SLOWING DOWN ACCELERATED APPROVAL: EXAMINING THE ROLE OF INDUSTRY INFLUENCE, PATIENT ADVOCACY ORGANIZATIONS, AND POLITICAL PRESSURE ON FDA DRUG APPROVAL

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The U.S. Food and Drug Administration (FDA) has been revered as the gold standard in pharmaceutical safety and efficacy review since the 1960s. More recently, partly in response to the HIV/AIDS epidemic and the pressing need for new treatments, the FDA established an accelerated approval process to hasten the review of new drug applications so that drugs could be approved and brought to market as soon as possible. Although accelerated approval has led to the availability of new treatments for patients with few other options, this Note argues that, today, the FDA grants accelerated approval too hastily and may be sacrificing scientific rigor in doing so.

On June 7, 2021, the FDA announced the accelerated approval of Aduhelm™ (aducanumab), sponsored by pharmaceutical manufacturer Biogen, for the treatment of Alzheimer's disease. This approval occurred despite intense criticism of the drug's efficacy from the scientific community and concerns about potentially dangerous side effects. Using Aduhelm as a case study, this Note illustrates the benefits and risks of the FDA's accelerated approval process and proposes areas for improvement. It suggests revisions to the role of advisory committees that weigh in on whether a drug should be approved, offers ways to further incentivize pharmaceutical companies to confirm a new drug's clinical benefits, and theorizes how a controversial drug approval from the FDA could be challenged in court.

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INTRODUCTION

The U.S. Food and Drug Administration (FDA) regulates food, cosmetics, human and animal drugs, biological products, medical devices, products emitting radiation, and tobacco products pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA).[1] The FDA created accelerated approval to allow faster approval of drugs that fill an unmet medical need in treating serious

1. Ch. 675, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.).

illnesses.[2] On June 7, 2021, the FDA announced the accelerated approval of Aduhelm™ (aducanumab), sponsored by pharmaceutical manufacturer Biogen, for the treatment of Alzheimer's disease.[3] Aduhelm is a monoclonal antibody drug—the first therapeutic agent approved to treat Alzheimer's disease in nearly two decades.[4] Yet, rather than being celebrated as a breakthrough treatment for a challenging illness, the drug has been mired in controversy because its approval contradicted the recommendations of the FDA's own Peripheral and Central Nervous System Drugs Advisory Committee.[5]

Aduhelm's efficacy—if any—in the treatment of Alzheimer's remains unclear.[6] A data monitoring committee[7] stopped two clinical trials[8] early

2. Americans have become increasingly aware of the speedy approval of drugs in light of the COVID-19 pandemic and the approval of vaccines to combat the underlying coronavirus disease. *See Coronavirus Disease 2019 (COVID-19)*, U.S. FOOD & DRUG ADMIN. (Dec. 23, 2021), https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19 [https://perma.cc/MZ49-4L74]. It is important to distinguish the approval process for the COVID-19 vaccines from the process of accelerated approval, which is the subject of this Note. The FDA approved vaccines for COVID-19 in 2021 under Emergency Use Authorization (EUA). *See COVID-19 Vaccines*, U.S. FOOD & DRUG ADMIN. (Dec. 17, 2021), https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines [https://perma.cc/3GAR-FRNW]. EUA may be used during a public health emergency, such as the COVID-19 pandemic, in which the FDA may allow the use of unapproved medical products, including vaccines, to treat or prevent serious diseases when there are no adequate, approved, or available alternatives. *See Emergency Use Authorization for Vaccines Explained*, U.S. FOOD & DRUG ADMIN. (Nov. 20, 2020), https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained [https://perma.cc/2LX7-6YT6]. Thus, while COVID-19 vaccines did receive approval more quickly than they would have through the traditional FDA approval process, it is important to note that EUA is a mechanism that is separate from accelerated approval and used under different circumstances.

3. *See* Press Release, U.S. Food & Drug Admin., 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/WJ3T-6H78].

4. *See* Michael Specter, *The F.D.A.'s Extraordinary Approval of a Questionable Treatment for Alzheimer's*, NEW YORKER (June 14, 2021), https://www.newyorker.com/news/daily-comment/the-fdas-extraordinary-approval-of-a-questionable-treatment-for-alzheimers [https://perma.cc/JA9S-76BV].

5. *See* Nuriel Moghavem et al., *Medicare Should Not Cover Aducanumab as a Treatment for Alzheimer's Disease*, 90 ANNALS OF NEUROLOGY 331, 331 (2021).

6. *See* Pam Belluck & Rebecca Robbins, *F.D.A. Approves Alzheimer's Drug Despite Fierce Debate over Whether It Works*, N.Y. TIMES (July 20, 2021), https://www.nytimes.com/2021/06/07/health/aduhelm-fda-alzheimers-drug.html [https://perma.cc/H23G-K9QA] (noting that "clinical trials of the drug had provided incomplete evidence to demonstrate effectiveness").

7. A data monitoring committee is a "group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials." U.S. FOOD & DRUG ADMIN., GUIDANCE FOR CLINICAL TRIAL SPONSORS: ESTABLISHMENT AND OPERATION OF CLINICAL TRIAL DATA MONITORING COMMITTEES 1 (2006), https://www.fda.gov/media/75398/download [https://perma.cc/U7G8-2FDE].

8. *See 221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE)*, CLINICALTRIALS.GOV (Sept. 2, 2021) [hereinafter *ENGAGE Trial*], https://clinicaltrials.gov/ct2/show/study/NCT02477800 [https://perma.cc/XB2A-YY6D]; *221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (EMERGE)*, CLINICALTRIALS.GOV (Sept. 2, 2021) [hereinafter *EMERGE Trial*], https://clinicaltrials.gov/ct2/show/study/NCT02484547 [https://perma.cc/D5ZS-N9T3].

after a futility analysis[9] indicated that it was unlikely to show clinical benefit upon completion.[10] Nonetheless, the FDA approved the drug, which is expected to cost $56,000 a year, raising significant financial concerns for patients and payers.[11] In fact, the Centers for Medicare & Medicaid Services (CMS) announced that premiums for Medicare would increase by an estimated 15 percent in 2022 and specifically cited the approval of Aduhelm as one reason for the increase.[12] As one journalist noted, "One would have to go back nearly two decades to find decisions that might have as far-reaching an impact on the FDA's regulatory behavior."[13]

This Note uses Aduhelm as a case study to assess the benefits and risks of the FDA's accelerated approval process and to propose areas for improvement and revision. Part I provides the legal and scientific framework for understanding accelerated approval. Part II uses Aduhelm's approval to describe the appropriate role of the FDA as a regulatory agency, the influence of the accelerated approval process in steering the course of future medical research, and potential economic issues that accelerated approval can spark. Finally, Part III proposes three strategies for improving the accelerated approval pathway that could be implemented through the legislature, regulatory reform, or in the courts.

I. THE LEGAL AND SCIENTIFIC FRAMEWORKS UNDERLYING ACCELERATED APPROVAL

The FDA operates at the unique intersection of science, law, and public policy. Thus, to understand how accelerated approval works, one must first understand the legal and scientific frameworks that allowed the saga of Aduhelm's approval to unfold. This part lays the foundation for understanding accelerated approval from a legal and scientific perspective. Part I.A discusses the FDA's historical role in drug approval and where the need for an accelerated process came from. Part I.B describes how the

9. By performing a futility analysis, a data monitoring committee may recommend, based on a statistical assessment, that a clinical trial be terminated early because the trial is unlikely to meet its objectives, and there is therefore no basis for continuing enrollment and/or follow-up. *See* U.S. FOOD & DRUG ADMIN., *supra* note 7, at 16.

10. *See* Belluck & Robbins, *supra* note 6.

11. *See* Juliette Cubanski & Tricia Neuman, *FDA's Approval of Biogen's New Alzheimer's Drug Has Huge Cost Implications for Medicare and Beneficiaries*, KAISER FAM. FOUND. (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/F5NL-UYVS].

12. *See* Press Release, Ctrs. for Medicare & Medicaid Servs., CMS Announces 2022 Medicare Part B Premiums (Nov. 12, 2021), https://www.cms.gov/newsroom/press-releases/cms-announces-2022-medicare-part-b-premiums [https://perma.cc/MC9G-9EM8] ("There is significant uncertainty regarding the potential for future coverage of clinician-administered Alzheimer's drugs (i.e., Aduhelm™), requiring additional contingency reserves.").

13. Matthew Herper, *By Approving Biogen's Alzheimer's Drug, the FDA Is Shifting Its Rules. That Is a Giant Risk*, STAT (June 7, 2021), https://www.statnews.com/2021/06/07/by-approving-biogen-alzheimers-drug-fda-is-shifting-its-rules-that-is-a-giant-risk/ [https://perma.cc/BEQ5-FPJK].

accelerated approval pathway differs from traditional FDA drug application review. Part I.C addresses legal administrative concerns about how FDA approval decisions are made. Finally, Part I.D examines Aduhelm's approval and the reasons for its controversy.

A. The FDA's Historic Role in Drug Approval

The FDA's regulatory authority was originally based on the 1906 Pure Food and Drugs Act,[14] enacted to better regulate widespread use of over-the-counter medications that included ingredients such as opium, alcohol, and cocaine.[15] The statute tasked the Bureau of Chemistry (later renamed the Food and Drug Administration) with preventing the "manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious food, drugs, medicines, and liquors,"[16] but did not address how to ensure the safety or efficacy of regulated products.[17] As a result, many drugs continued to be sold without any preapproval clinical testing.[18]

The Federal Food, Drug, and Cosmetic Act was passed in 1938, largely in response to public outcry from the sulfanilamide debacle, when more than 100 people across the United States died after ingesting sulfanilamide to treat streptococcal infections.[19] The 1938 law contained a comprehensive regulatory scheme for marketing new drugs in the United States[20] and required companies to prove to the FDA that a drug was safe before it could be sold.[21] The statute remains the basis for FDA regulation today.[22]

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14. Ch. 3915, § 6, 34 Stat. 768, 769 (1906) (repealed 1938).

15. *See* Jonathan J. Darrow et al., *FDA Approval and Regulation of Pharmaceuticals, 1983–2018*, 323 JAMA 164, 165 (2020).

16. § 6, 34 Stat. at 768.

17. *See* Darrow et al., *supra* note 15, at 165.

18. *See, e.g.*, *Part II: 1938, Food, Drug, Cosmetic Act*, U.S. FOOD & DRUG ADMIN. (Nov. 27, 2018), https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-ii-1938-food-drug-cosmetic-act [https://perma.cc/T75Y-UJXN] (explaining that the lackluster 1906 law allowed dangerous products to remain on the market, including an eyelash dye that caused injuries including permanent blindness and a radium-containing tonic that killed consumers).

19. *See* Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAG. (June 1981), https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf [https://perma.cc/9XXE-LKS3]. Sulfanilamide had been used safely in tablet and powder form, but a pharmaceutical company created a liquid form of the drug by dissolving sulfanilamide in diethylene glycol. *See id.* The company did not test the new formulation for toxicity; there were no laws at the time requiring safety studies for new drugs. *See id.* After the American Medical Association received reports of deaths related to the new sulfanilamide formulation, it analyzed the mixture and discovered that diethylene glycol, a chemical normally used as an antifreeze, was a toxic ingredient. *See id.*

20. *See* 21 U.S.C. § 355.

21. *See id.* § 355(e) (allowing the FDA to withdraw approval of a drug if "clinical or other experience, tests, or other scientific data show that such drug is unsafe for use").

22. *See Part III: Drugs and Foods Under the 1938 Act and Its Amendments*, U.S. FOOD & DRUG ADMIN. (Feb. 1, 2018), https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-iii-drugs-and-foods-under-1938-act-and-its-amendments [https://perma.cc/G9K9-FM6W].

The FDA's global reputation for excellence in protecting public health was established in 1960, when Dr. Frances Oldham Kelsey, an FDA medical officer, refused to approve the drug thalidomide for sale in the United States.[23] Thalidomide was marketed to pregnant women for treating nausea.[24] Dr. Kelsey resisted corporate pressure from thalidomide's maker and raised concerns about the drug's effect on human embryos.[25] Based on Dr. Kelsey's analysis of the data, the FDA rejected the application for thalidomide approval, effectively saving the United States from a generation of severe congenital deformities and infant death, while cementing the FDA's reputation as the gold standard for pharmaceutical safety review.[26]

After the FDA steered the United States away from the potential thalidomide disaster, Congress strengthened laws governing pharmaceutical safety and efficacy.[27] In 1962, Congress passed the Kefauver-Harris Drug Amendments[28] to the FDCA, requiring that drug manufacturers provide "substantial evidence" that drugs were effective through "adequate and well-controlled investigations . . . on the basis of which it could fairly and responsibly be concluded . . . that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[29] The FDA's interpretation of what qualifies as substantial evidence has been "at least two adequate and well-controlled studies, each convincing on its own," because typically, a single clinical experimental finding of efficacy, unsupported by other independent evidence, is not adequate scientific support for a conclusion of effectiveness.[30] In practice, adequate and well-controlled

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23. *See* Melissa Marie Bean, *Fatal Flaws in the Food and Drug Administration's Drug Approval Formula*, 2003 UTAH L. REV. 881, 883.

24. *See* Leila McNeill, *The Woman Who Stood Between America and a Generation of 'Thalidomide Babies*,*'* SMITHSONIAN MAG. (May 8, 2017), https://www.smithsonianmag.com/science-nature/woman-who-stood-between-america-and-epidemic-birth-defects-180963165/ [https://perma.cc/Y5UM-SAWJ].

25. *See* Bean, *supra* note 23, at 883.

26. *See* McNeill, *supra* note 24. In Europe, Australia, and some South American countries, thalidomide was marketed extensively, resulting in birth defects in more than 10,000 infants and an unknown number of miscarriages. *See* Eric Fischer, *After 60 Years, Scientists Uncover How Thalidomide Produced Birth Defects*, DANA-FARBER CANCER INST. (Aug. 1, 2018), https://www.dana-farber.org/newsroom/news-releases/2018/after-60-years--scientists-uncover-how-thalidomide-produced-birth-defects/ [https://perma.cc/5JAV-ZRMD].

27. *See Part III: Drugs and Foods Under the 1938 Act and Its Amendments*, *supra* note 22.

28. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 U.S.C.).

29. 21 U.S.C. § 355(d).

30. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 3 (1998), https://www.fda.gov/media/71655/download [https://perma.cc/TLQ4-S23C]. Multiple independent trials offset the possibility that any single clinical trial may be subject to biases or only produced positive results by chance. *See id.* The FDA has also acknowledged in draft guidance that under certain circumstances, one adequate and well-controlled trial plus confirmatory evidence may be enough (e.g., if one trial involved many test subjects from multiple testing centers and demonstrated a very statistically persuasive effect on the primary

clinical investigations are blinded, randomized, placebo-controlled, and generate data that enable a direct assessment of clinical benefits.[31]

The law requires a sponsor[32] (generally, the pharmaceutical company) to submit an Investigational New Drug Application (IND) that summarizes preclinical trial data and other information about the drug's effects in animals.[33] The IND also requires the sponsor to establish protocols for human trials divided into three phases.[34] Importantly, the final phase involves randomized clinical trials that measure clinical endpoints to produce evidence that the drug in question has a positive balance of benefit and risk.[35] Clinical endpoints measure clinically meaningful outcomes related to the disease process—that is, "how a person feels, functions, or survives."[36] Evidence gathered during clinical trials becomes part of the New Drug Application (NDA) submitted to the FDA, which reviews the data acquired from clinical trials to determine whether the sponsor has shown adequate support for its safety and efficacy claims and can proceed to marketing the drug.[37] The FDA and the sponsor may meet throughout this process to

outcome). *See* U.S. FOOD & DRUG ADMIN., DEMONSTRATING SUBSTANTIAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS: GUIDANCE FOR INDUSTRY 9 (2019), https://www.fda.gov/media/133660/download [https://perma.cc/Q4F9-7FF6].

31. *See* EVA TEMKIN & JONATHAN TRINH, NAT'L ORG. FOR RARE DISORDERS, FDA'S ACCELERATED APPROVAL PATHWAY: A RARE DISEASE PERSPECTIVE 5 (2021), https://rarediseases.org/wp-content/uploads/2021/06/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf [https://perma.cc/GLU6-UG8U]; *see also* 21 C.F.R. § 314.126(a) (2022) ("The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.").

32. A sponsor is "a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization." Definitions and Interpretations, 21 C.F.R. § 312.3 (2022).

33. *See* IND Content and Format, 21 C.F.R. § 312.23 (2022); *see also* Darrow et al., *supra* note 15, at 166.

34. *See* Phases of an Investigation, 21 C.F.R. § 312.21 (2022); *see also* Darrow et al., *supra* note 15, at 166–67. Phase I studies are uncontrolled studies in humans and are generally intended to gather information about pharmacokinetics (time course of drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (relationship between drug concentration and the resulting effect). *See id.* at 166. Phase II trials evaluate adverse effects and efficacy in up to a few hundred participants with the condition being studied. *See id.* at 166–67. Phase III trials can include several hundred to several thousand patients and are intended to collect evidence of the benefit-risk relationship of the drug to obtain FDA approval. *See id.*

35. *See Surrogate Endpoint Resources for Drug and Biologic Development*, U.S. FOOD & DRUG ADMIN. (July 24, 2018), https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development [https://perma.cc/5CZE-YA4S].

36. Charlie McLeod et al., *Choosing Primary Endpoints for Clinical Trials of Health Care Interventions*, CONTEMP. CLINICAL TRIALS COMMC'NS, Dec. 2019, at 1, 2. For example, the six-minute walk test is widely used as a clinical endpoint for measuring functional exercise capacity in patients with cardiac and pulmonary diseases. *See* Lisa Lancaster et al., *Standardization of the 6-Min Walk Test in Clinical Trials of Idiopathic Pulmonary Fibrosis*, CONTEMP. CLINICAL TRIALS, Jan. 2021, at 1, 1.

37. *See* Darrow et al., *supra* note 15, at 167.

discuss various issues, such as the safety of proceeding to the next phase or the best way to analyze data.[38]

The traditional drug development process takes an average of twelve years from concept creation to market authorization.[39] One reason why drug development is so prolonged is that it can take an extended period of time to measure a drug's intended clinical benefit.[40] Concerns about this lengthy process led to the development of an accelerated pathway to expedite approval of treatments for the most serious diseases.[41]

B. The Modern Accelerated Approval Process

In the 1980s, the Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) epidemic dramatically increased pressure on the FDA to streamline the drug approval process as protesters from affected communities demanded less stringent efficacy requirements for new drugs intended to treat incurable and fatal diseases.[42] Dr. Gregg Gonsalves, an epidemiologist at Yale School of Public Health, recalled: "You had AIDS activists screaming that the FDA is killing us . . . . We were pushing for accelerated approval saying, look, we don't have time to wait for clinical access."[43] In response, the FDA established several reforms to the drug approval process,[44] including the accelerated approval pathway in 1992.[45] This section explains the structure of accelerated approval, beginning with the criteria that make a drug eligible for accelerated approval. Next, it reviews the critical role of advisory committees in the FDA's decision on whether to grant approval. Finally, this section considers the importance of

38. *See* Erin E. Kepplinger, *FDA's Expedited Approval Mechanisms for New Drug Products*, 34 BIOTECHNOLOGY L. REP. 15, 21 (2015).

39. *See* Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 170, 170 (2016).

40. *See Accelerated Approval*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval [https://perma.cc/RNU9-M372].

41. *See infra* Part I.B.

42. *See* Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America's Drug Constitution*, 42 AM. J.L. & MED. 687, 688–690 (2016). By the early 1980s, FDA review times had increased to more than thirty months and activists were fed up. *See* Darrow et al., *supra* note 15, at 165.

43. Joanne Silberner, *Accelerated Approval, the Path Used to Greenlight Biogen Alzheimer's Drug, Has a Checkered Track Record, Critics Say*, STAT (July 21, 2021), https://www.statnews.com/2021/07/21/biogen-alzheimers-accelerated-approval-confirmatory-trials/ [https://perma.cc/24DU-DN26].

44. Besides accelerated approval, the FDA established three other mechanisms to hasten the availability of drugs for serious diseases: fast-track designation, breakthrough therapy, and priority review. *See Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, U.S. FOOD & DRUG ADMIN. (Feb. 23, 2018), https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review [https://perma.cc/72CJ-D98E]. Although the names of these programs all imply speed, they are distinct approval pathways with different criteria and are not the focus of this Note.

45. *See* Kepplinger, *supra* note 38, at 24–25.

Phase IV post-marketing trials in confirming clinical benefits after a drug is granted accelerated approval.

1. What Is Accelerated Approval?

According to the FDA, accelerated approval hastens the review of NDA documentation so that approval can be made as soon as possible after data are gathered.[46] Under FDA regulations, the FDA may grant marketing approval for a new drug based on "adequate and well-controlled clinical trials establishing that the drug product has an effect on a *surrogate endpoint* that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit."[47]

Surrogate endpoints are key to the concept of accelerating approval of drugs in this pathway. A surrogate endpoint is an outcome (e.g., a laboratory measurement, radiographic image, or related physical sign) that is expected to predict patient survival or symptom improvement but that is not itself a direct measure of clinical benefit.[48] By using a surrogate endpoint instead of a clinical endpoint,[49] researchers can focus on events that occur earlier in time instead of waiting to see actual clinical benefits, resulting in shorter clinical trials.[50] For example, one clinical endpoint for researching a cancer drug would be mortality and would require waiting to see whether the drug extends the survival rate for cancer patients.[51] But under accelerated approval, the FDA may grant approval of the drug based on tumor shrinkage—a surrogate endpoint that is reasonably likely to predict the clinical benefit of delayed mortality.[52] Surrogate endpoints and the accelerated approval pathway have become important tools for the development of treatments for rare diseases, which can be challenging due to "small heterogeneous patient populations, long time-frames for disease progression, [and] a poor understanding of disease natural history."[53]

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46. *See* 21 C.F.R. § 314.500 (2022); *see also Accelerated Approval*, *supra* note 40. 21 C.F.R. § 314, subpart H governs accelerated approval of new drugs. *See* 21 C.F.R. § 314.500 (2022) (noting that accelerated approval applies to "certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)").

47. 21 C.F.R. § 314.510 (2022) (emphasis added).

48. *See* Alexandra Tsakopoulos et al., Note, *The Right to Try: An Overview of Efforts to Obtain Expedited Access to Unapproved Treatment for the Terminally Ill*, 70 FOOD & DRUG L.J. 617, 625 (2015); Kepplinger, *supra* note 38, at 29. For example, a laboratory measurement of bacteria in the blood may serve as a surrogate endpoint for clinical resolution of infection. *See id.*, at 29–30.

49. For an explanation of clinical endpoints, see *supra* Part I.A.

50. *See* Kepplinger, *supra* note 38, at 30.

51. *See* Tsakopoulos et al., *supra* note 48, at 625.

52. *See id.*

53. Emil D. Kakkis et al., *Recommendations for the Development of Rare Disease Drugs Using the Accelerated Approval Pathway and for Qualifying Biomarkers as Primary Endpoints*, ORPHANET J. OF RARE DISEASES, Feb. 2015, at 1, 1.

Although the accelerated approval process originally allowed for approval based on surrogate endpoints to speed up the availability of HIV/AIDS and cancer treatments, the pathway has recently been expanded to include treatments for other serious and rare diseases for which there are inadequate therapies.[54] In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act[55] (FDASIA), which amended the FDCA and encouraged the FDA to "utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs."[56] Congress found that "following the establishment of the accelerated approval mechanism . . . the FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions."[57] Thus, the FDASIA reflected Congress's intent that the FDA make greater use of accelerated approval and apply it to other diseases.[58]

President Barack Obama's Council of Advisors on Science and Technology released a report in 2012 encouraging the FDA to expand the scope of acceptable endpoints used to approve drugs for serious diseases with insufficient treatment options.[59] The report suggested that accelerated approval could be appropriate for diseases such as Alzheimer's disease, muscular dystrophy, and spinal muscular atrophy.[60] As of December 31, 2021, 278 drugs have entered the market via the accelerated approval pathway.[61] These drugs target a range of diseases including Alzheimer's disease, Duchenne muscular dystrophy, sickle cell disease, and various types of cancer.[62] Overall, the median time from an IND to FDA approval has been calculated to be 0.9 years shorter for drugs with an expedited program than for drugs without an expedited program.[63]

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54. *See* Frank J. Sasinowski & Alexander J. Varond, *FDA's Flexibility in Subpart H Approvals: Assessing Quantum of Effectiveness Evidence*, 71 FOOD & DRUG L.J. 135, 136 (2016).

55. Pub. L. No. 112-144, 126 Stat. 993 (2012) (codified as amended in scattered sections of the U.S.C.).

56. FDASIA § 901(b), 126 Stat. at 1085.

57. FDASIA § 901(a)(1)(B)–(C), 126 Stat. at 1082.

58. *See* Kyle T. Edwards, *The Role of Patient Participation in Drug Approvals: Lessons from the Accelerated Approval of Eteplirsen*, 72 FOOD & DRUG L.J. 406, 421 (2017).

59. *See* PRESIDENT'S COUNCIL OF ADVISORS ON SCI. & TECH., REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION 59 (2012), https://www.broadinstitute.org/files/sections/about/PCAST/2012%20pcast-fda.pdf [https://perma.cc/B27R-VP9Z].

60. *See id.* at 59–60.

61. *See* U.S. FOOD & DRUG ADMIN., CDER DRUG AND BIOLOGIC ACCELERATED APPROVALS BASED ON A SURROGATE ENDPOINT AS OF DECEMBER 31, 2021 (2021), https://www.fda.gov/media/151146/download [https://perma.cc/Q73Q-F4XJ].

62. *See id.*

63. *See* Thomas J. Hwang et al., *The FDA's Expedited Programs and Clinical Development Times for Novel Therapeutics, 2012–2016*, 318 JAMA 2137, 2138 (2017) (analyzing FDA-approved drugs between 2012 and 2016).

2. Advisory Committees: A Critical Part of Accelerated Approval

Advisory committees are established to advise the FDA on the "safety and effectiveness, including the labeling and advertising . . . and on the scientific standards appropriate for a determination of safety and effectiveness in that class of drugs."[64] Generally, an advisory committee is a group of individuals "possessing recognized expertise and judgment in a specific field . . . [who] have the training and experience necessary to evaluate information objectively and to interpret its significance."[65] Anyone can nominate an individual or themselves for committee membership, and qualified candidates are appointed as members for terms of one to four years.[66] Per the Federal Advisory Committee Act,[67] membership in advisory committees must be "fairly balanced in terms of the points of view represented and the functions to be performed."[68] Advisory committee members are often physician-scientists whose specialties or research areas involve the type of product being reviewed, but they can also be statisticians, industry representatives, or consumer representatives from patient advocacy organizations (PAO).[69]

Advisory committee meetings may occur at any stage of the drug approval review process—typically, meetings are held to assist the FDA with interpretation when questions related to trial data arise.[70] The advisory committee reviews and debates evidence presented by the FDA and product sponsors during a public hearing, hears comments from members of the public, and usually holds formal votes before writing recommendations for the FDA's consideration.[71] Advisory committees provide valuable scientific expertise, which "serve[s] to legitimize and lend credibility to the decisions of the agency as scientifically founded."[72] Notably, the FDA is not bound to

64. 21 C.F.R. § 14.160(a) (2022); *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY ADVISORY COMMITTEES: IMPLEMENTING SECTION 120 OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997, at 1 (1998), https://www.fda.gov/media/72297/download [https://perma.cc/YXU5-NFJ6] ("Advisory committees provide independent advice and recommendations to the [FDA] on scientific and technical matters related to the development and evaluation of products regulated by the Agency.").

65. U.S. FOOD & DRUG ADMIN., *supra* note 64, at 2.

66. *See Learn About FDA Advisory Committees*, U.S. FOOD & DRUG ADMIN. (Oct. 19, 2020), https://www.fda.gov/patients/about-office-patient-affairs/learn-about-fda-advisory-committees [https://perma.cc/35HT-ZTQK].

67. 5 U.S.C. app.

68. *Id.* § 5(b)(2).

69. *See Advisory Committees: Critical to the FDA's Product Review Process*, U.S. FOOD & DRUG ADMIN. (May 4, 2016), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/advisory-committees-critical-fdas-product-review-process [https://perma.cc/N2QE-E4W2].

70. *See Learn About FDA Advisory Committees*, *supra* note 66.

71. *See* Audrey D. Zhang et al., *Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008–2015*, 97 MILBANK Q. 796, 797 (2019); Mara Sanders, Note, *Sex, Drugs, and Advisory Committees: An Analysis of Pharmaceutical Industry Manipulation of FDA Vulnerability to Sociopolitical Influences on Matters of Women's Health*, 48 COLUM. HUM. RTS. L. REV. 149, 161 (2017).

72. Sanders, *supra* note 71, at 161.

the advisory committee's recommendations but follows them most of the time.[73] One study of advisory committee meetings between 2008 and 2015 found that only 22 percent of the actions taken by the FDA contradicted the recommendations set forth by the advisory committees.[74]

3. Phase IV Post-Marketing Trials: Well-Intentioned but Poorly Executed

Accelerated approval permits approval of a drug earlier in the drug development process but ultimately holds the drug to the same safety and efficacy standards that the standard approval process would. After a drug is granted accelerated approval based on studies using surrogate endpoints, the pharmaceutical company is required to continue performing studies to ultimately prove a clinical benefit—these post-approval clinical studies are known as Phase IV post-marketing trials.[75] The FDA evaluates evidence from Phase IV post-marketing trials "to ensure that any remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved."[76] The FDA notes that the sponsor should also submit "evidence that a proposed surrogate endpoint . . . is reasonably likely to predict the intended clinical benefit of a drug."[77] These trials must be completed with due diligence, which the FDA has interpreted to mean that the protocol for the trial should be developed as early as possible, and timelines for enrollment and trial completion should be specified.[78] Generally, the Phase IV trial would evaluate a clinical endpoint that directly measures the clinical benefit that the surrogate endpoint was supposed to predict.[79]

If the post-marketing trials validate the surrogate endpoints and verify clinical benefit, accelerated approvals are generally converted to traditional approvals.[80] However, if the Phase IV trials fail to show a benefit, the FDA may remove the drug from the market or impose additional labeling requirements.[81] If the FDA determines there are grounds for withdrawal, it may ask the sponsor to request withdrawal of approval or notify the sponsor of an opportunity for a hearing.[82] In most cases, the sponsor voluntarily withdraws the drug in question from the market before the FDA acts.[83]

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73. *See* Zhang et al., *supra* note 71, at 796–97.
74. *See id.* at 807.
75. *See* Kepplinger, *supra* note 38, at 36.
76. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 19 (2014), https://www.fda.gov/media/86377/download [https://perma.cc/L7S2-PFHZ].
77. *See id.*
78. *See id.* at 22.
79. *See id.* at 23.
80. *See* Temkin & Trinh, *supra* note 31, at 14.
81. *See id.* at 16.
82. *See* 21 C.F.R. §§ 314.530(a)–(c), 601.43(c)(1) (2022).
83. *See* Aaron S. Kesselheim et al., *Pharmaceutical Policy in the United States in 2019: An Overview of the Landscape and Avenues for Improvement*, 30 STAN. L. & POL'Y REV. 421, 452 (2019); *see also* Recall Policy, 21 C.F.R. § 7.40(c) (2022) (noting that rather than the FDA itself taking a drug off the market, the sponsor's voluntary "[r]ecall is generally more appropriate and affords better protection for consumers than seizure, when many lots of product have been widely distributed").

Unless withdrawal procedures are initiated, drugs may continue to be marketed as accelerated approval drugs.[84] In practice, pharmaceutical companies do not consider withdrawal to be a credible threat unless there is a serious safety concern.[85] The FDA may also seek civil monetary penalties from sponsors who do not comply with Phase IV post-marketing trial requirements.[86] However, the FDA has been slow to take remedial action—fines are rarely invoked due to administrative complexity.[87]

Contrary to the expected process, many sponsors fail to comply with full completion of the required Phase IV post-marketing trials[88] or only conduct small, inconclusive trials.[89] This failure is partly attributable to the fact that after approval, it becomes increasingly difficult to recruit patient participants, who question why they should risk being placed in a placebo group when the drug is already available on the market.[90] This is an especially pertinent concern for drugs that are granted accelerated approval because of the ethical questions raised for serious illnesses.[91] One analysis of accelerated approval drugs brought onto the market in 2009 and 2010 found that, by 2015, only 54 percent of required post-marketing studies had been completed and that 20 percent had not even been started.[92] Failure to execute required post-marketing studies means that some drugs with no proven clinical benefit

84. *See* Temkin & Trinh, *supra* note 31, at 14; Julia A. Beaver & Richard Pazdur, *"Dangling" Accelerated Approvals in Oncology*, 384 NEW ENG. J. MED. e68(1), e68(1) (2021).

85. *See* Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 337–38 (2006).

86. *See* Kesselheim et al., *supra* note 83, at 448.

87. *See id.*

88. *See, e.g.*, Michael S. Sinha & Stephen Latham, *Patient Advocacy Organizations and FDA Drug Approval: Lessons from Aduhelm*, STAT (July 23, 2021), https://www.statnews.com/2021/07/23/patient-advocacy-organizations-lessons-from-aducanumab/ [https://perma.cc/737T-QRLS] (noting that Exondys 51, a $300,000-a-year treatment, remains on the market even after missing its post-marketing trial deadline in May 2021).

89. *See* Silberner, *supra* note 43.

90. *See* Stephanie Cajigal, *What FDA's Controversial Accelerated Approval of Aducanumab Means for Other Neurology Drugs*, NEUROLOGYTODAY (Aug. 5, 2021), https://journals.lww.com/neurotodayonline/fulltext/2021/08050/what_fda_s_controversial_accelerated_approval_of.1.aspx [https://perma.cc/XP5S-9W5F]; *see also* Robert A. Bohrer, *Drug Prices, Dying Patients, and the Pharmaceutical Marketplace: A New Conditional Approval Pathway for Critical Unmet Medical Needs*, 12 DREXEL L. REV. 1, 18 (2019) ("[F]or those drugs that go through the accelerated approval . . . there is a lower standard of evidence for approval and, as a result, even less certainty provided to doctors and patients that the benefits of the drugs do in fact exceed their risks." (footnotes omitted)).

91. *See* Steenburg, *supra* note 85, at 372 ("Because Phase IV studies by definition involve products that FDA has concluded to be safe and effective (albeit subject to confirmation of some sort), any trial involving a conventional placebo arm raises serious ethical questions.").

92. *See* Steven Woloshin et al., *The Fate of FDA Postapproval Studies*, 377 NEW ENG. J. MED. 1114, 1114 (2017). Reasons for incomplete or unfulfilled studies included difficulty recruiting patients, or the FDA freeing the sponsor from obligation to conduct the study because it was no longer feasible or would no longer provide useful information. *See id.* at 1115–16.

may stay on the market and may be used by patients who rely on the FDA to assess the safety and efficacy of their treatments.[93]

C. Legal Administrative Concerns of FDA Decisions

The FDA is supposed to work closely with the pharmaceutical companies it regulates and it inevitably faces industry pressure to approve drugs, but ultimately, the agency must base its decisions on objective evidence to maintain scientific integrity. Once the FDA makes a decision, it is difficult to overturn it. This section first describes regulatory capture and regulatory reactivity, two phenomena which make it difficult for the FDA to remain unbiased. This section then describes tools of administrative law for challenging federal agency decision-making.

1. Regulatory Capture and Regulatory Reactivity: When Agencies and Industry Get Too Cozy

Regulatory capture refers to the phenomenon where "regulated interests exert such an influence over their regulators that they essentially control the agencies, at the expense of the intended beneficiaries of the regulatory system."[94] Regulatory capture is sometimes used as an accusation that an agency failed to serve the public interest as Congress intended.[95] For example, Dr. Michael Carome, Director of the Health Research Group at Public Citizen, a consumer advocacy nonprofit, has criticized the approval of Aduhelm as a result of regulatory capture.[96] One explanation for regulatory capture is the "revolving door" practice of industry executives taking senior appointments at the FDA, thereby increasing the likelihood that the FDA will take positions that favor the regulated industry.[97]

When making the decision to approve new drugs, the FDA must consider the trade-off between speeding up availability of drugs for which there is an

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93. *See* Bishal Gyawali et al., *Regulatory and Clinical Consequences of Negative Confirmatory Trials of Accelerated Approval Cancer Drugs: Retrospective Observational Study*, BRIT. MED. J., Sept. 2021, at 1, 7.

94. Diana R.H. Winters, *Intractable Delay and the Need to Amend the Petition Provisions of the FDCA*, 90 IND. L.J. 1047, 1081 (2015).

95. *See* Sidney A. Shapiro, *Blowout: Legal Legacy of the Deepwater Horizon Catastrophe: The Complexity of Regulatory Capture: Diagnosis, Causality, and Remediation*, 17 ROGER WILLIAMS U. L. REV. 221, 223 (2012).

96. *See* Jeffrey Toobin, *The Road to Aduhelm: What One Ex-FDA Adviser Called 'Probably the Worst Drug Approval Decision in Recent US History' for an Alzheimer's Treatment*, CNN (Sept. 27, 2021, 10:01 AM), https://www.cnn.com/2021/09/26/politics/alzheimers-drug-aduhelm-fda-approval/index.html [https://perma.cc/L6D3-CAWB] (detailing that, according to Dr. Carome, members of the FDA "were not objective, unbiased regulators" and instead "became a partner with Biogen").

97. *See* Allison Parr, Note, *Agribusiness and Antibiotics: A Market-Based Solution*, 73 FOOD & DRUG L.J. 338, 350 (2018); *see also* Sydney Lupkin, *A Look at How the Revolving Door Spins from FDA to Industry*, NPR (Sept. 28, 2016, 10:48 AM), https://www.npr.org/sections/health-shots/2016/09/28/495694559/a-look-at-how-the-revolving-door-spins-from-fda-to-industry [https://perma.cc/D5TS-KFQY] (describing one study which found that about 27 percent of FDA reviewers in the hematology-oncology field left the agency from 2001 to 2010 to work for pharmaceutical companies).

urgent need and ensuring the safety and efficacy of the drug in question.[98] But when the FDA is driven by a particular short-term goal (e.g., the approval of a certain drug), it may use the "flexibility afforded by an expedited pathway to issue an authorization or approval when, in light of available data and guiding principles, such authorization or approval should not be issued."[99] Professor Yaniv Heled and other scholars coined the term "regulatory reactivity" to describe this phenomenon.[100] It is "a mode of agency decision-making that occurs: 1) when an agency does not adhere to predetermined principles, standards, and/or operative procedures in reaching its decision; 2) in direct reaction to pressure . . .; 3) resulting in the furtherance of short-term agendas rather than public health goals."[101] Decisions characterized by regulatory reactivity fail to capture the true costs and risks of a given marketing approval.[102] Existing review frameworks, such as *Chevron* and *Auer* deference,[103] allow for agency discretion but do not give courts tools to spot when regulatory reactivity decisions have been made because the agency can provide seemingly credible justifications for the adoption of a given measure.[104]

2. The *Chevron* Doctrine

Congress delegates much regulatory authority to administrative agencies by enacting broad statutes with the expectation that the agencies will fill in the gaps via rulemaking, adjudication, and informal guidance.[105] When an agency wants its policy to have the effect of law, it must promulgate a rule.[106] In notice-and-comment rulemaking, the agency informs the public about a proposed rule, at which point members of the public may provide opinions and suggestions for the agency's consideration.[107] Before the agency enacts the final, legally enforceable rule, the federal Office of Management and Budget (OMB) must review the rule to determine whether the agency engaged in a proper cost-benefit analysis.[108] Because incorporating public feedback and waiting for OMB review can be time-consuming, the FDA has

98. *See* Yaniv Heled et al., *Regulatory Reactivity: FDA and the Response to COVID-19*, 76 FOOD & DRUG L.J. 318, 319–20 (2021).
99. *Id.* at 321.
100. *See id.*
101. *Id.* See *infra* Part I.D for a discussion on Aduhelm's approval, arguably an example of regulatory reactivity.
102. *See* Heled et al., *supra* note 98, at 322.
103. *See infra* Part I.C.2.
104. *See* Heled et al., *supra* note 98, at 322.
105. *See* K.M. Lewis, *Informal Guidance and the FDA*, 66 FOOD & DRUG L.J. 507, 507 (2011).
106. *See* 5 U.S.C. § 551(4).
107. *See* Lauren Kostman, Note, *The "Natural" Response for Adjudicating Current Litigation When the Creation of a Related Agency Rule Is Simultaneously Underway*, 41 CARDOZO L. REV. 353, 363 (2019).
108. *See* Nicholas R. Parrillo, *Should the Public Get to Participate Before Federal Agencies Issue Guidance?: An Empirical Study*, 71 ADMIN. L. REV. 57, 79 (2019).

been criticized for being too slow.[109] As a result, the FDA largely relies on issuing informal guidance and treats guidance documents as if they were binding rules, despite not being required to subject the guidance to the more stringent notice-and-comment procedure.[110]

The Administrative Procedure Act[111] (APA) grants federal courts jurisdiction to review administrative decisions.[112] The *Chevron* test, first set forth in *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*,[113] calls for a two-step analysis to evaluate an agency's interpretation of ambiguous statutory language.[114] First, courts must determine whether Congress has spoken directly on the question at issue.[115] "If the intent of Congress is clear, that is the end of the matter; the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress."[116] If Congress has not expressed a view on the question at issue, then courts must determine "whether the agency's answer is based on a permissible construction of the statute."[117]

Since the establishment of the *Chevron* doctrine, courts have expanded the level of deference given to agencies to include the agency's interpretation of its own ambiguous regulations.[118] In *Auer v. Robbins*,[119] the U.S. Supreme Court held that an agency's interpretation of its own regulation is "controlling

109. *See* Kostman, *supra* note 107, at 363–64; *see also* Parrillo, *supra* note 108, at 80 (interviewing agency officials who believed that issuing guidance instead of notice-and-comment rulemaking was faster because it avoided OMB review). One study analyzing rules on medical products between 2000 and 2012 found that the FDA took a median time of 7.3 years to issue a final rule. *See* Thomas J. Hwang et al., *Quantifying the Food and Drug Administration's Rulemaking Delays Highlights the Need for Transparency*, 33 HEALTH AFFS. 309, 311 (2014).

110. Chad Landmon et al., *Open the Floodgates: The Potential Impact on Litigation Against FDA If the Supreme Court Reverses or Curtails* Chevron *Deference*, 74 FOOD & DRUG L.J. 358, 359 (2019); *see also* Chase Weidner, *The Guidance Document Dilemma: Reforming the FDA's Use of Guidance Documents for the 21st Century*, 75 N.Y.U. ANN. SURV. AM. L. 137, 143 (2020) (noting that because the FDA holds great leverage over regulated entities, "the reality in practice is that the guidance documents often do function like legislative rules even though they are neither the result of adjudication nor the byproduct of formal or informal rulemaking").

111. 5 U.S.C. §§ 551–559, 701–706.

112. *See id.* § 706 ("[T]he reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action.").

113. 467 U.S. 837 (1984).

114. *Id.* at 842–43. In this landmark case, the Supreme Court held that the Environmental Protection Agency (EPA) could treat all pollution-emitting devices within the same industrial grouping as though they were encased within a single "bubble" because the EPA based its treatment on a permissible interpretation of the term, "stationary source," in an environmental statute. *Id.* at 845. In doing so, the Supreme Court established the test, known as the *Chevron* doctrine, for deciding whether a court should defer to a government agency's interpretation of a statute. *See id.* at 842.

115. *See id.* at 842–43.

116. *See id.*

117. *Id.* at 843.

118. *See* Landmon et al., *supra* note 110, at 361.

119. 519 U.S. 452 (1997).

unless 'plainly erroneous or inconsistent with the regulation.'"[120] The *Chevron* doctrine has continued to evolve in response to growing concerns about regulatory capture.[121]

The Supreme Court articulated what is now known as hard look review in *Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Insurance*.[122] Hard look review requires an agency to show that at the time it took the action in question, the agency had a contemporaneous rationale sufficient to satisfy the requirements of "reasoned decisionmaking."[123] Nowadays, hard look review is the most common reason why courts vacate federal agencies' actions.[124] Further, in *Encino Motorcars, LLC v. Navarro*,[125] the Court highlighted the connection between the *Chevron* doctrine and agency procedure, holding that an agency can lose the opportunity for *Chevron* deference if it uses defective procedures in its decision-making.[126] Importantly, failure to explain an inconsistency is a "reason for holding an interpretation to be an arbitrary and capricious change from agency practice," and arbitrary action "is itself unlawful and receives no *Chevron* deference."[127]

Courts are usually deferential to agency discretion and rely heavily on the FDA's expertise, especially regarding technical or scientific decisions.[128] In fact, suing the FDA under the *Chevron* test has been described as a "David versus Goliath-like battle [e]xcept here, David almost never wins."[129] Perhaps that is appropriate, as proponents of the *Chevron* doctrine argue that agencies have more expertise to say what the law is when it comes to

120. *Id.* at 461 (quoting Robertson v. Methow Valley Citizens Council, 490 U.S. 332, 359 (1989)).

121. *See* John Blevins, *License to Uber: Using Administrative Law to Fix Occupational Licensing*, 64 UCLA L. REV. 844, 885 (2017) (noting that arbitrary and capricious review grew in response to concerns from courts and the legal academy about agency capture).

122. 463 U.S. 29 (1983). In this case, the Supreme Court concluded that the National Highway Traffic Safety Administration's decision to rescind its requirement that passive restraints be installed in new cars was flawed because the agency had failed to consider all relevant factors and alternatives. *See id.* at 45, 48, 55–56.

123. *Id.* at 52. Under *State Farm*, an agency's decision would be deemed arbitrary and capricious if the agency (1) based its decision on factors that "Congress has not intended it to consider," (2) failed to address "an important aspect of the problem," (3) provided an explanation that "runs counter to the evidence before the agency," or (4) provided an explanation that was "so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Id.* at 43. The agency explanation must have a "rational connection between the facts found and the choice made." *Id.* (quoting Burlington Truck Lines, Inc. v. United States, 371 U.S. 156, 168 (1962)).

124. *See* Blevins, *supra* note 121121, at 885.

125. 136 S. Ct. 2117 (2016). In this case, employees at an auto dealership sued the dealership alleging that it violated the Fair Labor Standards Act by not paying overtime compensation. *See id.* at 2121. At issue was the U.S. Department of Labor's interpretation of the term "salesman" and whether the plaintiff auto service advisors were included. *See id.* at 2122.

126. *See id.* at 2125.

127. *Id.* at 2126.

128. *See* Sanders, *supra* note 71, at 158.

129. Landmon et al., *supra* note 110, at 358.

administrative decisions.[130] On the other hand, judicial review is necessary as a last-resort check on virtually unrestrained agency discretion.[131] If a plaintiff were to challenge FDA decisions to approve a drug or require certain labeling, courts would likely require that the FDA only "articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'"[132] Overall, courts are reluctant to intervene in agency decision-making unless there is robust evidence that the agency decision was made with improper motives.[133] This is potentially problematic because it sets the stage for FDA agents to justify their decisions as entirely scientific, earning great deference from courts, even where their decisions may also be influenced by other invalid reasons.[134]

D. The Decision to Approve Aduhelm

The FDA has granted accelerated approval to hundreds of drugs, but few drugs have generated as much controversy as Aduhelm has in the time since its accelerated approval.[135] To understand why Aduhelm does not fit the accelerated approval criteria as seamlessly as the FDA purports, this section first explains Alzheimer's disease before diving into the saga culminating in Aduhelm's controversial approval.

1. Alzheimer's Disease and the Pressure for New Treatments

Alzheimer's disease is a progressive neurodegenerative disorder characterized by the degeneration of brain cells, cognitive and behavioral impairment, social and occupational dysfunction, and death.[136] As the disease progresses, patients experience a decline in thinking and independence in personal daily activities, becoming increasingly reliant on

130. *See id.* at 363; *see also* Lisa Schultz Bressman, Chevron*'s Mistake*, 58 DUKE L.J. 549, 561 (2009) ("*Chevron* directs courts to accept the legislative assignment of interpretive authority and defer to reasonable agency interpretations. . . . Agencies possess more expertise than courts for handling regulatory schemes that are 'technical and complex' and for reconciling the 'competing interests' that regulatory decisions often involve." (quoting Chevron U.S.A. Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837, 865 (1984))).

131. *See* Patrick Garry, *The Values and Viewpoints Affecting Judicial Review of Agency Actions: A Focus on the Hard-Look Doctrine*, 53 WASHBURN L.J. 71, 81–82 (2013).

132. Motor Vehicle Mfrs. Ass'n of the United States, Inc. v. State Farm Mutual Auto. Ins. Co., 463 U.S. 29, 43 (1983) (quoting Burlington Truck Lines v. United States, 371 U.S. 156, 168 (1962)); *see also* Sanders, *supra* note 71, at 158–59 (noting that although courts are generally deferential to agency discretion, they may still engage in closer review of FDA decision-making where the decision appears to be the product of political forces rather than scientific or technical judgment).

133. *See* Sanders, *supra* note 71, at 160.

134. *See id.*

135. *See* Alice Park, *Biogen's Controversial Alzheimer's Drug Was Connected to a Patient Death, Just as the Company Presented Its Final Study Data*, TIME (Nov. 12, 2021, 11:21 AM), https://time.com/6116870/aduhelm-alzheimers-drug-death-new-data/ [https://perma.cc/64C4-B5JY].

136. *See* Francesco Panza et al., *A Critical Appraisal of Amyloid-β-Targeting Therapies for Alzheimer Disease*, 15 NATURE REVS. NEUROLOGY 73, 73 (2019).

their caregivers[137] for daily tasks.[138] In the United States, an estimated 6.2 million people over the age of sixty-five live with Alzheimer's disease—by 2050, that number is projected to rise to 12.7 million.[139] The Alzheimer's Association estimates that in 2021, the United States spent $355 billion on Alzheimer's costs, including $239 billion in Medicare and Medicaid payments.[140] There is no cure for Alzheimer's, although there are drugs for the treatment of some symptoms.[141] The average life expectancy of patients with Alzheimer's is four to eight years; over these years, caregivers can suffer significant negative physical, financial, and emotional stress from the strain of caregiving.[142] The devastation and prevalence of the disease have led to a rush of investment in potential treatments, with federal government spending on Alzheimer's research reaching $3.1 billion in 2021, compared to $450 million in 2005.[143] Research institutions and pharmaceutical companies have also poured substantial resources into slowing down or stopping the progression of Alzheimer's.[144]

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137. Caregiving includes assistance with activities of daily living, emotional support, coordinating care with health-care providers, and managing the patient's health conditions. *See* ALZHEIMER'S ASS'N, 2021 ALZHEIMER'S DISEASE FACTS AND FIGURES 36 (2021). 83 percent of the help provided to older adults in the United States comes from unpaid caregivers (family members and friends); nearly half of those caregivers provide help for Alzheimer's and dementia patients. *See id.*

138. *See* Zeinab Breijyeh & Rafik Karamen, *Comprehensive Review on Alzheimer's Disease: Causes and Treatment*, MOLECULES, Dec. 2020, at 1, 4. In the presymptomatic stage, one may experience mild memory loss but no functional impairment in daily activities. *See id.* Early stage symptoms of Alzheimer's include loss of concentration and memory, disorientation of place and time, mood changes, and depression. *See id.* In the moderate stage, patients may experience increased memory loss, loss of impulse control, and difficulty reading and speaking. *See id.* Finally, in late stage Alzheimer's disease, patients may not be able to recognize family, become bedridden with difficulties in swallowing and urination, and eventually die. *See id.*

139. *See Facts and Figures*, ALZHEIMER'S ASS'N, https://www.alz.org/alzheimers-dementia/facts-figures [https://perma.cc/UHT4-5YSC] (last visited Mar. 4, 2022).

140. *See id.* Costs include insurance payments, nursing home care, and adult day services. *See id.*

141. *See* U.S. FOOD & DRUG ADMIN., COMBINED FDA AND APPLICANT PCNS DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT 12 (2020), https://fda.report/media/143503/PCNS-20201106-CombinedFDABiogenBackgrounder_0.pdf [https://perma.cc/T639-LDF3]. Currently approved Alzheimer's disease treatments include cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine. *See id.* These drugs have different mechanisms but all are approved for the treatment of dementia due to Alzheimer's disease. *See* Kristina Nikl et al., *Alzheimer's Disease: Current Treatments and Potential New Agents*, U.S. PHARMACIST (Jan. 18, 2019), https://www.uspharmacist.com/article/alzheimers-disease-current-treatments-and-potential-new-agents [https://perma.cc/S37M-WX4K]. However, none of these treatments halt, slow, or cure the underlying pathology of Alzheimer's. *See* U.S. FOOD & DRUG ADMIN., *supra*, at 12. The treatments' effects are reversible and lessen over time due to the continued progression of the disease process. *See id.*

142. *See* INST. FOR CLINICAL & ECON. REV., REPORT AT A GLANCE: ALZHEIMER'S DISEASE 2 (2021).

143. *See* Toobin, *supra* note 96.

144. *See* Michael Greicius & G. Caleb Alexander, Opinion, *People Want an Alzheimer's Drug. This Isn't the One.*, N.Y. TIMES (May 28, 2021), https://www.nytimes.com/2021/05/28/opinion/alzheimer-treatment-FDA-aducanumab.html [https://perma.cc/AXQ5-ZJAA] (describing the immense pressure on the FDA from pharmaceutical companies and PAOs to

One theory has dominated the field of Alzheimer's research for more than twenty-five years: the "amyloid hypothesis," which posits that the accumulation of the peptide amyloid-β in the brain triggers neurodegenerative processes and causes Alzheimer's disease.[145] Since the amyloid hypothesis was first proposed, scientific journals and professional societies have promoted and rewarded research targeting amyloid-β plaques to the point where one National Institutes of Health (NIH) researcher called the hypothesis "an almost religious belief system, where people stopped being skeptical or even questioning."[146] Today, the amyloid hypothesis remains controversial, with critics pointing out that amyloid-β plaques are found in the brains of many elderly people with and *without* Alzheimer's.[147] Importantly, data supporting a connection between the amount of amyloid-β plaque present in the brain and cognitive function are weak and inconsistent at best.[148] Moreover, many drugs targeting amyloid-β plaques have failed to slow cognitive decline in clinical trials.[149] One study pooled together data from fourteen clinical trials of drugs targeting amyloid-β plaque (including the Aduhelm trials) and found that reduction in amyloid levels was unlikely to have meaningful cognitive benefits within the time frame of typical trials.[150] Although this does not conclusively invalidate the amyloid hypothesis, it does suggest that the "use of anti-amyloid drugs is not a viable

approve of a new treatment for Alzheimer's disease, with proponents arguing that any treatment would be "better than nothing").

145. *See* Simon Makin, *The Amyloid Hypothesis on Trial*, 559 NATURE S4, S5 (2018) ("The aggregation of amyloid-β is thought to trigger a cascade of disease-causing processes such as inflammation, . . . synapse dysfunction and cell death, which ultimately leads to dementia.").

146. Sharon Begley, *The Maddening Saga of How an Alzheimer's 'Cabal' Thwarted Progress Toward a Cure for Decades*, STAT (June 25, 2019), https://www.statnews.com/2019/06/25/alzheimers-cabal-thwarted-progress-toward-cure/ [https://perma.cc/7TD6-MYG4]; *see also* Daniel R. George & Peter J. Whitehouse, *Alzheimer's, Inc.: When a Hypothesis Becomes Too Big to Fail*, SCI. AM. (Aug. 25, 2021), https://www.scientificamerican.com/article/alzheimers-inc-when-a-hypothesis-becomes-too-big-to-fail/ [https://perma.cc/5BE2-FE32] (describing the "field's inability to modify or abandon the amyloid hypothesis in light of contravening evidence").

147. *See* Makin, *supra* note 145, at S5.

148. *See* Hedva Barenholtz Levy, *Accelerated Approval of Aducanumab: Where Do We Stand Now?*, ANNALS PHARMACOTHERAPY, 2021, at 1, 3 ("The impact of reducing [amyloid-β plaque] accumulation and at what stage of development is unknown. Statistical significance found in clinical trials is based on small changes on clinical rating scales that may not translate to clinically significant improvement."); Makin, *supra* note 145, at S5 (listing examples of clinical trials for therapies targeting amyloid-β which had to be halted due to lack of efficacy or severe side effects).

149. *See* Pam Belluck, *Many Alzheimer's Experts Say Use of Aduhelm Should Be Sharply Limited*, N.Y. TIMES (Sept. 2, 2021), https://www.nytimes.com/2021/06/21/health/aduhelm-alzheimers-drug.html [https://perma.cc/C9JG-34NJ]; Panza et al., *supra* note 136, at 77 (explaining that in all clinical trials of drugs that decrease production of plaque or increase plaque brain clearance, treatments failed to improve cognitive outcomes despite reducing plaque; some drugs even worsened clinical status compared with placebo).

150. *See* Sarah F. Ackley et al., *Effect of Reductions in Amyloid Levels on Cognitive Change in Randomized Trials: Instrumental Variable Meta-Analysis*, BRIT. MED. J., Feb. 2021, at 1, 7. Data were pooled together because it is possible that the benefit of amyloid reduction might be too small to detect within any individual trial. *See id.* at 2.

strategy for the prevention or treatment of Alzheimer's disease and that other potential targets may merit more attention."[151]

2. Aduhelm: A Drug Approved Based on Inconclusive Data

Despite the lack of evidence demonstrating a causal connection between amyloid-β plaques and Alzheimer's disease, Biogen pushed forward with its drug, aducanumab (commercially known as Aduhelm).[152] Like many failed Alzheimer's therapeutic agents before it, Aduhelm is an immunotherapy that induces clearance of amyloid-β plaques from the brain.[153] Alzheimer's patients require monthly intravenous infusions, whereby Aduhelm is injected, sticking to the amyloid-β molecules and essentially tricking the body's immune system into thinking that the plaques are foreign invaders, leading the body to remove them.[154]

To move forward in the drug development process, Biogen had to collect evidence supporting Aduhelm's safety and efficacy.[155] To that end, Biogen conducted two trials for Aduhelm, called ENGAGE (Study 301)[156] and EMERGE (Study 302),[157] that were practically identical in their design and had an eighteen-month duration among patients with a mean age of seventy years who had mild cognitive impairment or early symptomatic Alzheimer's disease.[158] Both trials were global, randomized, double-blind, placebo-controlled studies designed to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of Aduhelm.[159] In total, over 3200 participants were randomly assigned to Aduhelm (high-dose or low-dose) or a placebo.[160]

The primary clinical outcome measured was the change in mean score on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB).[161] The CDR-SB assesses cognition and function through an interview with the patient, where the patient receives a score in six categories: memory, orientation, problem-solving, community affairs, hobbies, and personal

151. *Id.* at 6.

152. *See* George & Whitehouse, *supra* note 146.

153. *See* Rudolph E. Tanzi, *FDA Approval of Aduhelm Paves a New Path for Alzheimer's Disease*, 12 ACS CHEM. NEUROSCIENCE 2714, 2714 (2021).

154. *See* Andrew E. Budson, *A New Alzheimer's Drug Has Been Approved. But Should You Take It?*, HARV. HEALTH PUBL'G (July 15, 2021), https://www.health.harvard.edu/blog/a-new-alzheimers-drug-has-been-approved-but-should-you-take-it-202106082483 [https://perma.cc/ML38-5VT6].

155. *See supra* Part I.A for an explanation of the drug development process.

156. *See ENGAGE Trial*, *supra* note 8.

157. *See EMERGE Trial*, *supra* note 8.

158. *See* Lewis H. Kuller & Oscar L. Lopez, *ENGAGE and EMERGE: Truth and Consequences?*, 17 ALZHEIMER'S & DEMENTIA 692, 692 (2021).

159. *See* U.S. FOOD & DRUG ADMIN., *supra* note 141, at 28.

160. *See ENGAGE Trial*, *supra* note 8; *EMERGE Trial*, *supra* note 8.

161. *See* GRACE A. LIN ET AL., INST. FOR CLINICAL AND ECON. REV., ADUCANUMAB FOR ALZHEIMER'S DISEASE: EFFECTIVENESS AND VALUE 9 (2021), https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf [https://perma.cc/9DSE-ENNW].

care.[162] A total possible score ranges from zero to eighteen, with higher scores indicating greater disease severity.[163] Notably, the minimal clinically important difference is estimated to be one to two points.[164]

In ENGAGE, neither treatment group (i.e., those receiving high-dose and low-dose Aduhelm) had statistically significant[165] differences on either primary or secondary efficacy endpoints from those receiving a placebo—essentially, the data failed to show that either the low or high dose of Aduhelm significantly reduced the CDR-SB score in test subjects.[166] Although the EMERGE trial did show a statistically significant change where high-dose participants scored 0.39 points lower on CDR-SB than placebo participants, it is important to note that this change was less than the one-to-two point change that is considered clinically significant among the scientific community.[167]

Both trials were halted in March 2019 based on an interim analysis that was conducted by an independent data monitoring committee[168] and that concluded, based on data collected through October 2018, that Aduhelm was unlikely to benefit Alzheimer's patients compared to placebo.[169] At the time, the decision was an enormous disappointment to Biogen and the scientific community because Aduhelm "was supposed to be the drug that finally proved [the amyloid hypothesis] after multiple other failures."[170] The decision was a devastating blow to Biogen as shares fell 29 percent and erased almost $16 billion in market value.[171]

However, in October 2019, reanalysis of data from EMERGE combined with additional late evidence confirmed that participants in the high-dose Aduhelm group declined less in cognition and function over eighteen months

162. *See id.*

163. *See id.*

164. *See id.* In the scientific literature, a clinically significant outcome, not to be confused with a statistically significant outcome, is defined as the smallest difference in score that patients perceive as beneficial and that would mandate a change in the patient's management. *See* J. Scott Andrews et al., *Disease Severity and Minimal Clinically Important Differences in Clinical Outcome Assessments for Alzheimer's Disease Clinical Trials*, 5 ALZHEIMER'S & DEMENTIA: TRANSLATIONAL RSCH. & CLINICAL INTERVENTIONS 354, 354 (2019). Interestingly, the FDA "accepts a statistically significant change on an inherently meaningful instrument such as CDR-SB as evidence of a clinically meaningful effect." U.S. FOOD & DRUG ADMIN., *supra* note 141, at 34.

165. Statistical significance refers to whether any differences observed between groups being studied are reliable or whether they are simply due to random chance. *See Statistical Significance*, INST. FOR WORK & HEALTH (Apr. 2005), https://www.iwh.on.ca/what-researchers-mean-by/statistical-significance [https://perma.cc/3HZE-T978].

166. *See* Lin et al., *supra* note 161, at 10.

167. *See id.* at 9.

168. A clinical trial data monitoring committee is a group of individuals with pertinent expertise that regularly reviews accumulating data from ongoing trials to advise the sponsor on the safety of trial subjects and the continuing scientific merit of the trial. *See* U.S. FOOD & DRUG ADMIN., *supra* note 7, at 1.

169. *See* Adam Feuerstein, *Biogen Halts Studies of Closely Watched Alzheimer's Drug, A Blow to Hopes for New Treatment*, STAT (Mar. 21, 2019), https://www.statnews.com/2019/03/21/biogen-eisai-alzheimer-trial-stopped/ [https://perma.cc/U5S4-6A29].

170. *See id.*

171. *See id.*

compared to the placebo group.[172] According to Biogen, the larger dataset from the EMERGE trial showed that, ultimately, EMERGE was a "positive study, providing the primary contribution to the substantial evidence of the effectiveness of [Aduhelm.]"[173] Biogen announced that it planned on submitting Aduhelm for FDA approval, with Biogen's then Chief Medical Officer, Al Sandrock, stating that the "futility analysis was incorrect . . . because it was from a smaller dataset that looked at patients with less exposure to high dose [Aduhelm]."[174]

In light of all the clinical trial data, on November 6, 2020, the FDA convened the Peripheral and Central Nervous System Drugs Advisory Committee, which consisted of eleven voting members,[175] various non-voting FDA participants, and open public hearing speakers.[176] In the briefing document given to the advisory committee, the FDA stated that the results of the EMERGE trial were "highly persuasive and . . . a strongly positive study on multiple distinct and important clinical measures."[177] However, the advisory committee was concerned that the EMERGE trial "could not be viewed without consideration of [the ENGAGE trial] since [ENGAGE] was designed to be identical to [EMERGE] but was negative."[178] Several committee members cited the FDA's own statistical reviewer, who concluded that because "[t]here is only one positive study at best and a second study which directly conflicts with the positive study. . . . substantial evidence has not been met in this application."[179]

In both trials at the high and low dose, Aduhelm effectively removed amyloid-β plaques,[180] but the advisory committee expressed uncertainty as to whether plaque reduction actually conferred cognitive improvement.[181] Also concerning was the fact that more than 40 percent of participants in

172. *See* Matthew Herper, *In Shocking Reversal, Biogen to Submit Experimental Alzheimer's Drug For Approval*, STAT (Oct. 22, 2019), https://www.statnews.com/2019/10/22/biogen-to-submit-aducanumab/ [https://perma.cc/LGH3-6HUS]. The post hoc nature of these analyses resulted in a loss of randomization, which limits the conclusions that can be drawn from them. *See* Lin et al., *supra* note 161, at 20.

173. U.S. FOOD & DRUG ADMIN., *supra* note 141, at 56.

174. Herper, *supra* note 172.

175. *See* U.S. FOOD & DRUG ADMIN., TRANSCRIPT FOR THE NOVEMBER 6, 2020, MEETING OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE 2–7 (2020), https://www.fda.gov/media/145691/download [https://perma.cc/SH7K-QAJW].

176. *See* U.S. FOOD & DRUG ADMIN., FINAL SUMMARY MINUTES OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING 2 (2020), https://www.fda.gov/media/145690/download [https://perma.cc/96KV-BPBW].

177. U.S. FOOD & DRUG ADMIN., *supra* note 141, at 57.

178. U.S. FOOD & DRUG ADMIN., *supra* note 176, at 4.

179. TRISTAN MASSIE, CTR. FOR DRUG EVAL. AND RSCH., STATISTICAL REVIEW AND EVALUATION 10 (2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000StatR_Redacted.pdf [https://perma.cc/P59Q-FM5W]; *see also* Kelly Servick, *Biogen's Alzheimer's Drug Candidate Takes a Beating from FDA Advisers*, SCI. (Nov. 6, 2020), https://www.science.org/content/article/biogen-s-alzheimer-s-drug-candidate-takes-beating-fda-advisers [https://perma.cc/NER4-A8JJ] (describing more issues that the advisory committee had with the EMERGE and ENGAGE results).

180. *See* Lin et al., *supra* note 161, at ES1.

181. *See* U.S. FOOD & DRUG ADMIN., *supra* note 176, at 5.

EMERGE and ENGAGE receiving the FDA-approved dose developed amyloid-related imaging abnormalities (ARIAs), compared to 10 percent in the placebo groups.[182] Ultimately, ten members of the advisory committee voted against approval, concluding that there was insufficient evidence to show that Aduhelm could slow cognitive decline, while the eleventh member voted "uncertain."[183] After the advisory committee's damning vote against approval, it appeared that Aduhelm's journey had come to an end and that FDA approval was unlikely.[184]

3. The FDA's Approval Decision Causes Controversy

While the FDA's decision on approval was delayed because of COVID-19, many thought that if Aduhelm was approved, it would be "an eyebrow-raising departure, and would likely be met with confusion and criticism."[185] After the advisory committee's overwhelming vote against traditional approval, the FDA shockingly granted accelerated approval on June 7, 2021.[186] Here, accelerated approval was based on a different endpoint than the focus of the November 2020 advisory committee meeting: instead of the CDR-SB cognitive scale that was used in the ENGAGE and EMERGE trials, the FDA based approval on MRI findings of amyloid-β plaque.[187] This was a surprise because at the November 2020 meeting, the FDA had told the advisory committee that the agency was "not using the amyloid as a surrogate for efficacy."[188] In fact, the FDA's decision directly contradicted its earlier 2018 guidance document, wherein the agency stated that for early stage Alzheimer's disease trials, there was "no sufficiently reliable evidence that any observed treatment effect on such biomarker

182. *See* Moghavem et al., *supra* note 5, at 331. ARIAs manifest via symptoms including headache, confusion, nausea, and gait disturbances. *See id.*

183. Andrew Joseph, *Member of FDA's Expert Panel Resigns over Controversial Alzheimer's Therapy Approval*, STAT (June 8, 2021), https://www.statnews.com/2021/06/08/fda-expert-panel-resigns-alzheimers-approval/ [https://perma.cc/PXA8-72LP].

184. *See* Jacob Bell et al., *5 Takeaways From the FDA's High-Stakes Meeting for Biogen's Alzheimer's Drug*, BIOPHARMA DIVE (Nov. 9, 2020), https://www.biopharmadive.com/news/fda-alzheimers-biogen-aducanumab-takeaways/588653/ [https://perma.cc/TQ26-RHLZ].

185. *See id.* (quoting several commentators who were skeptical about Aduhelm's prospects after the November 2020 advisory committee meeting).

186. *See* Press Release, U.S. Food & Drug Admin., *supra* note 3.

187. *See* Patricia Cavazzoni, *FDA's Decision to Approve New Treatment for Alzheimer's Disease*, U.S. 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/UD7K-EPKL] (explaining that even though the advisory committee did not discuss accelerated approval, the FDA ultimately granted Aduhelm accelerated approval "based on . . . reduction of amyloid plaque in the brain"); *see also* Reshma Ramachandran & Joseph S. Ross, Opinion, *New Alzheimer's Drug Sets Dangerous Precedent*, CNN (June 17, 2021, 2:37 PM), https://www.cnn.com/2021/06/17/opinions/biogen-alzheimers-drug-opinion-ramachandra-ross/index.html [https://perma.cc/LP25-WDKD] (noting that the "FDA changed the rules in the middle of the game" by switching to amyloid-β plaque as a surrogate for efficacy).

188. U.S. FOOD & DRUG ADMIN., *supra* note 175, at 140.

measures would be reasonably likely to predict clinical benefit."[189] Given the FDA's sharp reversal of the advisory committee's vote, several committee members resigned, citing concerns over the lack of evidence that the drug was effective in reducing Alzheimer's symptoms while having significant adverse reactions,[190] and criticizing the FDA's approval based on considerations that were not part of the advisory committee's discussions.[191] One agency adviser who resigned from his committee post in protest called it "probably the worst drug approval decision in recent U.S. history."[192]

Of primary concern for the advisory committee was the FDA's approval based on a surrogate endpoint instead of the primary endpoint used in the Aduhelm trials.[193] An effective surrogate endpoint should be "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit,"[194] but FDA statistical review of the ENGAGE and EMERGE trials found no evidence that amyloid changes correlated with cognitive or functional changes.[195] While surrogate endpoints allow patients to try promising drugs without waiting for years of clinical trials, critics argue against placing drugs on the market that have not yet demonstrated the ability to produce direct, meaningful benefits to patients.[196] A study on surrogate endpoints used in oncological trials demonstrated that the strength of association between the surrogates used and clinically meaningful outcomes is often unknown or weak, and attempts to validate surrogates are rarely undertaken, suggesting that the benefits of

189. U.S. FOOD & DRUG ADMIN., EARLY ALZHEIMER'S DISEASE: DEVELOPING DRUGS FOR TREATMENT, GUIDANCE FOR INDUSTRY 6 (2018), https://www.fda.gov/files/drugs/published/Alzheimer%E2%80%99s-Disease---Developing-Drugs-for-Treatment-Guidance-for-Industy.pdf [https://perma.cc/3YZT-3BHF].

190. *See* Moghavem et al., *supra* note 5, at 331 (describing ARIAs found during clinical trials for Aduhelm).

191. *See* Letter from Aaron S. Kesselheim, Professor of Med., Brigham & Women's Hosp./Harv. Med. Sch., to Janet Woodcock, Acting Comm'r, U.S. Food & Drug Admin. (June 10, 2021), https://pbs.twimg.com/media/E3jKN4GWYAUGj9U.png [https://perma.cc/3HYT-32N6].

192. Matthew Herper et al., *Newly Disclosed FDA Documents Reveal Agency's Unprecedented Path to Approving Aduhelm*, STAT (June 22, 2021), https://www.statnews.com/2021/06/22/documents-reveal-fda-unprecedented-aduhelm-decision/ [https://perma.cc/T2Y8-5H4Q].

193. *See* G. Caleb Alexander et al., *Revisiting FDA Approval of Aducanumab*, 385 NEW ENG. J. MED. 769, 769 (2021) (criticizing the FDA's late-stage decision to grant accelerated approval for Aduhelm and noting that, before approval, "the FDA had not indicated that it considered beta-amyloid . . . an acceptable surrogate end point for clinical trials").

194. 21 C.F.R. § 314.510 (2022).

195. *See* Alexander et al., *supra* note 193, at 770 (noting that the FDA determined it was "not clear that there is any linkage between reduction in plaque and long term clinical change").

196. *See* Edwards, *supra* note 58, at 418; *see also* Oriana Ciani et al., *Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward*, 20 VALUE IN HEALTH 487, 493 (2017) ("Surrogates can result in market access for technologies that turn out to offer no true health benefit—or even harm—to patients and can result in overestimation of treatment effects, which can lead to inappropriate decisions on coverage.").

many approved drugs are uncertain at best.[197] Basing FDA approval on surrogate endpoints is controversial because they may not have strong predictive power for outcomes of interest.[198]

In 2009, the U.S. Government Accountability Office (GAO) investigated FDA oversight of surrogate marker studies and concluded that the FDA was failing to enforce verification of surrogate endpoints.[199] For example, at the time of the GAO investigation, the FDA had still not withdrawn the drug ProAmatine after the drug spent almost thirteen years on the market following its accelerated approval, despite the lack of required post-marketing studies.[200] Yet, this criticism from the GAO has ostensibly failed to reform FDA procedures.[201] In fact, the FDA rejected the GAO's recommendation to clarify the conditions under which the FDA would expedite withdrawal of drugs approved under the accelerated approval process if sponsors either failed to complete post-marketing studies or demonstrate clinical effectiveness of the drug.[202] According to Dr. Gonsalves, the "entire system completely disincentivizes the need to show clinical benefit . . . . It's driving drug development in the wrong direction."[203]

In basing accelerated approval on the amyloid-β plaque surrogate endpoint, the FDA overruled the advisory committee and skirted the issue of the conflicting CDR-SB clinical endpoint results in the Aduhelm trials. Granted, the FDA is not required by law or regulation to follow its advisory committees' recommendations.[204] However, previous overrulings have generally occurred when advisory committee votes were closer between the

197. *See* Robert Kemp & Vinay Prasad, *Surrogate Endpoints in Oncology: When Are They Acceptable for Regulatory and Clinical Decisions, and Are They Currently Overused?*, BMC MED., July 2017, 1, 2; Bishal Gyawali et al., *Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval*, 179 JAMA INTERNAL MED. 906, 906 (2019) (finding that out of ninety-three cancer treatments granted accelerated approval from 1992 to 2017, only nineteen showed improvement in overall patient survival).

198. *See* Austin B. Frakt, *The Risks and Benefits of Expedited Drug Reviews*, 320 JAMA 225, 226 (2018).

199. *See* U.S. GOV'T ACCOUNTABILITY OFF., GAO-09-866, NEW DRUG APPROVAL: FDA NEEDS TO ENHANCE ITS OVERSIGHT OF DRUGS APPROVED ON THE BASIS OF SURROGATE ENDPOINTS 29 (2009), https://www.gao.gov/assets/gao-09-866.pdf [https://perma.cc/7BZF-4LMH] (finding that the "FDA has not fully utilized its available enforcement tools, even when sponsors have failed to complete required studies").

200. *See id.* at 33–34; Silberner, *supra* note 43.

201. *See* ANNA KALTENBOECK ET AL., INST. FOR CLINICAL AND ECON. REV., STRENGTHENING THE ACCELERATED APPROVAL PATHWAY: AN ANALYSIS OF POTENTIAL POLICY REFORMS AND THEIR IMPACT ON UNCERTAINTY, ACCESS, INNOVATION, AND COSTS, 19 (2021), https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway-_-ICER-White-Paper-_-April-2021.pdf [https://perma.cc/NY95-QHNJ] (noting that the FDA did not change any internal procedures in response to GAO concerns about the FDA underenforcing accountability for disclosing the results of post-marketing studies).

202. *See* U.S. GOV'T ACCOUNTABILITY OFF., *supra* note 199, at 63–64.

203. Silberner, *supra* note 43.

204. *See* U.S. FOOD & DRUG ADMIN., *supra* note 64, at 1 ("Although the [advisory] committees provide recommendations to the Agency, final decisions are made by FDA."); *see also supra* note 74 and accompanying text.

experts who approved and those who did not.[205] The FDA approval of Aduhelm signifies a sharp departure from this pattern. Notably, Aduhelm's approval breaks with FDA precedent because accelerated approval is traditionally used for drugs that have not yet proven themselves in large clinical trials.[206] However, Aduhelm went through two Phase III trials that yielded conflicting evidence.[207] Nonetheless, the FDA justified its decision by citing the FDCA, which gives the FDA the authority to use accelerated approval on any treatment "upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit."[208] The agency concluded that reducing amyloid plaque is a surrogate endpoint reasonably likely to predict clinical benefit in Alzheimer's disease.[209]

Since its approval, some major American health systems have announced that they do not plan on administering Aduhelm, citing the current data regarding the drug's safety and efficacy.[210] Other doctors have noted that Aduhelm's potential side effects (brain swelling and hemorrhages) must be monitored carefully and that doctors should disclose to patients that there are many unknowns about the drug, including whether it can provide any benefit.[211] Dr. Paul Aisen, director of the Alzheimer's Therapeutic Research Institute at the University of Southern California, noted that "[i]t is impossible to determine on an individual patient level whether someone is benefiting or not."[212]

In response to public criticism of the FDA's decision to approve Aduhelm, Patrizia Cavazzoni, director of the FDA's Center for Drug Evaluation and Research, stated that the FDA granted accelerated approval because "the Agency concluded that the benefits of Aduhelm for patients with Alzheimer's disease outweighed the risks of the therapy."[213] She insisted that the FDA had not deviated from the usual course of action when reviewing NDAs.[214] Importantly, she failed to mention one issue that made Aduhelm quite unusual in the context of FDA regulatory decisions: there

205. *See* Zhang et al., *supra* note 71, at 813 (finding an increasing likelihood of discordance between advisory committee recommendations and FDA action associated with a decreasing degree of consensus among advisory committee members); *see also* Joseph, *supra* note 183.

206. *See* Herper et al., *supra* note 192.

207. *See id.*

208. 21 U.S.C. § 356.

209. *See* Billy Dunn et al., *An Appropriate Use of Accelerated Approval—Aducanumab for Alzheimer's Disease*, 385 NEW ENG. J. MED. 856, 856 (2021) (arguing that "there is compelling evidence that [Aduhelm] reduces plaque; and this reduction by a monoclonal antibody targeting aggregated amyloid is reasonably likely to predict clinical benefit—benefit supported by two controlled trials").

210. *See* Pam Belluck, *Cleveland Clinic and Mount Sinai Won't Administer Aduhelm to Patients*, N.Y. TIMES (Sept. 2, 2021), https://www.nytimes.com/2021/07/14/health/cleveland-clinic-aduhelm.html [https://perma.cc/7GAJ-FYE6].

211. *See* Belluck, *supra* note 149.

212. *Id.*

213. Cavazzoni, *supra* note 187; *see also* Specter, *supra* note 4.

214. *See* Cavazzoni, *supra* note 187.

appeared to be an alarming intimacy between Biogen and the FDA in the lead-up to Aduhelm's accelerated approval decision.

STAT, a media company that specializes in journalism focusing on the pharmaceutical industry, was the first to break the news of Project Onyx, an off-the-books campaign to resurrect Aduhelm after the EMERGE and ENGAGE clinical trials were halted for futility in March 2019.[215] STAT reported that after a meeting between Biogen and the FDA on June 14, 2019, a memo was sent to Biogen in which the FDA suggested the possibility of accelerated approval for Aduhelm.[216] The fact that accelerated approval was discussed as early as June 2019 is significant because it was never brought to the attention of the advisory committee when it met in November 2020.[217] An anonymous Biogen employee told STAT, "I knew from the interest levels within FDA that the agency was always going to find a way to approve Aduhelm."[218] A former FDA official who watched the advisory committee meeting called the FDA officials' actions and tone "very promotional," which was inappropriate because the FDA "should not be trying to lead the panel to an outcome . . . . [The] FDA should be as unbiased as they can be."[219]

As further evidence of the controversial nature of the FDA's approval of Aduhelm, the U.S. Department of Health and Human Services' Office of Inspector General has begun to investigate Aduhelm's approval and examine generally the accelerated approval pathway, but it is not yet clear what it will conclude.[220] In a separate inquiry on September 1, 2021, lawmakers from the House Committee on Oversight and Reform and the House Committee on Energy and Commerce requested data from the FDA on its Aduhelm approval decision, emphasizing the government's concern about "apparent anomalies in FDA's processes surrounding its review of Aduhelm."[221] Specifically, the House Committee's request to the FDA included (1) the body of evidence that the agency relied on to determine that amyloid-β

215. *See* Adam Feuerstein et al., *Inside 'Project Onyx': How Biogen Used an FDA Back Channel to Win Approval of Its Polarizing Alzheimer's Drug*, STAT (June 29, 2021), https://www.statnews.com/2021/06/29/biogen-fda-alzheimers-drug-approval-aduhelm-project-onyx/ [https://perma.cc/8F6C-2NBR].

216. *See id.*

217. *See id.*

218. *Id.*

219. *Id.*

220. *See Review of the FDA's Accelerated Approval Pathway*, U.S. DEP'T OF HEALTH & HUM. SERVS. OFF. OF INSPECTOR GEN., https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp [https://perma.cc/8NLC-C337] (last visited Mar. 4, 2022). Any reports from this investigation are expected to be issued in 2023. *See id.*

221. Letter from Frank Pallone, Jr., Chairman, Comm. on Energy and Com. & Carolyn B. Maloney, Chairwoman, Comm. on Oversight and Reform, to Janet Woodcock, Acting Comm'r, U.S. Food & Drug Admin. (Sept. 1, 2021), https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/EC%20COR%20FDA%20Aduhelm%20Letter%209.1.21.pdf [https://perma.cc/ZKF3-9TF8]; *see also* Rachel Cohrs, *Congress Demands Documents from FDA on Controversial Approval of Biogen's Alzheimer's Drug*, STAT (Sept. 2, 2021), https://www.statnews.com/2021/09/02/congress-demands-documents-fda-biogens-alzheimers-drug/ [https://perma.cc/ZGU5-2EJ2].

plaque was an appropriate endpoint, (2) the clinical trial data that convinced the FDA that Aduhelm should receive accelerated approval, (3) historical information about approvals in contravention of the advisory committee's recommendation, and (4) internal reviews of coordination between the FDA and Biogen.[222]

II. THE EFFECT OF THE FDA'S DECISION TO APPROVE ADUHELM

The FDA's decision to grant accelerated approval to Aduhelm shocked the pharmaceutical and health-care industries and will have consequences for pharmaceutical companies, medical researchers, and patients with and without Alzheimer's. This part describes the weaknesses of the accelerated approval pathway as seen through the story of Aduhelm. Part II.A questions what the appropriate role of the FDA should be, considering how closely the FDA worked with Biogen and PAOs leading up to Aduhelm's approval. Part II.B then describes how Aduhelm has already begun to influence the course of medical research both in and beyond Alzheimer's disease. Finally, Part II.C explains the economic impact of Aduhelm's approval. As discussed later, these connections raise numerous questions about the appropriate role of sponsors and PAOs in the accelerated approval process.

A. The Appropriate Role of the FDA as a Regulatory Agency

The accelerated approval of Aduhelm is a prime example of what can result when the FDA is pressured to usher in new treatments by industry and patients alike. Although it is important for the FDA to work with sponsors and listen to patient perspectives to ensure that new drugs move through the approval process efficiently, this section examines the deleterious effect that accelerated approval has on the FDA's role as a regulatory agency.

1. Responding to Industry Pressure

Although early engagement between the FDA and sponsors is officially encouraged,[223] Project Onyx provides an example of regulatory capture and how the FDA can abuse its discretion in carrying out the will of a sponsor to get a drug onto market.[224] The FDA arguably has a strong reason to help the very companies that it regulates, sometimes going as far as to blatantly consider the financial prospects of sponsors when making drug approval decisions.[225] The FDA, at least indirectly, considers pharmaceutical

222. *See* Cohrs, *supra* note 221.

223. *See* U.S. FOOD & DRUG ADMIN., *supra* note 189, at 5–6 (encouraging sponsors to discuss their plans with the FDA early in development when conducting research on Alzheimer's disease).

224. See *supra* Part I.D.3 for a discussion on Project Onyx, Biogen's off-the-books campaign to persuade the FDA to approve Aduhelm.

225. *See, e.g.*, Memorandum from Luciana Borio, Acting Chief Scientist, U.S. Food & Drug Admin., to Robert Califf, Comm'r of Food & Drugs, U.S. Food & Drug Admin. 16 (Sept. 16, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_redacted.pdf [https://perma.cc/9Z3D-HG8E] (noting that the FDA's Dr.

companies' financial health because it is closely tied to the FDA's own revenue stream.[226] Pharmaceutical companies pay user fees to support their regulators, a practice stemming from the idea that if companies benefit from the FDA's decisions, the companies should cover the FDA's costs.[227] Although user fees provide the FDA with much-needed funding and enable the agency to significantly cut down on median approval time for NDAs, user fees may present a glaring conflict of interest in which the FDA faces pressure to approve the drugs made by the very companies that provide the FDA's revenue stream.[228] Some critics argue that only regulatory capture can explain why increased speed alone would cause the FDA to too quickly approve, and not simply review, new drugs.[229]

2. Working with Patient Advocacy Organizations

Besides industry perspectives, the FDA also seeks input from patients who suffer from the disease in question.[230] PAOs[231] are formally organized nonprofit groups that serve people affected by a specific medical condition and raise awareness about the disease, treatment options, and new research on the disease.[232] PAOs are vital to the drug development process because they are a strong voice for more government resources and faster FDA drug approval, particularly on behalf of patients with devastating diseases for which there are few or no treatment options.[233] They also help

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Janet 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 pipeline").

226. *See* Toobin, *supra* note 96.

227. *See* James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 262 (2005) (explaining that user fees were developed so that the FDA could obtain more revenue, hire more employees to decrease NDA review times, and speed up the public's access to new drugs); *see also* FDA AT A GLANCE, U.S. FOOD & DRUG ADMIN. (2021), https://www.fda.gov/media/154548/download [https://perma.cc/H9EN-YKFJ] (noting that in 2020, 46 percent of the FDA's budget, or $2.8 billion, was paid for by industry user fees).

228. *See* Michael Gabay, *The Prescription Drug User Fee Act: Cause for Concern?*, 53 HOSP. PHARMACY 88, 88 (2018).

229. *See* Zelenay, *supra* note 227, at 310 (arguing that user fees inappropriately place the FDA in industry's pocket); *see also* Patrick O'Leary, *Funding the FDA: Assessing the User Fee Provisions of the FDA Safety and Innovation Act of 2012*, 50 HARV. J. ON LEGIS. 239, 257 (2013) (arguing that even if there is no actual regulatory capture, the appearance of capture is itself problematic because the FDA's ability to protect the public depends on its credibility).

230. *See FDA Patient Engagement Overview*, U.S. FOOD & DRUG ADMIN. (Sept. 14, 2020), https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-engagement-overview [https://perma.cc/YE6T-D5DX] (describing the various FDA initiatives that connect patients with FDA decision-making).

231. PAOs are also called advocacy groups, disease advocacy groups, health advocacy groups, and health consumer groups, which are all meant to highlight their focus on the patient perspective and distinguish them from professional organizations. *See* Susannah L. Rose, *Patient Advocacy Organizations: Institutional Conflicts of Interest, Trust, and Trustworthiness*, 41 J.L. MED. & ETHICS 680, 685 n.1 (2013).

232. *See id.* at 680.

233. *See, e.g.*, Anne-Laure Winkler & David Finegold, *Giving Patients a Say: How to Work with Patient Advocacy Groups*, NATURE BIOTECHNOLOGY, Jan. 2008, at 1, 1 (noting that

pharmaceutical companies and regulators identify patients and develop the best primary and secondary endpoints for clinical trials.[234] In certain research areas, including those covering Alzheimer's disease and Parkinson's disease, PAOs, rather than pharmaceutical companies, fund an increasing share of scientific research.[235]

On the other hand, PAOs are sometimes so effective at voicing their perspectives to the FDA that both parties may lose sight of upholding scientific rigor and protecting public health. After the advisory committee voted against approving Aduhelm in its November 2020 meeting, the Alzheimer's Association scheduled a listening session with Cavazzoni, the then acting director of the FDA's Center for Drug Evaluation and Research, on January 20, 2021.[236] The listening session included testimonials from patients and caregivers about their experiences with Alzheimer's disease and discussion on how much risk they would be willing to accept when trying a new treatment.[237] Peter Stein, director of the FDA's Office of New Drugs, said that the FDA "heard very clearly from patients that they're willing to accept some uncertainty to have access to a drug that could provide meaningful benefit in preventing the progression of [Alzheimer's] disease."[238] In the wake of Aduhelm's approval, PAOs for other diseases have already begun to push for approval of new treatments and more relaxed standards.[239] Critics argue that, "under steady pressure from the pharmaceutical industry and the patient groups it funds, the F.D.A. has

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a PAO for muscular dystrophy, which consisted of 3000 parents of sick children, helped pass the MD-Care Act in 2001 that mandated that the NIH promote research for muscular dystrophy); T. Joseph Mattingly II & Linda Simoni-Wastila, *Patient-Centered Drug Approval: The Role of Patient Advocacy in the Drug Approval Process*, 23 J. OF MANAGED CARE & SPECIALTY PHARMACY 1078, 1078 (2017) (describing the controversial approval of eteplirsen in 2016, when then FDA Commissioner Dr. Robert Califf received nearly 3000 emails from patient advocates alone urging for the approval of a drug that the advisory committee had mostly voted against).

234. *See* Raymond A. Huml et al., *Accelerating Rare Disease Drug Development: Lessons Learned from Muscular Dystrophy Patient Advocacy Groups*, 55 THERAPEUTIC INNOVATION & REGUL. SCI. 370, 374–75 (2020).

235. *See* Sinha & Latham, *supra* note 88; *see also* Margaret Goldberg, *Patient Advocacy Groups and Innovators Must Partner to Advance New Treatments*, STAT (July 6, 2021), https://www.statnews.com/2021/07/06/patient-advocacy-groups-and-innovators-must-partner-to-advance-new-treatments [https://perma.cc/Z4U4-GF3R] (noting that the Michael J. Fox Foundation, a PAO for Parkinson's disease, has partnered with pharmaceutical companies to fund research which led to FDA approval of at least two treatments in 2020 alone).

236. *See* Derrick Gingery, *Patient Support May Have Helped Push Aduhelm Toward Approval*, PINK SHEET (June 7, 2021), https://pink.pharmaintelligence.informa.com/PS144438/Patient-Support-May-Have-Helped-Push-Aduhelm-Toward-Approval [https://perma.cc/GFD9-FGL6].

237. *See id.*

238. *Id.*

239. *See* Sinha & Latham, *supra* note 88 (regarding the FDA's decision to approve Aduhelm, Neil Thakur, chief mission officer of the ALS Association, said "we need [FDA] to do the same for people with ALS [amyotrophic lateral sclerosis] immediately").

progressively lowered its standards of effectiveness and safety required for drug approvals."[240]

B. Steering the Course of Medical Research

The accelerated approval of Aduhelm has opened the door for drugs with similar mechanisms of action to follow. This is not necessarily a problem; it is possible that after Aduhelm's approval, subsequent amyloid-targeting treatments will improve upon Aduhelm and provide even greater benefits for patients.[241] One drug development consultant has noted that the tide is already turning in terms of renewed interest in neurodegenerative disease research investment.[242] Indeed, lecanemab, an investigational anti-amyloid agent similar to Aduhelm, was granted breakthrough therapy designation by the FDA in June 2021.[243]

However, the opposing view is the concern that Aduhelm's accelerated approval will lead to less innovative drug development.[244] Aduhelm's approval may have a ripple effect on the pharmaceutical industry, potentially lowering the bar for FDA approval of other drugs.[245] Scientists argue that the "approval [of Aduhelm] could lower standards for future drugs, allowing

240. 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 [https://perma.cc/N5U4-KDDC].

241. For example, azidothymidine (AZT) was the first treatment for HIV/AIDS and faced serious doubts about its safety and efficacy, but FDA approval led to continued investment and research in that drug class, paving the way for the development of new, safer, and more effective generations of antiretroviral drugs. *See Antiretroviral Drug Discovery and Development*, NAT'L INST. OF ALLERGY & INFECTIOUS DISEASES, https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development [https://perma.cc/Q5UL-FNQL] (Nov. 26, 2018).

242. *See* Asher Mullard, *Alzheimer's Drug Approval Could Affect Other Diseases*, 595 NATURE 162, 162 (2021).

243. *See* Press Release, Biogen, EISAI and Biogen Inc. Announce U.S. FDA Grants Breakthrough Therapy Designation for LECANEMAB (BAN2401), an Anti-Amyloid Beta Protofibril Antibody for the Treatment of Alzheimer's Disease (June 23, 2021), https://investors.biogen.com/news-releases/news-release-details/eisai-and-biogen-inc-announce-us-fda-grants-breakthrough-therapy [https://perma.cc/SH2P-BCJA]. Other anti-amyloid antibodies being researched include Roche's gantenerumab and Lilly's donanemab. *See* Adam Feuerstein, *In Reversal, Eli Lilly Now Intends to Seek Fast Approval for Alzheimer's Treatment*, STAT (June 24, 2021), https://www.statnews.com/2021/06/24/eli-lilly-seek-fast-approval-for-alzheimers-treatment/ [https://perma.cc/7ENK-3B6Z] (announcing that Eli Lilly and Company's plans on seeking accelerated approval for its drug, donanemab, based on the "unprecedented regulatory path established by Biogen").

244. *See* 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/UX5M-Q2ZY].

245. *See id.*; Robert Langreth, *All Wall Street Cares About Today Is Lilly's Alzheimer's Drug*, BLOOMBERG (Aug. 3, 2021, 12:15 PM), https://www.bloomberg.com/news/articles/2021-08-03/all-wall-street-cares-about-today-is-lilly-s-alzheimer-s-drug?sref=kGAyuRSx [https://perma.cc/9EG8-X3UX] (quoting Eli Lilly and Company's chief scientific officer as saying that "Aduhelm's approval . . . pav[es] the way for Lilly to apply for approval of its drug sooner than expected" and that "Lilly hopes donanemab can also gain accelerated approval on the basis of its ability to remove amyloid").

them onto the market before experts in the field are convinced the benefits outweigh any safety risks."[246] The FDA's approval of Aduhelm provides tacit support for the controversial amyloid hypothesis and "opens the door for other plaque-clearing anti-amyloid antibodies . . . to pursue similar accelerated approval without having to first demonstrate clinical efficacy."[247] After Aduhelm's approval, pharmaceutical companies are incentivized to invest in something that has already been FDA-approved, potentially overlooking other more fruitful theories.[248]

Moreover, it may become more difficult to conduct research to test new Alzheimer's drugs now that Aduhelm is available.[249] Scholars predict that patients and their families will choose to be treated with the approved Aduhelm instead of joining an observational study or participating in a clinical trial of an unapproved treatment.[250] Thus, the approval and availability of Aduhelm could make Alzheimer's patients less willing to enroll in trials for other promising therapies.[251] On top of a lack of patient willingness to participate in studies, pharmaceutical companies have little incentive to even try to recruit subjects for post-marketing studies—after all, a patient in a clinical trial does not pay for the drug, but a patient getting a prescription through a doctor does. Indeed, Biogen does not appear motivated to recruit subjects for its required post-marketing study: it recently launched a direct-to-consumer marketing campaign pushing readers to ask their doctors whether they may have undiagnosed mild cognitive impairment.[252] The campaign, a paid post in the *New York Times*, directed

246. *See* Belluck & Robbins, *supra* note 6; *see also* Lin et al., *supra* note 161, at 53 (noting that "sponsors of [amyloid-clearing] drugs may assume that it is not necessary to have outcomes data beyond amyloid clearance before applying for regulatory approval").

247. Erik S. Musiek et al., *Aducanumab for Alzheimer Disease: The Amyloid Hypothesis Moves from Bench to Bedside*, J. CLINICAL INVESTIGATION, Oct. 15, 2021, 1, 2.

248. *See id.* (noting that the availability of Aduhelm might jeopardize future clinical trials of potentially more effective Alzheimer's treatments).

249. *See* Sarah S.P. DiMagno et al., *Accelerated Approval of Cancer Drugs—Righting the Ship of the US Food and Drug Administration*, 179 JAMA INTERNAL MED. 922, 923 (2019) ("Approval of ineffective drugs also crowds out innovation that might produce 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.").

250. *See* M.W. Weiner et al., *How Will Aducanumab Impact AD Research?*, 8 J. PREVENTION ALZHEIMER'S DISEASE 391, 392 (2021).

251. *See* Fiona Rutherford, *Alzheimer's Drug Discord Puts FDA Accelerated System Under Fire*, BLOOMBERG (June 30, 2021, 7:30 AM), https://www.bloomberg.com/news/articles/2021-06-30/alzheimer-s-drug-discord-puts-fda-accelerated-system-under-fire [https://perma.cc/3J7A-EN9Y].

252. *See* Biogen, *When Memory Fades*, N.Y. TIMES (2021), https://www.nytimes.com/paidpost/biogen-memory/its-time-we-know/when-memory-fades.html [https://perma.cc/6QGZ-C2M9] (paid post sponsored by Biogen and Eisai); Madhav Thambisetty, *'When Memory Fades': Misinformation About Alzheimer's Disease and Aduhelm Must Be Limited*, STAT (July 21, 2021), https://www.statnews.com/2021/07/21/when-memory-fades-misinformation-about-alzheimers-disease-and-aduhelm-must-be-limited/ [https://perma.cc/F5BC-QQV9].

readers to Alzheimer's specialists and made no mention of recruitment into clinical trials.[253]

Much of the uncertainty over Aduhelm's efficacy stems from the fact that the FDA granted accelerated instead of traditional approval. Because Aduhelm's accelerated approval was based on a surrogate endpoint (the drug's ability to reduce amyloid-β plaque),[254] Biogen was temporarily allowed to defer submitting robust evidence of clinical benefits—it has until February 2030 to finish a Phase IV post-marketing trial on Aduhelm's efficacy.[255] However, David Whitrap, vice president for communications at the Institute for Clinical and Economic Review (ICER), has stated that "[i]f approval would've been withheld and the company was just asked to run a third trial to provide further insight into whether the drug works, that trial surely could've been accomplished far sooner than 2030."[256] Once accelerated approval was granted and Biogen was allowed to sell Aduhelm, there became considerably less incentive for Biogen to do the research that would tell other pharmaceutical companies and medical researchers whether it is worthwhile to continue pursuing amyloid-targeting treatments.

C. Economic Impact: Aduhelm's Ripple Effect on American Taxpayers

Biogen originally set the price of Aduhelm at $56,000 per patient per year[257] before decreasing the price to $28,200 after a disappointing commercial launch.[258] The true annual cost for Aduhelm will likely be higher because the standard price was calculated based on dosing for a patient weighing about 163 pounds, which is below average for American adults.[259] ICER, an independent nonprofit research institute that studies drugs and medical services, estimates that the drug's yearly price will actually be

253. *See* Thambisetty, *supra* note 252 (describing the "slick paid post" as a "direct-to-consumer marketing campaign that seeks to greatly expand the target population of people that are candidates for Aduhelm").

254. *See* Cavazzoni, *supra* note 187.

255. *See* Letter from Billy Dunn, Dir., Off. of Neuroscience, Ctr. for Drug Evaluation & Rsch., to Priya Singhal, Vice President, Global Safety and Regul. Scis., Biogen (June 7, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761178Orig1s000ltr.pdf [https://perma.cc/Y5B4-CGDE]; *see also* Rutherford, *supra* note 251. Biogen has announced that it expects to begin the Phase IV post-marketing trial for Aduhelm in May 2022. *See* Damian Garde & Adam Feuerstein, *As Aduhelm Faces Doubts, Biogen Plans Another Pivotal Trial for 2022*, STAT (Dec. 16, 2021), https://www.statnews.com/2021/12/16/as-aduhelm-faces-doubts-biogen-plans-another-pivotal-trial-for-2022/ [https://perma.cc/A3S4-9HY3].

256. Rutherford, *supra* note 251.

257. *See* Josh Katz et al., *New Drug Could Cost the Government as Much as It Spends on NASA*, N.Y. TIMES (June 23, 2021), https://www.nytimes.com/2021/06/22/upshot/alzheimers-aduhelm-medicare-cost.html [https://perma.cc/RS7J-AYER].

258. *See* Adam Feuerstein, *Biogen Slashes Price of Alzheimer's Drug Aduhelm in Half, Plans $500M in Cost-Cutting*, STAT (Dec. 20, 2021), https://www.statnews.com/2021/12/20/biogen-slashes-price-of-alzheimers-drug-aduhelm-in-half-plans-500m-in-cost-cutting/ [https://perma.cc/82TU-GMND].

259. *See* Alex Ruoff & Jasmine Ye Han, *Drugmakers to Pay Billions for Wasted Drugs Under Senate Deal*, BLOOMBERG L. (Aug. 5, 2021, 5:15 AM), https://news.bloomberglaw.com/bloomberg-law-news/drugmakers-to-pay-billions-for-wasted-drugs-under-senate-deal [https://perma.cc/N24G-8JQS].

between $3000 and $8400.[260] In an analysis of long-term cost effectiveness of Aduhelm, ICER also determined that "despite the tremendous unmet need for new treatments for Alzheimer's disease . . . the current evidence [is] insufficient to demonstrate that aducanumab slows cognitive decline, while it is clear that it can harm some patients."[261]

Aduhelm's approval has already begun to impact the country economically through its close connection to Medicare patients. Although there are many drugs on the market with similar or greater price tags, Aduhelm is unique in that it has an excessive cost *and* it is a drug with potentially millions of customers who are expected to take the drug for the rest of their lives.[262] About 80 percent of the patients eligible for Aduhelm are old enough to receive coverage under Medicare.[263] Because Aduhelm is an infusion drug that must be administered in doctors' offices and clinics, rather than taken at home, it is covered under Medicare Part B.[264] Medicare does not set its own rates for drugs covered under Part B and instead reimburses providers 103 percent of the wholesale acquisition cost until an average sales price (ASP) is determined, at which point Medicare reimburses providers 106 percent of the ASP.[265] Patients without a supplemental insurance plan would have to pay the 20 percent Part B coinsurance[266]: $5640 for the $28,200 drug. Patients with supplemental plans may see their premiums rise in response to the increased costs of Aduhelm.[267] As one doctor put it, "[A]ll of us, one

260. *See* Press Release, Inst. for Clinical & Econ. Rev., ICER Publishes Final Evidence Report and Policy Recommendations on Aducanumab for Alzheimer's Disease (Aug. 5, 2021), https://icer.org/news-insights/press-releases/icer-publishes-final-evidence-report-and-policy-recommendations-on-aducanumab-for-alzheimers-disease/ [https://perma.cc/DL2R-Y9E9]. ICER's price range represents the highest U.S. price Biogen should charge for Aduhelm, based on the amount of improvement in overall health seen in clinical trials, when a higher price would cause disproportionately greater losses in health among other patients in the health system due to rising overall costs of health care and health insurance—essentially, it is the "top price range at which a health system can reward innovation and better health for patients without doing more harm than good." *Id.*

261. *Id.*; *see also supra* note 182 (discussing ARIAs).

262. *See* Katz et al., *supra* note 257.

263. *See* 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 [https://perma.cc/2C3E-D9VL].

264. *See* Nicholas Bagley & Rachel Sachs, *The Drug That Could Break American Health Care*, ATLANTIC (June 11, 2021), https://www.theatlantic.com/ideas/archive/2021/06/aduhelm-drug-alzheimers-cost-medicare/619169/ [https://perma.cc/LP5N-F4SH] (explaining that Medicare Part B generally covers FDA-approved physician-administered medications that are reasonable and necessary for the patient).

265. *See* Cubanski & Neuman, *supra* note 11. Medicare is currently prohibited from negotiating prescription drug prices, but President Joe Biden has proposed in his Build Back Better Framework making drugs eligible for negotiation once they have been on the market for nine to twelve years. *See* Press Release, White House, President Biden Announces Prescription Drug Pricing Plan in Build Back Better Framework (Nov. 2, 2021), https://www.whitehouse.gov/briefing-room/statements-releases/2021/11/02/president-biden-announces-prescription-drug-pricing-plan-in-build-back-better-framework/ [https://perma.cc/C65C-MSRQ].

266. *See* Moghavem et al., *supra* note 5, at 332.

267. *See id.*

way or another, are going to feel this expense."[268] In fact, CMS announced in November 2021 that Medicare Part B monthly premiums would increase by $21.60 in 2022, the largest increase in the program's history,[269] specifically citing the approval of Aduhelm as one rationale.[270]

In response to the looming costs of Aduhelm treatment, doctors have called for CMS to restrict coverage to only certain Medicare beneficiaries (such as those meeting inclusion criteria for the Aduhelm clinical trials) or for CMS to not cover Aduhelm at all, citing scientific evidence on the lack of efficacy and risk of harm.[271] Technically, Medicare may refuse to pay for medical care that is "not reasonable and necessary for the diagnosis or treatment of illness or injury."[272] However, historically, it has only denied about 3 percent of claims submitted by hospitals and physicians.[273] In January 2022, CMS shocked the scientific community by doing exactly what doctors had been calling for: CMS proposed that Medicare would cover Aduhelm, but only for patients enrolled in certain CMS-approved clinical trials.[274] This marked the first time that CMS limited Medicare beneficiaries' access to an FDA-approved drug in this way.[275] The proposal did not contain details on whether patients would be required to pay to participate in the trials or whether patients would know if they were in a placebo or treatment group.[276] If the decision is finalized in the spring of 2022, it would effectively limit the use of Aduhelm to an estimated few thousand patients enrolled in randomized trials over the next three to five years, as the majority

268. Lawrence H. Price, *Aducanumab: Boon or Bust?*, BROWN UNIV. PSYCHOPHARMACOLOGY UPDATE, Nov. 2021, at 7, 7.

269. *See* Dena Bunis, *Medicare Part B Premium Increase for 2022 Largest Ever*, AM. ASS'N RETIRED PERSONS (Nov. 15, 2021), https://www.aarp.org/health/medicare-insurance/info-2021/part-b-premiums-increase.html [https://perma.cc/9YQV-FG73].

270. *See* Press Release, Ctrs. for Medicare & Medicaid Servs., *supra* note 12. In January 2022, Department of Health and Human Services Secretary Xavier Becerra directed CMS to reconsider its decision to raise premiums after Biogen decreased Aduhelm's price to $28,200. *See* Rachel Cohrs, *Becerra Orders Medicare to Reconsider Premium Hike Following Price Drop for Biogen's Aduhelm*, STAT (Jan. 10, 2022), https://www.statnews.com/2022/01/10/becerra-medicare-aduhelm-reconsider-price/ [https://perma.cc/CY3N-NYXK].

271. *See* Moghavem et al., *supra* note 5, at 332 (noting that "[a]lthough it would be highly unusual for CMS to decline to cover a drug approved by the FDA, the accelerated approval of aducanumab was itself highly unusual").

272. *See* 42 U.S.C. § 1395y(a)(1)(B).

273. *See* Joshua D. Gottlieb et al., *The Complexity of Billing and Paying for Physician Care*, 37 HEALTH AFFS. 619, 624 (2018) (analysis of Medicaid and Medicare data showing that, in 2015, the denial rate in Medicare Advantage was 3 percent).

274. *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Jan. 11, 2022), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305 [https://perma.cc/9K9F-G8B3]. The proposal is not final and may change before it is finalized in the spring of 2022. *See id.*

275. *See* Belluck, *supra* note 263.

276. *See* Rachel Cohrs, *No One Has Any Idea How Much Money Seniors Could Pay for New Alzheimer's Drug*, STAT (Jan. 14, 2022), https://www.statnews.com/2022/01/14/no-one-has-any-idea-how-much-money-seniors-could-pay-for-new-alzheimers-drug/ [https://perma.cc/5X9V-XELG].

of patients who meet FDA approval criteria would not be covered by Medicare.[277]

The astronomical costs are not limited to just Aduhelm itself. In an op-ed, two experts at the Yale School of Medicine warned that "the approval of [Aduhelm] has unleashed a perilous precedent that could usher in the approval of countless, costly treatments of uncertain benefit and even harm."[278] Aduhelm's approval increases the likelihood that other drugs targeting amyloid-β plaques will be approved, potentially compounding the financial strain that Aduhelm already presents.[279]

III. STRATEGIES TO SLOW DOWN ACCELERATED APPROVAL

The saga of Aduhelm highlights how accelerated approval allows drugs with unproven clinical benefit to linger in the market, steering the course of medical research and calling into question whether the FDA is yielding too easily to industry pressure. This part contains three proposals to prevent the FDA from using accelerated approval to authorize another drug like Aduhelm. Part III.A suggests revisions to the operations of FDA advisory committees. Part III.B discusses ways to incentivize pharmaceutical companies to complete Phase IV post-marketing trials. Part III.C theorizes how plaintiffs may challenge a questionable FDA approval decision in court. The proposed regulatory reforms are ripe for implementation, as the FDA's drug, generic drug, biosimilar, and device user fee programs expire in September 2022, at which time Congress must pass new legislation for the FDA to continue collecting fees and doing its work.[280] Some scholars have emphasized that because reauthorization legislation is essential for the FDA to continue operating, it is a "natural vehicle for other FDA legislative reforms."[281]

A. Suggested Revisions to the Role of Advisory Committees

The approval process for Aduhelm eroded public confidence in the FDA.[282] Although the advisory committee, an independent group of experts, strongly voted against approval, the FDA still approved the drug without

277. *See* Belluck, *supra* note 263.

278. Ramachandran & Ross, *supra* note 187.

279. For examples of other anti-amyloid antibodies with mechanisms similar to Aduhelm, see *supra* note 243.

280. *See PDUFA VII: Fiscal Years 2023–2027*, U.S. FOOD & DRUG ADMIN. (Aug. 23, 2021), https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027 [https://perma.cc/L3PY-NTNQ].

281. Keith Flanagan, *Congress Should Fix FDA's Accelerated Approval Program for the Next 30 Years*, STAT (Aug. 12, 2021), https://www.statnews.com/2021/08/12/congress-fix-accelerated-approval-program-for-next-30-years/ [https://perma.cc/5J8J-QPAW].

282. *See* Steve Usdin, *FDA's Aducanumab Decision Will Erode Public Trust: An Editor's Commentary*, BIOCENTURY (June 7, 2021, 7:51 PM), https://www.biocentury.com/article/637011 [https://perma.cc/L8HS-S26C]; DHIRAJ KUMAR ET AL., TOPICAL INSIGHTS INTO THE POST-APPROVAL CONTROVERSIES OF ADUCANUMAB 2 (2021) (noting that "any future congressional hearings on NIH funding, the FDA's decision, and Medicare reimbursement for Aduhelm would all show a negative influence on faith in the agency").

disclosing any data showing a patient-level correlation between amyloid clearance and cognitive outcomes from clinical trials.[283] As Dr. Aaron Kesselheim, one of the advisory committee members who resigned after Aduhelm's approval, wrote in his resignation letter, the FDA "needs to reassess its decision-making processes, including . . . how Committee recommendations are used (or ignored) by FDA officials. When clear [advisory committee] recommendations against a drug are overruled by FDA administrators . . . the agency owes it to the nation to provide a detailed justification."[284]

The FDA should issue new guidance requiring the agency to follow the advisory committee's recommendations or to submit detailed justification for deviating from such recommendations. Currently, FDA guidance regarding advisory committees simply states that the "rationale for decisions and reasons for no decisions should be documented."[285] If the FDA wants to disregard the advisory committee's concerns—particularly when the vote is so skewed toward disapproval—it should support its position by providing a scientific explanation to refute the evidence that the advisory committee relied on. For consistency, ICER has proposed that the FDA create a template that would include a structured explanation for why accelerated approval was deemed more appropriate than regular review.[286] Developing a formal and public template would lead to more disciplined reporting and increased transparency among stakeholders.[287] This would represent the FDA "tak[ing] concrete steps to become clearer about the way it engages its advisory committees and to be transparent and consistent in . . . the timing of its decisions to use the accelerated approval pathway."[288]

Formally requiring the FDA to follow the advisory committee's recommendations or to provide detailed justification for overriding the advisory committee would take away some of the flexibility that the FDA currently has in its decision-making. However, it would also help fulfill the FDA's mission of maintaining public trust for the benefit of all patients. A lack of trust can lead the public to refuse certain medicines or vaccines and encourage people to turn to alternative non-FDA-approved products because they believe there are more trustworthy health experts out there.[289]

283. *See* Lin et al., *supra* note 161, at 52.
284. Kesselheim, *supra* note 191.
285. U.S. FOOD & DRUG ADMIN., *supra* note 64, at 5.
286. *See* KALTENBOECK ET AL., *supra* note 201, at 25.
287. *See id.* at 19.
288. Lin et al., *supra* note 161, at 52.
289. *See, e.g.*, Dan Diamond, *'I'm Still Not Planning to Get It': Approval Not Swaying Some Vaccine Holdouts*, WASH. POST (Aug. 25, 2021, 3:59 PM), https://www.washingtonpost.com/health/2021/08/25/fda-approval-vaccine-holdouts/ [https://perma.cc/C8RD-XWXN]; Selena 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/MC79-ZZER] (describing a poll which found that only 52 percent of Americans trust the Centers for Disease Control and Prevention (CDC) and that only 37 percent of Americans trust the NIH or the FDA).

Additionally, requiring the FDA to publish its reasoning for overriding the advisory committee's recommendation would provide future litigants with the necessary information to challenge FDA decisions in court.[290]

B. Incentivizing Pharmaceutical Companies to Complete Phase IV Post-Marketing Trials

It is unlikely that Biogen will ever complete the required Phase IV post-marketing trials to show Aduhelm's clinical benefit.[291] The Food and Drug Administration Modernization Act of 1997[292] authorizes the FDA to use expedited procedures to withdraw accelerated approval of drugs and biological products if sponsors fail to conduct required post-approval Phase IV studies with due diligence or the investigations fail to verify clinical benefits.[293] Currently, sponsors with ongoing post-marketing studies for accelerated approvals already provide periodic reports to the FDA that include information about the progress of the study and whether the anticipated milestones have been met.[294] The FDA also has the power to issue administrative action letters, assess financial penalties, and withdraw approval should expected evidence not materialize in post-marketing Phase IV trials.[295]

The FDA should exercise its existing powers more aggressively. This is easier said than done: the FDA may hesitate to remove a drug from the market because the FDA would thereby hurt the revenue streams of the companies that pay the user fees that make up the FDA's own budget. Additionally, if the FDA were to take a drug off the market for a disease with few available treatments, such as Alzheimer's, it might draw intense backlash from patients and the broader public. Even with its existing powers in place, the FDA needs additional ways to further incentivize pharmaceutical companies to actually conduct and complete post-marketing studies. For example, the FDA could wait to grant accelerated approval until there is proof that confirmatory trials are either initiated or in progress.[296] This would require the FDA to devote more resources to monitoring the progress of post-marketing trials more closely. The cost of increasing monitoring efforts would be worthwhile because, without approval, companies cannot begin to profit—the ultimate incentive to comply with the FDA.

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290. *See infra* Part III.C.

291. *See supra* Part II.B.

292. Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of the U.S.C.).

293. *See* 21 U.S.C. § 356(b)(3); Steenburg, *supra* note 85, at 331.

294. Required information includes, in relevant part: (1) the date of the post-marketing study requirement; (2) a description of the post-marketing study requirement; (3) the schedule for completing and reporting of the post-marketing study requirement; (4) the current status of the post-marketing study requirement—as pending, ongoing, delayed, terminated, or submitted; and (5) an explanation of the status. 21 C.F.R. §§ 314.81(b)(2)(vii)(a), 601.70(b) (2022).

295. *See* Anne Kaltenboeck et al., *Potential Policy Reforms to Strengthen the Accelerated Approval Pathway*, 10 J. COMPAR. EFFECTIVENESS RSCH. 1177, 1180 (2021).

296. *See id.*

Some scholars have suggested requiring Biogen to provide Aduhelm at the pure cost of producing the drug plus a maximum profit of 5 percent—a reasonable reimbursement given the uncertainty around Aduhelm's safety and effectiveness.[297] Such minimal profits would incentivize Biogen to complete Phase IV post-marketing trials quickly because the company would be entitled to their desired $28,200 price only if post-marketing trials provided enough evidence of the drug's clinical benefits.[298] As some experts have written, the "paradigm must be shifted from 'any drug at any cost' to 'the best drug at the right cost.'"[299] For this proposal to work, pharmaceutical companies would have to report their costs of researching and producing the drug to the government to determine how much they could be reimbursed through Medicare and Medicaid. This would be another way to use financial incentives to ensure that pharmaceutical companies actually do the work to show a clinical benefit in their drugs even after being granted accelerated approval. The danger would be that pharmaceutical companies might be discouraged from pouring millions of dollars into research and development if it is unclear whether they could immediately profit just as much, if not more, after being granted accelerated approval. However, there are mathematical methods to incorporate the value of innovation into drug prices—pharmaceutical companies may be rewarded for being the first in a new drug class instead of adding to a drug class that already addresses a satisfied need.[300]

Finally, new legislation could impose a moratorium on direct-to-consumer pharmaceutical advertising[301] until Phase IV post-marketing trials are complete. Restricting companies from conducting direct-to-consumer advertising would strongly incentivize them to complete Phase IV post-marketing trials in a timely manner, effectively requiring companies to first find participants for trials before being allowed to find customers for the same drug. Alternatively, the FDA could issue new regulations requiring that if an accelerated approval drug is to be advertised, there must be a warning that states the drug in question has only been preliminarily approved and that a study showing clinical benefit has not been completed yet.

C. Challenging FDA Decisions in Court

Scholars have argued that existing judicial review frameworks allow agencies to make decisions that lack evidentiary support, reliability, and

297. *See* Leonard M. Fleck, *Alzheimer's and Aducanumab: Unjust Profits and False Hopes*, 51 HASTINGS CTR. REP. 9, 11 (2021).

298. *See id.*

299. Sinha & Latham, *supra* note 88.

300. *See, e.g.*, Santiago G. Moreno & Joshua A. Ray, *The Value of Innovation Under Value-Based Pricing*, 4 J. MKT. ACCESS & HEALTH POL'Y 1, 2 (2016) (proposing a modification to conventional cost-effectiveness analysis to include the value of innovation in new drug development).

301. See *supra* Part II.B for a discussion of Biogen's direct-to-consumer pharmaceutical advertising.

accountability, and that are prone to conflicts of interest.[302] Some propose that, to combat regulatory reactivity, courts should "employ a diminished level of *Chevron* deference when agencies act in ways that go against expert advice or scientific understanding of the issue at hand but are nonetheless justified by reasoning that evades characterization of the decision as 'arbitrary or capricious.'"[303] When the FDA deviates from the recommendations of scientific experts, such as in the case of Aduhelm, "the court would no longer be required to follow step two of the *Chevron* test but would instead apply a non-deferential standard of review."[304] Professor Heled believes that, under the traditional *Chevron* framework, the bar is low for the FDA to justify its approval of Aduhelm before a court.[305] The FDA itself has given a number of facially plausible reasons for its decision to approve Aduhelm: "Alzheimer's is a serious disease with substantial unmet need; . . . there is compelling evidence that [aducanumab] reduces plaque[] and this reduction . . . is reasonably likely to predict clinical benefit."[306] Such justification would likely be enough for a court but would not adequately reflect the FDA's disregard for scientific expertise.[307] Members of the FDA advisory committee, Medicare and Medicaid, and organizations concerned about drug pricing (e.g., Alzheimer's patient advocacy groups and Public Citizen) may have standing to sue the FDA and challenge its decision to approve a drug like Aduhelm in court.[308]

Because an FDA approval decision has never been challenged in court in this way, it is difficult to theorize whether such litigation would be successful for plaintiffs seeking to challenge the accelerated approval of Aduhelm. There would be clear difficulties in challenging Aduhelm's approval in court: First, courts have been generally unwilling to question the FDA's judgment regarding standards for assessing safety and efficacy.[309] Additionally, there might be public backlash from patients who are willing to accept the risk of Aduhelm's questionable safety and efficacy in exchange for the hope of one more weapon against Alzheimer's disease.[310]

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302. *See supra* Part I.C.2; Yaniv Heled et al., Opinion, *Regulatory Reactivity in FDA's Approval of Aduhelm*, REGUL. REV. (July 6, 2021), https://www.theregreview.org/2021/07/06/heled-rutschman-vertinsky-regulatory-reactivity-fda-approval-aduhelm/ [https://perma.cc/W343-7ZZK].

303. Heled et al., *supra* note 302. Under the *Chevron* doctrine, courts would give judicial deference to agency interpretation of its statutory powers where Congress has not spoken directly on the issue. *See* Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, 468 U.S. 837, 842 (1984).

304. *See* Heled et al., *supra* note 302.

305. *See* Interview with Yaniv Heled, Professor of L., Ga. State Univ. (Nov. 2, 2021).

306. Dunn et al., *supra* note 209, at 856.

307. *See* Interview with Yaniv Heled, *supra* note 305.

308. *See id.* Issues such as the injury-in-fact requirement are beyond the scope of this Note; this Note merely operates arguendo that plaintiffs can establish standing.

309. *See* Steenburg, *supra* note 85, at 334.

310. *See, e.g.*, Dylan Scott, *The Harrowing New Reality for Alzheimer's Patients*, VOX (July 19, 2021, 8:30 AM), https://www.vox.com/policy-and-politics/22577776/alzheimers-disease-dementia-symptoms-aduhelm-drug [https://perma.cc/3B2S-4V6J] (describing Alzheimer's patients and family members who were enthusiastic about Aduhelm even after reading negative news coverage about the drug's unproven effectiveness, noting that their

Nonetheless, instead of employing a diminished level of *Chevron* deference as Professor Heled has suggested, courts should instead incorporate *State Farm* hard look review into the *Chevron* analysis where the agency has not engaged in "reasoned decisionmaking."[311] Under *State Farm*, agencies must provide detailed and reasoned explanations of their decisions, explain deviations from precedent, and make policy choices that are objectively reasonable under the circumstances.[312] The current attorney general, Merrick Garland, once described hard look review in this way: "[H]ard look demands that the agency show that the course it chose was reasonable in light of the relevant policies, alternatives, and facts."[313]

Encino Motorcars is instructive of this idea, whereby a court could scrutinize the FDA's decision to grant accelerated approval to Aduhelm. There, the Supreme Court stated that when an agency changes its policy course, it must give adequate reasoning for its decision-making.[314] Here, the FDA has arguably not given adequate reasoning for its decision to grant accelerated approval to Aduhelm based on its ability to remove amyloid-β plaque from patients' brains. In particular, plaintiffs could argue that under hard look review, the FDA's explanation that it approved Aduhelm based on its ability to reduce amyloid-β plaque "runs counter to the evidence before the agency"[315] that this surrogate endpoint is not reasonably likely to predict clinical benefit.[316] There was ample discussion of the advisory committee's skepticism over the ENGAGE and EMERGE clinical data at the November 2020 meeting, and yet the FDA defied the near-unanimous opinion of the independent group of experts.[317] Additionally, plaintiffs may argue that the FDA's purported reasoning for approving Aduhelm was "so implausible that it could not be ascribed to a difference in view or the product of agency expertise."[318] After all, the agency's reliance on Aduhelm's ability to reduce plaque in the brain contradicted its own guidance on the reliability of amyloid-β plaques as a surrogate endpoint.[319] Thus, the agency should not be given *Chevron* deference, a finding that would return the case to the FDA to make a different, more informed decision or to provide more detailed

"hope and the adrenaline of that hope outweighs all of their reason and they are clamoring for the drug").

311. See *supra* note 123 for the factors to be considered in *State Farm* hard look analysis.

312. *See* Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 34–51 (1983).

313. Merrick B. Garland, *Deregulation and Judicial Review*, 98 HARV. L. REV. 505, 554 (1985).

314. *See* Encino Motorcars, LLC v. Navarro, 136 S. Ct. 2117, 2125 (2016) (citing *State Farm*, 463 U.S. at 43) (explaining that the agency's reasoning should be clear enough to show "a rational connection between the facts found and the choice made").

315. *State Farm*, 463 U.S. at 43.

316. For a discussion on the reasons why the FDA's decision to grant accelerated approval based on a surrogate endpoint contradicted scientific evidence, see *supra* Part I.D.3.

317. See *supra* Part I.D.3 for a discussion on how the approval decision lacked scientific reasoning and generated controversy.

318. *State Farm*, 463 U.S. at 42.

319. For a discussion on how the decision to approve Aduhelm lacked scientific reasoning and generated controversy, see *supra* Part I.D.3.

scientific reasoning for approving Aduhelm. This reasoning could be used not just in the case of Aduhelm, but any time the FDA grants accelerated approval based on a surrogate endpoint with a weak connection to clinical benefit.

CONCLUSION

The success of accelerated approval is grounded in ensuring a balance between speed and scientific accuracy. In the decades since the FDA has begun using accelerated approval to get treatments out faster to HIV/AIDS and cancer patients, there has been a gradual erosion in the level of scientific rigor the FDA finds acceptable to show safety and efficacy. In the wake of the FDA's controversial approval, Biogen has been struggling to sell Aduhelm, reporting just $300,000 made from Aduhelm in the first full quarter since its approval, an amount far below the originally predicted $14 million.[320] Consequently, Biogen had to plan its largest layoff ever, with more than 1000 employees expected to lose their jobs in early 2022.[321] This is a testament to the impact of the advisory committee members who resigned in protest and to the subsequent public backlash against the FDA's approval decision.

Today, it has become too easy for drugs to enter the market via the accelerated approval pathway—Aduhelm was the drug that finally alerted the public to the need for reform of the accelerated approval process. Going forward, the FDA should be required to provide science-based justifications for overriding the advisory committee's recommendations. The FDA should also further incentivize pharmaceutical companies to complete Phase IV post-marketing trials. As a last resort, concerned scientists and PAOs should consider challenging controversial FDA approval decisions in court; this Note's proposed changes regarding judicial approaches to agency actions can help give these lawsuits more weight.

320. *See* Damian Garde & Adam Feuerstein, *Biogen's Aduhelm Sales Fall Dramatically Below Wall Street's Expectations*, STAT (Oct. 20, 2021), https://www.statnews.com/2021/10/20/biogens-aduhelm-sales-dramatically-below-wall-street-expectation/ [https://perma.cc/4VQG-4BEK].

321. *See* Adam Feuerstein & Damian Garde, *Biogen's Reckoning: How the Aduhelm Debacle Pushed a Troubled Company and Its Fractured Leadership to the Brink*, STAT (Dec. 8, 2021), https://www.statnews.com/2021/12/08/biogen-aduhelm-al-sandrock-michel-vounatsos-company-reckoning/ [https://perma.cc/TVE7-P4CF].