Richard A. Merrill & Alan M. Kirschenbaum, *The Standard of Evidence Required for Premarket Approval Under the Medical Device Amendments of 1976*, 47 *FOOD & DRUG L.J.* 605, 609-11 (1992) (describing Congress's and FDA's thinking on innovation when the modern regulatory regime for devices was created).

⁵⁰ Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 388.

⁵¹ *Id.* at 347 (“If a century ago the goal of drug regulation was to protect people from poisons, today drug regulation guides the development of information that turns poisons, used advisedly, into drugs.”).

⁵² *Id.*; see also Thomas J. Moore, Hanzhe Zhang, Gerard Anderson & G. Caleb Alexander, *Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016*, 178 *JAMA INTERNAL MED.* 1451, 1451 (2018) (finding that average cost of pivotal efficacy trials was \$19 million); Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, 2 *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 *J. HEALTH ECON.* 20, 27 (2016) (finding that average total cost of developing a new drug was between \$2.3 billion and \$2.8 billion).

particular type⁵³ of expensive, information-generating innovation with the reward of market access.⁵⁴

Policymakers continue to debate whether and how much information-generating innovation firms must engage in to obtain FDA approval. Legislative directives for FDA to implement or at least study the use of “real-world evidence” nudge FDA to decrease its reliance on traditional clinical trials in favor of other data sources.⁵⁵ Although Agency officials have attempted to clarify both the potential uses and limitations of real-world evidence,⁵⁶ many members of Congress continue to push ahead with expansions of its use.⁵⁷

Similarly, FDA has long interpreted the FDCA to restrict the ability of drug manufacturers to promote drugs for so-called “off-label” uses that the Agency has not approved.⁵⁸ At the same time that manufacturers’ *promotion* of off-label

⁵³ FDA not only requires that these trials occur but oversees their conduct as well. In this space, FDA guidelines on what kinds of trial designs efficiently produce sufficient evidence of drug effectiveness shape how trials are conducted. *See, e.g.*, FDA, DIGITAL HEALTH TECHNOLOGIES FOR REMOTE DATA ACQUISITION IN CLINICAL INVESTIGATIONS: DRAFT GUIDANCE 12-14 (2021), <https://www.fda.gov/media/155022/download> [<https://perma.cc/484N-A5MT>] (discussing clinical endpoints); Scott Gottlieb, *FDA’s Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation*, FOOD & DRUG ADMIN. (Aug. 29, 2018), <https://www.fda.gov/news-events/fda-voices/fdas-comprehensive-effort-advance-new-innovations-initiatives-modernize-innovation> [<https://perma.cc/K559-ZCLS>] (discussing innovative trial designs).

⁵⁴ Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 370; *see also* Sharkey, *supra* note 41, at 368 (describing FDA’s innovation role with respect to genetic testing devices).

⁵⁵ *See, e.g.*, Rebecca S. Eisenberg, *Shifting Institutional Roles in Biomedical Innovation in a Learning Healthcare System*, 14 J. INSTITUTIONAL ECON. 1139, 1149 (2018).

⁵⁶ *See, e.g.*, Rachel E. Sherman et al., *Real-World Evidence — What Is It and What Can It Tell Us?*, 375 NEW ENG. J. MED. 2293, 2293 (2016) (noting that real-world evidence can provide data more efficiently than clinical trials but may also generate unreliable conclusions due to poor study design and researchers without methodologic experience).

⁵⁷ *See* Mary Ellen Schneider, *Accelerated Approval: Experts Weigh In on the Role of RWE in Confirmatory Trials*, RAPS (Aug. 8, 2022), <https://www.raps.org/news-and-articles/news-articles/2022/8/accelerated-approval-experts-weigh-in-on-the-role>.

⁵⁸ Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124, 126, 129 (2016). FDA’s ability to restrict off-label promotion has taken some recent hits from courts finding increasingly vigorous First Amendment protections for commercial speech. *See, e.g.*, *United States v. Caronia*, 703 F.3d 149, 152 (2d Cir. 2012); *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015); Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO ST. L.J. 1053, 1054 (2017) [hereinafter Zettler, *Indirect Consequences*]; Christopher Robertson & Aaron S. Kesselheim, *Regulating Off-Label Promotion — A Critical Test*, 375 NEW ENG. J. MED. 2313, 2313 (2016); Amy Kapczynski, *The Lochnerized First Amendment and the FDA: Toward a More Democratic Political Economy*, 118 COLUM. L. REV. ONLINE 179, 181 (2018). *Cf.* Barbara J. Evans, *FDA Regulation of Physicians’ Professional Speech*, J. FREE SPEECH L. (forthcoming 2024) (manuscript at 31-32) (available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4501746) (investigating a potential First Amendment challenge to FDA’s approach to clinical decision support software).

uses generally leads to violations of the FDCA, FDA generally does not restrict the ability of health care professionals to *prescribe* drugs for off-label uses.⁵⁹ This Agency position arguably reflects the Agency's statutory authority.⁶⁰ But from a consumer protection perspective this is an odd juxtaposition, at least at first glance—why not protect patients from unapproved uses by directly prohibiting prescribing drugs for such uses?⁶¹ One reason that FDA itself has offered is that restricting manufacturers' ability to promote off-label uses serves public health by creating incentives for manufacturers to develop the costly information demonstrating that the off-label use is in fact safe and effective before promoting it.⁶² This, too, is a form of innovation that FDA drives while performing its core safety and effectiveness review function.

The requirement that FDA approve new drugs as safe and effective for their intended use is not the only example of the ways that FDA's core public health functions shape biopharmaceutical innovation. For instance, FDA regulates the manufacturing of approved drugs to ensure their quality. FDA's choices about drug manufacturing requirements, such as permitting (or encouraging) continuous manufacturing rather than old-fashioned batch manufacturing, affect

⁵⁹ There are exceptions. For example, section 303(e) of the FDCA directly prohibits knowingly prescribing, dispensing, or administering human growth hormone for off-label uses, while FDA's authority to require Risk Evaluation and Mitigation Strategies can indirectly limit off-label prescribing and dispensing. *See, e.g.*, Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 454-67 (2015).

⁶⁰ *See generally* Cortez, *supra* note 58. For discussion of FDA's authority to restrict off-label prescribing and dispensing, rather than promotion, and examples where the Agency has done so, *see, for example*, Zettler, *Indirect Consequences*, *supra* note 58, at 1080-86. *See also* Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 845 (2017) (laying out arguments for FDA's nonregulation of the practice of medicine). *But see id.* at 885-86 (noting that FDA has more power and does more regulation in this space than is commonly assumed); Myrisha S. Lewis, *Innovating Federalism in the Life Sciences*, 92 TEMP. L. REV. 383, 391 (2020) (describing federal and state regulation of medical products and practice).

⁶¹ *See, e.g.*, Caronia, 703 F.3d at 166; *see also* Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 476 (2009) (highlighting some of the problems associated with off-label use, including "lack of data, costs, and unfavorable risk-benefit ratios"); David A. Simon, *Off-Label Speech*, 72 EMORY L.J. 549, 549 (2023) (arguing that FDA should regulate off-label promotion on a scale from less to more restrictive, depending on how much evidence supports the promoted use).

⁶² FDA Off-Label Use Memo, *supra* note 36, at 4-5; *see also* Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 371-72 (citing *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 71-74 (D.D.C. 1998)) (calling FDA's incentivization argument in *Washington Legal* "remarkable"); Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past and Future*, 102 MINN. L. REV. 2357, 2366 (2018). *Cf.* David A. Simon, *Off-Label Innovation*, 56 GA. L. REV. 701, 740 (2022) (considering ways to incentivize health care professionals, rather than drug manufacturers, to produce information on off-label uses).

innovation in drug manufacturing, if not as directly as its oversight of clinical trials.⁶³

B. Ministerial Innovation Judgments

In contrast to the ways FDA's extensive regulation of drugs unavoidably affects innovation, sometimes FDA is more actively involved in innovation incentives. FDA's responsibility for administering a set of exclusivity periods is, perhaps, the clearest example of Congress delegating innovation authority to FDA which the Agency then implements in a relatively ministerial fashion. Under this authority, the Agency awards manufacturers of newly approved drugs certain periods of market or data exclusivity. During these statutorily specified periods of time, FDA is limited in its ability to review and approve follow-on versions of innovator products. Although the details of these exclusivity periods differ from each other slightly, they function very similarly in practice. Congress created the first of these periods in the 1983 Orphan Drug Act, which prohibited FDA from approving a new version of an approved drug for a rare disease or condition for seven years after the first drug's approval.⁶⁴ In the Hatch-Waxman Act of 1984, Congress created a five-year period of data exclusivity for small-molecule drugs, preventing generic drug applicants from relying on the innovator drug's clinical trial data during that period.⁶⁵ In the Biologics Price Competition and Innovation Act of 2010, passed as part of the Affordable Care Act, Congress created the most recent major exclusivity period, providing

⁶³ See *Advanced Manufacturing*, FOOD & DRUG ADMIN. (June 7, 2023), <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing> [<https://perma.cc/PL3R-4VNZ>] (describing important new developments in advanced manufacturing, including the White House's National Strategy for Advanced Manufacturing); W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 491-92, 502 (2014) (arguing innovation in drug manufacturing can be spurred through FDA regulation); NAT'L ACADS. OF SCIS., ENG'G, & MED., CONTINUOUS MANUFACTURING FOR THE MODERNIZATION OF PHARMACEUTICAL PRODUCTION: PROCEEDINGS OF A WORKSHOP 6 (Joe Alper Rapporteur, 2019) (describing how Dr. Woodcock noted that FDA has begun "to adopt the role of advocate for change rather than be an obstacle to change" by removing barriers to continuous manufacturing); NAT'L ACADS. OF SCIS., ENG'G, & MED., INNOVATIONS IN PHARMACEUTICAL MANUFACTURING ON THE HORIZON: TECHNICAL CHALLENGES, REGULATORY ISSUES, AND RECOMMENDATIONS 1-6 (2021) (discussing how FDA could further promote manufacturing innovation). Some of these choices are congressionally encouraged, such as the 21st Century Cures Act's provision of grants for studying continuous manufacturing. Pub. L. No. 114-255, § 3016, 130 Stat. 1033 (2016).

⁶⁴ 21 U.S.C. § 360cc(a). The Orphan Drug Act applies to incentives for a "rare disease or condition," statutorily defined as "affect[ing] less than 200,000 persons in the United States," or affecting a larger number under certain market conditions, as discussed in Section I.C. § 360bb(a)(2)(A).

⁶⁵ 21 U.S.C. § 355(c)(3)(E)(ii). This exclusivity period is reduced to four years if the generic filer makes what is known as a "Paragraph IV challenge," in which they claim that either existing patents are invalid or will not be infringed by the generic product. *Id.* § 355(c)(3)(E)(ii), (b)(2)(A)(iv).

twelve years of data exclusivity for innovator biologic drugs.⁶⁶ Congress has also established a set of shorter exclusivity periods,⁶⁷ such as three years for the approval of a new use of an existing drug,⁶⁸ or add-on exclusivity periods, such as six months for the performance of studies in pediatric populations,⁶⁹ or five years of exclusivity, added to certain already-provided exclusivities, for some antimicrobial drugs.⁷⁰

Scholars have considered the many ways in which these exclusivity periods both strongly resemble patents and are dissimilar in important ways.⁷¹ Describing exclusivity periods as “FDA-administered pseudo-patents,” Eisenberg has argued that FDA’s oversight of these periods “serves a function traditionally relegated to the patent system: promoting and rewarding

⁶⁶ 42 U.S.C. § 262(k)(7)(A). This exclusivity period is measured from the innovator product’s approval to the biosimilar’s approval. *Id.* For a discussion of how Congress came to pass the Biologics Price Competition and Innovation Act of 2009, see, for example, Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671 (2010).

⁶⁷ One exclusivity period beyond the focus of this Article is the 180-day exclusivity period provided to the first generic applicant to file a Paragraph IV certification. 21 U.S.C. § 355(j)(5)(B)(iv)(I). The purpose of this exclusivity period was to incentivize generic manufacturers to challenge the patents of the branded product. David E. Korn, Erika Lietzan & Shaw W. Scott, *A New History and Discussion of 180-Day Exclusivity*, 64 FOOD & DRUG L.J. 335, 335 (2009); Erika Lietzan & Julia Post, *The Law of 180-Day Exclusivity*, 71 FOOD & DRUG L.J. 327, 327 (2016). But scholars have also noted the ways in which generic manufacturers may “park” the exclusivity to delay generic entry. See Victor L. Van de Wiele, Jonathan J. Darrow & Aaron S. Kesselheim, *No Parking Here: A Review of Generic Drug 180-Day Exclusivity and Recent Reform Proposals*, 20 YALE J. HEALTH POL’Y L. & ETHICS 131, 133 (2021). Cf. Rebecca E. Wolitz, Aaron S. Kesselheim & Jonathan J. Darrow, *Government Patent Use to Promote Public Health in the United States: Overcoming Nonpatent Exclusivities*, 112 AM. J. PUB. HEALTH 1110, 1110 (2022) (considering potential pathways for increasing drug accessibility during exclusivity periods).

⁶⁸ 21 U.S.C. § 355(j)(5)(F)(iii). Experts argue, however, that this exclusivity period may have more limited effects than the others. As Eisenberg has pointed out, new use patents or additional exclusivity periods for new uses do not protect manufacturers against generic competition that may exist for the older use, which now lacks exclusive protection. Eisenberg, *The Problem of New Uses*, *supra* note 42, at 720. State generic substitution laws may then lead to the dispensation of the generic for the newer, patented indication. *Id.* at 729.

⁶⁹ 21 U.S.C. § 355a(b)(1)(A)(i)(I). For an overview of how this incentive has worked to promote pediatric trials—and what opportunities still remain for improving such research—see Allan M. Joseph, *Kid Tested, FDA Approved: Examining Pediatric Drug Testing*, 72 FOOD & DRUG L.J. 543 (2017).

⁷⁰ 21 U.S.C. § 355f.

⁷¹ See, e.g., Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 359; Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 424 (2012); Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 104-05 (2016); Lisa Larrimore Ouellette, *Erika Lietzan on the Myths of Data Exclusivity*, WRITTEN DESCRIPTION (Nov. 12, 2015, 11:54 AM), <https://writtendescription.blogspot.com/2015/11/erika-lietzan-on-myths-of-data.html> [<https://perma.cc/ERT5-78JN>].

investments in innovation by granting valuable exclusionary rights.⁷² This is by design: exclusivity periods can function as a patent-like guarantee of market exclusivity for products that may not be able to receive patent protection⁷³ or whose patents may have expired. But for the vast majority of new drugs, exclusivity periods and patents are likely to run concurrently for some period of time after the drug is approved.⁷⁴

However, there are important differences between patents and FDA exclusivity periods. One set of key differences relates to enforceability: in order to enforce their patent rights, drug manufacturers must not only expend resources to identify potential infringers, but must also take steps to enforce their patents through litigation, a costly process that may result in the invalidation of their patents.⁷⁵ But FDA exclusivity periods are enforced by FDA, and more precisely by its *inaction*, or failure to approve applications for marketing. They generally require no resource commitments from manufacturers,⁷⁶ and it is not typical for generic manufacturers to challenge their issuance. A second set of differences relates to scope: FDA exclusivity periods are tied specifically to the approved product and often its indication,⁷⁷ while patents do not map precisely onto particular products. Patents may be broader, covering a class of compounds that includes the approved product, or narrower, covering a method of use or aspect of an approved drug.⁷⁸

The history behind these laws supports the claim that Congress's intent in establishing these exclusivity periods was to encourage innovation. Representative Henry Waxman played critical roles in the development and

⁷² Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 359, 361.

⁷³ See Rachel E. Sachs, *The Uneasy Case for Patent Law*, 117 MICH. L. REV. 499, 519 (2018) (identifying obstacles to patenting microbiome-based therapies); Mark A. Lemley & Jacob S. Sherkow, *The Antibody Paradox*, 132 YALE L.J. 994, 998-99 (2023) (identifying obstacles to patenting antibody-based therapies).

⁷⁴ Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 360.

⁷⁵ Heled, *supra* note 71, at 431-32; see also Russ Krajec, *Current Patent Litigation Costs Are Between \$2.3 to \$4M - from the BlueIron Blog*, ASSOCIATED PRESS (July 10, 2020, 8:02 AM), <https://apnews.com/press-release/news-direct-corporation/technology-business-intellectual-property-patents-a5dd5a7d415e7bae6878c87656e90112>; Filko Prugo, Scott McKeown & Jon Tanaka, *Orange, Purple Book Patentees Hone PTAB Survival Skills*, BLOOMBERG L. (June 13, 2018, 10:38 AM), <https://news.bloomberglaw.com/ip-law/insight-orange-purple-book-patentees-hone-ptab-survival-skills-1> (finding a validity rate of about 76% for Orange Book patents, as defined in Section I.D., at both the Patent Trial and Appeal Board and district court).

⁷⁶ Manufacturers do sometimes object to FDA interpretations of the marketing exclusivity provisions of the FDCA. See, e.g., *Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs.*, 66 F. Supp. 3d 217, 220 (D.D.C. 2014). These lawsuits, however, are brought against the government, underscoring the fact that manufacturers generally do not themselves need to enforce exclusivity periods to reap its benefits, as they do for patents.

⁷⁷ Heled, *supra* note 71, at 459-60.

⁷⁸ See Lisa Larrimore Ouellette, Note, *How Many Patents Does It Take to Make a Drug? Follow-on Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299, 300 (2010) (noting small-molecule drugs averaged 3.5 patents per drug in 2005).

passage of all three of these laws: the Orphan Drug Act and Hatch-Waxman Act as the chair of the House Energy & Commerce Committee's Subcommittee on Health and the Environment, and the Affordable Care Act as the chair of the full House Energy & Commerce Committee.⁷⁹ Writing about his efforts to develop and pass the Orphan Drug Act, Representative Waxman explained:

[O]ur bill encompassed three major incentives for pharmaceutical companies, each addressing a specific impediment to orphan drug development that we had uncovered in our survey and hearings. The first component eliminated the patent problem by providing a "market exclusivity provision" guaranteeing the drug's manufacturer a seven-year monopoly—in addition the clock would not start ticking until much later in the regulatory process, after the drug had received FDA approval.⁸⁰

The House Energy & Commerce Committee's report on the law reflected Representative Waxman's views, noting that the bill "includes an exclusive marketing right for the sponsor" of an orphan drug "[i]n order to provide some incentive for the development" of these products.⁸¹ The law as ultimately passed embodied these goals, including enacted legislative findings⁸² in which Congress concluded that "some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws . . . to provide financial incentives to develop such drugs."⁸³ FDA, likewise, understood that "[t]he main purpose of the Orphan Drug Act is to stimulate innovation."⁸⁴

Although Congress created these exclusivity periods to provide drug developers with innovation incentives and charged FDA with their administration, Congress did not direct FDA to actively consider innovation in its decisions.⁸⁵ In deciding whether to approve a new drug (and therefore to

⁷⁹ MINORITY STAFF OF H. COMM. ON ENERGY & COM., REP. HENRY A. WAXMAN'S RECORD OF ACCOMPLISHMENT 7, 9 (2014).

⁸⁰ HENRY WAXMAN, THE WAXMAN REPORT: HOW CONGRESS REALLY WORKS 63 (2009). The law also created a special program of grants for research into rare diseases and a new tax credit for qualifying clinical trial costs for orphan-designated drugs, in addition to existing research and development tax credit programs. Orphan Drug Act, Pub. L. No. 97-414, § 4-5, 96 Stat. 2053-57 (1983) (codified at 26 U.S.C. § 44H, 21 U.S.C. § 360ee). Although the original bill included a 90% tax credit, *see* WAXMAN, *supra*, at 63, as enacted the law contained a 50% tax credit. Orphan Drug Act § 4. The 2017 Tax Cuts and Jobs Act reduced this tax credit to 25%. Tax Cuts and Jobs Act, Pub. L. No. 115-97, § 13401(a), 131 Stat. 2133 (2017) (codified at I.R.C. § 45C(a)).

⁸¹ H.R. Rep. No. 97-840, pt. 1, at 11 (1982).

⁸² Jarrod Shobe, *Enacted Legislative Findings and Purposes*, 86 U. CHI. L. REV. 669, 674 (2019) (noting courts often ignore these findings).

⁸³ Orphan Drug Act § 1(b)(5).

⁸⁴ Orphan Drug Regulations, 56 Fed. Reg. 3338, 3338 (proposed Jan. 29, 1991) (to be codified at 21 C.F.R. pt. 316).

⁸⁵ FDA's administration of four programs for expedited drug approval—the Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review programs—is another example of congressionally created innovation policy in legislation which FDA implements

provide it with the associated exclusivity period), FDA is not itself instructed to decide whether doing so would promote innovation or not.⁸⁶

Nevertheless, these programs are important to consider as part of the range of FDA's innovation-related judgments. After all, even ministerial decisions can involve *some* judgment, and the line between what is simply administering an innovation program and what becomes an innovation-related judgment is blurry. For example, FDA administers a resource called the Approved Drug Products with Therapeutic Equivalence Evaluations—widely known as the Orange Book—that lists patent and exclusivity information for approved drugs.⁸⁷ Orange Book listings play a key role in resolving patent disputes under the Hatch-Waxman Act.⁸⁸ FDA, and courts, tend to describe the Agency's administration of the Orange Book as “purely ministerial”—simply listing the patents that drug manufacturers provide to FDA without policing whether they are correct.⁸⁹ At the same time, however, FDA does ban the listing of certain kinds of patents that it views as unrelated to the drug product or its use.⁹⁰ In this way, FDA arguably may be making innovation judgments about what kinds of technologies can block generic competition, even when the Agency views itself as having a ministerial role.

ministerially. See FDA, EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY 7-8 (2014), <https://www.fda.gov/media/86377/download> [<https://perma.cc/KX7Z-BLG7>].

⁸⁶ Some of the above-described exclusivity periods do require FDA to make judgments that may not be automatic. The three-year new use exclusivity period, for instance, 21 U.S.C. § 355(j)(5)(F)(iii), requires FDA to determine whether the studies in question are “essential to the approval of the application,” § 355(c)(2)(E)(iii), and the pediatric exclusivity period, § 355a(b)(1), requires FDA to determine whether “information relating to the use of a new drug in the pediatric population may produce health benefits in that population.” But these are inevitable innovation judgments as discussed in Section I.A, rather than those which require FDA to actively consider innovation.

⁸⁷ *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, FOOD & DRUG ADMIN. [hereinafter FDA, *Orange Book*], <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm> (last updated Feb. 2024). See generally FDA, ORANGE BOOK: QUESTIONS AND ANSWERS: DRAFT GUIDANCE FOR INDUSTRY (2020), <https://www.fda.gov/media/138389/download> [<https://perma.cc/RMK8-MVNR>]. For further discussion of the Orange Book, see *infra* Section IV.A.

⁸⁸ See *infra* Section VI.A.

⁸⁹ See, e.g., *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 237, 243 (4th Cir. 2002).

⁹⁰ FDA has long done this. In 2021, Congress passed the Orange Book Transparency Act, Pub. L. No. 116-290, 134 Stat. 4889-92 (2021) (codified as amended at 21 U.S.C. § 355), which amended the FDCA to codify FDA's long-standing approach (described in 21 C.F.R. § 314.53), by expressly prohibiting the listing of any patents that do not claim the drug substance, the drug product, or a method of use included in the New Drug Application. For critiques of FDA's position that its administration of the Orange Book is purely ministerial, see Jacob S. Sherkow, *Adminstrating Patent Litigation*, 90 WASH. L. REV. 205, 216-17 (2015); Jacob S. Sherkow & Patricia J. Zettler, *EpiPen, Patents, and Life and Death*, 96 N.Y.U. L. REV. ONLINE 164, 176 (2021).

As another example, even if the Agency's administration of an innovation program is ministerial, the Agency may have innovation-related views about the program, as an ongoing policy debate illustrates. A 2021 Eleventh Circuit decision rejected FDA's interpretation of the scope of market exclusivity under the Orphan Drug Act, under which the Agency had approved a competitor to Ruzurgi, a drug still within its exclusivity period, on the grounds that the competitor was seeking approval for an indication distinct from the indication for which Ruzurgi was approved, though Ruzurgi's orphan designation was for a broader population that included the competitor's approved indication.⁹¹ More specifically, although Ruzurgi had received an orphan *designation* for treating Lambert-Eaton Myasthenic Syndrome (a rare autoimmune disease) generally, its *approval* was limited to treating that disease in adults only, and the competitor sought approval to treat the disease in children.⁹² The decision prevents the Agency from granting additional approvals during the market exclusivity period for a drug possessing a broader orphan drug *designation*, even where its actual approved *indication* is narrower and leaves other patients with the disease without approved products. Although the Agency's oversight of these exclusivity periods is nominally ministerial, FDA took the position that the court's decision would harm innovation, arguing in its briefs that a ruling against the Agency would "threaten[] to discourage and delay the investment in orphan drugs that Congress specifically sought to boost."⁹³ After the ruling, FDA officials testifying before Congress warned that the decision "will send a chill into the development of rare diseases,"⁹⁴ even asking Congress to change the law in a way that would reverse the court's decision.⁹⁵

C. *Actively Considering Innovation*

As the previous Section demonstrates, in many cases, when Congress allocates new innovation-related responsibilities to FDA, those new responsibilities do not necessarily require FDA to actively make innovation-related judgments. At other times, however, Congress asks FDA to actively

⁹¹ *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299, 1306 (11th Cir. 2021).

⁹² *Id.* at 1304-05.

⁹³ Response Brief for Federal Defendants-Appellees at 32-33, *Catalyst*, 14 F.4th 1299 (No. 20-13922); *see also* Orphan Drug Regulations, 57 Fed. Reg. 62076, 62077 (Dec. 29, 1992) (to be codified at 21 C.F.R. pt. 316) (explaining the final rule "protect[s] the incentives of the Orphan Drug Act"); Orphan Drug Regulations, 56 Fed. Reg. 3338, 3338 (proposed Jan. 29, 1991) (to be codified at 21 C.F.R. pt. 316) (discussing the Agency's views on sameness as they relate to the Orphan Drug Act's innovation purpose).

⁹⁴ Zachary Brennan, *CDER Director on Accelerated Approval Reforms and a Court Decision That Will 'Send a Chill' Across Rare Disease Drug Development*, ENDPOINTS NEWS (Apr. 29, 2022, 1:53 PM), <https://endpts.com/cder-director-on-accelerated-approval-reforms-and-a-court-decision-that-will-send-a-chill-across-rare-disease-drug-development/>.

⁹⁵ Versions of the 2022 user fee legislation—although not the version that passed—did contain provisions that would have addressed this issue. *See, e.g.*, Food and Drug Amendments of 2022, H.R. 7667, 117th Cong. § 812 (2022).

consider innovation. This Section first describes two situations in which Congress has explicitly asked FDA to make innovation-related judgments: in the Orphan Drug Act, and for the grant of certain priority review vouchers. It then discusses FDA's undertaking of innovation-related judgments regarding the development of future products not currently before the Agency without a clear congressional requirement that it do so, briefly reviewing the examples discussed in Part I.

1. Congressionally Required Innovation Judgments

As noted above, the Orphan Drug Act is intended to increase manufacturers' incentives to develop drugs for "rare disease[s] or condition[s]."⁹⁶ This term is defined in the statute to include a numerical threshold: the Act primarily applies to conditions that "affect[] less than 200,000 persons in the United States."⁹⁷ However, the Act *also* applies to another set of conditions: those that "affect[] more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."⁹⁸

The Orphan Drug Act therefore sometimes requires FDA to determine whether this second standard is met—whether there is "no reasonable expectation" that the company can recoup its costs. In promulgating regulations implementing the Act, FDA has specified the data that sponsors requesting to use this pathway must provide, including both "[d]ata on all costs that the sponsor has incurred in the course of developing the drug for the U.S. market" and "[a]n estimate of and justification for the expected revenues from sales of the drug in the United States during its first 7 years of marketing," including "[a] projection of and justification for the price at which the drug will be sold."⁹⁹ This pathway has been rarely used, with FDA granting orphan designations on this basis to just three drugs in the Act's history¹⁰⁰—a topic to which we return in Section II.B.

In 2007, Congress instructed FDA to award priority review vouchers ("PRVs") to companies when their products are approved for the treatment of any of a particular set of tropical diseases.¹⁰¹ Under FDA's pre-2007 Priority Review program, the Agency aimed to speed review (from ten months to six

⁹⁶ 21 U.S.C. § 360bb(a).

⁹⁷ *Id.* § 360bb(a)(2).

⁹⁸ *Id.*

⁹⁹ 21 C.F.R. § 316.21(a)(2), (c)(1), (c)(6), (c)(6)(ii) (2024).

¹⁰⁰ See Kurt R. Karst, *The Rarely Used "Cost Recovery" Path to Orphan Drug Designation and Approval*, FDA L. BLOG (Feb. 1, 2009), <https://www.thefdalawblog.com/2009/02/the-rarely-used-cost-recovery-path-to-orphan-drug-designation-and-approval/> [<https://perma.cc/7KSX-EPHQ>]; Kao-Ping Chua & Rena M. Conti, *Orphan Drugs for Opioid Use Disorder: An Abuse of the Orphan Drug Act*, HEALTH AFFS. FOREFRONT (July 26, 2019), <https://www.healthaffairs.org/doi/10.1377/forefront.20190724.795814/full/>.

¹⁰¹ 21 U.S.C. § 360n(a)(1).

months) of drug applications for products intended to treat a serious condition that would provide a significant improvement in safety or effectiveness if approved.¹⁰² Under the new voucher program, a PRV bearer may present the voucher to FDA to shorten the review process for any drug that would not otherwise qualify for Priority Review.¹⁰³ The shortened review process has a range of benefits, including allowing the drug to spend more time on the market while under patent protection and possibly enabling its manufacturer to beat competitors to market. As such, the transferable PRV can be worth hundreds of millions of dollars,¹⁰⁴ in theory providing a powerful incentive for companies to invest in treatments for otherwise-neglected conditions.¹⁰⁵

When first established, the list of conditions meriting a PRV overlapped largely with the World Health Organization's ("WHO") list of Neglected Tropical Diseases.¹⁰⁶ But Congress foresaw that FDA might wish to add diseases to the PRV list, and it authorized FDA to designate by regulation "[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations" as PRV eligible.¹⁰⁷ FDA has added nine diseases to this list since the creation of the PRV,¹⁰⁸ on grounds that we return to in Section II.B. Although Congress would

¹⁰² See FDA, EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY, *supra* note 85, at 24-25.

¹⁰³ If the drug could have qualified for Priority Review under the pre-2007 criteria, there would be no need to use the PRV. A PRV can thus be used to give priority review to a product that would not otherwise meet those criteria, either because the condition it aims to treat is not serious or because it is not projected to provide a significant improvement.

¹⁰⁴ The highest known sale price to date for a PRV has been \$350 million, though as more PRVs have entered the market and become available for sale, the price has settled closer to \$100 million. See Michael Mezher, Zachary Brennan & Alexander Gaffney, *Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers*, REGUL. FOCUS (Feb. 25, 2020), <https://www.raps.org/news-and-articles/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know> [<https://perma.cc/9UDE-KFUD>].

¹⁰⁵ The PRV program was proposed by scholars for this purpose. See David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, 25 HEALTH AFFS. 313, 318 (2006).

¹⁰⁶ Congress's list included malaria and tuberculosis, which are not considered "neglected" under the WHO's definition, but did not include conditions like Chagas disease and cysticercosis, which are on the WHO list. *Neglected Tropical Diseases*, WORLD HEALTH ORG., <https://www.who.int/health-topics/neglected-tropical-diseases> [<https://perma.cc/6W82-3FUR>] (last visited Feb. 3, 2024).

¹⁰⁷ 21 U.S.C. § 360n(a)(3)(S). Over time, Congress has itself added diseases to this list, adding filoviruses (a class of diseases including Ebola) and Zika virus in 2014 and 2016, respectively. *Id.* § 360n(a)(Q)-(R); Adding Ebola to the FDA Priority Review Voucher Program Act, Pub. L. No. 113-233, § 2(1)(B), 128 Stat. 2127 (2014); Adding Zika Virus to the FDA Priority Review Voucher Program Act, Pub. L. No. 114-146, § 2(3), 130 Stat. 357 (2016).

¹⁰⁸ *Tropical Disease Priority Review Voucher Program*, FOOD & DRUG ADMIN. (July 15, 2020), <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program> [<https://perma.cc/RTJ4-8HRT>].

later create two additional PRV programs—one for rare pediatric diseases¹⁰⁹ and one for medical countermeasures¹¹⁰—neither statute includes lists of specific diseases, and neither explicitly empowers FDA to add additional diseases to the programs on innovation-related grounds.¹¹¹

In both of these cases, Congress has tasked FDA with making innovation judgments. For the Orphan Drug Act, when a company is seeking orphan drug designation on the ground that there is “no reasonable expectation” that it can recoup its costs, FDA must determine whether that is true—that is, the Agency must determine whether granting the designation is necessary for the company to invest in research and development of the potential treatment.¹¹² And for the PRV program, FDA must determine whether there is a significant enough market to spur innovation on its own, or whether the grant of a PRV is needed to incentivize innovation. But Congress has provided relatively little guidance or support for the Agency as it seeks to answer these questions.

2. Agency-Initiated Innovation Judgments

Along with congressionally directed innovation-related judgments in the context of overseeing innovation incentive programs, FDA appears to also sometimes consider innovation incentives when it is not clearly required to do so, in an effort to support the development of future products and the broader innovation ecosystem for drugs. The Agency’s Aduhelm and Exondys 51 approvals, discussed in Part I, provide two particularly striking examples.

But these examples don’t stand alone. For decades, FDA officials have considered innovation promotion a core part of their work.¹¹³ In 1983, FDA’s Chief Counsel explained that although FDA “does not directly consider patents in any of its decisions, [and] regards its own approval system as independent of the patent system, . . . that doesn’t mean FDA doesn’t take into account or

¹⁰⁹ Food & Drug Administration Safety & Innovation Act, Pub. L. No. 112-114, § 908, 126 Stat. 1094 (2012) (codified at 21 U.S.C. § 360ff).

¹¹⁰ 21st Century Cures Act, Pub. L. No. 114-255, § 3086, 130 Stat. 1145 (2016) (codified at 21 U.S.C. § 360bbb-4a).

¹¹¹ The rare pediatric voucher program does note that the disease in question must qualify as a “rare disease or condition” under the Orphan Drug Act, 21 U.S.C. § 360ff(a)(3)(B), which includes an innovation-related nonprofitability condition as discussed *infra* Section II.B.1. And for the medical countermeasure voucher program, HHS and the Department of Homeland Security identify “material threats” that may qualify for the program, but not on innovation grounds. U.S. GOV’T ACCOUNTABILITY OFF., DRUG DEVELOPMENT: FDA’S PRIORITY REVIEW VOUCHER PROGRAMS 7 tbl.1 (2020).

¹¹² 21 C.F.R. § 316.21(a)(2) (2024).

¹¹³ This Article is primarily focused on innovation judgments made by FDA in the context of individual, product-level decisions, such as in the examples of Aduhelm and Exondys 51. As noted in this paragraph, however, FDA may engage in broader policymaking efforts that are motivated by innovation promotion. This Article does not provide a full treatment of the similarities and differences between the two types of decision-making processes, and there may be reasons to analyze them differently. For example, individual product-level decisions may lack the public engagement and transparency involved in broader policymaking efforts.

cannot take into account incentives to innovate.”¹¹⁴ In 2003, FDA announced a public workshop to discuss scientific and clinical developments in drug and biologic delivery systems, explaining that the workshop was “part of a broad effort to increase the development of novel medical technologies.”¹¹⁵ And in 2017, FDA announced a comprehensive policy for regenerative medicine products, as well as a period in which FDA would exercise its discretion not to enforce requirements to allow developers time to come into compliance.¹¹⁶ In announcing the policy, FDA’s Commissioner explained:

We need to provide a clear, efficient pathway for product developers, while making sure that we meet our obligation to help ensure the safety and efficacy of these medical products so that patients can benefit from these novel therapies.

. . . Our aim is to make sure we’re being nimble and creative when it comes to fostering innovation, while taking steps to protect the safety of patients.¹¹⁷

In 2022, after this enforcement discretion period ended, Peter Marks, the director of FDA’s Center for Biologics Evaluation and Research, announced that FDA is considering an “intermediate pathway” for certain cell- and tissue-based products that would be something short of approval through a biologics license application, reportedly “to underscore [FDA’s] continued commitment to work with those who share [the] goal of advancing the development of safe and effective regenerative medicine products.”¹¹⁸ The Agency had a webpage devoted entirely to “Innovation at FDA,” providing links to innovation news, speeches and testimony, and reports and factsheets, among other things.¹¹⁹

¹¹⁴ *Drug Labeling and Advertising and New Drug Application: Hearing on H.R. 1554 and H.R. 3605 Before the Subcomm. on Health and the Env’t of the H. Comm. on Energy and Com.*, 98th Cong. 20 (1983).

¹¹⁵ Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical, and Regulatory Challenges Public Workshop, 68 Fed. Reg. 33723, 33724 (June 5, 2003). This workshop was held by FDA’s Center for Devices and Radiologic Health, as drug and biologic delivery systems are generally considered to be devices.

¹¹⁶ Press Statement, Scott Gottlieb, Comm’r, FDA, Statement on FDA’s Comprehensive New Policy Approach to Facilitating the Development of Innovative Regenerative Medicine Products to Improve Human Health (Nov. 15, 2017), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-comprehensive-new-policy-approach-facilitating> [<https://perma.cc/JH6D-CYV2>].

¹¹⁷ *Id.*

¹¹⁸ Sue Sutter, *US FDA to Explore New Regulatory Pathways for Some Cellular Products*, PINK SHEET (May 23, 2022), <https://pink.citeline.com/PS146208/US-FDA-To-Explore-New-Regulatory-Pathways-For-Some-Cellular-Products> [<https://perma.cc/E8FQ-2YMY>].

¹¹⁹ *Innovation at FDA*, FOOD & DRUG ADMIN. (Dec. 12, 2017), <https://web.archive.org/web/20200319122322/https://www.fda.gov/about-fda/innovation-fda>. The webpage, however, has not been updated since 2017 and has been taken down.

Taken together, these examples—which are by no means exhaustive¹²⁰—suggest that FDA is considering innovation on its own initiative in a broad range of regulatory activities.¹²¹ The Agency doing so may reflect a kind of mission creep—as Congress has increasingly tasked the Agency with administering innovation incentive programs, the Agency has increasingly considered innovation elsewhere as well. Or it may reflect the Agency’s view that innovation is integral to its public health mission,¹²² the political reality in which the Agency operates (in which it often faces critiques that it is hindering innovation),¹²³ or some combination of these.

II. FDA’S INNOVATION PERFORMANCE

Given that FDA has assumed a wide range of innovation-related functions, this Part considers how well the Agency is suited to these responsibilities. First, this Part considers the case for broadly exercising innovation-related judgment at FDA: given the Agency’s specialized knowledge and its oversight of drugs throughout their innovation lifecycles, it would seem a natural fit for this role. Second, this Part considers potential challenges with FDA’s assumption of these roles, as the Agency seems to lack a reasoned theory of innovation and may suffer from resource constraints. Finally, this Part notes how FDA’s innovation-

¹²⁰ For example, FDA also has invoked innovation-related reasoning in decision making and discussions regarding nondrug products within its jurisdiction. When FDA announced a “comprehensive plan” for regulating tobacco and nicotine products in 2017, it also announced it would delay enforcing certain requirements for novel tobacco products, like e-cigarettes, “to encourag[e] innovations.” News Release, FDA Announces Comprehensive Regulatory Plan to Shift Trajectory of Tobacco-Related Disease, Death (July 27, 2017), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm568923.htm> [<https://perma.cc/SQ3Y-E82G>]. *But see* Micah L. Beran, *The Faltering Promise of FDA Tobacco Regulation*, 12 ST. LOUIS U. J. HEALTH L. & POL’Y 145, 160 (2018) (critiquing FDA’s position that this policy would encourage innovation). In June 2022, FDA’s Commissioner called for Congress to give FDA new food authorities to better “support innovation without sacrificing [the Agency’s] standards.” Robert M. Califf, Comm’r, FDA, Remarks to the 2022 FDLI Annual Conference (June 14, 2022) (prepared remarks available at <https://www.fda.gov/news-events/speeches-fda-officials/remarks-commissioner-califf-2022-fdli-annual-conference-06142022> [<https://perma.cc/3GF3-D2NW>]).

¹²¹ *But cf.* Memorandum from Robert M. Califf, *supra* note 26, at 7 (describing rise of patient-centered drug development as part of environment in which FDA approved Exondys 51); LEWIS A. GROSSMAN, CHOOSE YOUR MEDICINE: FREEDOM OF THERAPEUTIC CHOICE IN AMERICA 193 (2021) (linking evolutions in FDA’s incorporation of patient voices into risk-benefit assessment to the AIDS movement).

¹²² *Cf.* 21 U.S.C. § 393(b) (providing that FDA’s mission includes “promot[ing] the public health”).

¹²³ *See, e.g.*, Nathan G. Cortez, I. Glenn Cohen & Aaron S. Kesselheim, *FDA Regulation of Mobile Health Technologies*, 371 NEW ENG. J. MED. 372, 372 (2014); Kapczynski, *supra* note 62, at 2360-63; *see also* Peter B. Hutt, *The Evolution of Federal Regulation of Human Drugs in the United States: An Historical Essay*, 44 AM. J.L. & MED. 403, 420 (2018) (broadly describing the history of U.S. drug regulation, including criticisms about slowing innovation that FDA faced early in its implementation of the modern drug approval regime).

related decisions may conflict with other policy goals, in ways that should affect our assessment of the Agency's role in this area.

A. *FDA's Innovation Advantages*

Innovation in the drug ecosystem—that is, the development of drugs that actually work—serves FDA's public health mission.¹²⁴ There are at least two reasons why FDA is arguably ideally suited for the innovation-related functions that Congress has delegated to it, or that it has assumed, in recent years: first, FDA has expertise in understanding the complex scientific process needed to bring new drugs to market, and second, FDA exercises oversight of drugs across their lifecycles. This Section discusses each of these advantages in turn.

1. Understanding Drug Development

FDA is the federal administrative agency with the greatest expertise in understanding the complex scientific process needed to bring new drug products (or uses) to market. To be sure, patents are often viewed as the primary federal tool for promoting innovation, and the PTO accordingly is the Agency generally tasked with “driv[ing] U.S. innovation.”¹²⁵ But there is widespread agreement that biomedical innovation poses challenges distinct from those in many other fields, and patent law—with its one-size-fits-all approach to encouraging innovation across many areas—is insufficient to the challenges in the biopharmaceutical space.¹²⁶ For example, the effective duration of patents for drugs may be shorter than that for some other products because of the time-consuming research that must be conducted before a drug may be marketed.¹²⁷ The time devoted to premarket research shortens the time during which a manufacturer can market its product with patent protection. These kinds of timing challenges helped prompt Congress to create the patent-like innovation

¹²⁴ See, e.g., Toni Clarke, *In Swansong, FDA Chief Defends Drug Approval Process*, REUTERS (Mar. 27, 2015, 8:25 PM), <https://www.reuters.com/article/us-fda-commissioner-speech/in-swansong-fda-chief-defends-drug-approval-process-idUSKBN0MO00V20150328> [<https://perma.cc/4HE5-TGVY>] (quoting Commissioner Margaret Hamburg as explaining that “[i]n the race for the newest treatment we must remember the point that innovation doesn't matter if the product doesn't work”).

¹²⁵ *U.S. Patent and Trademark Office*, U.S. DEP'T OF COM., <https://www.commerce.gov/bureaus-and-offices/uspto> [<https://perma.cc/MV6G-KZLB>] (last visited Feb. 4, 2024); see also Rebecca E. Wolitz, *States, Preemption, and Patented Drug Prices*, 52 SETON HALL L. REV. 385, 392 (2021) (“[T]he federal patent system is best understood as being charged with sufficiently incentivizing innovation.”); U.S. Const. art. I, § 8, cl. 8 (providing Congress with the power “[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors [certain] exclusive Right[s]”).

¹²⁶ See, e.g., Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 4, at 351; Erika Lietzan & Kristina M.L. Aciri née Lybecker, *Distorted Drug Patents*, 95 WASH. L. REV. 1317, 1326 (2020); W. Nicholson Price II, *The Cost of Novelty*, 120 COLUM. L. REV. 769, 771 (2020).

¹²⁷ See, e.g., Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. REV. 672, 752 (2014).

incentives, discussed in Section I.B, which promote innovation in drug development in ways similar to patent law.

Moreover, while patent law focuses on the creation of new technologies based on the assumption that patent incentives alongside market forces will drive technological improvement over time,¹²⁸ FDA's drug authority focuses on the creation of new technologies *that work*.¹²⁹ This is important because current health care markets by themselves are ill-suited to drive *quality* innovation in drug development.¹³⁰ Although prescription drug purchasing decisions are shaped by sophisticated entities, insurers, health care systems, and even health care professionals—let alone patients!—are generally unable to evaluate the safety, effectiveness, and quality of drugs.¹³¹ Deciding when drugs are supported by sufficient evidence of effectiveness, and how to incentivize the development of novel drugs that work, are complicated questions involving nuanced judgments.

The accelerated approval pathway, through which FDA approved both Aduhelm and Exondys 51—described in Part I—provides an example of the kinds of nuanced decisions required to effectively promote beneficial innovation in the biopharmaceutical market. While FDA may have made the wrong choices with respect to promoting innovation by approving these two products, as we discuss more thoroughly below, these kinds of approval decisions do involve case-specific considerations that are difficult to second-guess. For example, Exondys 51 is approved for certain patients with Duchenne muscular dystrophy, a rare disease affecting a small number of people in the United States. The manufacturer of Exondys 51 and FDA were criticized for, among other things, the small size of the pivotal clinical trial supporting approval—which included just twelve patients—because of the possibility that the approval would encourage other manufacturers to seek approval based on such small trials, particularly where the evidence itself was not strong.¹³² On the other hand, the

¹²⁸ Price, *The Cost of Novelty*, *supra* note 126, at 772.

¹²⁹ The FDCA does not, however, require that drugs be more effective than those already on the market, which, from an innovation perspective, is at least a debatable stance. See Daniel J. Hemel & Lisa Larrimore Ouellette, *Valuing Medical Innovation*, 75 STAN. L. REV. 517, 525 (2023) (arguing for rewarding drugs based on value relative to existing standard of care); Dmitry Karshedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 IOWA L. REV. 1129, 1192-98 (2019) (proposing a comparative efficacy standard).

¹³⁰ See, e.g., Kapczynski, *supra* note 62, at 2358-59 (arguing that markets cannot produce adequate third-party validators of evidence about medicines); Hemel & Ouellette, *supra* note 129, at 525; see also Cortez et al., *supra* note 123, at 372 (making a similar point about FDA's device authorities).

¹³¹ See Kapczynski, *supra* note 62, at 2368 (“Unregulated markets can neither produce balanced information about drugs nor rigorously evaluate evidence produced about drugs.”).

¹³² Kesselheim & Avorn, *supra* note 25, at 2357.

size of the Exondys 51 trial was not without precedent¹³³ and, if FDA were to set trial size expectations too large for rare diseases, that might discourage companies from entering the rare disease space altogether.¹³⁴ Given its deep scientific expertise, FDA may be best suited—and better suited than the PTO, at least—to understand innovation in the biopharmaceutical space, and to make decisions that drive the development of effective new products or uses.

2. Regulating Across Drugs' Lifecycles

A second reason FDA may be well suited to making innovation-related judgments is that, unlike other biopharmaceutical innovation actors,¹³⁵ FDA oversees a drug's entire lifecycle—from preclinical studies, to clinical trials, to approval, to marketing and the drug's use in the practice of medicine. This affords FDA the opportunity to adopt a comprehensive approach to promoting innovation in drug development. It can implement “push” incentives that can ease and speed drug development before approval.¹³⁶ These incentives include expedited approval programs, such as accelerated approval in addition to priority review, fast-track designation, and breakthrough designation.¹³⁷ FDA can also implement “pull” incentives which reward drug manufacturers once they create a product receiving FDA approval, such as through administering exclusivity periods and granting PRVs.¹³⁸

FDA can also shape innovation in ways that may not neatly fit into either a push or pull category. For example, the Agency can issue guidance meant to shape drug development in particular areas of public health importance, such as

¹³³ Frank J. Sasinowski, Erika B. Panico & James E. Valentine, *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014*, 49 THERAPEUTIC INNOVATION & REGUL. SCI. 680, 690, 692 (2015) (discussing six-person study for Juxtapid and thirteen-person study for Anascorp); Frank J. Sasinowski, *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs*, 46 DRUG INFO. J. 238, 239 (2012) (“The examination of 135 orphan drugs found that 90 approvals were based on some exercise of flexibility by FDA.”).

¹³⁴ Cf. S. Claiborne Johnston et al., *It's Time to Harmonize Clinical Trial Site Standards*, NAT'L ACAD. OF MED. (Oct. 9, 2017), <https://nam.edu/its-time-to-harmonize-clinical-trial-site-standards/> [<https://perma.cc/66HM-65TA>] (“Climbing costs and lengthy time frames of clinical trials are significant bottlenecks in medical product development. Despite the fact that scientific discoveries yield many new possible targets for developing into therapies, the capacity and resources with which to develop these targets are limited, thereby leaving potentially valuable discoveries undeveloped and unrealized.”).

¹³⁵ See, e.g., Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. 1991, 1997-2013 (2018) (discussing the National Institutes of Health's role as an innovation actor).

¹³⁶ *Id.* at 2005-06.

¹³⁷ *Id.*

¹³⁸ E.g., Sachs, *Administering Health Innovation*, *supra* note 135, at 2005.

antibiotics, analgesics, or COVID-19 vaccines.¹³⁹ Where such guidance can speed drug development by providing regulatory certainty and making more transparent the Agency's expectations for research design and the kinds of evidence needed for approval, it may serve as a push incentive. But in some of these cases, such as a guidance that requires companies to conduct larger trials or look for previously unstudied safety signals, transparency may *increase* costs beyond what might have been expected, even if it provides regulatory clarity. In either case, by establishing the Agency's views on what constitutes sufficient evidence of effectiveness for drug classes or therapeutic areas, such guidance can reduce uncertainty and set goals for innovation going forward.

Other government agencies administer more limited innovation levers at particular points in a drug's lifecycle. For example, although the National Institutes of Health ("NIH") has awarded a small number of prizes (pull incentives) for certain biomedical innovations, most of its innovation promotion comes in the form of pushes—grants awarded for basic or translational research, which happens early in a drug's lifecycle or might even precede drug development.¹⁴⁰ As another example, the Centers for Medicare and Medicaid Services ("CMS")—by paying for drugs that FDA has approved for patients covered by Medicare and Medicaid—offers pull incentives later in a drug's lifecycle, which reward companies that successfully develop drugs.¹⁴¹ Although the NIH and CMS have quite different roles, they are similarly limited in the kinds of innovation promotion in which they engage and in the points of a drug's lifecycle at which they promote innovation.¹⁴² In contrast, FDA's ability to regulate across a drug's lifecycle, coupled with its deep knowledge of the drug development process, positions it well to make innovation-related decisions for the biopharmaceutical market.

¹³⁹ *E.g.*, FDA, ANTIBACTERIAL THERAPIES FOR PATIENTS WITH AN UNMET MEDICAL NEED FOR THE TREATMENT OF SERIOUS BACTERIAL DISEASES: GUIDANCE FOR INDUSTRY (2017), <https://www.fda.gov/files/drugs/published/Antibacterial-Therapies-for-Patients-With-an-Unmet-Medical-Need-for-the-Treatment-of-Serious-Bacterial-Diseases.pdf> [<https://perma.cc/UBW2-EQE3>]; FDA, DEVELOPMENT OF NONOPIOID ANALGESICS FOR ACUTE PAIN: DRAFT GUIDANCE FOR INDUSTRY (2022), <https://www.fda.gov/media/156063/download>; FDA, DEVELOPMENT AND LICENSURE OF VACCINES TO PREVENT COVID-19: GUIDANCE FOR INDUSTRY (2020), <https://www.fda.gov/media/139638/download> [<https://perma.cc/RGP7-3MNR>].

¹⁴⁰ Sachs, *Administering Health Innovation*, *supra* note 135, at 1997-98. *See generally* W. Nicholson Price II, *Grants*, 34 BERKELEY TECH. L.J. 1 (2019).

¹⁴¹ Sachs, *Administering Health Innovation*, *supra* note 135, at 2012.

¹⁴² There are also examples outside HHS, including U.S. military efforts to support and develop new biomedical technologies. *See, e.g.*, Efthimios Parasidis, *Justice and Beneficence in Military Medicine and Research*, 73 OHIO ST. L.J. 723, 730 (2012). *Cf.* Tammi S. Etheridge, *What's the Beef? The FDA, USDA, and Cell-Cultured Meat*, 78 WASH. & LEE L. REV. 1729, 1761 (2022) (discussing USDA's role in food innovation).

B. *FDA's Innovation Disadvantages*

Although FDA has certain innovation advantages, there also are reasons to be concerned about the Agency making innovation-related judgments, whether at Congress's direction or on its own initiative. The broadest disadvantage, which runs throughout this piece, is that promoting innovation may be in tension with FDA's primary, constitutive public health mission of ensuring the safety and effectiveness of medical products, and introducing innovation as a consideration may undermine public trust in and the legitimacy of FDA decision making. We return to this tension at its tautest in the next Part. Nevertheless, there are two other disadvantages the Agency faces as an innovation agency, even setting aside the tension between different goals. First, FDA has not publicly articulated a strategy for promoting innovation. The apparent lack of such a strategy has the potential to create conflicting judgments both over time and across the wide range of regulatory decisions that the Agency makes. Second, as a resource-constrained agency, the very act of focusing on innovation judgments may take away from FDA's performance of its core functions in ways that even the Agency itself might oppose.

1. Lack of a Transparent Strategy

Although there are many types of innovation and varied contestable innovation strategies, at a minimum, FDA ought to make transparent its strategy for promoting innovation, and apply that strategy in a fair, consistent, and internally coherent way.¹⁴³ As the following three examples of FDA's innovation-related arguments demonstrate, however, FDA often has not met even this minimum expectation, regardless of what one thinks of the merits of FDA's decisions.¹⁴⁴

The first returns to the examples that began the Introduction: although the Agency's core function—to determine whether new drugs are safe and effective for their intended purpose—does not contemplate the implications of an approval decision for innovation incentives for the development of future products not currently before the Agency, in high-profile cases in recent years,

¹⁴³ See Erika Lietzan, *Access Before Evidence and the Price of the FDA's New Drug Authorities*, 53 U. RICH. L. REV. 1243, 1285 (2019); Yoav Dotan, *Making Consistency Consistent*, 57 ADMIN. L. REV. 995, 1001 (2005); Shalini Bhargava Ray, *Immigration Law's Arbitrariness Problem*, 121 COLUM. L. REV. 2049, 2098 (2021); Christopher J. Walker, *How to Win the Deference Lottery*, 91 TEX. L. REV. SEE ALSO 73, 80 (2013).

¹⁴⁴ Although we focus on pharmaceutical innovation in this paper, others have similarly questioned FDA's innovation-related judgments in other product areas. For example, Micah L. Berman has criticized FDA's decision to delay enforcing premarket review requirements for certain tobacco products to "encourage innovations." Berman noted FDA applied its enforcement discretion *only* to those products that were already being marketed, and that, "[b]y definition, delaying review of products that are already being sold does nothing to promote innovation." Micah L. Berman, *The Faltering Promise of FDA Tobacco Regulation*, 12 ST. LOUIS U. J. HEALTH L. & POL'Y 145, 160 (2018).

FDA officials have referred to such innovation impacts as reasons to either approve or reject a new drug application.

The most explicit of these innovation-related justifications came during FDA's 2016 approval of Sarepta's Exondys 51 (eteplirsen), indicated for the treatment of a subset of patients with Duchenne muscular dystrophy.¹⁴⁵ Exondys 51 was the first drug approved specifically for Duchenne muscular dystrophy patients—but the approval was highly controversial. The advisory committee that was convened to review the data supporting the drug voted 7-3 against granting a traditional approval on the grounds that there was insufficient evidence of clinical efficacy, and 7-6 against granting an accelerated approval on the grounds that the drug did not produce sufficient muscle proteins to translate into a clinical benefit.¹⁴⁶ Although the Agency's primary scientific reviewers also opposed approving the drug, they were overruled by Dr. Janet Woodcock, then director of FDA's CDER, and the FDA Commissioner declined to overturn her decision.¹⁴⁷

Yet internally, Dr. Woodcock appears to have made the case for approving Exondys based not only on the clinical trials involved, but also on the approval's impact on future innovation. Internal FDA briefing documents noted the following:

In her presentation to the [Scientific Dispute Resolution] Board, Dr. Woodcock suggested that, in making the decision, she was looking at the broader picture for the development of these types of drugs for very limited patient populations in the United States (between 600 and 1300) and that there needed to be some path forward for such innovative products. She opined that Sarepta in particular "needed to be capitalized." She noted that the sponsor's stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its

¹⁴⁵ FDA, Exondys 51 (eteplirsen) Label (2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf [<https://perma.cc/S925-KXAC>]; News Release, FDA, FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy (Sept. 19, 2016), <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy>.

¹⁴⁶ Exondys 51 Summary Minutes, *supra* note 24, at 7-8, 10; Kesselheim & Avorn, *supra* note 25, at 2357. An advisory committee vote is, by definition, just that: advisory and not binding on the Agency. Additionally, internal disagreement at FDA is to be expected—the Agency is tasked with making regulatory decisions that are often difficult and involve complicated scientific and public health judgments about which reasonable experts can disagree. Accordingly, we do not intend to suggest that FDA decisions that differ from what an advisory committee recommends are necessarily suspect, nor that internal disagreement necessarily means the Agency reached the wrong decision in any instance. Rather, we use the Exondys 51 and Aduhelm examples to highlight the ways that the Agency seems to have used broad innovation considerations to help it resolve difficult questions about these particular drugs.

¹⁴⁷ Exondys 51 Summary Minutes, *supra* note 24, at 7-8.

pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would “lapse into a position of” self-treatment.¹⁴⁸

More generally, the internal documents note Dr. Woodcock’s focus on “the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases).”¹⁴⁹

Dr. Ellis Unger, the Director of the Office of Drug Evaluation, took a sharply different view of the innovation ramifications of the decision. He argued that approving the drug would *harm* innovation for at least two reasons. First, he argued that “approval of an ineffective therapy has the potential to discourage or inhibit the development of other drugs that *are* effective,” giving the example “of a related drug with far greater potential to promote dystrophin production in patients with [Duchenne muscular dystrophy].”¹⁵⁰ He noted that patients would have to agree to stop treatment on Exondys 51 for a manufacturer to complete clinical trials on this potential new product, “and few patients may be willing to do so.”¹⁵¹ Second and more broadly, he warned that “[w]ith accelerated approval of this NDA, there would be highly detrimental effects on drug development” in which “the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence of effectiveness.” For companies, “[t]here would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of failure would provide a disincentive to conduct such trials.”¹⁵²

Dr. Woodcock’s statements in particular were widely criticized. In declining to overturn her decision, Commissioner Califf noted that he was “troubled” by the statements in the reviewing “memo that Dr. Woodcock’s decision to approve eteplirsen may have been inappropriately motivated by concerns over the sponsor’s financial well-being,” though after discussing the issue with Dr. Woodcock, he concluded “that her decision was based on the science.”¹⁵³ Dan Carpenter, the author of a canonical history of FDA drug regulation and public trust,¹⁵⁴ disagreed, arguing that Dr. Woodcock “began to think about the drug review process as one in which the incentives and culture for future innovations had to be protected,” taking into account the implications of one drug’s approval

¹⁴⁸ See Memorandum from Luciana Borio, *supra* note 27, at 16.

¹⁴⁹ *Id.* at 10.

¹⁵⁰ Agency Scientific Dispute Appeal from Ellis F. Unger, Dir., Off. of Drug Evaluation, Ctr. for Drug Rsch. & Eval., FDA, to G. Mathew Warren, Dir., Off. of Sci. Integrity, FDA 22 (July 18, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_redacted.pdf [<https://perma.cc/7A7M-XLHE>].

¹⁵¹ *Id.*

¹⁵² *Id.* at 22-23.

¹⁵³ Memorandum from Robert M. Califf, *supra* note 26, at 8 n.23.

¹⁵⁴ DANIEL CARPENTER, REPUTATION AND POWER (2010).

for innovation incentives more broadly.¹⁵⁵ In Carpenter’s view, this perspective is “not in keeping with the spirit of the 1938 Food, Drug and Cosmetic Act, to tether these decisions, basically give one drug a pass so that somehow you think that there will be better incentives for developing others in the future.”¹⁵⁶ Pharmaceutical journalist Matthew Herper argued that although Woodcock’s observations about Sarepta’s financial situation were “probably true, . . . [i]t’s also not a reason to approve a drug.”¹⁵⁷ Another outlet emphasized that these financial considerations are “not supposed to play a role in FDA decisionmaking.”¹⁵⁸ Even the *Wall Street Journal* editorial board, which praised the approval itself, noted that these financial considerations were “irrelevant to approval.”¹⁵⁹ Dr. Unger’s comments also received criticism, with Herper noting that Dr. Unger was worried about the cost of the drug, which is not supposed to factor into FDA decision making.¹⁶⁰

Five years later, the Agency’s controversial approval of Aduhelm referred less explicitly to innovation, at least publicly.¹⁶¹ FDA’s approval announcement emphasized that “the accelerated approval pathway can bring therapies to patients faster while spurring more research and innovation,”¹⁶² while a (highly unusual) *Washington Post* opinion piece from FDA officials defending the decision highlighted that the accelerated approval program “ha[s] propelled progress forward,” particularly in the cancer space.¹⁶³

¹⁵⁵ Sarah Karlin-Smith, *She Didn’t Need to Be Commissioner: Janet Woodcock’s Transformative Legacy*, PINK SHEET (Dec. 1, 2021), <https://pink.pharmaintelligence.informa.com/PS145327/She-Didnt-Need-to-Be-Commissioner-Janet-Woodcocks-Transformative-Legacy> [<https://perma.cc/GL73-JD47>].

¹⁵⁶ *Id.*

¹⁵⁷ Herper, *supra* note 22.

¹⁵⁸ Derrick Gingery, *Woodcock’s Consideration of Sarepta Financial Issues Raises Eyebrows*, PINK SHEET (Sept. 19, 2016), <https://pink.pharmaintelligence.informa.com/PS119158/Woodcocks-Consideration-of-Sarepta-Financial-Issues-Raises-Eyebrows>.

¹⁵⁹ Opinion, *The Boys Who Beat the FDA*, WALL ST. J. (Sept. 19, 2016, 7:49 PM), <https://www.wsj.com/articles/the-boys-who-beat-the-fda-1474328940>.

¹⁶⁰ Herper, *supra* note 22.

¹⁶¹ As with Exondys 51, there was some internal disagreement about whether to approve the drug, although seemingly not as heated, nor did disagreement publicly appear to include innovation-related arguments. The review team consisted of the Office of Neuroscience, Office of Clinical Pharmacology, Office of Translational Sciences, and Office of Biostatistics, all within CDER. The Office of Biostatistics recommended against approval without publicly discussing innovation, while all the other offices recommended approval, again without publicly noting innovation-related concerns, and the directors of the Office of New Drugs and of CDER concurred with the approval recommendations. See *Drug Approval Package: Aduhelm (aducanumab-avwa)*, FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000TOC.cfm [<https://perma.cc/P5SQ-V5A8>] (last updated June 28, 2021).

¹⁶² News Release, FDA, FDA Grants Accelerated Approval for Alzheimer’s Drug, *supra* note 18.

¹⁶³ Cavazzoni et al., *supra* note 18.

At one level, the dispute between Drs. Woodcock and Unger is an empirical one: Will approvals like Exondys 51 and Aduhelm lead to more approved drugs, or fewer, and what will the health benefits of those drugs be?¹⁶⁴ That is, as Dr. Unger worried, it could be the case that approvals like these do lead to an increased *number* of newly approved drugs—but also that those drugs offer weak or no clinical benefits. FDA has not publicly advanced a framework for analyzing this question, but many scholars agree with Dr. Unger’s view. As Holly Fernandez Lynch notes, companies “will have little incentive to prove that [their drugs work] definitively if FDA doesn’t make them.”¹⁶⁵

Others, for example, pointed to FDA’s January 2023 accelerated approval of Leqembi (lecanemab) for Alzheimer’s Disease—an approval which, like Aduhelm’s, was based on a showing that the drug reduced amyloid plaques in the brain—as evidence supporting Dr. Unger’s view.¹⁶⁶ In July 2023 FDA then converted Leqembi to traditional approval, after the Agency determined a subsequent trial confirmed clinical benefit.¹⁶⁷ This chain of events, and the debates about how to understand it, perhaps, serve to underscore the difficult empirical task of assessing a given approval’s impact on the development of future products.¹⁶⁸

Experts also echoed Unger’s concerns that the approval of one drug may make it more difficult to conduct clinical trials, with one recent study noting that “[a]pproval of ineffective drugs also crowds out innovation that might produce

¹⁶⁴ There are other empirical questions beyond simply more or fewer drug approvals, including what kinds of surrogate or clinical endpoints companies choose to study in clinical trials, what disease areas companies choose to invest in, whether the resulting approved drugs provide patients meaningful clinical benefits, and how industry spending on research and development changes. More generally, this dispute contributes to ongoing discussions about how the Agency makes decisions in the face of uncertainty.

¹⁶⁵ Scott, *supra* note 21.

¹⁶⁶ See Elisabeth Mahase, *Alzheimer’s Disease: FDA Approves Lecanemab amid Cost and Safety Concerns*, 380 *BMJ* 73, 73 (2023). Although researchers conducting the relevant clinical trial found that study participants also had “moderately less decline on measures of cognition and function,” Christopher H. van Dyck et al., *Lecanemab in Early Alzheimer’s Disease*, 388 *NEW ENG. J. MED.* 9, 9 (2023), FDA’s approval decision was “based on the observed reduction of amyloid beta plaque.” News Release, FDA, FDA Grants Accelerated Approval for Alzheimer’s Disease Treatment (Jan. 6, 2023), <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment> [<https://perma.cc/9FND-8NG5>].

¹⁶⁷ News Release, FDA, FDA Converts Novel Alzheimer’s Disease Treatment to Traditional Approval (July 6, 2023), <https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval> [<https://perma.cc/X339-7YJN>]. At the time of writing, FDA is considering a third application for a drug intended to treat Alzheimer’s Disease by clearing amyloid plaques, donanemab, though this drug reportedly significantly slowed clinical disease progression in a clinical trial that would support approval. John R. Sims et al., *Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial*, 330 *JAMA* 512, 512 (2023).

¹⁶⁸ As discussed *supra* note 31, the drugs that have followed Exondys 51 might likewise highlight the challenges in assessing such impacts.

effective treatment. Once a drug has been approved for a certain indication, other companies and researchers might not invest resources in treatments related to the condition, believing that there is no market.¹⁶⁹ This may also be true if patients are unwilling to enroll in follow-on trials, as Lynch notes.¹⁷⁰ In short, the rosy picture of innovation painted by some FDA officials is hardly accepted as a model for the Agency to follow, to say nothing of its irrelevance to assessing the scientific evidence regarding whether a drug candidate is “safe and effective” for its intended use.

Second, as noted in Section I.C, when Congress created the PRV program for tropical diseases in 2007, it instructed FDA to designate by regulation for receipt of a voucher “[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations.”¹⁷¹ FDA has added a total of nine diseases to this list since 2007, making changes on three separate occasions.¹⁷²

FDA made its first additions to the list in 2015, adding Chagas disease and neurocysticercosis.¹⁷³ In that 2015 final order, FDA set forth its interpretation of the statutory criteria and explained how it would analyze whether to add applicable infectious diseases to the PRV list going forward. FDA both specified the factors it intends to consider in interpreting the statute and applied those factors to the two diseases at issue. In deciding what it means for there to be “no significant market” for a particular drug, FDA proposed to consider two factors: the disease’s occurrence in developed nations and the existence of an indirect market for the relevant drug, such as through the military.¹⁷⁴ In its view, there is “no significant market” for a drug in developed countries if its prevalence is less than 0.1% of the population of those countries. According to FDA, at these rates “it is unlikely that ordinary market forces will offer a sufficient incentive to drive the development of new preventions or treatments.”¹⁷⁵ Further, there can be no

¹⁶⁹ Sarah S. P. DiMugno, Aaron Glickman & Ezekiel J. Emanuel, *Accelerated Approval of Cancer Drugs — Righting the Ship of the US Food and Drug Administration*, 179 JAMA INTERNAL MED. 922, 923 (2019); see also Karlin-Smith, *supra* note 155 (quoting Carpenter as saying, “There’s no evidence in the social science literature that says, ‘oh, if you let one drug through, that’s kind of iffy, all of a sudden, you’re going to get a lot of other therapies, and they’re going to be really good’”).

¹⁷⁰ Scott, *supra* note 21. Moreover, for gene therapies, patients might be not only unwilling, but also *unable*, to participate in future trials or receive later-developed products. For example, if a patient develops antibodies to the viral vector used to deliver the gene therapy, that patient may be unable to receive any gene therapy using the same or a similar vector in the future. See Carolyn Riley Chapman et al., *What Compassionate Use Means for Gene Therapies*, 37 NATURE BIOTECHNOLOGY 352, 353 (2019).

¹⁷¹ 21 U.S.C. § 360n(a)(3)(S).

¹⁷² See FDA, *Tropical Disease Priority Review Voucher Program*, *supra* note 108.

¹⁷³ Designating Additions to the Current List of Tropical Diseases, 80 Fed. Reg. 50559, 50559 (Aug. 20, 2015) (codified at 21 C.F.R. pt. 317).

¹⁷⁴ *Id.* at 50560.

¹⁷⁵ *Id.* at 50561.

indirect market for the drug from governmental sources, as sometimes occurs where governments maintain stockpiles for public health or military reasons.¹⁷⁶

In addition, a qualifying disease must “disproportionately affect[] poor and marginalized populations.”¹⁷⁷ In making this determination, FDA proposed to consider four factors: (1) “the proportion of global disability-adjusted life years for the disease that is attributable to developing countries,” (2) “the relative burden of the disease in the most impoverished populations within the countries in which it is found,” (3) “the relative burden of the disease in infants, children, or other marginalized segments of the population . . . within the countries in which it is found,” and (4) “designation by the World Health Organization as a Neglected Tropical Disease.”¹⁷⁸ FDA’s analysis of this provision is more holistic than its “no significant market” analysis, as it does not provide benchmark figures that would presumptively qualify a drug under this provision. FDA found that these criteria were met for both Chagas disease—which affects “just over 300,000 persons” in the United States—and neurocysticercosis, which affects a much smaller number, given that both diseases have disproportionate impacts on marginalized populations in developing countries.¹⁷⁹

From an innovation perspective, the way FDA specifies these criteria is puzzling. First and foremost, FDA offers no explanation for the prevalence threshold it sets, at 0.1% of the population—in the United States, a bit more than 300,000 people¹⁸⁰—also leaving unexplained why there is “no significant market” for a drug at fewer than 300,000 people in the United States. In some ways, this threshold even seems to conflict with the Orphan Drug Act, which set its statutory threshold for receiving special incentives at 200,000 people in the United States.¹⁸¹ One result is to create a class of infectious diseases affecting between 200,000 and 300,000 Americans where the condition is not

¹⁷⁶ *Id.*

¹⁷⁷ 21 U.S.C. § 360n(a)(3)(S).

¹⁷⁸ Designating Additions to the Current List of Tropical Diseases, 80 Fed. Reg. at 50561.

¹⁷⁹ *Id.* at 50562. In 2018, FDA applied these same criteria from 2015 in adding four diseases to the PRV list: Chikungunya virus, Lassa fever, rabies, and cryptococcal meningitis. Designating Additions to the Current List of Tropical Diseases, 83 Fed. Reg. 42904, 42904-08 (Aug. 24, 2018). In 2020, FDA again applied these criteria in adding three additional diseases to the PRV list: brucellosis, opisthorchiasis, and paragonimiasis. Designating Additions to the Current List of Tropical Diseases, 85 Fed. Reg. 42860, 42860-62 (July 15, 2020); Designating Additions to the Current List of Tropical Diseases, 85 Fed. Reg. 42883, 42883-86 (July 15, 2020).

¹⁸⁰ See Brynn Epstein & Daphne Lofquist, *U.S. Census Bureau Today Delivers State Population Totals for Congressional Apportionment*, U.S. CENSUS BUREAU (Apr. 26, 2021), <https://www.census.gov/library/stories/2021/04/2020-census-data-release.html> [<https://perma.cc/K72H-R8VH>].

¹⁸¹ The source of the 200,000-person threshold is reportedly “that companies were unwilling to manufacture drugs for narcolepsy or multiple sclerosis, each believed to affect approximately 200,000 persons.” Peter S. Arno, Karen Bonuck & Michael Davis, *Rare Diseases, Drug Development, and AIDS: The Impact of the Orphan Drug Act*, 73 MILBANK Q. 231, 234 (1995).

presumptively eligible for the Orphan Drug Act's incentives (and must prove its inability to be profitable under the exceptions clause of the Act) but is presumptively eligible for the PRV list. May companies rely on this order in asking FDA to designate a condition affecting 250,000 Americans or primarily impacting marginalized populations as a rare disease under the Orphan Drug Act's nonprofitability clause?

At the same time, FDA's interpretation of the "no significant market" requirement may be too narrowly focused on the simple prevalence of a disease. Sometimes there may be "no significant market" for a drug *because* a disease affects poor or marginalized populations, who may be un- or under-insured, even if they are relatively numerous. FDA could have considered not only the size of the relevant patient population in developed countries, but also its ability to pay in considering whether there is a significant market for a particular drug.¹⁸² Because the Agency has not publicly explained why it adopted a prevalence threshold of 0.1% of the population, it is difficult to assess the merits of that approach against other potential approaches, such as one that would have accounted for ability to pay.

FDA also has chosen alternative frames for its own analysis in at least some of its decisions rejecting adding other diseases to the PRV list.¹⁸³ In 2020, FDA rejected adding coccidioidomycosis (perhaps better known as Valley Fever) to the PRV list.¹⁸⁴ FDA noted that "the annual number of persons potentially considered for treatment for coccidioidomycosis in the United States is currently below 0.1 percent of the population," recognizing that the *treatment* of this disease appears to fall within the "no significant market" threshold set forth in its 2015 order.¹⁸⁵ FDA emphasized, however, that "a sizeable direct market may exist for products to *prevent* coccidioidomycosis (e.g., vaccines) in developed nations," and declined to add the disease to the PRV list on that basis.¹⁸⁶ In FDA's view, the market for prevention had not been a relevant consideration for the other conditions that it had agreed to add to the list, as they are "principally imported diseases."¹⁸⁷ But experts have recognized the ways in which existing

¹⁸² Cf. Rachel E. Sachs, *Prizing Insurance*, 30 HARV. J.L. & TECH. 153, 193 (2016) (arguing that prescription drug insurance can serve as an innovation incentive).

¹⁸³ FDA has also rejected adding diseases to the list on the grounds that they were not for "infectious" diseases and therefore were categorically ineligible for addition. See Letter from Patrizia Cavazzoni, Dir., Ctr. for Drug Evaluation & Rsch., to Lorna Speid, Founder & President, Putting Rare Diseases & Patients First! 2 (Sept. 17, 2021), https://downloads.regulations.gov/FDA-2020-P-1674-0022/attachment_1.pdf [<https://perma.cc/BB39-RKGS>].

¹⁸⁴ Notice of Decision Not to Designate Coccidioidomycosis as an Addition to the Current List of Tropical Diseases, 85 Fed. Reg. 42871, 42871 (July 15, 2020).

¹⁸⁵ *Id.* at 42873.

¹⁸⁶ *Id.* (emphasis added). This was also FDA's rationale for declining to add pneumocystis pneumonia to the list. Notice of Decision Not to Designate Pneumocystis Pneumonia as a Tropical Disease, 83 Fed. Reg. 42896, 42897 (Aug. 24, 2018).

¹⁸⁷ Notice of Decision Not to Designate Coccidioidomycosis as an Addition to the Current List of Tropical Diseases, 85 Fed. Reg. at 42873.

incentives to develop vaccines are particularly weak relative to incentives to develop treatments. Thus, it would be concerning from an innovation perspective for FDA to apply the same numerical threshold for market significance for a vaccine and a treatment, as the Agency appears to have done here.¹⁸⁸

Third, FDA has admitted that it erred in granting one of the three¹⁸⁹ orphan designations it has made on the basis of the nonprofitability pathway in the statute.¹⁹⁰ In 1994, FDA granted orphan drug status using this pathway to Subutex (buprenorphine hydrochloride) for the treatment of opioid dependence.¹⁹¹ Suboxone (a combination of buprenorphine and naloxone), also indicated for the treatment of opioid dependence, was one of the other two products to receive an orphan designation through this pathway, having received the designation in 1994.¹⁹² In the 1990s, although FDA recognized that the potential market for the drugs was larger than 200,000 Americans, FDA may not have thought that such drugs would be in high demand, and the Agency accepted the manufacturers' representations about the lack of a market for their products.¹⁹³ Subutex was officially approved in a sublingual tablet form¹⁹⁴ in 2002,¹⁹⁵ receiving seven years of orphan drug exclusivity. Its manufacturer would withdraw the drug from the market in 2011,¹⁹⁶ after earning roughly \$285

¹⁸⁸ See, e.g., Qiwei Claire Xue & Lisa Larrimore Ouellette, *Innovation Policy and the Market for Vaccines*, 7 J.L. & BIOSCIENCES 1, (2020) (noting that vaccines are not purchased repeatedly and thus are less profitable than treatments).

¹⁸⁹ Karst, *supra* note 100. There are several reasons why this nonprofitability pathway has been rarely used since the statute's passage. A company may not want to effectively certify to its investors that it is investing in products it does not believe to be profitable. The company also may not want to disclose information to FDA about its cost structure and expected pricing. Arno et al., *supra* note 181, at 234.

¹⁹⁰ See Letter from Lowell Schiller, Principal Assoc. Comm'r for Pol'y, FDA, to Lassman L. & Pol'y, Couns. to Braeburn, Inc. 11 (Nov. 7, 2019), https://downloads.regulations.gov/FDA-2019-P-1679-0079/attachment_1.pdf [<https://perma.cc/6SEA-HHL2%5D>]; Ed Silverman, *FDA Admits It Goofed When Granting Orphan Status to an Opioid Addiction Treatment*, STAT (Nov. 8, 2019), <https://www.statnews.com/pharmalot/2019/11/08/fda-orphan-drug-opioids-indivior/>.

¹⁹¹ Letter from Marlene E. Haffner, Dir., Off. of Orphan Prods. Dev., FDA, to Charles O'Keeffe, Exec. Vice President, Reckitt & Colman Pharms., Inc. 1 (June 15, 1994), <https://www.thefdalawblog.com/wp-content/uploads/archives/docs/subutex---cost-recovery.pdf> [<https://perma.cc/7ZTM-T6KD>]; Karst, *supra* note 100.

¹⁹² Karst, *supra* note 100.

¹⁹³ See Diane Dorman, *Orphan Drug Act's 'Nonprofitability' Loophole Needs to Be Closed*, STAT (Dec. 19, 2019), <https://www.statnews.com/2019/12/19/orphan-drug-act-nonprofitability-loophole-needs-closing/> [<https://perma.cc/3FLN-6GC9>].

¹⁹⁴ The patient would place the tablet under their tongue, where it would dissolve, rather than being swallowed as a more traditional pill.

¹⁹⁵ Karst, *supra* note 100.

¹⁹⁶ Determination That SUBUTEX (Buprenorphine Hydrochloride) Sublingual Tablets, Were Not Withdrawn from Sale for Reasons of Safety or Effectiveness, 80 Fed. Reg. 8088, 8088 (Feb. 13, 2015).

million in sales (Suboxone earned billions of dollars).¹⁹⁷ But in November 2017, FDA then approved a once-monthly injectable formulation of Subutex, now named Sublocade.¹⁹⁸ In approving Sublocade, FDA Commissioner Scott Gottlieb noted the benefits of the drug's once-monthly administration (including potential increased adherence) “[g]iven the scale of the opioid crisis, with millions of Americans already affected.”¹⁹⁹ Yet FDA also went on to grant Sublocade seven years of orphan drug exclusivity, relying in 2017 on the Agency's 1994 judgments about whether a treatment for opioid dependence could be profitable,²⁰⁰ despite the fact that Subutex and Suboxone had already earned significant revenue.

In November 2019, FDA revoked Sublocade's orphan designation and market exclusivity²⁰¹ after a would-be competitor filed a citizen petition asking FDA to do so.²⁰² The petition argued (among other claims) that not only should Sublocade not be eligible for orphan designation in 2017 when “blockbuster” revenues were expected, but also that the original 1994 orphan designation for Subutex was incorrect, based on “inaccurate information and unreasonable assumptions” about the drug's potential market.²⁰³ FDA largely agreed, concluding that the Agency had “erroneously granted” the original orphan drug designation request, and that “on the basis of the facts and circumstances as of the date of the orphan designation request, it was unreasonable to conclude that there would be no cost recovery from sales of [the drug] in the United States.”²⁰⁴ More specifically, the Agency concluded that “it was not reasonable to assume that the market size would remain constant for the first seven years of marketing” of the drug—a number which Indivior had benchmarked at 104,000 patients, and which FDA had already rejected on the grounds that over a million

¹⁹⁷ Kao-Ping Chua & Rena M. Conti, *Orphan Drugs for Opioid Use Disorder: An Abuse of the Orphan Drug Act*, HEALTH AFFS. FOREFRONT (July 26, 2019), <https://www.healthaffairs.org/doi/10.1377/forefront.20190724.795814/full/>.

¹⁹⁸ News Release, FDA, FDA Approves First Once-Monthly Buprenorphine Injection, a Medication-Assisted Treatment Option for Opioid Use Disorder (Nov. 30, 2017), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-once-monthly-buprenorphine-injection-medication-assisted-treatment-option-opioid> [<https://perma.cc/R6JF-P2JX>].

¹⁹⁹ *Id.*

²⁰⁰ Dorman, *supra* note 193.

²⁰¹ See Letter from Lowell Schiller, *supra* note 190, at 1.

²⁰² Citizen Petition from Scott M. Lassman, Couns. to Braeburn, Inc., Requesting the Food and Drug Administration (“FDA”) to Revoke Orphan Drug Designation for Sublocade (Buprenorphine Extended Release) Injection for Treatment of Opiate Addiction in Opiate Users 1 (Apr. 5, 2019), <https://braeburnrx.com/wp-content/uploads/2019/04/Sublocade-Orphan-Designation-Petition.pdf> [<https://perma.cc/MS5M-Z9KH>]; see also Chua & Conti, *supra* note 197.

²⁰³ Citizen Petition from Scott M. Lassman, *supra* note 202, at 1, 15-16. The competitor even asserted that “[t]he available evidence thus strongly suggests that Indivior knew the assumptions it was providing to FDA in 1993 and 1994 were highly inaccurate.” *Id.* at 17.

²⁰⁴ Letter from Lowell Schiller, *supra* note 190, at 2.

patients were estimated to suffer from opioid dependence.²⁰⁵ The citizen petition notes the ways in which Indivior itself had lobbied Congress to pass a 2000 law that dramatically expanded the possibilities for using buprenorphine-based treatment,²⁰⁶ but FDA had simply accepted (and never reevaluated) Indivior's statement that the number of patients eligible for treatment would not substantially increase.²⁰⁷

Perhaps more concerning than FDA's seeming unwillingness to closely examine Subutex's manufacturer's assumptions is its 2019 statement that "FDA will . . . not revoke a cost recovery based orphan-drug designation solely because the drug has become profitable."²⁰⁸ Although FDA admits that this limitation "is not explicitly stated in the regulation," the Agency noted in finalizing a set of Orphan Drug Act regulations in 1992 that:

FDA rejected a comment that suggested "orphan-drug designation and exclusive marketing should be revoked when FDA determines that a drug that it has designated is later proved to have commercial potential" because "legislation that would have authorized FDA to take such actions was vetoed by the President in 1990."²⁰⁹

Except that's not what the vetoed legislation would have done. The quoted 1992 regulation considers comments suggesting that orphan-exclusivity periods should be revoked "when FDA determines that a drug that it has designated is later proved to have commercial potential *or when the prevalence of the indicated rare disease or condition later exceeds 200,000 people.*"²¹⁰ The 1992 regulation does go on to say that such legislation was vetoed in 1990. But the text of the vetoed legislation was *only* focused on the changing prevalence of the disease, and made no mention of the cost-recovery provisions of the law.²¹¹ Only years later did Congress consider a proposed bill that would have revoked exclusivity periods for drugs which had reached a certain sales threshold, but that bill never came to a vote in Congress.²¹² FDA may be choosing to view the President's veto broadly, as in doing so, President Bush expressed concern that "[w]eakening the current 7-year exclusivity provision would certainly discourage development of desperately needed new orphan drugs."²¹³ But FDA

²⁰⁵ *Id.* at 11-12.

²⁰⁶ Citizen Petition from Scott M. Lassman, *supra* note 202, at 17.

²⁰⁷ Letter from Lowell Schiller, *supra* note 190, at 13.

²⁰⁸ *Id.* at 4.

²⁰⁹ *Id.* (quoting Orphan Drug Regulations, 57 Fed. Reg. 62076, 62082 (Dec. 29, 1992) (to be codified at 21 C.F.R. pt. 316)).

²¹⁰ Orphan Drug Regulations, 57 Fed. Reg. at 62082 (emphasis added).

²¹¹ Orphan Drug Amendments of 1990, H.R. 4638, 101st Cong. § 2; *see also* Carolyn H. Asbury, *The Orphan Drug Act: The First 7 Years*, 265 JAMA 893, 896 (1991).

²¹² Orphan Drug Amendments of 1992, S. 2060, 102d Cong.; *Attempts to Revise Orphan Drug Law Stall*, 48 CQ ALMANAC 429, 430 (1992).

²¹³ Memorandum of Disapproval for the Orphan Drug Amendments of 1990, 2 PUB. PAPERS 1587, 1587 (Nov. 8, 1990).

is not obligated to treat a presidential veto as foreclosing its use of regulatory authority in this area, and it is a further choice to adopt an expansive reading of the veto.

2. Exacerbating Resource Constraints

Other concerns about FDA's expertise in making innovation-related judgments stem from its resource constraints. FDA has limited resources, and using them on innovation-related tasks, ministerial or otherwise, leaves fewer resources for its other functions. Consider the rare pediatric disease PRV program. A 2016 Government Accountability Office review of the program describes and analyzes FDA's concerns, concluding that while FDA officials "strongly support the goal of incentivizing drug development for rare pediatric diseases, they have seen no evidence that the program is effective" and "do not support the program's continuation."²¹⁴ More generally, FDA officials offered several concerns about the program's impact "on the Agency's ability to determine its public health priorities."²¹⁵

First, FDA officials noted the ways in which the program "places a substantial strain" on Agency workload.²¹⁶ "[P]erforming a priority review on a drug that would otherwise merit a standard review requires the Agency to conduct significant work in a compressed timeframe." Thus, "in order to meet the required shortened timeframe for review, staff must divert attention from other important work or management must assign more reviewers to review an application."²¹⁷ The program also limits FDA's ability "to effectively manage its own workload." Because the Agency "is organized into separate review divisions with specific areas of expertise and . . . cannot quickly train new

²¹⁴ U.S. GOV'T ACCOUNTABILITY OFF., GAO-16-319 HIGHLIGHTS, RARE DISEASES: TOO EARLY TO GAUGE EFFECTIVENESS OF FDA'S PEDIATRIC VOUCHER PROGRAM (2016), <https://www.gao.gov/assets/gao-16-319-highlights.pdf> [<https://perma.cc/T7SP-RATQ>]. Congress has nevertheless extended the program on several occasions since then. *See, e.g.*, Advancing Hope Act of 2016, Pub. L. No. 114-229, § 2, 130 Stat. 943 (2016); 21st Century Cures Act, Pub. L. No. 114-255, § 3013, 130 Stat. 1093 (2016); Consolidated Appropriations Act, 2021, Pub. L. No. 116-260, § 321, 134 Stat. 2932 (2020) (reauthorizing the program until 2024).

²¹⁵ U.S. GOV'T ACCOUNTABILITY OFF., GAO-16-319, RARE DISEASES: TOO EARLY TO GAUGE EFFECTIVENESS OF FDA'S PEDIATRIC VOUCHER PROGRAM 13-14 (2016).

²¹⁶ *Id.*

²¹⁷ *Id.* Congress foresaw the potential for this and created a special user fee that companies must pay to redeem a PRV, in theory providing the Agency with the resources to hire more staff. But "FDA noted that the funding mechanism does not provide the agency the resources required to review the particular voucher priority application." *Id.* at 15. In other words:

[T]here is a disconnect in the timing of its collection of the additional user fee and the time it takes the agency to hire, orient, and train additional reviewers to assist with the additional reviews. Furthermore, the additional user fee is a one-time payment and does not provide the funding needed to sustain the longer-term employment of additional staff hired to assist with conducting the priority review.

Id.

staff[,] [t]here is not a pool of review staff that can be moved from one review division to another review division on an ad hoc basis to complete priority reviews for the application based on the rare pediatric review vouchers.”²¹⁸

Ultimately, FDA officials concluded that:

[I]f the number of pediatric vouchers awarded and redeemed continues to increase, the agency’s ability to meet its public health mission and other commitments will be adversely affected, including monitoring postmarket safety, engaging with patient and stakeholder groups, and advising drug sponsors on their development programs, including those focused on pediatric drugs.²¹⁹

Relatedly, FDA officials argued that “the program interferes with its ability to set priorities on the basis of public health needs by requiring FDA to provide priority reviews of new drug applications that would not otherwise qualify.”²²⁰ Because PRV holders use the vouchers to expedite what would otherwise be a standard ten-month review process for a drug that either does not treat a serious condition or provide significant improvement in safety or efficacy, FDA officials view these priority reviews as coming “at the expense of other important public health work in FDA’s portfolio, which undermines FDA’s public health mission and the morale of its professional review staff.”²²¹ This innovation-justified line-jumping exacerbates the resource constraint by forcing the Agency to focus on an innovation-based outcome rather than what it sees as more core priorities.

These agency comments, published in March 2016, come after the Agency had awarded just six rare pediatric disease vouchers (in addition to three tropical disease vouchers in 2009, 2012, and 2014)²²² and had processed just three redeemed vouchers.²²³ But from the release of the GAO report through the end of 2019, FDA awarded twenty-six more vouchers (two medical countermeasure, eight tropical disease, and sixteen rare pediatric disease).²²⁴ It is reasonable to think the Agency’s concerns have persisted and even increased, as at least twelve PRVs were redeemed from 2017 through 2019.²²⁵

Importantly, these PRV-related resource constraints stem from the Agency’s implementation of the PRV program as a whole, not from the Agency’s specific exercise of innovation-related judgment as part of its implementation of the

²¹⁸ *Id.* at 14-15.

²¹⁹ *Id.* at 15.

²²⁰ *Id.* at 14.

²²¹ *Id.*

²²² See Mezher et al., *supra* note 104.

²²³ U.S. GOV’T ACCOUNTABILITY OFF., GAO-20-251 HIGHLIGHTS, DRUG DEVELOPMENT: FDA’S PRIORITY REVIEW VOUCHER PROGRAMS (2020). One additional voucher is listed by GAO as having been redeemed in 2016, but it is unclear whether that was redeemed before or after the 2016 report. *Id.*

²²⁴ See Mezher et al., *supra* note 104.

²²⁵ U.S. GOV’T ACCOUNTABILITY OFF., *supra* note 223.

program. These concerns began to arise with the Agency's governance of the rare pediatric PRV program, which is *motivated by* innovation-related goals but does not in itself require FDA to actively consider innovation, because unlike the neglected diseases PRV, it does not authorize the Agency to designate eligible diseases. But the resource constraint themes raised by agency officials would likely be present when the Agency actively considers innovation as well. When Congress directs the Agency to make innovation-related judgments without giving the Agency sufficient additional resources to do so, that may similarly alter the Agency's ability to set its own priorities on the basis of public health needs.²²⁶

C. Potentially Competing Policy Considerations

Thus far, we have considered FDA's expertise advantages and disadvantages that make it both well and poorly suited for innovation-related judgments. Particularly for the Agency's expertise disadvantages, there may be relatively clear potential solutions: for example, Congress could provide FDA additional resources to enable the Agency to develop innovation expertise and a reasoned innovation theory, while also reducing overall resource constraints. But even assuming Congress saw fit to do so, there are other, relatively fixed policy considerations that may raise concerns about FDA's current role in making innovation-related judgments. Here, we consider two examples: the innovation-related consequences that FDA's decisions have for other institutional actors and the possibility that FDA considering innovation in its decisions will affect public trust in the Agency.

1. Impacts on Other Actors

When FDA decides to approve a new drug, that decision has ramifications for other actors. Within the federal government, it principally has implications for CMS, which (like FDA) is an agency within HHS.²²⁷ Medicare must cover most and in many cases all newly approved drugs,²²⁸ and state Medicaid programs must cover essentially all FDA-approved drugs as well.²²⁹ Even where FDA approves a drug with uncertain clinical benefits, as with both Aduhelm and

²²⁶ Resource concerns may be less relevant when the Agency considers innovation on its own initiative because the Agency presumably considers its own resource availability when it decides to consider innovation. But to the extent the Agency feels practical or political pressure to make innovation-related judgments where it might not otherwise chose to do so, *see* discussion *supra* notes 121-123 and accompanying text, that likewise may raise concerns about resource constraints.

²²⁷ *HHS Organizational Charts Office of Secretary and Divisions*, DEP'T OF HEALTH & HUM. SERVS., <https://www.hhs.gov/about/agencies/orgchart/index.html> [<https://perma.cc/WW96-7957>] (last updated Aug. 17, 2023).

²²⁸ *See* Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307, 2314-16 (2018).

²²⁹ *See id.* at 2316-18. Although prescription drugs are formally an optional category of coverage for state Medicaid programs, all states have chosen to cover them. *Id.* at 2316-17.

Exondys 51, it is difficult for Medicare and Medicaid to decline to cover the drug.²³⁰ Coverage for these drugs therefore creates financial burdens on other actors, including Medicare, Medicare beneficiaries prescribed the drug who may have high out-of-pocket-costs associated with it,²³¹ Medicare beneficiaries *not* prescribed the drug whose premiums may rise because of its existence,²³² and state Medicaid programs.²³³

FDA doesn't bear those costs if a drug it approves turns out not to have meaningful clinical benefits. Instead, those costs are externalized onto these other actors.²³⁴ To be sure, the Agency generally disclaims authority to consider

²³⁰ CMS has confirmed that state Medicaid programs must cover drugs approved through the accelerated approval pathway. CTR. FOR MEDICAID & CHIP SERVS., MEDICAID DRUG REBATE PROGRAM NOTICE: STATE MEDICAID COVERAGE OF DRUGS APPROVED BY THE FDA UNDER ACCELERATED APPROVAL PATHWAY (June 27, 2018); Paige Minemyer, *CMS Official Says Medicaid Must Cover Aduhelm as Industry Awaits National Coverage Decision*, FIERCE HEALTHCARE (Sept. 23, 2021, 12:12 PM), <https://www.fiercehealthcare.com/payer/cms-says-medicaid-must-cover-aduhelm-as-industry-awaits-its-national-coverage-decision> [https://perma.cc/Q7PX-8CX6]. By contrast, Medicare may be able to issue a National Coverage Determination restricting coverage for the drug, but these decisions are extremely rare. *See, e.g.*, Pam Belluck, *Medicare Proposes to Sharply Limit Coverage of the Alzheimer's Drug Aduhelm*, N.Y. TIMES (Jan. 11, 2022), <https://www.nytimes.com/2022/01/11/health/aduhelm-medicare-alzheimers.html>.

²³¹ For seniors without supplemental coverage, Medicare beneficiaries are responsible for 20% of the costs of drugs administered through Part B, which is the case for Aduhelm. *See, e.g.*, Juliette Cubanski & Tricia Neuman, *FDA's Approval of Biogen's New Alzheimer's Drug Has Huge Cost Implications for Medicare and Beneficiaries*, KFF (June 10, 2021), <https://www.kff.org/medicare/issue-brief/fdas-approval-of-biogens-new-alzheimers-drug-has-huge-cost-implications-for-medicare-and-beneficiaries/> [https://perma.cc/3M9Y-JP9T].

²³² Medicare Part B premiums rose significantly from 2021 to 2022, with CMS ascribing a large portion of this increase to the need to pay for Aduhelm. Tami Luhby, *Aduhelm, Priced at \$56,000 a Year, Is a Key Factor Driving Up Medicare Premiums*, CNN (Nov. 16, 2021, 11:52 AM), <https://www.cnn.com/2021/11/16/politics/aduhelm-alzheimer-medicare-increase/index.html> [https://perma.cc/5EM5-2GT2].

²³³ Matt Salo, *Much Adu(helm) About Nothing: New Alzheimer's Drug Threatens State Medicaid Budgets*, STAT (Oct. 12, 2021), <https://www.statnews.com/2021/10/12/new-alzheimers-drug-threatens-state-medicaid-budgets/> [https://perma.cc/P9EE-KE4L] (explaining that if Medicare does not cover Aduhelm, the cost of coverage will fall on state Medicaid programs).

²³⁴ Although the Inflation Reduction Act enables CMS to directly negotiate prescription drug prices, other countries generally give their insurance regulators greater ability to negotiate lower prices for prescription drugs in their jurisdictions, which minimizes these externalities. *See* Sachs, *Delinking Reimbursement*, *supra* note 228, at 2339-41. And, in August 2023, the Biden Administration announced the first ten drugs selected for Medicare drug price negotiations. Press Release, White House, Biden-Harris Administration Announces First Ten Drugs Selected for Medicare Price Negotiation (Aug. 29, 2023), <https://www.whitehouse.gov/briefing-room/statements-releases/2023/08/29/fact-sheet-biden-harris-administration-announces-first-ten-drugs-selected-for-medicare-price-negotiation/> [https://perma.cc/VM73-LHP7].

price as part of its approval process²³⁵ and FDA's decision as to whether a drug is "safe" and "effective" does not necessarily require consideration of price (though, to be fair, it also does not necessarily include an innovation assessment).²³⁶ But those costs exist all the same.

2. Public Trust

FDA administering innovation-related programs and actively considering innovation (separately from drug safety and effectiveness) may also affect public perceptions of FDA. To the extent that FDA is criticized for slowing innovation,²³⁷ FDA undertaking these roles may improve perceptions of the Agency, at least among certain audiences.²³⁸ Another possibility, however, is that FDA engaging in innovation-related reasoning will undermine public trust in the Agency—suggesting that the Agency is captured by industry,²³⁹ or otherwise making decisions that deviate from its public health mission. After the start of the COVID-19 pandemic, public trust in FDA seemed to be at a low moment,²⁴⁰ and some examples of the Agency engaging in innovation-related decision making discussed above, such as the Aduhelm approval, have been cited as contributing to this lack of public trust.²⁴¹

²³⁵ See, e.g., *Frequently Asked Questions About CDER*, FOOD & DRUG ADMIN. (Oct. 28, 2019), <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/frequently-asked-questions-about-cder> [<https://perma.cc/L8DR-73EW>] ("FDA has no legal authority to investigate or control the prices set by manufacturers, distributors and retailers.") *But see* Sherkow & Zettler, *supra* note 90, at 178-80 (arguing that FDA has, in fact, considered price in at least one instance and may have the authority to do so when price affects patient access). For additional discussion of FDA considering the relationship between a drug's price and patient access, see Lietzan, *supra* note 143, at 1277-78 and Rachel E. Sachs & Carolyn A. Edelstein, *Ensuring the Safe and Effective FDA Regulation of Fecal Microbiota Transplantation*, 2 J.L. & BIOSCIENCES 396, 404-05 (2015).

²³⁶ Sachs, *Administering Health Innovation*, *supra* note 135, at 2039-40.

²³⁷ See, e.g., Nathan Cortez, *Digital Health and Regulatory Experimentation at the FDA*, 21 YALE J.L. & TECH. 4, 12 (2019).

²³⁸ Cf. Patricia J. Zettler, Micah L. Berman & Efthimios Parasidis, *Drug and Vaccine Development and Access*, in 2 COVID-19 POLICY PLAYBOOK: LEGAL RECOMMENDATIONS FOR A SAFER, MORE EQUITABLE FUTURE 142, 143 (Scott Burris et al. eds., 2021) ("FDA . . . may lose public trust if the agency is viewed as either unresponsive to patients' concerns [about access] or as moving too quickly . . . based on insufficient data.")

²³⁹ It is also possible that the Agency actually *is* captured by industry to some extent, which would justifiably hinder public trust and would also weigh against FDA's active role in considering innovation. The complex dynamics of agency capture are outside our scope.

²⁴⁰ Selena Simmons-Duffin, *Trust in CDC and FDA Is at a Low*, NPR (Sept. 25, 2020, 3:57 PM), <https://www.npr.org/2020/09/25/917014322/trust-in-cdc-and-fda-is-at-a-low> [<https://perma.cc/3PU9-YHRR>] (discussing how "mixed messaging from the top of the administration and political interference by appointees and advisors" negatively impacted public trust of FDA during COVID-19 pandemic).

²⁴¹ See, e.g., Jason Karlawish & Joshua D. Grill, *The Approval of Aduhelm Risks Eroding Public Trust in Alzheimer Research and the FDA*, 17 NATURE REV. NEUROLOGY 523 (2021);

The reality, of course is that innovation and public health are not completely separate or separable. FDA regulation inevitably shapes the biopharmaceutical market, and efficient innovation in biopharmaceutical products can be vitally important to public health. The development of COVID-19 vaccines serves as a recent salient example of innovation matching an urgent public health need, where the Agency's public health mission and its innovation goals were closely aligned (though even there, the Agency has faced criticism).²⁴² The approval of Aduhelm, on the other hand, appears to be a key instance where innovation goals ran counter to safety and effectiveness concerns. In considering FDA's innovation role, the impact on public trust is crucial. The Agency's ability to protect and promote public health derives in no small part from its reputation for establishing the global "gold standard" for drug safety and effectiveness,²⁴³ and the Agency itself has identified improving public trust as an important public health goal on its agenda.²⁴⁴

In the preceding Parts, we have laid out the opportunities and challenges of FDA's role in managing innovation incentives and incorporating broader innovation ecosystem considerations into its decisions, as well as the reality that FDA in fact spends substantial effort performing this role. We draw two major implications from this analysis. First, there are some appropriate limits to FDA's focus on innovation: FDA should not use broad innovation concerns as a justification to lower safety and effectiveness standards and therefore should not

Rachel Sachs, *The FDA's Approval of Aduhelm: Potential Implications Across a Wide Range of Health Policy Issues and Stakeholders*, HEALTH AFFS. FOREFRONT (June 10, 2021), <https://www.healthaffairs.org/content/forefront/fda-s-approval-aduhelm-potential-implications-across-wide-range-health-policy-issues>.

²⁴² See, e.g., Rachel E. Sachs, Jacob S. Sherkow, Lisa Larrimore Ouellette & Nicholson Price, *How Will the FDA's New COVID-19 Vaccine Guidance Affect Development Efforts?*, WRITTEN DESCRIPTION (July 10, 2020, 11:59 AM), <https://writtendescription.blogspot.com/2020/07/how-will-fdas-new-covid-19-vaccine.html> [<https://perma.cc/VJ9X-VGUN>] (describing how more rigorous clinical trial requirements could increase FDA's ability to make accurate judgments while delaying patients' access); Rachel E. Sachs, Jacob S. Sherkow, Lisa Larrimore Ouellette & Nicholson Price, *How Are COVID-19 Vaccine Manufacturers Aiming to Encourage Trust in the FDA's Approval Process?*, WRITTEN DESCRIPTION (Oct 2, 2020, 10:10 AM), <https://writtendescription.blogspot.com/2020/10/how-are-covid-19-vaccine-manufacturers.html> [<https://perma.cc/PZQ5-U3TB>] (arguing more transparency could increase trust in the approval process); Jerry Avorn & Aaron S. Kesselheim, *Up Is Down — Pharmaceutical Industry Caution vs. Federal Acceleration of Covid-19 Vaccine Approval*, 383 NEW ENG. J. MED. 1706, 1706-08 (2020).

²⁴³ See generally CARPENTER, *supra* note 154 (discussing FDA's reputation and its regulation of pharmaceutical manufacturing).

²⁴⁴ See, e.g., *Remarks by Commissioner Califf*, *supra* note 120 (discussing public trust in essential scientific work). Cf. Allison M. Whelan, *Executive Capture of Agency Decisionmaking*, 75 VAND. L. REV. 1787, 1788-90 (2022) (discussing the ways political interference with FDA decision making can undermine trust).

weigh future product development in decisions currently before the Agency about a specific product's safety and effectiveness, such as approval decisions. In Part III, we lay out why FDA should not separately consider such future innovation concerns when evaluating a product's safety and effectiveness (and explain what this does and does not entail).

Second, even for those innovation decisions that FDA is clearly statutorily required to undertake, such as decisions about PRVs or orphan drug act incentives, the Agency is not currently well constituted to make those decisions. We remain at least somewhat agnostic about whether those active innovation decisions should remain with FDA, and recognize that policymakers could prefer a vision that either limits, or bolsters, FDA's role in such decisions. Accordingly, we offer two complementary paths. If FDA *shouldn't* be focused on these innovation questions, then it should probably stop doing a number of things in that space. And if FDA *should* be focused on these innovation questions, then it should probably have more authority and a suite of innovation-focused tools and capacities to explicitly consider those concerns more broadly. In Parts V and VI, we consider what it might look like to either reduce FDA's role in considering other innovation questions or enhance its ability to answer those questions well.

III. WEIGHING INNOVATION AGAINST SAFETY AND EFFECTIVENESS

FDA should not promote innovation by considering the potential development of future products not before the Agency in decisions about a specific product's safety and effectiveness.²⁴⁵ The Agency appeared to do just that in the approval decision for Exondys 51, and perhaps for Aduhelm, leading to justifiable criticism. Such innovation should not come into play in safety and effectiveness decisions for at least two reasons.²⁴⁶ First, considering innovation against safety and effectiveness is likely to damage public trust. And second,

²⁴⁵ This is not to say innovation isn't an important goal. Of course it is. But in this Article, we're investigating whether and when innovation ought to be a goal of FDA's—that is, when the Agency should make innovation judgments.

²⁴⁶ As noted in Part I, this Article does not tackle the statutory question of whether or to what extent Congress has authorized FDA to consider such innovation in reviewing a product's safety and effectiveness. *Cf.* Konnoth, *supra* note 43, at 171 (arguing that FDA should consider a broad range of drugs' "collateral effects" in its regulatory decisions); Paradise, *supra* note 31, at 66-73 (describing amendments to the Federal Food, Drug, and Cosmetic Act to increase patient-focused drug development); Sherkow & Zettler, *supra* note 90, at 177-78 (arguing FDA might be able to consider drug price when it impacts patient access); Zettler et al., *supra* note 43, at 224 ("[T]he Federal Food, Drug, and Cosmetic Act authorizes FDA to take [a] broad approach in its drug approval and withdrawal decisions."). That said, the plain language of the approval standard does not expressly describe innovation as a factor in FDA's approval decisions. 21 U.S.C. § 355(d). Of course, if FDA lacks statutory authority to consider certain kinds of innovation in its approval or other safety and effectiveness decisions, that would be a compelling reason—to say the least—that it ought not make such innovation judgments as part of those decisions.

such considerations are likely to have problematic dynamic effects on later innovation.

Before diving into the arguments against FDA weighing such innovation against safety and effectiveness, we consider the contours of the question. As noted above, sometimes innovation cuts in the same direction as promoting safety and effectiveness and thereby public health (developing initial COVID-19 vaccines), and sometimes those factors cut in opposite directions (Aduhelm and Exondys 51). Should we only be worried some of the time, in the latter cases? In short, no. Putting innovation into the balancing either doesn't matter, or it matters in a bad way. If innovation considerations align with safety and effectiveness considerations, or if safety and effectiveness considerations alone are sufficient to determine the outcome, then considering innovation separately isn't necessary. If, on the other hand, innovation incentives for future product development are a *necessary* thumb on the scale—a but-for cause of approval when safety and effectiveness would not have supported it alone—then the below arguments come into play. In either case, better to leave innovation out of the decision.

First, uplifting innovation to the detriment of safety and effectiveness is likely to harm public trust, no matter how well and accurately FDA considers innovation. FDA is the “gold standard” of biomedical regulators for a reason: it is cautious and careful, demanding rigorous evidence of safety and effectiveness for approval.²⁴⁷ Patients, physicians, and other actors in the health-care ecosystem rely on FDA approval as a certification that a drug does, in fact, work and is safe. A certification that the drug works well enough and safely enough that innovation benefits for future products push it over the line is unlikely to carry the same heft. And once that's the case for a few drugs, the value of approval as a (relatively) unquestioned seal diminishes sharply. This is not to say safety and effectiveness determinations are purely objective—FDA must make subjective judgments about when benefits outweigh risks.²⁴⁸ This is only to say FDA risks undermining public trust when it is perceived to be making decisions on grounds other than its best judgment about safety and effectiveness.²⁴⁹

²⁴⁷ See generally CARPENTER, *supra* note 154. But see Aaron S. Kesselheim & Jerry Avorn, Opinion, *The F.D.A. Has Reached a New Low*, N.Y. TIMES (June 15, 2021), <https://www.nytimes.com/2021/06/15/opinion/alzheimers-drug-aducanumab-fda.html> (arguing FDA is damaging its reputation, particularly by approving Aduhelm).

²⁴⁸ See Holly Fernandez Lynch, Steven Joffe & Matthew S. McCoy, *The Limits of Acceptable Political Influence over the FDA*, 27 NATURE MED. 188, 189 (2021) (“FDA’s approval and authorization decisions for specific products similarly are informed by data about safety and efficacy, but the Agency must also balance normative considerations about speed and certainty in light of disease severity and medical need.”).

²⁴⁹ This likely applies outside the innovation context as well. For example, during the COVID-19 pandemic, polls have found low trust in public health agencies, with some citing concerns about political interference with agency decision making. See, e.g., Selena

Second, using innovation effects to shape safety and effectiveness standards is likely to itself harm innovation. Innovation incentives should be dynamic, reflecting developments in the market and in science. But approval decisions are sticky, with long-lasting impacts. Consider Aduhelm. FDA's approval included acceptance of reduction in amyloid plaques as a biomarker for Alzheimer's, despite the scientific controversy over that biomarker. So approving Aduhelm doesn't just convey to other companies that there are rewards available in the Alzheimer's space. It conveys that a biomarker with limited scientific support is now fair game, perhaps as evidenced by the January 2023 approval of Leqembi based on that drug's effect on amyloid plaques.²⁵⁰ In other words, if FDA approves one drug based on its effect on a problematic but relatively straightforward biomarker, it is likely to be asked to approve additional drugs on the same kind of evidence. The negative impact of initial approval would not be ameliorated; it would multiply.

To be fair, FDA seemingly has recognized and sought to mitigate this problem. In FDA Commissioner Califf's memo regarding the approval of Exondys 51, he explained: "I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of the data and information."²⁵¹

While it is true that approval decisions are drug specific and FDA has substantial discretion to determine the kinds of evidence sufficient to demonstrate safety and effectiveness,²⁵² FDA, nevertheless, is likely limited in its ability to mitigate the precedential impact of approval decisions. Under the FDCA, for a drug to meet the safe and effective standard for approval, a drug need not be more effective than drugs already on the market for the relevant condition.²⁵³ This suggests that FDA is not free to refuse to approve future similarly situated new drug applications supported by the same, or very similar, safety and effectiveness data as supported a previous approval, without risking violating the Administrative Procedure Act's prohibition on arbitrary and capricious agency actions.²⁵⁴ And despite the Commissioner's statements about the Exondys 51 approval, in 2019 and in 2021 FDA again approved new drugs for Duchenne muscular dystrophy, from the same manufacturer as Exondys 51,

Simmons-Duffin, *Poll Finds Public Health Has a Trust Problem*, NPR (May 13, 2021, 12:01 AM), <https://www.npr.org/2021/05/13/996331692/poll-finds-public-health-has-a-trust-problem> [<https://perma.cc/P6BW-8CXF>] (finding 52% had a great deal of trust in the CDC and only 37% had a great deal of trust in FDA and the NIH).

²⁵⁰ See *supra* notes 166 and 167 and accompanying text.

²⁵¹ Memorandum from Robert M. Califf, *supra* note 26, at 11.

²⁵² 21 C.F.R. § 314.105(c) (2024); see also Zettler et al., *supra* note 43, at 236-37.

²⁵³ 21 U.S.C. § 355(d) (conventional approval standard); § 356 (accelerated approval standard).

²⁵⁴ See, e.g., *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 31 (D.D.C. 1997) (explaining that FDA failing to treat similarly situated products similarly is arbitrary and capricious conduct in violation of the Administrative Procedure Act).

again based on the drug's effects on dystrophin production—and again amid concerns about sufficient safety and effectiveness data.²⁵⁵ Using innovation as a reason to approve a problematic product doesn't just increase prior incentives: it opens the door to similarly problematic products in the future.

Luckily, the fix for FDA weighing innovation concerns regarding future product development in the context of safety and effectiveness decisions is fairly straightforward: the Agency should not do it. The most high-profile version of such a decision comes in the drug approval context. FDA could not and should not rely on innovation incentives for future products when deciding whether to approve marginal drugs, but rather should justify them solely on the merits of that individual approval and on the scientific evidence of the drug's safety and effectiveness.²⁵⁶

IV. DESIGNING AN INNOVATION-AGNOSTIC FDA

Beyond the context of considering an individual drug's safety and effectiveness, if policymakers were to decide that the downsides of FDA making innovation-related judgments outweigh the potential opportunities, what would it look like from an institutional design perspective to implement such a vision, in which FDA would be largely innovation-agnostic? In this Part we present two versions of an innovation-agnostic FDA. One option would be to retain a ministerial role for FDA, in which many innovation-relevant programs could remain within FDA's purview, but the Agency would not use significant discretion to shape the innovation process. Much of this could be done by FDA itself, though some statutory changes would be required. A second option would be for Congress to remove innovation-focused programs from FDA, relocating them in other agencies with explicit innovation mandates such as the NIH, the PTO, or a potential centralized innovation agency.

A. *Retaining a Ministerial Role for FDA*

If policymakers think FDA should no longer make its own innovation-related judgments, the Agency could get much of the way there through fairly minor changes, some on its own initiative. In some instances, either FDA itself or courts have limited FDA's discretionary ability to take innovation (or other considerations) into account in applying its powers.

²⁵⁵ See Paradise, *Federal Right to Try*, *supra* note 31, at 81; Angus Liu, *FDA Waves Through a 3rd Sarepta DMD Drug, Once Again Based on Questionable Biomarker Data*, FIERCE PHARMA (Feb. 26, 2021, 10:56 AM), <https://www.fiercepharma.com/marketing/fda-waves-through-third-sarepta-dmd-drug-once-again-based-questionable-biomarker-data> [<https://perma.cc/7ZWW-WQ8W>]. It is worth noting that the trial supporting the 2021 approval was larger than that supporting the Exondys 51 approval—forty-three patients—and was double-blinded and placebo-controlled. News Release, FDA, FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation, *supra* note 31.

²⁵⁶ Even if policymakers were to find these arguments unconvincing, FDA still lacks robust expertise in making these sorts of innovation-weighting decisions and therefore should still be augmented as described in Part V.

The Orange Book serves as one example of a tool that FDA *could* use to shape innovative change—but generally doesn't.²⁵⁷ A bit of background first. From an innovation point of view, the key feature of the document formally known as Approved Drug Products with Therapeutic Equivalence Evaluations but widely called the Orange Book is its listing of patents associated with a drug. If a company wishes to obtain approval for a generic version of a drug, the Hatch-Waxman Act requires them to address any listed patents associated with the drug. An assertion that any extant patents are invalid or not infringed by the generic drug triggers a stylized litigation procedure including an automatic thirty-month stay of generic approval, for which there is no need for the challenger to establish likelihood of success or irreparable harm.²⁵⁸ Thus, any patent listed in the Orange Book—no matter how feeble—is typically protected for two-and-a-half years, a substantial barrier against competition.²⁵⁹ And indeed, many patents that innovator drug companies list in the Orange Book are

²⁵⁷ *But see* Sherkow & Zettler, *supra* note 90, at 176 (arguing FDA shapes innovation in certain circumstances through administering the Orange Book by allowing device patents to be listed and issuing guidance to that effect).

²⁵⁸ There also are no negative consequences for the patent holder—the innovator drug company—if a delay in generic entry is determined not to be justified by the patent claim. Additionally, there are complexities around how the thirty-month stay operates in specific circumstances. *See, e.g.*, C. Scott Hemphill, *Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem*, 81 N.Y.U. L. REV. 1553, 1566 (2006). But we leave those complexities aside.

²⁵⁹ *See* Nora Xu, *AIA Proceedings: A Prescription for Accelerating the Availability of Generic Drugs*, 66 EMORY L.J. 1007, 1010 (2017). *But see* Sunand Kannappan, Jonathan J. Darrow, Aaron S. Kesselheim & Reed F. Beall, *The Timing of 30-Month Stay Expirations and Generic Entry: A Cohort Study of First Generics, 2013–2020*, 14 CLINICAL & TRANSLATIONAL SCI. 1917, 1917 (2021) (finding that the thirty-month stays typically expired well in advance of generic entry, suggesting a lower impact of the stay).

of dubious strength or applicability for various reasons.²⁶⁰ They are often held invalid or not infringed in litigation.²⁶¹

Orange Book listing of patents is thus a substantial innovation influencer: making generic entry harder, increasing the incentives for initial drug developers,²⁶² and creating incremental incentives for drugs with more potentially patentable aspects.²⁶³ One might think that if Orange Book patents are a substantial innovation influence, and that FDA thinks about influencing innovation, it would take an active role administering the Orange Book, carefully considering what patents get listed.²⁶⁴ Not so! FDA has repeatedly asserted that its role in administering the Orange Book is purely ministerial;

²⁶⁰ See, e.g., S. Sean Tu & Mark A. Lemley, *What Litigators Can Teach the Patent Office About Pharmaceutical Patents*, 99 WASH. U. L. REV. 1673, 1682 (2022) (“Patentees try to extend patent lifecycles by creating large patent thickets and ‘evergreening’ their patents, adding new patents on minor variants as the basic patents expire. . . . Those later patents are often weaker, and they are more frequently challenged by generic firms. But the structure of the regulatory regime means that any patent, no matter how weak, poses a significant obstacle to generic market entry.”); These are not the only problematic patents associated with drugs. For instance, many patents on manufacturing methods for drugs or biologics are of dubious strength. See W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1036-37 (2016). But such patents are not listed in the Orange Book or the equivalent for biologics (the Purple Book). See FDA, *Orange Book, supra* note 88; *Background Information: List of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book)*, FOOD & DRUG ADMIN. (Aug. 3, 2020), <https://www.fda.gov/drugs/biosimilars/background-information-list-licensed-biological-products-reference-product-exclusivity-and> [<https://perma.cc/G7BM-EH9P>].

²⁶¹ Tu & Lemley, *supra* note 260, at 1673 (“[A]bout 25% of active Orange Book patents were invalidated in court.”).

²⁶² Karshedt, *supra* note 129, at 1152 (“Because the pharmaceutical industry is one that typically requires a high amount in upfront investments, a drug maker’s ability to recoup those outlays by charging supracompetitive prices made possible by patent exclusivity is critical for preserving incentives for pharmaceutical innovation.”); see also Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685, 709-12 (2009) (“Creative patent holders have found several ways to convert [the Orange Book’s] regulatory framework into an exclusionary tool.”).

²⁶³ Cf. Price, *The Cost of Novelty, supra* note 126, at 828 (arguing for incentives based on comparative effectiveness).

²⁶⁴ Indeed, others have proposed that Orange Book listings be actively managed to promote innovation. See, e.g., Karshedt, *supra* note 129, at 1203; Rebecca S. Eisenberg & Daniel A. Crane, *Patent Punting: How FDA and Antitrust Courts Undermine the Hatch-Waxman Act to Avoid Dealing with Patents*, 21 MICH. TELECOMM. & TECH. L. REV. 197, 218-20 (2015); Jacob S. Sherkow, *Administrating Patent Litigation*, 90 WASH. L. REV. 205, 214-15, 250-53 (2015).

firms decide what patents to list, and FDA lists them without decision or discretion.²⁶⁵ It has taken this position in litigation and been upheld.²⁶⁶

FDA's attempts to use exclusivity tools to shape innovation have also, in some cases, been denied by courts as outside the Agency's power. In 2006, Depomed requested that FDA designate its gabapentin product, Gralise, as an orphan drug for the treatment of postherpetic neuralgia, with the goal of receiving the Orphan Drug Act's seven-year exclusivity period.²⁶⁷ There was just one problem: another gabapentin drug, Neurontin, had been approved for the treatment of seizures in 1993 and then for the treatment of postherpetic neuralgia in 2002; dozens of generic versions of Neurontin had entered the market.²⁶⁸ Neurontin's sponsor, Pfizer, had never sought orphan drug exclusivity.²⁶⁹ FDA denied Depomed's request for orphan drug designation for Gralise, stating that because the earlier gabapentin drug Neurontin was already approved "there is no rationale for supporting, with taxpayer monies, the clinical development of an identical product for an identical indication as one which has been approved after the most thorough evaluation possible."²⁷⁰ This represented an explicit innovation policy rationale—why grant exclusivity when it wasn't necessary because a treatment already existed? But the court rejected FDA's argument, holding that the statutory mechanism was mandatory, not discretionary, and that whatever the policy merits (about which the court was less worried),²⁷¹ FDA lacked the power to deny orphan drug exclusivity to Gralise.²⁷²

These examples demonstrate the possibility of limiting FDA's discretionary innovation abilities. That same logic could be applied to other agency powers, placing FDA into a more ministerial role, at least with respect to the innovation-related powers described above.

For instance, take another aspect of the *Depomed* case. Once a drug is approved as an orphan drug, FDA may not approve another marketing application for "the same drug for the same disease or condition" for seven years.²⁷³ That's all the statute requires. But FDA, in rulemaking, read a pro-innovation gloss onto the statute. In implementing regulation, FDA stated a new drug *could* be approved within the seven-year exclusivity period if it had the

²⁶⁵ See, e.g., *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 237 (4th Cir. 2002). But see *Sherkow & Zettler*, *supra* note 90, at 176 ("[W]hile that may be how the Agency sees its role, it is also the case that the FDA already bans listing various patents unrelated to the drug product in the Orange Book." (footnote omitted)).

²⁶⁶ *aaiPharma*, 296 F.3d at 230.

²⁶⁷ *Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs.*, 66 F. Supp. 3d 217, 224 (D.D.C. 2014); see also *supra* Section I.C (discussing Orphan Drug Act exclusivity).

²⁶⁸ *Depomed*, 66 F. Supp. 3d at 223-24.

²⁶⁹ *Id.*

²⁷⁰ *Id.* at 224.

²⁷¹ *Id.* at 236 ("[FDA's] policy concerns appear to be somewhat overblown.").

²⁷² *Id.* at 230.

²⁷³ 21 U.S.C. § 360cc(a)(2).

same active ingredient but was “clinically superior” to the already approved orphan drug, defined as having “a significant therapeutic advantage over and above” the older drug.²⁷⁴ The court had no problem with this requirement generally,²⁷⁵ though it didn’t apply to Gralise because Neurontin had never received exclusivity.²⁷⁶ This innovation-focusing interpretation by FDA wasn’t required by the statute; indeed, a 2001 court decision found the statute’s use of the term “drug” ambiguous, leaving room for FDA’s interpretation.²⁷⁷ An innovation-agnostic FDA could still administer certain innovation incentive programs in a ministerial fashion. For instance, the Agency could revise the implementing regulations to remove the clinical superiority exception to orphan-drug exclusivity, applying exclusivity to all drugs with the same active ingredient for the same condition, whether or not they represented an improvement.²⁷⁸

Put more broadly, FDA could simply *not* exercise its discretion in ways that take innovation into account, even in contexts outside the safety and effectiveness decisions mentioned above.

Some FDA programs might need congressional tweaking to remove this discretion. For instance, the PRV program evinces congressional concerns about innovation and FDA’s role in implementing those concerns. FDA is allocated the authority to identify diseases to add to the list for which priority review vouchers are an available incentive;²⁷⁹ this is an innovation-shaping role. But Congress could choose to shift that role to another agency, such as the Centers for Disease Control and Prevention (“CDC”) or the NIH, while still leaving the bulk of the program to be administered—ministerially!—by FDA. Or, if it wanted, Congress could eliminate neglected disease PRV discretion, as it has done with the other PRV programs, and avoid the challenges of interagency collaboration.

Overall, there is much that could be done to remove many innovation-focused decisions from FDA’s purview, while leaving intact its role in administering programs more mechanically.

B. *Removing Innovation Programs from FDA*

Another vision for an innovation-agnostic FDA would focus on removing innovation-focused programs (those identified above in Sections II.B and II.C.1)

²⁷⁴ *Depomed*, 66 F. Supp. 3d at 222-23; 21 C.F.R. § 316.3(b)(14) (2024) defining “same drug”); § 316.3(b)(3) (defining “clinically superior”).

²⁷⁵ *Depomed*, 66 F. Supp. 3d at 235; *see also* *Baker Norton Pharms., Inc. v. FDA*, 132 F. Supp. 2d 30, 37-38 (D.D.C. 2001) (upholding FDA’s definition of the term “same drug”).

²⁷⁶ *Depomed*, 66 F. Supp. 3d at 232.

²⁷⁷ *Baker Norton*, 132 F. Supp. 2d at 36.

²⁷⁸ We take no position on whether this would be a good decision.

²⁷⁹ The Agency may designate “[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations.” 21 U.S.C. § 360n(a)(3)(S).

from FDA entirely and relocating them to other agencies, as necessary. Decisions about what diseases merit a priority review voucher²⁸⁰ could be allocated to another agency, as could decisions about whether to designate a drug as treating an orphan disease.²⁸¹ FDA's focus could rest entirely on its health and safety mission instead (which, as we have noted, itself involves some forms of innovation, just not those about incentives for future products).²⁸²

Different agencies could make these innovation decisions instead. The CDC could be an option for questions about orphan diseases or tropical diseases,²⁸³ for instance; the NIH, on the other hand, likely has greater expertise in identifying which areas need greater incentives for fundamental research (though other mechanisms, such as the NIH's grant programs,²⁸⁴ may be better suited). Alternately, a new centralizing innovation agency, such as that proposed by Stuart Benjamin and Arti Rai,²⁸⁵ could take on these innovation functions as well.

There would certainly be complexities in removing some innovation programs from FDA because enforcement or reward mechanisms will still involve the Agency. For instance, even if the CDC or the NIH take over decisions about how priority review vouchers are determined and awarded, that review itself still happens at FDA. Similarly, orphan drug exclusivity is effectuated by FDA's refusal to approve another version of the previously approved orphan drug for the same indication.²⁸⁶ FDA would, at some level, still need to be involved. But the decision could be determinedly ministerial, with discretion explicitly committed to another agency.²⁸⁷ FDA's administration of

²⁸⁰ See *supra* Section I.C.

²⁸¹ See *Designating an Orphan Product: Drugs and Biological Products*, FOOD & DRUG ADMIN. (Aug. 7, 2022), <https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products> [<https://perma.cc/J2N7-3V45>].

²⁸² See *supra* Section I.A.

²⁸³ See, e.g., *Parasitic Infections in the United States*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/parasites/npi/index.html> [<https://perma.cc/4AV7-6AAR>] (last updated Nov. 20, 2020).

²⁸⁴ See Price, *Grants*, *supra* note 140, at 21-25.

²⁸⁵ See Stuart Minor Benjamin & Arti K. Rai, *Fixing Innovation Policy: A Structural Perspective*, 77 GEO. WASH. L. REV. 1, 61-62 (2008).

²⁸⁶ See *supra* Section I.B.

²⁸⁷ Such a setup, however, may not be seamless. There is a similar division of labor between the NIH and FDA in administering ClinicalTrials.gov, which lists information about clinical trials that trial sponsors are required to report. Studies are registered with and trial results are reported to the NIH, and the NIH is permitted to withhold grant funds from grantees who fail to comply with relevant requirements. FDA is otherwise tasked with enforcing failures to register or report required information. FDA and the NIH have both been criticized for a lack of enforcement activities, perhaps partly because of a diffusion of responsibility. See, e.g., Reshma Ramachandran, Christopher J. Morten & Joseph S. Ross, *Strengthening the FDA's Enforcement of ClinicalTrials.Gov Reporting Requirements*, 326 JAMA 2131, 2131 (2021).

the Orange Book—as the Agency has construed it—follows this pattern. FDA does administer the Orange Book; it adds entries when companies ask it to and uses those entries to process Abbreviated New Drug Application filings.²⁸⁸ But the PTO makes the determinations about which inventions receive patents, not FDA. FDA merely implements the PTO’s decision (as mediated by the company’s choice to list the patent).²⁸⁹

Removing these programs, or at least their innovation aspects, explicitly from FDA would not only shift the locus of the theoretical decision from FDA, but would also emphasize that the creating and shaping of innovation incentives should not be FDA’s focus. Along these lines, even if all innovation programs that can be removed from FDA are in fact removed, the Agency would still need to commit not to take innovation incentives into account for decisions that remain, such as the decision to approve a drug with an eye to future developments in that class.²⁹⁰

Neither of these visions of an innovation-agnostic FDA would completely remove innovation from the Agency’s mindset. Core functions of FDA, such as approving drugs or helping oversee clinical trial design, will still influence innovation. But whether by agency choice or by congressional relocation of explicitly innovation-focused programs, FDA could be shifted away from its deep involvement in actively setting incentives for future innovation.

V. DESIGNING AN INNOVATION-FOCUSED FDA

How might FDA look if policymakers decided to more fully support the Agency’s role in managing innovation incentives? As we note above, some problems arise both because of contradictory decisions and because of challenging coordination between FDA and other agencies. In this Part, we explore those two principal challenges. First, Congress could consider buttressing FDA’s expertise in the innovation policy space. Second, Congress could reevaluate the interactions between FDA and other agencies to facilitate more effective innovation decisions.

²⁸⁸ See *supra* Section I.B.

²⁸⁹ Indeed, this separation of innovation focus can be particularly problematic if the other agency *also* doesn’t take innovation into account. The lack of coordination between FDA and the PTO, for instance, has recently become the subject of scholarly, judicial, and Congressional attention. See, e.g., Price & Rai, *supra* note 260, at 1052 (identifying differences between FDA and PTO, such as FDA’s ability to police supplementary disclosure with greater efficiency than PTO); Letter from Patrick Leahy, U.S. Sen., & Thom Tillis, U.S. Sen., to Andrew Hirshfeld, Dir., PTO (Sept. 9, 2021), <https://web.archive.org/web/20220826061315/https://www.leahy.senate.gov/imo/media/doc/20210909%20Letter%20to%20PTO%20on%20FDA%20submissions.pdf> (expressing concern patent applicants make different statements to FDA and PTO); *Belcher Pharms., LLC v. Hospira, Inc.*, 1 F.4th 1374, 1381 (11th Cir. 2021) (finding inequitable conduct resulting from Belcher’s inconsistent FDA and PTO disclosures).

²⁹⁰ See *supra* Section I.B.

A. *The Role of Expertise*

The statement that “FDA” makes decisions based on innovation elides an underlying question: *Who*, precisely, at FDA considers those innovation incentives? The examples described above evince concern from high-level FDA personnel for innovation in decisions like the Aduhelm approval.²⁹¹ And the administration of priority review vouchers, orphan drug exclusivity, and other innovation-related programs involves innovation considerations, which are presumably made by individuals involved in the relevant programs. Additionally, in 2019, FDA Commissioner Scott Gottlieb announced a plan to create an innovation-focused office within CDER.²⁹² But according to current organization charts, this office did not come to fruition,²⁹³ and to the best of our knowledge, there are no individuals at FDA specifically tasked with broadly considering innovation, across all drugs or all products within FDA’s purview. If FDA is to best fill a role as an innovation-focused agency, perhaps there should be precisely such individuals with innovation-oriented expertise.

An internal office could aid innovation in several ways. First, the office could collect and analyze the data necessary to make effective innovation decisions. Knowing the impacts of FDA choices on innovation requires knowing the state of the industry, the effect of similar interactions in the past, the underlying science, and other similar information. For instance, in the case of Aduhelm, what were the underlying economics of research into Alzheimer’s? Were innovation challenges principally shaped by the lack of incentives for approved products, by the difficulty of the underlying science,²⁹⁴ or by challenges in clinical trial design for such a long-term illness?²⁹⁵ An innovation office with relevant expertise could collect and analyze such data.

Second, an FDA innovation office could develop expertise in making decisions for *effective* innovation impacts. Were the innovation incentives in the Alzheimer’s space actually such that an approval of Aduhelm would make a meaningful positive impact in the development of *high-quality* products—or all

²⁹¹ See *supra* Part I.

²⁹² Matthew Herper, *FDA Plans to Create a New Office to Leverage Cutting Edge Science*, STAT (Jan. 7, 2019), <https://www.statnews.com/2019/01/07/fda-plans-to-create-a-new-office-to-leverage-cutting-edge-science/>.

²⁹³ *Center for Drug Evaluation and Research Organization Chart*, FOOD & DRUG ADMIN. (Sept. 8, 2023), <https://www.fda.gov/about-fda/fda-organization-charts/center-drug-evaluation-and-research-organization-chart> [<https://perma.cc/Z3KR-KLXT>].

²⁹⁴ Fuyuki Kametani & Masato Hasegawa, *Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer’s Disease*, FRONTIERS IN NEUROSCIENCE, Jan. 2018, at 1, 1 (describing deficiencies of amyloid hypothesis).

²⁹⁵ See Eric Budish, Benjamin N. Roin & Heidi Williams, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044, 2044, 2049 (2015); Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. REV. 672, 672 (2013) (arguing that a longer time-to-market is associated with a reduced likelihood of patents stifling subsequent innovation).

potential Alzheimer's products, including products of dubious efficacy?²⁹⁶ Multiple disciplines focus on shaping innovation effectively, and FDA could acquire this exact expertise.

Third, and perhaps most significant, an FDA office of innovation could serve an independent and centralizing role.²⁹⁷ Currently, innovation decisions seemingly are often ad hoc and sometimes of contestable justifiability.²⁹⁸ An innovation office would both help to coordinate those ad hoc decisions and also serve to express the congressional determination that innovation decisions are in fact within FDA's purview.

Developing internal agency innovation expertise has solid precedent.²⁹⁹ The PTO is explicitly concerned with innovation, but even an entirely innovation-focused agency is best operated when it can rely on high-quality data and modeling of potential decisions. Accordingly, Congress created the Office of the Chief Economist within the PTO in 2010.³⁰⁰ That Office collects research datasets, considers the economic implications of intellectual property policy, and helps study how intellectual property shapes innovation.³⁰¹ Should policymakers decide that FDA should maintain a central role in shaping biomedical innovation, acquiring similar expertise would be a substantial step forward.

B. *Deepening Interagency Support*

Envisioning an innovation-focused FDA would also require reconsidering the relationships between FDA and other institutional actors.³⁰² For example, in Section II.C, we considered the ways in which a decision by FDA to approve a new drug has financial ramifications for Medicare and Medicaid, in addition to

²⁹⁶ See Scott, *supra* note 21.

²⁹⁷ Cf. Christi J. Guerrini, Jacob S. Sherkow, Michelle N. Meyer & Patricia J. Zettler, *Self-Experimentation, Ethics, and Regulation of Vaccines*, 369 *SCIENCE* 1570, 1572 (2020) (arguing for FDA office with citizen science expertise); Christi Guerrini, Alex Pearlman & Patti Zettler, *The Biden-Harris FDA Should Make Friends with Independent Researchers*, *STAT* (Jan. 26, 2021), <https://www.statnews.com/2021/01/26/the-biden-harris-fda-should-make-friends-with-independent-researchers/> [<https://perma.cc/MJ64-78WP>] (arguing for the same partly because “[r]eorganizing and creating new offices or divisions is a way the FDA can change its own internal culture”).

²⁹⁸ See *supra* Parts II & III.

²⁹⁹ Cf. Nathan Cortez & Jacob S. Sherkow, *Presidential Administration and FDA Guidance: A New Hope*, 2021 *U. ILL. L. REV. ONLINE* (SPECIAL ISSUE: PRESIDENT BIDEN'S FIRST 100 DAYS) 179, 180 (2021) (describing how FDA can “pursue policy experiments via guidance”).

³⁰⁰ Sarah Tran, *Policy Tailors and the Patent Office*, 46 *U.C. DAVIS L. REV.* 487, 507 (2012).

³⁰¹ *Office of the Chief Economist*, U.S. PAT. & TRADEMARK OFF. (last visited Feb. 5, 2024), <https://www.uspto.gov/about-us/organizational-offices/office-policy-and-international-affairs/office-chief-economist> [<https://perma.cc/BW36-TNWY>].

³⁰² Cf. Catherine M. Sharkey, *Agency Coordination in Consumer Protection*, 2013 *U. CHI. LEGAL F.* 329, 356 (“Where agency missions are in conflict, coordination may be contrary to congressional intent and counterproductive . . .”).

patients covered by those programs.³⁰³ At present, FDA does not consider those costs (or the price of the drug in question) as part of its analysis. But if FDA's decision to approve certain products is based partly on its view that doing so will encourage additional innovation, and not based solely on the evidence of efficacy, administrators might also think differently about whether public funds should be spent to pay for that drug. Some might argue that because insurance reimbursement itself functions much like an innovation prize,³⁰⁴ insurers ought to cover the drug, as doing so is necessary to instantiate the innovation incentive. At the same time, however, it is not clear that public funders should be required to pay (possibly at all, or at least whatever the manufacturer demands) for a product where the supporting evidence is weak.³⁰⁵ An innovation-focused view of not only the FDA approval process but also the role of health insurance as an innovation incentive might counsel in favor of balancing these objectives for products where innovation is a key concern, as has been proposed in the context of gene therapies.³⁰⁶

Another set of connections might involve FDA's relationship with the PTO. As noted in Part III, FDA currently perceives its role in administering the Orange Book listing of patents as largely ministerial on the grounds "that it lacks both the resources and the expertise to" take a more active role.³⁰⁷ But an FDA that both possessed an internal office focused on developing innovation expertise and was focused on deepening existing collaborations with administrative agencies could choose a different approach. An FDA that chose—or was instructed—to take a stronger view of innovation across its functions might change that perspective, in several substantive ways.³⁰⁸ FDA might actively manage Orange Book listings, as several scholars have called for, to ensure that only valid patents promoting innovation incentives are listed.³⁰⁹ A September

³⁰³ See *supra* Section II.C.

³⁰⁴ See Sachs, *Prizing Insurance*, *supra* note 182, at 159.

³⁰⁵ On one view of this argument, insurers should not pay at all if it is not clear that the drug is effective. But where there is some indication that the drug *may* be effective to support its approval, another version of this argument would say that insurers should retain significant ability to decide what they will pay for the product rather than tipping the balance of negotiating power strongly in the pharmaceutical company's favor as we currently do. Recent proposals to align Medicare payment with a drug's clinical benefits, at least for accelerated approval drugs, reflect these concerns. See MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: MEDICARE AND THE HEALTH CARE DELIVERY SYSTEM 89 (2022).

³⁰⁶ See Bill Cassidy, *How Will We Pay for the Coming Generation of Potentially Curative Gene Therapies?*, STAT (June 12, 2019), <https://www.statnews.com/2019/06/12/paying-for-coming-generation-gene-therapies/> [<https://perma.cc/5NKF-NSVJ>].

³⁰⁷ *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 237 (4th Cir. 2002).

³⁰⁸ A 2021 law already strengthens FDA's ability to identify and remove patents from the Orange Book that have been invalidated, but the proposals we include here go further. Orange Book Transparency Act of 2020, Pub. L. No. 116-290, 134 Stat. 4889.

³⁰⁹ See, e.g., Karshedt, *supra* note 129, at 1203; Sherkow, *supra* note 264, at 250-53. One intermediate solution would enable FDA to actively manage Orange Book listings to ensure

2021 letter from then Acting FDA Commissioner Janet Woodcock to the PTO, in which Dr. Woodcock lays out a series of areas for potential collaboration between the agencies,³¹⁰ is one potential template. As one example, the letter identifies FDA's concerns around the use of secondary patents to delay generic competition, and "whether some of these patenting practices encourage innovation that is meaningful for patients."³¹¹ Both FDA and the PTO could take a more active role in identifying and addressing these issues.

FDA's relationships with the NIH are perhaps the best starting point for this type of work. FDA and the NIH already have strong bonds, including on innovation-focused projects in regulatory science.³¹² But FDA's focus on health care technologies (pharmaceuticals and medical devices) and jurisdictional limits on considering the role of nonpharmaceutical interventions, including dietary changes and surgical methods, means that the Agency's relationship with the NIH has important blind spots. During the COVID-19 pandemic, for instance, financial investment focused on the development of pharmaceutical interventions, to the detriment of nonpharmaceutical interventions. While vaccines have been an astonishing success story, we still lack important data on the most appropriate applications of nonpharmaceutical interventions, such as masking, ventilation, and social distancing, and patients still struggle with access to many of these tools.³¹³ The innovation picture could be improved by an explicit recognition that in a coordinating role, other agencies should push innovation in *non*pharmaceutical innovations to compensate for FDA's focus.

To be sure, we do not mean to suggest that there would be no disadvantages to reconsidering FDA's relationships with other agencies and even resituating FDA's innovation responsibilities within other innovation actors. Other innovation actors may be similarly resource constrained,³¹⁴ and may lack FDA's unique ability to view innovation incentives across a drug's entire lifecycle.³¹⁵ There may be disadvantages specific to dividing responsibilities across multiple agencies that are currently sited primarily or exclusively within a single agency. Our point is primarily that policymakers should actively consider these tradeoffs

that listed patents meet the statutory standards without making active innovation judgments. See Eisenberg & Crane, *supra* note 264, at 218-20.

³¹⁰ Letter from Janet Woodcock, Comm'r, FDA, to Mr. Andrew Hirshfeld, Dir., PTO 4 (Sept. 10, 2021), <https://www.fda.gov/media/152086/download>.

³¹¹ *Id.*

³¹² *FDA-NIH Joint Leadership Council Charter*, FOOD & DRUG ADMIN. (Mar. 29, 2018), <https://www.fda.gov/science-research/advancing-regulatory-science/fda-nih-joint-leadership-council-charter> [<https://perma.cc/L9HP-99DR>].

³¹³ See, e.g., Lisa Larrimore Ouellette, Nicholson Price, Rachel Sachs & Jacob S. Sherkow, *Nonexcludable Innovations and COVID-19*, WRITTEN DESCRIPTION (May 27, 2020, 3:00 PM), <https://writtendescription.blogspot.com/2020/05/nonexcludable-innovations-and-covid-19.html> [<https://perma.cc/D8SB-EYPJ>] (noting that many nonpharmaceutical COVID-19 interventions are not protectable by intellectual property law and are thus underincentivized).

³¹⁴ See *supra* Section II.B.2.

³¹⁵ See *supra* Section II.A.2.

both within and outside FDA as they make decisions about FDA's own innovation judgments.

Existing scholarship has considered the ways in which interagency innovation challenges like these might be addressed, including through creating a centralized innovation regulator.³¹⁶ Benjamin and Rai have argued that the existing decentralization of innovation functions creates problems that can be addressed through centralizing an innovation office within the executive branch.³¹⁷ Although there may be reasons to house a health-specific innovation coordinator within HHS,³¹⁸ the parent agency to FDA, CMS, and NIH, such a coordinator might find it more difficult to work with the Department of Commerce-based PTO.³¹⁹ This supports the case for an executive branch-based regulator—though perhaps one with staffers developing expertise in particular technological areas.³²⁰

CONCLUSION

FDA plays a key role in shaping the development of biopharmaceutical products. In addition to the inevitable ways that FDA's extensive regulation of drugs influences innovation, FDA also makes a variety of innovation-related judgments, from the relatively ministerial to actively incorporating innovation into its regulatory decisions. Unfortunately, this latter set of activities is poorly conceptualized, and the Agency's capabilities are an imperfect match to the scope of its innovation-shaping decisions. Policymakers should decide whether FDA is best viewed as an active shaper of innovation, and whether the Agency's design and resources should be recalibrated so it can optimally play that role to the benefit of patients, developers, and the biopharmaceutical innovation system as a whole. Better conceptualizing the intersection of FDA's public health mission and its innovation functions, and adjusting its design accordingly, may be necessary to help ensure that FDA can continue to be a vital institution for public health.

FDA's innovation role also occurs within an ecosystem of other innovation actors, both active and potential, with different institutional strengths. Congress can make more or less detailed innovation decisions, and indeed some of its broader decisions have created the FDA-located innovation programs discussed above. Would Congress guide the biopharmaceutical innovation process better than

³¹⁶ See, e.g., Benjamin & Rai, *supra* note 285, at 6.

³¹⁷ *Id.* at 57.

³¹⁸ See Sachs, *Administering Health Innovation*, *supra* note 135, at 2045.

³¹⁹ See *Bureaus and Offices*, U.S. DEP'T OF COMMERCE, <https://www.commerce.gov/bureaus-and-offices> [<https://perma.cc/7RN9-VQ7G>] (last visited Feb. 3, 2024).

³²⁰ See Sachs, *Administering Health Innovation*, *supra* note 135, at 2043.

FDA is doing?³²¹ The PTO?³²² Courts, which are taking a more active role in innovation policy than before?³²³ Fully weighing the merits of innovation judgments at FDA requires considering what would and should happen in the absence of those judgments.

Finally, understanding the ways that innovation has crept into FDA decision making, either at Congress's instruction or on the Agency's own initiative, and the effects of that creep raises current questions about impacts beyond FDA. FDA's decisions about drugs have effects on other agencies—such as CMS, which generally must pay for those drugs whether they have proven clinical benefits or not. Considering how to promote agency harmonization when agencies' decisions might also impose negative externalities on each other could inform our understanding of interagency coordination more broadly. Likewise, much government regulation affects innovation, from environmental regulation to workplace protections, whether inevitably or more actively, and investigating FDA's innovation judgments can serve as a starting point for examining the broader landscape of regulatory shaping of innovation.

³²¹ To be sure, Congress faces tremendous political economy problems with respect to detailed innovation oversight. On the other hand, the need for regular renewals of FDA-related acts like the user-fee legislation already results in frequent congressional attention to the space. See Paradise, *Citizen Pharma*, *supra* note 46, at 319 (noting five-year reauthorization requirement of user-fee legislation had led to Congress only considering reform every five years).

³²² See *supra* note 19 and accompanying text.

³²³ Many scholars expressed concern that recent court decisions regarding mifepristone could harm innovation. See, e.g., Patricia J. Zettler, Eli Y. Adashi & I. Glenn Cohen, *Alliance for Hippocratic Medicine v. FDA — Dobbs's Collateral Consequences for Pharmaceutical Regulation*, 388 *NEW ENG. J. MED.* 1, 3 (2023); Abbe Gluck, *The Mifepristone Case and the Legitimacy of the FDA*, 329 *JAMA* 2121, 2121 (2023); David S. Cohen, Greer Donley & Rachel Rebouche, *Abortion Pills*, 76 *STAN. L. REV.* (forthcoming 2024) (manuscript at 16) (available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4335735); Margaret Hamburg & Joshua Sharfstein, *Judicial Interference with Mifepristone*, 380 *SCIENCE* 223, 223 (2023); Wendy K. Mariner, *Science v. Ideology in Court: Mifepristone and the U.S. Food and Drug Administration*, 176 *ANNALS INTERNAL MED.* 857, 857 (2023); Greer Donley & Rachel Sachs, *The Stakes in the Texas Abortion Medication Suit Are Broader than Just One Pill*, *WASH. POST* (Mar. 3, 2023, 7:45 AM), <https://www.washingtonpost.com/opinions/2023/03/03/antiabortion-pill-suit-drug-development-access/>. Some, however, have dismissed these concerns. See, e.g., Lars Noah, *Listening to Mifepristone*, 80 *N.Y.U. ANN. SURV. AM. L.* 33, 58 (2023) (dismissing concerns of innovation impacts as “entirely hyperbolic”). *But see* Greer Donley & Patricia J. Zettler, *Response to Listening to Mifepristone*, 80 *N.Y.U. ANN. SURV. AM. L.* 63, 68-69 (2023).