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# Public Citizen's Advocacy Campaign Opposing FDA Approval of Aducanumab for Alzheimer's Disease: The Fight Against Regulatory Capture

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THE OLIVER C. SCHROEDER, JR. SCHOLAR-IN-RESIDENCE LECTURE

# PUBLIC CITIZEN'S ADVOCACY CAMPAIGN OPPOSING FDA APPROVAL OF ADUCANUMAB FOR ALZHEIMER'S DISEASE: THE FIGHT AGAINST REGULATORY CAPTURE†

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Good afternoon - I am honored to give this year's Oliver C. Schroeder, Jr. Scholar-in-Residence Lecture.

For 50 years, Public Citizen's Health Research Group, which was founded by my colleague Dr. Sidney Wolfe, has engaged in independent, research-based advocacy targeting the Food and Drug Administration (FDA) and the pharmaceutical industry. In testimony before hundreds of FDA advisory committee meetings, we have opposed approval of numerous new drugs that, in our judgment, had unfavorable risk-benefit profiles. Through citizen petitions to the FDA, we have sought the removal of more than 40 drug products from the market because they were too dangerous and the addition of stronger warnings to the labeling for several dozen other drugs. In many cases, the agency granted our petitions.[1]

† Edited from the annual Oliver C. Schroeder, Jr. Scholar-in-Residence Lecture sponsored by the Law-Medicine Center on October 4, 2021, at Case Western Reserve University School of Law. This version has been edited for publishing purposes and does not contain the lecture in its entirety. The full transcript is on file with the editors of Health Matrix. Please direct all inquiries to h-matrix@case.edu.

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1. For examples of the Food and Drug Administration granting in full or in part a petition from Public Citizen's Health Research Group, *see* Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Rsch., to Sidney M. Wolfe, Pub. Citizen's Health Rsch. Grp., (July 23, 2018) (on file with the U.S. Food & Drug Admin.) (granting in part our December 6, 2017, petition to place cesium chloride on list of bulk drug substances that present significant safety risks and therefore may not be compounded under the agency's interim

Today, I would like to tell the story of drugmaker Biogen's development of aducanumab for the treatment of Alzheimer's disease; the FDA's unprecedented, inappropriately close collaboration with the company before and after the submission of its biologics license application (BLA) for the drug; and the agency's subsequent approval of the drug under the Accelerated Approval pathway.[2] I will describe our group's advocacy campaign over the past year opposing FDA approval of aducanumab and seeking to hold the agency accountable for its

guidance); Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Rsch., to Sammy Almashat, Researcher, Pub. Citizen's Health Rsch. Grp. (Aug. 7, 2017) (on file with the U.S. Food & Drug Admin.) (granting our December 21, 2016, petition to require that the label of repaglinide-containing medications include information on a serious drug-drug interaction with clopidogrel that could result in severe hypoglycemia); Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Rsch, to Sidney M. Wolfe & Michael A. Carome, Pub. Citizen's Health Rsch. Grp. (Aug. 4, 2014) (on file with the U.S. Food & Drug Admin.) (granting in part our Oct. 26, 2011, petition to require a boxed warning in the label for the antibiotic Tygacil); Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Rsch., to Eric Nellis et al., Pub. Citizen's Rsch. Grp. & Helge L. Waldum, Trondheim University Hospital (Oct. 31, 2014) (on file with the U.S. Food & Drug Admin.) (granting in part our August 23, 2011, petition to require the addition of boxed warnings and other safety information to the labels of all proton pump inhibitors); Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Rsch., to Sidney M. Wolfe, Dir., Pub. Citizen's Health Rsch. Grp. (Jan. 5, 2011) (on file with the U.S. Food & Drug Admin.) (granting our December 3, 2009, petition to ban the weight loss drug Meridia (sibutramine)); Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Rsch., to Arnold L. Widen & Babs Waldman, Ill. Att'y Gen.'s Off. & Jay Parkinson & Sidney M. Wolfe, Pub. Citizen's Health Rsch. Grp. (July 24, 2008) (on file with the U.S. Food & Drug Admin.) (granting in part our August 29, 2006, petition to, among other things, add a boxed warning to the product labeling of all fluoroquinolone antibiotics about the risk of tendinopathy and tendon rupture).

2. News 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/HT5G-PQHU].

inappropriately close collaboration with Biogen and for its reckless decision to approve the drug — one of the worst decisions in the agency's history. I will present events regarding the development and review of aducanumab as they become publicly known. I will conclude with some reflections on how the FDA reached this new low point as a regulatory agency.

*Background on Aducanumab*

Aducanumab is a recombinant human monoclonal antibody targeting amyloid-beta multimers.[3] The drug was developed primarily by Biogen, in partnership with Eisai, as a treatment of Alzheimer's disease.[4]

Like the prior 22 unsuccessful experimental drugs targeting amyloid-beta that were pursued as potential treatments for Alzheimer's disease over the past two decades, use of aducanumab is predicated on the still-unproven "amyloid hypothesis," which was introduced in the early 1990s and posits that deposition of amyloid plaques in the brain *causes* the neuronal degeneration seen in Alzheimer's disease.[5]

After completing two phase 1 trials of aducanumab (Study 101 and Study 103), Biogen in 2015 launched two identical phase 3, randomized, double-blind, placebo-controlled clinical trials to evaluate the safety and efficacy of two dosing regimens of aducanumab (Study 301 [ENGAGE] and Study 302 [EMERGE]).[6] By early 2019, Studies 301 and 302 each had

3. Francesco Panza et al., *Emerging Drugs to Reduce Abnormal β-amyloid Protein in Alzheimer's Disease Patients*, 21(4) EXPERT OPINION ON EMERGING DRUGS 377, 385 (2016).

4. *Biogen and Eisai Discontinue Phase 3 ENGAGE and EMERGE Trials of Aducanumab in Alzheimer's Disease*, BIOGEN (Mar. 21, 2019) [hereinafter *Biogen and Eisai Discontinue Phase 3*], https://investors.biogen.com/news-releases/news-release-details/biogen-and-eisai-discontinue-phase-3-engage-and-emerge-trials [https://perma.cc/E7S6-GSDX].

5. Abass Alavi et al., *Suboptimal Validity of Amyloid Imaging-Based Diagnosis and Management of Alzheimer's Disease: Why it is Time to Abandon the Approach*, 47 EUR. J. NUCL. MED. MOL. IMAGING 2, 225-30 (2019).

6. U.S. FOOD & DRUG ADMIN., COMBINED FDA AND APPLICANT PCNS DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT (2020) [hereinafter COMBINED FDA AND APPLICANT BRIEFING DOCUMENT].

enrolled approximately 1,650 subjects with mild cognitive impairment attributed to Alzheimer's disease or mild Alzheimer's disease dementia.[7]

On March 21, 2019, Biogen and its partner Eisai announced the decision to terminate both pivotal phase 3 trials after a prespecified interim futility analysis by an independent data-monitoring committee indicated that the trials were unlikely to meet their primary efficacy endpoint upon completion.[8] That action should have marked the end of aducanumab as a potential treatment for Alzheimer's disease, at least as it pertained to the studies thus far completed.

*Subsequent Unprecedented Close Collaboration Between the FDA and Biogen*

Following this, on October 22, 2019, Biogen shocked the medical community when it announced in another press release plans to seek FDA approval for aducanumab based on a series of post hoc analyses of data from Studies 301 and 302, including additional data collected after the announced termination of the trials.[9] The company stated in the press release that new analyses had been "conducted by Biogen in consultation with the FDA."[10]

On December 5, 2019, Biogen presented topline results of Studies 301 and 302 at the Clinical Trials on Alzheimer's Disease 2019 conference. The post hoc analyses conducted by Biogen in collaboration with the FDA showed that in Study 301 aducanumab at both the low and high dosing regimens did *not* show improvement in the trial's primary efficacy endpoint, whereas in Study 302 the drug at only the high dosing regimen resulted in small, statistically significant — but not clinically meaningful — improvement in the primary efficacy endpoint.[11]

7. *Id.*

8. *Biogen and Eisai Discontinue Phase 3, supra* note 4.

9. *Biogen Plans Regulatory Filing for Aducanumab in Alzheimer's Disease Based a New Analysis of Larger Dataset From Phase 3 Studies*, BIOGEN (Oct. 22, 2019), https://investors.biogen.com/news-releases/news-release-details/biogen-plans-regulatory-filing-aducanumab-alzheimers-disease [https://perma.cc/LG4M-ACHT].

10. *Id.*

11. *EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients with Early Alzheimer's Disease*,

In a July 8, 2020, press release publicizing the completion of its BLA submission for aducanumab to the FDA, Biogen noted that the "submission followed ongoing collaboration with the FDA."[12]

On November 4, 2020, the FDA posted on its website the briefing documents for the agency's Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee meeting on November 6, 2020. Disturbingly, the primary briefing document for the meeting had been written jointly by the FDA and Biogen, with most content apparently written by the company.[13]

In our experience attending or participating in hundreds of FDA advisory committee meetings, we could not recall ever seeing an advisory committee meeting briefing document that was explicitly written jointly by the FDA and the sponsor of the medical product being considered by the committee.

The joint advisory committee briefing document revealed further details of the close collaboration that had occurred between the FDA and Biogen following the company's March 2019 decision to terminate the phase 3 trials of aducanumab. For example, the briefing document stated that Biogen had a June 2019 meeting with the FDA that included a discussion of post hoc analyses of data from Study 302 conducted after termination of the study showing apparently positive results.[14] According to Biogen, the FDA stated the following at this meeting:

> It is imperative that extensive resources be brought to bear on achieving a maximum understanding of the existing data. Given the wholly unique situation that is the current state of the aducanumab development program . . . , those

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BIOGEN (Dec. 5, 2019), https://investors.biogen.com/static-files/ddd45672-9c7e-4c99-8a06-3b557697c06f [https://perma.cc/8KA5-67KM].

12. *Biogen Completes Submission of Biologics Licensing Application to FDA for Aducanumab as a Treatment for Alzheimer's Disease*, BIOGEN (July 8, 2020), https://investors.biogen.com/news-releases/news-release-details/biogen-completes-submission-biologics-license-application-fda [https://perma.cc/6PL4-2BXZ].

13. COMBINED FDA AND APPLICANT BRIEFING DOCUMENT, *supra* note 6.

14. *Id.*

> further analyses would best be conducted as part of a **bilateral effort involving the Agency and sponsor, i.e., through a 'workstream' or a 'working group' collaboration.**[15]

Of note, key details regarding the extent of this FDA-Biogen collaboration would not become known until after the FDA approved aducanumab in June 2021.

Typically, sponsors conduct their own statistical analyses of clinical trial data supporting new drug applications (NDAs) and BLAs, and the FDA then conducts its own independent analyses of the data following submission of these applications for approval. Such appropriate separation between the clinical trial data analyses conducted by the sponsor and those conducted by the FDA is critical to maintaining the independence and integrity of the FDA's review of the data.

In the case of aducanumab, the close collaboration between the FDA and Biogen in the post hoc analyses of clinical trial data and the subsequent joint authorship of the primary briefing document for the November 6, 2020, PCNS Drugs Advisory Committee meeting resulted in a one-sided consensus briefing document.[16] That document overwhelmingly emphasized the post hoc analyses that yielded positive results suggesting that high-dose aducanumab was an effective treatment for Alzheimer's disease (primarily the analyses of Study 302), but significantly downplayed the results of post hoc analyses showing that aducanumab was not effective for treating Alzheimer's disease (the analyses of Study 301).

The FDA characterized the results of Study 302 as being "highly persuasive," "strongly positive," and "capable of providing the primary contribution to a demonstration of substantial evidence of effectiveness of aducanumab," while simply acknowledging that Study 301 was a "negative study."[17]

Note that the FDA's usual standards for approval of new drugs include "substantial evidence of effectiveness," which generally requires demonstration of effectiveness in two, well-

15. *Id.*

16. *Id.*

17. *Id.*

designed, completed, randomized, phase 3 clinical trials, particularly for drugs used to treat common diseases like Alzheimer's disease.[18]

Relying on dubious statistical gymnastics, Biogen and the FDA in their joint review document sought to discount the discordance between the negative results of Study 301 and the partially positive results of Study 302 and portray the post hoc analyses of Study 302 data (with supporting data from the small phase 1 Study 103 that was not even designed to assess efficacy, but did assess safety and the effect of aducanumab on brain amyloid-beta) as representing the true picture of aducanumab's effectiveness in treating Alzheimer's disease. This "cherry-picking" approach was neither statistically nor scientifically appropriate.

Appended to the joint briefing document for the PCNS Drugs Advisory Committee meeting was a draft statistical review document written by FDA Mathematical Statistician Tristan Massie, Ph.D., that highlighted numerous serious flaws in the post hoc data analyses of Studies 301, 302, and 103 that had been conducted by Biogen in collaboration with *other* FDA staff.[19] Dr. Massie made the following conclusions:

> The totality of the data does not seem to provide sufficient evidence to support the efficacy of the high dose. There is much inconsistency and no replication. There is only one positive study at best and a second study which directly conflicts with the positive study. Both studies were not fully completed . . . and had sporadic unblinding for dose management of ARIA [amyloid-related imaging abnormalities] cases[,] which was much higher in the [aducanumab] group . . . there is no convincing evidence of delaying clinical progression.[20]

18. U.S. Food & Drug Admin., Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, Guidance For Industry (Draft) (2019).

19. Combined FDA and Applicant Briefing Document, *supra* note 6.

20. *Id.*

Unsurprisingly, the prerecorded and live presentations by Biogen and all FDA reviewers, *except the FDA statistician Dr. Massie*, for the PCNS Drugs Advisory Committee meeting were completely concordant with the one-sided joint briefing document. Dr. Billy Dunn, Director, Office of Neuroscience, Office of New Drugs, Center for Drug Evaluation and Research (CDER) — whose office is responsible for reviewing Alzheimer's disease drugs — gave the FDA's summary presentation at the meeting.[21] The language he used, as reflected in the following representative excerpts, made him sound more like a consultant hired by Biogen to endorse the company's BLA for aducanumab, than like an independent and objective federal regulator paid by American taxpayers:

> **The effect of aducanumab in Study 302 is robust and exceptionally persuasive** on several of the instruments used to evaluate efficacy . . . [22]
>
> When considered on its own, **Study 302 would appear to be a home run** . . . [23]

During the meeting, advisory committee members unleashed a torrent of appropriately harsh criticism of the post hoc analyses of Studies 301, 302, and 103; the nature and organization of the questions posed by the FDA; and the one-sided joint briefing document.

For example, Scott Emerson, M.D., Ph.D., Professor Emeritus of Biostatistics, University of Washington, Seattle, Washington,[24] said the following:

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21. U.S. Food & Drug Admin. Ctr. Drug Evaluation & Rsch., Final Summary Minutes of the Peripheral And Central Nervous System Drugs Advisory Committee Meeting (2020) [hereinafter Meeting Summary Minutes).

22. U.S. Food & Drug Admin., Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee Webcast Recording (2020) [hereinafter Meeting Webcast Recording], https://collaboration.fda.gov/p2uew93ez7dw/ [https://perma.cc/KUK5-KW5S] (available at 02:12:36-02:12:43).

23. *Id.* (available at 02:17:01-02:17:06).

24. U.S. Food & Drug Admin. Ctr. Drug Evaluation & Rsch., Peripheral and Central Nervous System Drugs Advisory

> This analysis seems to be subject to the **Texas sharpshooter fallacy**, a name for the joke of someone first firing a shotgun at a barn and then painting a target around the bullet holes.[25]

Likewise, G. Caleb Alexander, M.D., M.S., Professor of Epidemiology and Medicine,[26] Johns Hopkins Bloomberg School of Public Health, Center for Drug Safety and Effectiveness, Baltimore, Maryland, offered the following comment:

> I find the materials that the FDA has provided strikingly incongruent, and I have a very hard time understanding . . . how the FDA could conclude that there are substantial evidence of effectiveness and, in particular, that Study 302 provides 'a robust and exceptionally persuasive study,' and it just feels to me like the audio and the video on the TV are out of sync. And there are literally a dozen different red threads that suggest concerns about the consistency of evidence.[27]

*Our Advocacy Work Opposing FDA Approval of Aducanumab and Seeking to Hold FDA Accountable for its Inappropriately Close Collaboration with Biogen Prior to FDA Approval of the Drug*

Our advocacy work opposing FDA approval of aducanumab began on November 5, 2020, with a press statement previewing our testimony before the FDA's PCNS Drugs Advisory Committee the following day. The statement noted that "[t]he overall tenor of the FDA's briefing document for [the] meeting reveals that the agency is actively working hand-in-hand with Biogen . . . to rush to market an unproven biologic drug to treat

COMMITTEE MEETING ROSTER (2020) [hereinafter MEETING ROSTER].

25. MEETING WEBCAST RECORDING, *supra* note 22 (available at 01:00:28-01:00:39).

26. MEETING ROSTER, *supra* note 24.

27. MEETING WEBCAST RECORDING, *supra* note 22 (available at 03:35:28-03:36:15).

Alzheimer's disease that could bankrupt our health care system."[28]

In our testimony before the PCNS Drugs Advisory Committee on November 6, we urged the committee to recommend that the FDA not approve aducanumab for treatment of Alzheimer's disease.[29] We argued that the post hoc analyses of the phase 3 clinical trials of the drug had been highly susceptible to bias, had not provided substantial evidence of effectiveness, and should only have been used to generate hypotheses for possible future trials. We highlighted the FDA statistical reviewer's statement in his prerecorded presentation that "if we select only the better study, our [efficacy] estimate is very likely biased, and we already know not consistently repeatable . . . Thus, excluding data from a large trial without sufficient justification is unscientific, statistically inappropriate and misleading." We concluded that the FDA must demand another large premarket randomized, placebo-controlled trial of aducanumab and that FDA approval of the drug, absent substantial evidence of efficacy, would further damage the agency's already diminished credibility.

On the key voting question posed to the advisory committee — *In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease?* — the vote was 0 YES, 10

28. Press Statement, Pub. Citizen, FDA Approval of Aducanumab to Treat Alzheimer's Disease Would Be a Reckless Disregard for Science, Damage Agency's Credibility (Nov. 5, 2020), https://www.citizen.org/news/fda-approval-of-aducanumab-to-treat-alzheimers-disease-would-be-a-reckless-disregard-for-science-damage-agencys-credibility/ [https://perma.cc/9UMU-ZM78].

29. Michael A. Carome, *Testimony Before The FDA's Peripheral and Central Nervous System Drugs Advisory Committee: The FDA Must Reject BLA 761178 for Aducanumab for the Treatment of Alzheimer's Disease*, Pub. Citizen's Health Rsch. Grp. (Nov. 6, 2020), https://www.citizen.org/wp-content/uploads/2556.pdf [https://perma.cc/5ZQB-VPG6].

NO, 1 UNCERTAIN,[30] formally indicating near-unanimous opposition to FDA approval of aducanumab based on the available clinical trial data — opposition that was readily apparent throughout the meeting.

Following the meeting, we were hopeful that the advisory committee's overwhelming negative assessment of the aducanumab data would be the death knell for Biogen's BLA.

We also concluded that there must be an independent investigation of the unprecedented close collaboration that had occurred between the FDA and Biogen before and after the submission of the company's BLA for aducanumab. Therefore, on December 9, 2020, we submitted a formal, detailed complaint to the U.S. Department of Health and Human Services (HHS) Office of Inspector General (OIG) calling for such an investigation.[31] Citing the aforementioned details of the FDA-Biogen collaboration, we asserted that this collaboration dangerously compromised the independence and objectivity of senior staff and clinical reviewers in CDER's Office of Neuroscience during the agency's review of Biogen's BLA for aducanumab and key data from the clinical trials of the drug, which resulted in the FDA's unbridled enthusiasm for the drug. We noted that Office of Neuroscience Director Dunn "likely played a key role in the close FDA-Biogen collaboration."[32] We also argued that the FDA's close collaboration with Biogen was indicative of regulatory capture at the agency, which has resulted in the agency acting in ways that benefit the interests of the pharmaceutical industry rather than the public interest.[33]

30. MEETING SUMMARY MINUTES, *supra* note 21.

31. Letter from Michael A. Carome, Dir., Pub. Citizen's Health Rsch. Grp., to Christi A. Grimm, Principal Deputy Inspector General, Off. of Inspector General, U.S. Dept. of Health & Human Services (Dec. 9, 2020) (on file with Pub. Citizen's Health Rsch. Grp.) [hereinafter Letter from Carome to Grimm](requesting an Office of Inspector General investigation of the Food and Drug Administration's inappropriate close collaboration with Biogen before and after the submission of the biologics license application for aducanumab for treatment of Alzheimer's disease).

32. *Id.*

33. *Id.*

We listed for the OIG three major adverse consequences if the FDA were to approve aducanumab. First, approving a drug for Alzheimer's disease that has not been shown to be effective would provide false hope to millions of desperate patients with the disease and their families. Second, because the drug would be exorbitantly priced and used by potentially millions of patients for years, it would have a massive impact on health-care economics and potentially bankrupt the Medicare program, as well as many patients and their families. Third, the premature approval of aducanumab could impede the development of other experimental treatments for Alzheimer's disease for many years, potentially delaying progress on drugs that actually may turn out to be beneficial.

Also on December 9, we sent a separate letter to then-FDA Commissioner Stephen Hahn and then-Acting CDER Director (and now CDER Director) Patrizia Cavazzoni transmitting a copy of our letter to the HHS OIG and urging them to begin restoring public confidence in their agency and its review of aducanumab by taking the following actions:

> (1) Endorse our call for an OIG investigation; (2) Assign all further review and decision-making related to the BLA for aducanumab to CDER staff who were not involved in this close collaboration with Biogen; (3) Given that he supervised the FDA team reviewing the BLA for aducanumab and likely played a key role in the close collaboration with Biogen, temporarily remove Dr. Dunn from his position as Office of Neuroscience Director until the requested OIG investigation is completed; and (4) Assess whether any similar close collaborations have occurred with other sponsors that submitted NDAs or BLAs to the FDA, and if so, determine the extent to which the integrity of the review of those NDAs or BLAs had been compromised.[34]

34. Letter from Michael A. Carome, Dir., Pub. Citizen's Health Rsch. Grp., to Stephen M. Hahn, Commissioner, Food & Drug Admin., and Patrizia Cavazzoni, Acting Dir., Center for Drug Evaluation & Rsch., U.S. Food & Drug Admin. (Dec. 9, 2020) (on file with Pub. Citizen's Health Rsch. Grp.) (discussing the FDA's inappropriate close collaboration with Biogen before and after the

In our letter to the FDA, we also pressed that agency to take additional actions to prevent future inappropriate collaborations between agency staff and sponsors:

> As noted in our letter to the HHS OIG, we understand that it is not unusual for the FDA to meet with sponsors and provide advice regarding the development of drugs and biologics, the design of clinical trials, and the statistical analyses of trial data, among other things. Given the potential for these interactions to drift towards collaborations with sponsors that could undermine the integrity of agency reviews, as had occurred with aducanumab, the FDA in such cases should designate other staff, who were not involved in such interactions prior to the submission of an NDA or BLA, to review and make decisions on any subsequent NDAs and BLAs related to those drugs or biologics. To ensure the integrity of these reviews and decisions, a firewall should be created between the FDA staff involved in any presubmission interactions and those involved in the postsubmission NDA or BLA review and decision-making.[35]

Finally, we again urged the agency not to approve aducanumab.

The OIG on January 11, 2021 responded to us with a short pro forma letter stating, in part, the following:

> Safeguarding public health is one of the Department's Top Management and Performance Challenges, and OIG has responded by focusing on work that identifies opportunities to, among other things, ensure the integrity of agency review and decision making. OIG continuously engages in work planning and will include the collaboration issues you have raised in our ongoing work planning discussions.[36]

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submission of the biologics license application for aducanumab for treatment of Alzheimer's disease).

35. *Id.*

36. Letter from Christopher S. Seagle, Dir. External Affairs, Office of Inspector General, Dept. of Health & Human Services, to Michael

This initial response fell far short of committing to the type of OIG investigation that we had sought.

On January 28, 2021, we sent Dr. Janet Woodcock — shortly after her appointment as Acting FDA Commissioner — a letter identical to our December 9 missive to Drs. Hahn and Cavazzoni.[37] On February 11, 2021, Dr. Woodcock responded with a full-throated defense of the FDA's interactions with pharmaceutical companies during the drug development process.[38] She extolled the benefits of these interactions and ignored their potential downsides, which had been apparent in the agency's review of aducanumab.[39]

On January 29, 2021, Biogen and Eisai unexpectedly announced that the FDA had extended the review period for the companies' marketing application for aducanumab by three months (the planned decision date delayed from March 7 until June 7, 2021) after the agency had requested more data on the drug.[40] Worried that the FDA was searching for a way to approve aducanumab following the strong opposition to approval from its advisory committee, we promptly issued a press statement reiterating our position that the FDA should reject the application for aducanumab and demand that Biogen and Eisai conduct another large, placebo-controlled clinical trial before

A. Carome, Dir., Pub. Citizen Health Rsch. Grp. (Jan. 11, 2021) (on file with Pub. Citizen's Health Rsch. Grp.).

37. Letter from Michael A. Carome, Dir., Pub. Citizen's Health Rsch. Grp., to Janet Woodcock, Acting Commissioner, U.S. Food & Drug Admin. (Jan. 28, 2021) (on file with Pub. Citizen's Health Rsch. Grp.).

38. Letter from Janet Woodcock, Acting Commissioner, U.S. Food & Drug Admin., to Michael A. Carome, Dir., Public Citizen's Health Rsch. Grp. (Feb. 11, 2021) (on file with Pub. Citizen's Health Rsch. Grp.).

39. *Id.*

40. *Biogen And Eisai Announce FDA's 3-Month Extension of Review Period for the Biologics License Application for Aducanumab*, BIOGEN, https://www.globenewswire.com/news-release/2021/01/29/2166560/0/en/Biogen-and-Eisai-Announce-FDA-s-3-Month-Extension-of-Review-Period-for-the-Biologics-License-Application-for-Aducanumab.html [https://perma.cc/9XH6-4VNW] (last visited Feb. 27, 2022).

giving further consideration to approving the drug to treat Alzheimer's disease.[41]

Of note, through press releases and persistent media outreach during our advocacy campaign, we were able to partially frame the public debate regarding whether aducanumab should be approved by the FDA based on the available data and to bring public attention to our concern that the integrity of the FDA's review of the drug had been compromised by the agency's inappropriately close collaboration with Biogen.

We also wrote a letter to Secretary of Health and Human Services ("HHS") Xavier Becerra on April 1, 2021, two weeks after he had been confirmed by the Senate, urging him to ask his department's OIG to immediately investigate the FDA-Biogen collaboration.[42] We also warned that approval of aducanumab for treatment of Alzheimer's disease despite the lack of evidence of effectiveness would pose an unacceptable threat to the financial health of the Medicare program.[43] We asserted that "[g]iven the gravity of our concerns, more definitive, prompter actions by the OIG and HHS must be taken."[44]

*Our Advocacy Work Seeking to Hold FDA Accountable For its Reckless Decision to approve aducanumab*

Disappointingly, we were unsuccessful in stopping FDA approval of aducanumab. On June 7, 2021, the agency announced its decision to approve the drug under the brand name Aduhelm to treat patients with Alzheimer's disease using the Accelerated

41. *Statement: FDA Must Demand a New Clinical Trial of Experimental Alzheimer's Disease Treatment Following Inappropriate Collaboration,* PUB. CITIZEN (Jan. 29, 2021), https://www.citizen.org/news/statement-fda-must-demand-a-new-clinical-trial-of-experimental-alzheimers-disease-treatment-following-inappropriate-collaboration/ [https://perma.cc/NJT4-PXL9].

42. Letter from Michael A. Carome, Dir., Pub. Citizen's Health Rsch. Grp., to Xavier Becerra, Sec'y, Health & Human Serv. (Apr. 1, 2021) (on file with Pub. Citizen's Health Rsch. Grp.).

43. *Id.*

44. *Id.*

Approval pathway.[45] The agency claimed that the reduction in amyloid-beta plaques in the brains of subjects who received aducanumab in clinical trials — a surrogate endpoint — was "reasonably likely to result in clinical benefit."[46] The FDA mandated that Biogen complete a postmarket, randomized, placebo-controlled trial of the drug within 9 years.[47]

We immediately shifted our advocacy work to holding the FDA accountable for its reckless decision to approve aducanumab. Shortly after the FDA's announcement, we released a press statement condemning the decision and noting that it showed "a stunning disregard for science and eviscerate[ed] the agency's standards for approving new drugs" and that "[b]ecause of this reckless action, the agency's credibility has been irreparably damaged."[48]

The FDA's decision to approve aducanumab, combined with Biogen's announced price of $56,000 for a one-year treatment course of the drug,[49] sparked fierce backlash from many neurologists, academics, and Congress, among others, and prompted three members of the agency's PCNS Drugs Advisory

45. Patrizia 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/D3LG-MAYL].

46. *Id.*

47. Letter from Billy Dunn, Dir., Off. Of Neuroscience, Ctr. for Drug Evaluation & Rsch., to Priya Singhal, Vice Pres., Global Safety & Regulatory Sci., Biogen, Inc. (June 7, 2021) (on file with U.S. Food & Drug Admin.).

48. Press Statement, Pub. Citizen, FDA's Decision to Approve Aducanumab for Alzheimer's Disease Shows Reckless Disregard For Science, Severely Damages Agency's Credibility (June 7, 2021), https://www.citizen.org/news/statement-fdas-decision-to-approve-aducanumab-for-alzheimers-disease-shows-reckless-disregard-for-science-severely-damages-agencys-credibility/ [https://perma.cc/3SDV-2K4Y].

49. *Biogen and Eisai Launch Multiple Initiatives to Help Patients with Alzheimer's Disease Access Aduhelm,* BIOGEN (June 7, 2021), https://investors.biogen.com/news-releases/news-release-details/biogen-and-eisai-launch-multiple-initiatives-help-patients [https://perma.cc/XXK3-XMAN].

Committee to resign from the committee.[50] Many health insurers refused to cover the drug, and some health care systems, including the Cleveland Clinic, announced that they would not provide the drug to patients.[51]

On June 16, 2021, we again wrote to HHS Secretary Becerra and urged him to request the resignations or seek the removal of the three officials most responsible for the agency's indefensible decision to approve aducanumab for treatment of Alzheimer's disease, despite the lack of evidence that the drug provided any meaningful clinical benefit, plus the fact that the drug had a well-documented risk of potentially serious brain injury: Acting FDA Commissioner Woodcock, CDER Director Cavazzoni, and CDER's Office of Neuroscience Director Dunn.[52] In our letter, we emphasized that the currently available evidence — including evidence from the clinical trials of aducanumab itself — failed to show a meaningful correlation between changes in brain amyloid-beta and changes in clinical measures of cognitive function. We also highlighted the fact that during the November 6, 2020 PCNS Drugs Advisory Committee meeting, in response to a question from one committee member about the lack of correlation between the observed changes in amyloid-beta plaques in the brain and changes in measures of cognitive function in the clinical trials of aducanumab, Dr. Dunn explicitly stated that the agency was "not using the amyloid as a surrogate [endpoint] for

50. Bill Chappell, *3 Experts Have Resigned from an FDA Committee Over Alzheimer's Drug Approval*, NPR (June 11, 2021), https://www.npr.org/2021/06/11/1005567149/3-experts-have-resigned-from-an-fda-committee-over-alzheimers-drug-approval [https://perma.cc/5J8N-8UTY].

51. *Aducanumab FAQ*, Cleveland Clinic, https://my.clevelandclinic.org/departments/neurological/depts/brain-health/aducanumab-faq#:~:text=Based%20on%20the%20current%20data,for%20use%20in%20our%20patients [https://perma.cc/66TQ-XY2W] (last visited Feb. 27, 2022).

52. Letter from Michael A. Carome, Dir., Pub. Citizen's Health Rsch. Grp., to Xavier Becerra, Sec'y, Health & Human Services (June 16, 2021) (on file with Pub. Citizen's Health Rsch. Grp.).

efficacy."[53] Finally, we expressed dismay that the agency had approved the drug for anyone with Alzheimer's disease despite that fact the phase 3 clinical trials of the drug had been limited to patients with no more than mild Alzheimer's disease and, thus, there was a complete absence of any evidence that the drug was safe or effective for patients with moderate or severe Alzheimer's disease.

On June 25, the Chairs of the U.S. House of Representatives' Committee on Energy and Commerce and Committee on Oversight and Reform announced a joint investigation into the FDA's review and approval of aducanumab.[54] Shortly thereafter, we met with staff from the committees to share our concerns regarding the FDA-Biogen collaboration before and after the company submitted its marketing application for the drug.

Then, on June 29, 2021, the online media outlet STAT published a detailed exposé that provided stunning new disclosures about the extent to which key FDA staff in CDER's Office of Neuroscience collaborated with Biogen after the company terminated the phase 3 clinical trials of aducanumab in March 2019.[55] Among the most troubling disclosures in the STAT article were the following:

1. In early May 2019 — shortly after Biogen and Eisai had announced the decisions to terminate the two pivotal phase 3 clinical trials testing aducanumab and to end development of the drug — Biogen Chief Scientist, Al Sandrock, reached out to CDER's ON Director, Dr.

53. U.S. Food & Drug Admin., Peripheral & Central Nervous System Drugs Advisory Committee (PCNs) Meeting Transcript (2020).

54. Press Release, House Comm. on Oversight & Reform, Chairs Maloney and Pallone Announce Investigation of Biogen's Alzheimer's Drug Aduhelm (June 25, 2021), https://oversight.house.gov/news/press-releases/chairs-maloney-and-pallone-announce-investigation-of-biogen-s-alzheimer-s-drug [https://perma.cc/RN6R-RQQ8].

55. 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/LXD2-HJ93].

Dunn, with whom Sandrock "already had a longstanding professional relationship," and sat down with him for an "off-the-books" meeting while the two were attending a neurology conference in Philadelphia.[56] "Sandrock wanted to let Dunn know that Aduhelm — publicly declared ineffective — might actually be slowing the progression of Alzheimer's . . . And wanted to know if Dunn would be open to helping find a way to get the drug approved."[57]

2. "'It was clear that Billy Dunn was an ally, so the job for Biogen became figuring out how to support his efforts within the FDA,' a former Biogen employee told STAT."[58]

3. Following Sandrock's meeting with Dunn, Biogen "mounted a secret campaign, codenamed 'Project Onyx,' to resurrect the drug and convince the FDA to give it the green light. Central to their mission was an inside ally: Billy Dunn, the agency's top regulator of Alzheimer's drugs."[59]

4. "The FDA's support grew quickly. By June 2019, only a month after the crucial meeting with Dunn, agency officials in his Office of Neuroscience were so willing to advance Aduhelm that they proposed as one option a regulatory shortcut called 'accelerated approval,' according to meeting minutes read to STAT. The move stunned even Biogen's top executives, who had considered that out of the question for a host of reasons."[60]

5. "After the June 14, 2019, meeting [between Biogen and the FDA], Biogen and the FDA established a 'working group collaboration' consisting of company employees and agency review staff. The group met or

56. *Id.*

57. *Id.*

58. *Id.*

59. *Id.*

60. *Id.*

> communicated almost daily in June, July, and August of 2019, working to collect and analyze Aduhelm data for inclusion in the planned marketing submission. The group decided to pursue a standard FDA approval based on data on how patients had fared on cognitive surveys."[61]

The following day, June 30, 2021, we sent follow-up letters to the HHS OIG renewing our request for an independent investigation of the unprecedented FDA-Biogen collaboration[62] and to HHS Secretary Becerra again, calling for the resignations or removal of Acting Commissioner Woodcock and other senior FDA officials.[63] Both letters asserted that the circumstances described in the STAT exposé, if confirmed, painted a damning picture of FDA drug regulators who had surrendered their independence and objectivity, essentially began working on behalf of Biogen, and fostered regulatory capture at the agency.

On July 9, 2021, Dr. Woodcock surprisingly announced via Twitter that she had asked the HHS Acting Inspector General to independently review the "interactions between representatives of Biogen and the FDA during the process that led to the decision to approve" aducanumab for treatment of Alzheimer's disease.[64] We responded that same day with a press statement welcoming Dr. Woodcock's belated request for an independent IG investigation of her agency's inappropriately close collaboration with Biogen, as we had urged her to do nearly six months earlier,

61. *Id.*

62. Letter from Michael A. Carome, Dir., Pub. Citizen's Health Rsch. Grp., to Christi A. Grimm, Principal Deputy Inspector General, Off. of Inspector General, U.S. Dept. of Health & Human Serv. (June 30, 2021) (on file with Pub. Citizen's Health Rsch. Grp).

63. Letter from Michael A. Carome, Dir., Pub. Citizen's Health Rsch. Grp., to Xavier Becerra, Sec'y, Health & Human Services (June 30, 2021) (on file with Pub. Citizen's Health Rsch. Grp.).

64. @DrWoodcockFDA, TWITTER (July 9, 2021), https://twitter.com/DrWoodcockFDA/status/1413540801934774283 [https://perma.cc/98SZ-LJR2].

and noting that the requested OIG investigation must examine the role that Dr. Woodcock played in the matter.[65]

On August 4, 2021, the HHS OIG finally announced that in response to concerns raised about the FDA's process for reviewing and approving aducanumab — including "allegations of an inappropriately close relationship between the FDA and the industry"[66] — the OIG would review and assess how the FDA implemented the accelerated approval pathway for this drug and a sample of other drugs approved under this regulatory pathway.[67] That review will include an examination of the interactions between the FDA and "outside parties" [i.e., Biogen and other drug company personnel] during the review and approval process of these drugs. This was exactly the type of investigation that we had requested in our original December 9, 2020, letter to the OIG.[68] The OIG expects to issue its report in 2023.[69]

*Concluding Reflections: How Did the FDA Sink So Low?*

The FDA-Biogen collaboration regarding aducanumab and the agency's subsequent decision to approve the drug under the Accelerated Approval pathway exemplify the regulatory capture at the agency by the pharmaceutical industry. So how did we reach this point?

The origins of the FDA's decline as a pharmaceutical industry regulator date back to 1992 when Congress first passed the

65. Press Statement, Pub. Citizen, Woodcock's Role in Aducanumab's Approval Must Be Investigated as Part of IG Probe (July 9, 2021), https://www.citizen.org/news/statement-woodcocks-role-in-aducanumabs-approval-must-be-investigated-as-part-of-ig-probe/ [https://perma.cc/P2NK-UBSC].

66. *Review of the FDA's Accelerated Approval Pathway*, U.S. Dept. Health & Human Serv. Off. Inspector Gen. [hereinafter *Review of the FDA's Accelerated Approval Pathway*], https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp [https://perma.cc/3LA5-JWAR] (last visited Feb. 27, 2022).

67. *Id.*

68. Letter from Carome to Grimm, *supra* note 31.

69. *Review of the FDA's Accelerated Approval Pathway, supra* note 66.

Prescription Drug Use Fee Act (PDUFA).[70] PDUFA was intended to expedite the drug review process by providing the FDA with a new funding stream to hire additional medical officers and other staff to review NDAs. In exchange for this industry funding — which across all FDA user fee programs totaled nearly $1.2 billion dollars in fiscal year 2020 for review and oversight of human drugs[71] — Congress required that the FDA meet benchmarks for timeliness of review and final decision making for drug marketing applications.

In addition, each five-year reauthorization of PDUFA has provided an opportunity for drug companies and their well-paid advocates to lobby Congress for additional legislative provisions that have, and have had, nothing to do the actual user fees, but instead weakened the standards for approving new drugs. For example, PDUFA's reauthorization in 1997 provided the vehicle for passage of the Food and Drug Administration Modernization Act, which permitted drug approval based on a single phase 3 clinical trial (instead of two), created the Fast-Track program for facilitating the development and expediting the review of drugs for treatment of serious or life-threatening conditions, and established the use of surrogate endpoints in clinical trials, among other things.[72]

Concerns about declining FDA standards for drug approvals were raised by some FDA staff following PDUFA's enactment. For example, in a 1998 anonymous survey study of FDA medical officers conducted by Public Citizen's Health Research Group, among the 53 medical officers who responded to the survey (out of 172 officers to whom the survey had been mailed), 17 described the then-current standards for the review of drug safety and efficacy as being "lower" or "much lower" than those in existence prior to 1995, and 34 stated that there was "somewhat greater"

70. Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571.

71. U.S. Food & Drug Admin., Fiscal Year 2021 Justification of Estimates for Appropriations Committees (2021).

72. Peter Lurie & Sidney M. Wolfe, FDA Medical Officers Report Lower Standards Permit Dangerous Drug Approvals: A Public Citizen's Health Research Group Report 2 (1998) [hereinafter Lower Standards]; Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296.

or "much greater" pressure to approve a greater proportion of drugs than there was before 1995.[73] Likewise, a 2003 HHS OIG report found that among 136 CDER reviewers surveyed, 36% were not confident in FDA decisions regarding the safety of a drug.[74]

Most importantly, the introduction of user fees gradually resulted in a fundamental shift in the relationship between the FDA and the regulated pharmaceutical industry, such that the agency came to view drug companies as partners, rather than regulated entities. FDA leaders for several years now have been transparent about the agency's partnership with industry. For example, in a 2014 speech to drug company executives then-FDA Commissioner Margaret Hamburg touted a "new era of partnership" with the biopharmaceutical industry.[75]

Partnerships involve close cooperation between two or more entities seeking to advance shared interests and objectives. But the dynamics of a partnership are incompatible with the relationship that should exist between a regulatory agency and regulated industry. The pharmaceutical industry's primary interest is to maximize profits selling drugs, which can conflict with what should be the FDA's primary interest: protecting public health.

In 2018, ProPublica published an exposé describing the deeply entrenched industry-friendly culture within the FDA.[76] It reported that, according to former agency employees, as the FDA became more reliant on industry user fees to pay for drug reviews, it showed an increasing inclination to approve new drugs and

73. LOWER STANDARDS, *supra* note 72, at 3.

74. DEP'T OF HEALTH AND HUM. SERV. OFF. INSPECTOR GEN., FDA'S REVIEW PROCESS FOR NEW DRUG APP., PUB. OEI-01-01-00590 (2003).

75. Robert Weisman, *FDA Chief Urges 'New Era of Partnership*,' BOS. GLOBE (Apr. 5, 2014), http://www.bostonglobe.com/business/2014/04/04/fda-commissioner-calls-for-new-era-partnership-with-biopharma-industry/8676GZuMw8oEqaXt2HmkmK/story.html [https://perma.cc/4XBD-LPB5].

76. Caroline Chen, *FDA Repays Industry by Rushing Risky Drugs to Market*, PROPUBLICA (June 26, 2018), https://www.propublica.org/article/fda-repays-industry-by-rushing-risky-drugs-to-market [https://perma.cc/CE3G-L5NM].

adopted an industry-friendly posture.[77] For example, one former FDA medical team leader told ProPublica that FDA staff know "you don't get promoted unless you're pro-industry."[78]

As we told the HHS OIG in a July 13, 2021, follow-up letter, during Dr. Woodcock's leadership of CDER over the past three decades, the relationship between the FDA and the pharmaceutical industry grew ever cozier — resulting in regulatory capture on the part of the agency.[79] She undoubtedly helped foster the current culture at CDER that permitted and encouraged the type of inappropriately close collaboration that occurred between the FDA and Biogen and ultimately corrupted the integrity of the FDA's review of aducanumab for the treatment of Alzheimer's disease. Thus, the OIG must examine her role in this matter.

I close with this cartoon summing up the current state of the FDA and its relationship with the pharmaceutical industry and the potential resulting harm to patients that was posted on Twitter in response to Dr. Woodcock's July 9 tweet calling for an OIG investigation of the agency's review and approval of aducanumab.[80]

77. *Id.*

78. *Id.*

79. Letter from Michael A. Carome, Director, Pub. Citizen's Health Rsch. Group, to Christie A. Grimm, Inspector General (July 13, 2021) (on file with Pub. Citizen's Health Rsch. Grp.).

80. Matt Carmody, Cartoon of FDA in Bed with Drug Companies (c) 2004, *in* TUESDAY'S HORSE (Nov. 10, 2014), https://tuesdayshorse.wordpress.com/2014/11/10/pfizer-fights-for-more-protection-for-their-new-combo-drug-duavee-but-why/drugcompaniesinbed/ [https://perma.cc/E24D-BHNA]. Links to all our advocacy work related to aducanumab can be found on the Public Citizen website. *See Aducanumab*, PUB. CITIZEN'S HEALTH RSCH. GRP., https://www.citizen.org/article/aducanumab/ [https://perma.cc/H7JQ-LT8Q] (last visited Mar. 13, 2022).