

June 10, 2024

Robert M. Califf
Commissioner
Food and Drug Administration
Department of Health and Human Services,
Attention: FDA-2013-D-0077
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

SUBMITTED ELECTRONICALLY VIA
<https://www.regulations.gov>

Re: Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease (FDA-2013-D-0077)

Dear Commissioner Califf:

The American Geriatrics Society (AGS) appreciates the opportunity to comment to the Food and Drug Administration (FDA) on the draft guidance for *Early Alzheimer's Disease: Developing Drugs for Treatment - Guidance for Industry*. AGS is a nationwide not-for-profit organization dedicated to improving the health, independence, and quality of life of all older adults. Our 6000+ members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician assistants, pharmacists, internists, and others who are pioneers in advanced-illness care for older individuals, with a focus on championing interprofessional teams, eliciting personal care goals, and treating older people as whole persons. We provide leadership to healthcare professionals, policymakers, and the public by implementing and advocating for programs in clinical care, research, professional and public education, and public policy.

AGS' vision is a nation where we can all have a fair and equitable opportunity to contribute to our communities and maintain our health, safety, and independence as we age. AGS believes in a just society – one where we all are supported by and able to contribute to communities and where ageism, ableism, classism, homophobia, racism, sexism, xenophobia, and other forms of bias and discrimination no longer impact healthcare access, quality, and outcomes for older adults and their caregivers. We believe discriminatory policies—especially when they are perpetuated across the healthspan and lifespan—can have a negative impact on public health for us all as we age.

Geriatricians and other geriatrics health professionals care for older adults—many of whom are living with complicated medical issues and social challenges, including Alzheimer's disease (AD)—and they understand the heavy toll of AD on patients, caregivers, and their families. We are fully supportive of the FDA approving safe and effective new treatments as well as resources and guidance that best address the unique healthcare needs of older adults and reflects what is most appropriate for all of us as we age. In April 2024, we commented to the FDA on the importance of ensuring that clinical trials reflect the

diversity of the population being treated and its role in ensuring that older adults, including those living with multiple chronic conditions, should be represented in clinical trials.¹ We believe that it is important for the FDA to ensure that guidance that is specific to certain disease states reflect and emphasize that FDA is committed to its policies regarding inclusion and protecting the safety of all Americans.

We appreciate that the FDA is providing guidance to industry on enrollment of people who are in the early stages of AD. We are concerned about two specific elements of the draft guidance:

Staging of Alzheimer's Disease

In the draft guidance, FDA is proposing to redefine Alzheimer's disease to add the following stage:

- Stage 1: Patients with characteristic pathophysiological changes of AD but no evidence of clinical impact. These patients are truly asymptomatic with no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures. The characteristic pathophysiological changes are typically demonstrated by assessment of various biomarker measures (*Lines 104-108*).²

In making this proposal, the FDA cites that this new stage relies on consensus diagnostic criteria intended to establish the true biological presence of AD and jettison inclusion of clinical syndromes which have been a cornerstone of someone with AD. The FDA rationale for this proposed staging is that the approach will “avoid enrollment of a substantial number of subjects who would not actually have AD” (*Lines 73-77*) given the presence of biomarkers.

AGS recognizes the benefit of pursuing research on treatments directed at delaying, halting, or reversing the progression of AD before there are overt clinical symptoms (*Line 57*). However, this proposed new stage is predicated on there being large numbers of people who harbor biomarkers and who *will* progress to having the clinical symptoms associated with AD. While we agree that biomarkers are important in the diagnosis of AD, biomarkers alone are not sufficient. For beta amyloid, as an example, there has not been a study of a sufficiently large and representative cohort of asymptomatic people across a wide age range who have undergone positron emission tomography (PET) or lumbar puncture (LP) and then been followed to death. In light of that, it is still unclear how many biomarker-positive

¹ American Geriatrics Society. Letter to FDA on Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products Draft Guidance. Published April 29, 2024. Accessed June 5, 2024. [https://www.americangeriatrics.org/sites/default/files/AGS%20Comment%20on%20FDA%20Draft%20Guidance%20-%20Collection%20of%20Race%20and%20Ethnicity%20Data%20in%20Clinical%20Trials%20and%20Clinical%20Studies%20for%20FDA-Regulated%20Medical%20Products%20Final%20\(4%2029%2024\).pdf](https://www.americangeriatrics.org/sites/default/files/AGS%20Comment%20on%20FDA%20Draft%20Guidance%20-%20Collection%20of%20Race%20and%20Ethnicity%20Data%20in%20Clinical%20Trials%20and%20Clinical%20Studies%20for%20FDA-Regulated%20Medical%20Products%20Final%20(4%2029%2024).pdf)

² Food and Drug Administration. Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry (Draft Guidance). Published March 2024. Accessed June 5, 2024. <https://www.fda.gov/media/110903/download>

individuals will develop cognitive impairment.^{3,4,5,6} Given that biomarker positivity is associated with wide variations in cognitive trajectory, we urge the FDA to develop guidance that is specific as to how best to avoid assigning a clinical diagnosis of AD to biomarker-positive, asymptomatic individuals with normal cognition. Conveying a diagnosis of AD to asymptomatic, biomarker-positive individuals who may never go on to manifest cognitive decline or dementia symptoms may expose them to harms without clear benefit.

This proposed change would likely have significant unintended consequences for study participants, their families, clinicians, and researchers. Specifically, there has been inadequate attention thus far to its potential impact on personal identity or social and financial consequences (e.g., study participants diagnosed as having AD because of biomarker positivity may not have access to insurance, face discrimination by their employers, and be denied access to treatments for other diseases). Further, we know that the relationships between biomarkers, cognitive performance, and prognosis are heterogeneous and that important gaps remain in understanding individual and intersectional effects across different population groups (age, race/ethnicity, socioeconomic, morbidity, and others).

Outcome Measures – The Use of Surrogate Endpoints

FDA cites its accelerated approval of drugs producing a reduction in brain-amyloid burden as a surrogate endpoint that is “reasonably likely to predict clinical benefit” as an example of where such endpoints can form the basis for accelerated approval (*Lines 224-228*). We appreciate that FDA then encourages trialists to include clinical outcome assessments in clinical trials for early AD to assess early clinical changes that may potentially provide support for any changes observed on biomarkers (*Lines 239 – 242*).

AGS is supportive of studies that are of therapeutic interventions that show promise of clinical benefit for serious or life-threatening disease. We disagree, however, that there is sufficient evidence on the safety and efficacy of these agents to warrant approval on an accelerated pathway based on a reduction in beta amyloid as a surrogate indicator.^{7,8} While the currently available monoclonal antibodies directed against amyloid for the treatment of AD (mAbs) have been shown to reduce amyloid beta, the clinical

³ Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. *Alzheimer's Dement.* 2018;14(8):981-988. doi:[10.1016/j.jalz.2018.03.005](https://doi.org/10.1016/j.jalz.2018.03.005)

⁴ Roberts RO, et al. Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. *JAMA Neurol.* 2018;75(8):970-979. doi:[10.1001/jamaneurol.2018.0629](https://doi.org/10.1001/jamaneurol.2018.0629)

⁵ Jansen WJ, et al. Prevalence estimates of amyloid abnormality across the Alzheimer disease clinical spectrum. *JAMA Neurol.* 2022;79(3):228-243. doi:[10.1001/jamaneurol.2021.5216](https://doi.org/10.1001/jamaneurol.2021.5216)

⁶ Erickson P, et al. Prevalence and clinical implications of a β -amyloid–negative, tau-positive cerebrospinal fluid biomarker profile in Alzheimer disease. 2023;80(9):969-979. doi:[10.1001/jamaneurol.2023.2338](https://doi.org/10.1001/jamaneurol.2023.2338)

⁷ American Geriatrics Society. Letter to FDA on Review of Biogen's Drug Aducanumab for Alzheimer's Disease. Published June 2, 2021. Accessed June 5, 2024. https://www.americangeriatrics.org/sites/default/files/inline-files/American%20Geriatrics%20Society_Letter%20to%20FDA%20Biogen%20Drug%20for%20Alzheimer%27s%20%28June%202021%29%20FINAL%20%281%29.pdf

⁸ American Geriatrics Society. Letter to FDA on Review of Eisai's Drug Lecanemab for Alzheimer's Disease. Published December 22, 2022. Accessed June 5, 2024.

https://www.americangeriatrics.org/sites/default/files/inline-files/American%20Geriatrics%20Society_Letter%20to%20FDA%20Lecanemab%2012.22.22.pdf

trials report less decline in other measures (e.g., Clinical Dementia Rating-Sum of Boxes (CDR-SB))^{9,10} and do not meet the requirements for minimal clinically important differences (MCID) compared to placebo.¹¹ Given the reliance on a correlation between reduction in amyloid beta and improvement or stagnation in cognitive and functional decline in the approval for mAbs and the significant adverse events identified in the clinical trials without reports of the association of amyloid-related imaging abnormalities (ARIA) severity and clinical outcomes,¹² AGS is deeply concerned about the FDA signaling that it would potentially rely on a surrogate biomarker when determining whether a treatment should be approved on an accelerated pathway.

Equity Considerations

We are also concerned with FDA's statement (*Lines 135-136*) that "it is expected that biomarker evidence of disease will establish the reliable diagnosis of subjects in trials of early AD" and (*Lines 261-263*) that at Stage 1, "an effect on the characteristic pathophysiological changes of AD as demonstrated by an effect on various biomarkers, may be an appropriate measure." Much remains to be learned about how biomarkers perform as valid and reliable indicators of specific brain pathologies across different clinical populations, including those with various comorbid conditions.¹³ Considering the racial and ethnic disparities in the prevalence of AD and other dementias among the subpopulations and increasing diversity among older people, it is important to determine whether age, gender, and racial and ethnic representation in the data is sufficient to support generalizability.¹⁴ As stated in *Lines 235-237*, "a surrogate endpoint that is determined to be appropriate for use in a particular therapeutic clinical development program should not be assumed to be appropriate for use with a different product or trial population." The existing disparities in access to AD diagnosis and care must not be exacerbated by evidence based on non-representative participant populations. It would be critically important to understand the impact of biomarker-based diagnosis on different populations as well as any potential or unintended harms, including inequities in clinical trial enrollment and diagnosis, particularly for the historically minoritized populations that have been disproportionately affected by AD and disproportionately understudied and underdiagnosed.

In addition to FDA's encouragement for continued research in understanding the role of biomarkers in AD (*Lines 245-247*), we urge an explicit callout on the critical need for diversity and inclusion of underrepresented groups in AD trials and research. More biomarker studies representing diverse study populations would allow testing the validity of the cut-off values of biomarkers across different

⁹ van Dyck CH, et al. Lecanemab in early Alzheimer's disease. *NEJM*. 2023;388(1):9-21.

doi:[10.1056/NEJMoa2212948](https://doi.org/10.1056/NEJMoa2212948)

¹⁰ Institute for Clinical and Economic Review. Aducanumab for Alzheimer's disease: effectiveness and value draft evidence report. Published May 5, 2021. Accessed May 20, 2024. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf

¹¹ Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimer's Dement (N Y)*. 2019;5(1):354-363. doi:[10.1016/j.trci.2019.06.005](https://doi.org/10.1016/j.trci.2019.06.005)

¹² Thambisetty M, Howard R. Conveying risks of harm in Alzheimer disease by amyloid lowering. *JAMA*. Published online May 6, 2024. doi:[10.1001/jama.2024.7548](https://doi.org/10.1001/jama.2024.7548)

¹³ Mielke MM, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405. doi:[10.1038/s41591-022-01822-2](https://doi.org/10.1038/s41591-022-01822-2)

¹⁴ Matthews KA, Xu W, Gaglioti AH, Holt JB, Croft JB, Mack D, McGuire LC. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. *Alzheimer's Dement*. 2018;15(1):17-24. doi:[10.1016/j.jalz.2018.06.3063](https://doi.org/10.1016/j.jalz.2018.06.3063)

populations and age strata, including those with various comorbid conditions. While some of this work is underway with research funding, it is not yet sufficient to support firm conclusions. We also recognize that results of ongoing secondary prevention trials may one day justify interventions for asymptomatic individuals, but for now, this evidence is lacking. Further, there is no adequate observational study evidence base for people who are older, have chronic conditions, or from historically underrepresented groups to know how well these biomarkers reflect true AD pathology.

The rapid evolutions in our knowledge of AD will necessarily (and hopefully) lead to future shifts in clinical practice and revisions to how we diagnose, and label, conditions and pathologies associated with ADRD. While there is growing understanding of the biological mechanisms associated with cognitive disorders including dementias, the current evidence is not sufficient to guide the application of biomarker-based diagnosis of Alzheimer's disease in all populations.

Thank you for taking the time to review our feedback and recommendations. For additional information or if you have any questions, please do not hesitate to contact, Anna Kim at akim@americangeriatrics.org.

Sincerely,



Mark A. Supiano, MD, AGSF
President



Nancy E. Lundebjerg, MPA
Chief Executive Officer