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December 9, 2020

Stephen M. Hahn, M.D.  
Commissioner  
Food and Drug Administration  
U.S. Department of Health and Human Services  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Patrizia Cavazzoni, M.D.  
Acting Director  
Center for Drug Evaluation and Research  
Food and Drug Administration  
U.S. Department of Health and Human Services  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**RE: The FDA's inappropriate close collaboration with Biogen before and after the submission of the biologics license application for aducanumab for treatment of Alzheimer's disease**

Dear Commissioner Hahn and Dr. Cavazzoni:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to express its alarm regarding the unprecedented close collaboration between the Food and Drug Administration (FDA) and Biogen that occurred before and after the submission of Biogen's biologics license application (BLA) for the new biologic drug aducanumab for treatment of Alzheimer's disease. A detailed description of our concerns is provided in the enclosed letter to the Department of Health and Human Services (HHS) Office of Inspector General (OIG).

As noted in our letter to the OIG, such close collaboration — which was made fully transparent in press releases and presentation documents issued by Biogen and in the unprecedented joint briefing document prepared by the FDA and Biogen for the FDA's Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee meeting on November 6, 2020 — has dangerously compromised the independence and objectivity of senior staff and clinical reviewers in the agency's Office of Neuroscience (ON) in the Center for Drug Evaluation and Research's (CDER's) Office of New Drugs during the agency's review of Biogen's BLA for aducanumab and key data from the two identical pivotal phase 3 clinical trials of the drug. ON Director Billy Dunn, M.D., supervised the FDA team conducting this review and likely played a key role in the close FDA–Biogen collaboration.

The FDA's unbridled enthusiasm for aducanumab documented in the PCNS Drugs Advisory Committee meeting joint briefing document and echoed in Dunn's presentation at the November 6, 2020, advisory committee meeting was not supported by an objective review of data from the pivotal phase 3 clinical trials, which had been terminated early after enrollment had reached only 50% of the planned target enrollment because a planned prespecified interim analysis for futility showed the trials were unlikely to yield evidence that the drug was effective for treating Alzheimer's disease.

The circumstances surrounding the FDA's collaboration with Biogen before and after the submission of the BLA for aducanumab are a black eye for the agency, further undermining public confidence in the FDA, and demand your immediate attention. To begin restoring public confidence in the FDA and its review of aducanumab, we urge you to immediately take the following actions:

- (1) Endorse our call for an OIG investigation of the unprecedented close collaboration between the FDA and Biogen that occurred before and following the submission of Biogen's BLA for aducanumab for treatment of Alzheimer's disease;
- (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 ON Director until the requested OIG investigation is completed; and
- (4) Assess whether any similar close collaborations have occurred with other sponsors that submitted new drug applications (NDAs) or BLAs to the FDA, and if so, determine the extent to which the integrity of the review of those NDAs or BLAs was compromised.

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 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.

Finally, the FDA must not approve the BLA for aducanumab given the clear lack of substantial evidence that the drug is effective for treating Alzheimer's disease, the statutory requirement for drug approval. A decision by the FDA to approve aducanumab now would have several wide-ranging adverse consequences. First, approving a drug for Alzheimer's disease that has not been shown to be effective — and that in the end may turn out to be ineffective, assuming another pivotal phase 3 trial is conducted appropriately and completed — would provide false hope to

millions of desperate patients with the disease and their families. Second, because the drug would be exorbitantly expensive (therapy would be priced at about \$50,000 per year,<sup>1</sup> and that does not include the cost of the serial brain imaging tests, such as magnetic resonance imaging, that patients would need to undergo) 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. Such economic costs would only be justifiable for a drug that has definitive evidence of significant, clinically meaningful benefit. Finally, 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.

The FDA therefore must reject Biogen's BLA for aducanumab and issue a complete response letter requiring another large, premarket, randomized, placebo-controlled clinical trial of aducanumab in patients with Alzheimer's disease as a condition of any subsequent resubmission of this BLA.

Thank you for your attention to these urgent public health issues.

Sincerely,



Michael A. Carome, M.D.  
Director  
Public Citizen's Health Research Group

Enclosure

cc: Alex Azar, Secretary of Health and Human Services

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<sup>1</sup> Belluck P. F.D.A. panel declines to endorse controversial Alzheimer's drug. *The New York Times*. November 6, 2020. <https://www.nytimes.com/2020/11/06/health/aducanumab-alzheimers-drug-fda-panel.html>. Accessed November 30, 2020.