February 11, 2021

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Dear Dr. Carome:

I am writing to acknowledge your letter concerning the Food and Drug Administration's (FDA's or the Agency's) review of Biogen's biologics license application (BLA) for aducanumab, which is intended to treat Alzheimer's disease.

You allege in the letter that interactions and coordination between staff in the Center for Drug Evaluation and Research (CDER) and Biogen prior to and after the submission of Biogen's BLA were inappropriate. You specifically allege that CDER staff improperly collaborated with Biogen in preparing for and conducting the Advisory Committee meeting on November 6, 2020, regarding scientific and clinical issues related to the drug's safety and efficacy. You assert these interactions constituted "unprecedented close collaboration" between CDER and Biogen that "dangerously compromised the independence and objectivity of senior staff and clinical reviewers." You also mention and attach your December 9, 2020, letter to the Office of Inspector General (OIG) at the U.S. Department of Health and Human Services (HHS) requesting an investigation of your allegations.

Based on these allegations, you request that FDA take certain steps for the Biogen BLA review, including assigning further review and decision-making for the aducanumab BLA to CDER staff not previously involved in the Biogen development program. You also request that FDA not approve the BLA based on your assertion that there is not substantial evidence of aducanumab's effectiveness to treat Alzheimer's disease.

FDA takes the allegations in your letter very seriously and will continue to consider the issues you have raised. This letter does not respond to your specific allegations regarding this BLA. If the HHS OIG proceeds with an investigation into this matter, FDA will cooperate fully with that investigation.

In addition to your specific requests regarding the Biogen BLA, you propose that going forward, a firewall should be created between FDA staff involved in any pre-submission interactions with sponsors and FDA staff involved in the post-submission new drug application (NDA) or BLA review and decision-making. I wish to highlight several points regarding this proposal, as I believe adopting the proposal would cause significant negative repercussions for public health.

A key assumption in your letter is that FDA's interactions with sponsors during drug development have the potential to "undermine the integrity of agency reviews"—hence your statement that a firewall is needed, as described above, "[t]o ensure the integrity of [FDA's] reviews and decisions." Your letter overlooks the fact that FDA's interactions with sponsors are critically important to drug development. Drug development is a highly complex process, and FDA's interactions with sponsors are essential to set clear goals and expectations. In an increasingly scientifically complex landscape, the absence of these interactions would dramatically delay the availability of effective drugs for patients who need them. Not only do FDA's interactions with sponsors help ensure that pre-clinical and clinical development programs are appropriately designed to yield the data that would be needed to support an application, but also these interactions reduce the potential for duplicative or otherwise unnecessary testing in humans and animals. For FDA to make its expectations clear, staff involved in the review of applications must have a thorough understanding of the development program, from the pre-clinical phase through the clinical phase. The firewall you propose would significantly reduce the efficiency of FDA's review process and cause delays in drug development.

Nor is a firewall necessary to ensure the integrity of FDA's decision-making. FDA has a long history of conducting its scientific and regulatory processes, including reviews of investigational new drug applications and NDAs/BLAs, with integrity, focusing on public health considerations and ensuring independence and scientific excellence as the cornerstones of its work. As reflected in FDA's Staff Manual Guide 9001.1 (Scientific Integrity at FDA):

> FDA must rely on the best available science to make difficult decisions with respect to those products. In making those decisions, an unbiased presentation and full evaluation and analysis of the data, including its uncertainties, is absolutely critical. Establishing and maintaining integrity of the scientific process and of scientific data is crucial to the agency's ability to arrive at sound decisions and to maintain public trust.[1]

FDA is one of only a few drug regulatory agencies in the world that requires that primary study data be submitted in the drug application. FDA scientists thoroughly, and independently, analyze these data, developing their own interpretations—which at times align with and at other times differ from the sponsor's. These analyses often raise further questions and may lead to requests to the sponsor for further data or specific analyses, intended to ensure that the drug's safety and efficacy is fully evaluated. (Often, the sponsor has information on trial conduct or other key information that can be valuable in the interpretation of results.) Indeed, this iterative and interactive process provides FDA with a complete picture of the proposed drug that is essential for making the best regulatory decisions for patients.

The HHS OIG recognized the long-standing benefit of this interaction in its 2003 report entitled "FDA's Review Process for New Drug Applications."[2] In addition to noting that, in the context of formal meetings with sponsors, "FDA provides valuable advice to sponsors that can help speed up the drug development process," the report noted:

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[1] The guide is available at https://www.fda.gov/media/82932/download.
[2] The report is available at https://oig.hhs.gov/oei/reports/oei-01-01-00590.pdf.

FDA and sponsors also meet and discuss issues relating to the content and format of an NDA immediately prior to and during the review process. The purpose of this collaborative approach is to produce higher quality NDAs and more efficient reviews.

As Congress has recognized, these principles are particularly relevant for a sponsor's development and FDA's review of therapies for diseases such as Alzheimer's, ALS, and some cancers where drug development has not, on its own, advanced sufficiently quickly to meet patient needs. Often, in these situations, FDA employs additional resources to further the development of safe and effective treatments, consistent with the Agency's public health mission, while simultaneously maintaining integrity in its scientific and regulatory processes.

Opportunities for collaboration related to such therapies include the Agency's breakthrough therapy designation and fast-track designation programs, authorized by section 506 of the Federal Food, Drug, and Cosmetic Act. These programs allow sponsors to receive more intensive guidance and increased interactions and communications with FDA for therapies that meet certain conditions. Section 506 specifically contemplates that FDA will increase its interactions with drug developers—such as holding meetings to discuss trial designs, endpoints, and interpretations of earlier phase study results. These interactions are intended to make drug development both more efficient and more effective, and these interactions do not interfere with FDA's independent perspective.

I hope this elaboration of relevant FDA principles and practices has provided helpful information. As I noted, FDA is committed to maintaining scientific integrity, to reviewing results without bias, and to basing its regulatory decisions on the drug trial results and their implications for safety and effectiveness.

Sincerely,

Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs