

SINGLE ENDPOINT FOR NEW DRUG APPROVALS FOR ALZHEIMER'S DISEASE

George Vradenburg; Howard Fillit, M.D.; Dave Morgan, Ph.D.; Marwan Sabbagh, M.D., FAAN, CCRI.; Paul Aisen, M.D.; Richard Mohs, Ph.D.¹

Abstract/Summary: The Food and Drug Administration's (FDA) approach to approving new medicines for Alzheimer's disease since the 1990s has been to require a proven benefit on two independent primary endpoints of cognition and function, although this policy has not been formalized in the FDA rules or finalized FDA guidance. We argue that, in light of an improved scientific understanding of the continuous and progressive character of the disease and consistent with many recent oral expressions by agency leadership in public settings, the FDA should clarify for the field that a clinically meaningful benefit on a single primary endpoint of cognition or function is a sufficient basis for a New Drug Application filing. The time has come for the FDA to provide this needed level of clarity. Clinical meaningfulness should be assessed for each drug, weighing any safety risks against efficacy evidence from primary and secondary endpoints, sensitivity analyses, and patient input (the greater the risk, the greater the required benefit). Articulating a modernized standard in light of recent understandings would benefit patients with mild cognitive impairment and both early and mild-to-moderate Alzheimer's disease, provide needed clarity for the field, and thereby stimulate research and development for new Alzheimer's disease therapies.

About ResearchersAgainstAlzheimer's: ResearchersAgainstAlzheimer's (RA2) is a global network of more than 450 Alzheimer's researchers established by UsAgainstAlzheimer's to advocate for research funding and policy reform to stop Alzheimer's disease. The RA2 network believes that an effective treatment for Alzheimer's is within reach if governments, industry, and citizens are willing to commit the resources and institute the necessary policy changes. UsAgainstAlzheimer's and ResearchersAgainstAlzheimer's were co-founded by George Vradenburg. Drs. Fillit, Morgan, Sabbagh, Aisen and Mohs are members of ResearchersAgainstAlzheimer's.

¹ While authors of the analysis are affiliated with ResearchersAgainstAlzheimer's, the viewpoints published in the analysis may not reflect or represent the opinions or positions of all RA2 members.

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In December 2016, FDA Commissioner Dr. Robert Califf was among a group of authors who wrote that health regulatory statutes “evolved to meet the exigencies of particular moments in the history of medical product development” and who also highlighted the need for more modern approaches to lessen “uncertainty surrounding the approval or clearance of new therapies and their subsequent use in practice.”² As a partial response, we now make a constructive appeal to the FDA to modernize and clarify its standards for the approval of new treatments for Alzheimer’s disease – “the only disease among the top 10 causes of death in America that cannot be prevented, cured or even slowed”³ – based on recent learnings in the field.

This need for a modernized standard is particularly important at a time when new therapeutic options for Alzheimer’s disease are desperately needed. Admittedly, the principal obstacle in recent years for the approval of new therapies in Alzheimer’s disease has not been the FDA but rather the absence of effective new drug candidates. Yet the absence of a clear regulatory pathway to market is a factor adversely affecting venture investment in smaller biotech companies looking at possible investment in Alzheimer’s therapies. And with several new prevention and treatment therapies currently entering late-stage trials, following several prominent late-stage disappointments in the last year,⁴ this is an opportune time for the FDA to articulate publicly a clear, reasonable standard for the approval of a new therapy to address Alzheimer’s disease for populations at any and all points across the disease continuum. This is not only a condition with a rapidly-growing population of persons diagnosed with the disease, but also one whose pathogenesis begins up to 20 years before symptomatic presentation.

We argue that a modernized standard for drug approval in Alzheimer’s disease should more closely resemble the standard for drug approval in most other therapeutic areas – in particular, the requirement for a drug sponsor to demonstrate a statistically significant and clinically meaningful improvement on a *single* valid primary outcome measure on matters of importance to those receiving the intervention (*e.g.*, patient memories). As discussed further below, clinical meaningfulness should be assessed for each drug, weighing any safety risks against efficacy evidence from primary and secondary endpoints, sensitivity analyses, and patient input (the greater the risk, the greater the required benefit). This more straightforward requirement stands in sharp contrast to the historic and (in our view) archaic FDA requirement that a drug sponsor in Alzheimer’s disease demonstrate simultaneous clinically meaningful improvements on *two*

² Robert M. Califf, Rachel E. Sherman and Andrew Slavitt, “Knowing When and How to Use Medical Products: A Shared Responsibility for the FDA and CMS,” *JAMA*, 2016;316(23):2485-2486, p. 2485, abstract available at: <http://jamanetwork.com/journals/jama/article-abstract/2580955>

³ *2016 Alzheimer’s Disease Facts and Figures*, Alzheimer’s Association, 2016, http://www.alz.org/documents_custom/2016-facts-and-figures.pdf

⁴ These include phase 3 studies of the investigational drugs solanezumab, idalopirdine, verubecestat, and LTMX.

independent co-primary outcome measures, patient cognition *and* function. Instead, we believe that accelerated approval of a new drug in this area should be based on a single endpoint of cognition or function. This standard would apply across the range of clinical diagnoses, from mild cognitive impairment to early Alzheimer's disease to mild-to-moderate Alzheimer's disease. We thus encourage the FDA to update its guidance to reflect this proposed modernized standard.

To be clear, the historic requirement for co-primary outcome measures is not an official policy codified in statutes, regulations, or formally published guidance. Rather, the notion of requiring two co-primary endpoints is rooted in an informal departmental position articulated by the FDA's Neurologic Products division in the 1990s.⁵ While this informal standard may have seemed necessary during the time of approval of cholinesterase inhibitors⁶ (the first generation of drugs for Alzheimer's disease) targeted at mild to moderate populations, we believe it is now appropriate to revise that standard to a single primary endpoint in light of significant developments in both research and the standard of care of Alzheimer's patients over the last two decades.

A modernized FDA standard is well-justified in light of substantial changes in both the social impact of Alzheimer's disease since the 1990s and the imperative need for higher levels of investment to research new treatments. Since the first generation of drugs for Alzheimer's disease was approved, the burden of Alzheimer's disease on patients, caregivers, physicians and society as a whole has grown immensely and poses an even greater threat to public health in the decades ahead. Already the fifth leading cause of death for Americans above 65, Alzheimer's disease presents a very high burden on public finances and the economy as a whole. Medicare and Medicaid expenses in 2017 related to Alzheimer's disease and dementia are estimated to be \$175 billion; caregivers offered an estimated 18.2 billion hours of unpaid care in 2016, with an estimated value of \$230.1 billion.⁷ Without effective new therapies, the problem will only continue to grow.

Meanwhile, the success rate of drugs tested for Alzheimer's disease has been extraordinarily low when compared with drugs in other therapeutic areas. Of the 244 compounds that were tested in 413 clinical trials between 2002 and 2012, only one resulted in approval of a new chemical

⁵ See Leber P. Guidelines for the clinical evaluation of anti-dementia drugs, 1st draft. Rockville, MD: United States Food and Drug Administration, 1990; see also, Lon Schneider et al., "Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014," *Journal of Internal Medicine*, March 2014, 275(3): 251–283, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3956752/#R14>

⁶ Lon Schneider et al., "Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014," *Journal of Internal Medicine*, March 2014, 275(3): 251–283, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3956752/#R14>: "In 1993 the cholinesterase inhibitor tacrine, branded Cognex®, was the first drug approved 'for the treatment of mild to moderate dementia of the Alzheimer's type'; Cognex® received FDA approval on September 9, 1993, other drugs in this class include Aricept® (approved 1996, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022568s000ltr.pdf), Exelon® (approved 2000, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20823ltr.pdf), and Reminyl® (approved 2001, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2001/21169ltr.pdf).

⁷ 2017 Alzheimer's Disease Facts and Figures, Alzheimer's Association, 2017, https://www.alz.org/documents_custom/2017-facts-and-figures.pdf

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entity, in 2003.⁸ No others have been approved since that time; the failure rate in clinical trials conducted over the last decade exceeds 99.6%. This staggeringly high failure rate has adversely impacted investment in Alzheimer's disease research at precisely the time when new advances are most needed.

Last December, the highly anticipated results of EXPEDITION3 – a phase 3 clinical trial of the anti-amyloid therapy solanezumab in patients with mild Alzheimer's disease conducted by Eli Lilly – dealt yet another major blow to the prospect of approval of a disease-modifying drug.⁹ Lilly announced that solanezumab was well-tolerated but ultimately failed to demonstrate statistically significant improvements over placebo on the primary endpoint of the study, patients' scores at 80 weeks on ADAS-Cog₁₄ (a widely accepted cognitive scale). Solanezumab did show benefit on certain secondary endpoints, but the effect was not regarded by Lilly as clinically meaningful.¹⁰ Consequently, Lilly announced it would not submit a New Drug Application for approval.

For argument's sake, suppose that solanezumab had produced clinically meaningful improvements on its single primary endpoint of cognition, the hallmark feature of Alzheimer's disease and certainly an endpoint of importance to patients. Would the FDA have approved it under those circumstances? Most companies, physicians, researchers, and investors in this field believe that approval would have been likely. Irrespective of the degree of impact on secondary measures, the notion that the FDA would deny approval for a safe and well-tolerated drug candidate that achieves its primary endpoint of improving cognition in patients with Alzheimer's disease is almost unthinkable.

However, the answer is less clear under a straightforward interpretation of the informal approach applied by the FDA since the 1990s.¹¹ Consistent with the FDA's historic requirements, the original design of Lilly's EXPEDITION3 study included co-primary outcome measures of the ADAS-Cog₁₄ and a measure of functional ability known as the ADCS-iADL. However, in March 2016 Lilly made the unilateral decision to drop ADCS-iADL as a co-primary endpoint, pointing to “emerging scientific evidence” that “cognitive decline precedes and predicts functional decline in Alzheimer's disease, particularly in earlier stages of the disease” while at the same time commenting that regulators “will continue to view both cognitive and functional endpoints

⁸ Jeffrey L. Cummings, Travis Morstorf and Kate Zhong, “Alzheimer's disease drug-development pipeline: few candidates, frequent failures,” *Alzheimer's Research & Therapy*, July 2014, 6(4):37, <https://www.ncbi.nlm.nih.gov/pubmed/25024750>: “The Clinicaltrials.gov database demonstrates that relatively few clinical trials are undertaken for AD therapeutics, considering the magnitude of the problem. The success rate for advancing from one phase to another is low, and the number of compounds progressing to regulatory review is among the lowest found in any therapeutic area. The AD drug-development ecosystem requires support.”

⁹ Eli Lilly and Company, “Lilly Announces Top-Line Results of Solanezumab Phase 3 Clinical Trial,” November 2016, <https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871>

¹⁰ Eli Lilly and Company, “Lilly Announces Detailed Results of Solanezumab Phase 3 EXPEDITION3 Study at the Clinical Trials on Alzheimer's Disease (CTAD) 2016 Meeting,” December 2016, <http://www.prnewswire.com/news-releases/lilly-announces-detailed-results-of-solanezumab-phase-3-expedition3-study-at-the-clinical-trials-on-alzheimers-disease-ctad-2016-meeting-300375751.html>

¹¹ Leber P. Guidelines for the clinical evaluation of anti-dementia drugs, 1st draft. Rockville, MD: United States Food and Drug Administration, 1990.

as necessary for clinical trials in people with mild Alzheimer's dementia, and regulatory guidance has been to include these as co-primary endpoints.”¹²

Lilly's public statement suggests that the company believed the FDA would ultimately approve solanezumab if EXPEDITION3 succeeded in achieving a sole primary endpoint, notwithstanding the historic requirement for clinical trials to include two separate co-primary endpoints, either because of the emerging consensus¹³ regarding the predictive relationship between cognitive and functional decline or because cognition itself could serve as a decisive endpoint. Lilly's position could be read as relying on cognition as a standalone endpoint or possibly also as a surrogate for function.

We believe that Lilly was likely correct that the FDA would have approved solanezumab either without condition or for accelerated approval – particularly given the rare event of a compound succeeding in showing efficacy in addressing cognitive decline – but because EXPEDITION3 ultimately failed, we cannot know for sure. Why should trial sponsors be required to engage in regulatory guesswork? Lilly's multiple-theory position demonstrated uncertainty regarding the position of the regulatory agency, regulatory uncertainty that can chill much-needed investment in development of new treatments for Alzheimer's disease, particularly in smaller-capitalized companies and early stage venture investors.

Still, despite the desperate need for new therapeutic options for Alzheimer's disease, it is the FDA's role as a regulator to be cautious. Would a new requirement for only a single primary outcome unduly lower the bar for new drug approvals? The last decade of data suggests that this should not be a concern: of the many drugs that have failed in phase 3 trials for Alzheimer's disease, none has succeeded in demonstrating clinically meaningful, statistically significant benefits on *any* primary outcome measure. The real concern in developing clinical trials and standards for regulatory approval, therefore, should not be that a single primary outcome measure would be too permissive, but rather that the difficulty of demonstrating clinically meaningful and statistically significant benefits on *two* distinct primary endpoints may deter researchers from advancing potentially valuable treatments.

Indeed, in many ways the bar for approval has actually been raised, however unintentionally, over the course of the past two decades, particularly for patients with mild-to-moderate Alzheimer's disease. The first drugs approved for Alzheimer's disease, cholinesterase inhibitors, were compared in clinical trials to true placebo in the 1990s. By contrast, the majority of patients with Alzheimer's disease today take those first-generation drugs and thus experience on average a higher level of cognition and function than earlier patients who were on pure placebo.¹⁴ Long-

¹² Eli Lilly and Company, “Lilly Announces Change to Primary Endpoint of EXPEDITION3 Study,” March 2016, <https://investor.lilly.com/releasedetail.cfm?ReleaseID=960661>

¹³ Laura B. Zahodne et al., “Cognitive Declines Precede and Predict Functional Declines in Aging and Alzheimer's Disease,” *PLOS ONE*, September 2013, <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0073645>; Hong Liu-Seifert et al., “Cognitive Impairment Precedes and Predicts Functional Impairment in Mild Alzheimer's Disease,” *Journal of Alzheimer's Disease*, April 2015, <https://www.ncbi.nlm.nih.gov/pubmed/26402769>

¹⁴ Indeed, in previous clinical trials of cholinesterase inhibitors, cognitive change was quite predictive of later functional and patient-defined treatment outcome; this was particularly true for negative cognitive change early in treatment. Rockwood, Kenneth, et al., “Clinical Meaningfulness of Alzheimer's Disease Assessment Scale:

term care facilities, increased caregiver support, and enhanced access to behavioral health resources have further raised the functional status of Alzheimer's patients for a given stage of the disease relative to two decades ago. Given the growing body of evidence that cognitive decline precedes and predicts functional decline even in the mild-to-moderate stage of the disease,¹⁵ it has become much more difficult for a drug to demonstrate clinically meaningful improvements on a functional endpoint in mild-to-moderate Alzheimer's disease studies. This is particularly true given that over the course of a 6-, 12-, or 18-month clinical trial, a patient's function is heavily influenced by many confounding variables unrelated to the progression of Alzheimer's disease, ranging from falls to comorbidities to changes in caregiving. A modernized standard, therefore, would merely reflect changes in the field and in treatment since the 1990s.

This modernized standard would also flow naturally out of reasoning from the FDA's 2013 draft guidance on drug development for early Alzheimer's disease¹⁶ (before the onset of overt dementia). In this guidance, the FDA noted that "where only subtle cognitive deficits are present in the absence of any detectable functional impairment," a single primary efficacy measure of cognition could be used to support an application for accelerated marketing approval, requiring a post-approval study to demonstrate that the observed benefit persists and positively affects the overall course of a patient's condition.¹⁷ Given that, as discussed above, cognitive impairments are now increasingly understood to precede and predict functional impairment and are themselves a matter of importance to patients, improvements in those impairments should be regarded as a basis for final approval. And that should be the case both in patients with subtle cognitive benefits but also in patients with overt dementia, including those in the mild-to-moderate stage.

Of course, a treatment effect on a single primary outcome measure would still need to be carefully weighed against the safety or tolerability risks posed by a new unapproved chemical entity. We believe strongly that, even under the modernized standard proposed here, the FDA would need to evaluate each drug candidate on a case-by-case basis to ensure that the new drug delivers a clinically meaningful effect that outweighs any potential safety risks that drug poses.

When conducting this analysis of the extent of clinical benefit, the FDA should look at the totality of evidence for each drug, including the magnitude of the observed benefit in cognitive or functional improvement, outcomes on secondary endpoints, sensitivity analyses (such as cumulative distribution analysis), and input from patients. The FDA might also look to any dose-related effects on cognition and sustained cognitive benefit over time. These factors can be assessed holistically and measured against any safety risks posed by a drug (*e.g.*, the greater the safety risk, the higher the bar for magnitude of benefit), rather than looking at any one individual datapoint as a dispositive measure of clinical meaningfulness.

Cognitive Subscale change in relation to goal attainment in patients on cholinesterase inhibitors," *Alzheimer's & Dementia*, March 2017, 1-9, <https://www.ncbi.nlm.nih.gov/pubmed/28341540>

¹⁵ Id.

¹⁶ Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration, "Guidance for Industry: Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease (Draft Guidance)," February 2013, <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338287.pdf>

¹⁷ Id. at p. 4.

For therapies that may be disease modifying, once again, the experience of Lilly with the solanezumab EXPEDITION studies proves helpful in pointing to a future direction. Both the recent course of research in Alzheimer's disease and the EXPEDITION studies support the view that "[e]vidence of disease modification alone might, in part, support the clinical meaningfulness of a treatment. Such evidence could be supported by biomarker changes, a delayed start analysis, or an increasing effect over time during the double-blind portion of the trial."¹⁸

The ultimate perspective on clinical meaningfulness, of course, comes from the patient. A recent article has offered extremely helpful suggestions for revising the common understanding of clinical meaningfulness with respect to Alzheimer's disease in response to "FDA's emphasis on incorporating the patient voice into the determination of clinical meaningfulness."¹⁹ Efforts to identify what matters, what matters most and how much change matters to patients should become a priority for the field, focused on all stages of the disease. The requirements of the recently-passed 21st Century Cures Act²⁰ are instructive in this regard.²¹

The modernized standard proposed in this paper would also support the development of combination and adjunctive therapies. Many drugs in development for Alzheimer's disease have complementary mechanisms of action. Even if each of these might, individually, deliver a modest clinical benefit, when used in combination or adjunctively, the benefit could become more substantial. If the FDA were to reject, individually, several safe and well-tolerated therapies with complementary mechanisms of action that each demonstrate a modest clinical benefit, it would unwittingly deprive patients of potentially substantial advances in the quality of treatment over the long run with a combination of therapies. Most researchers believe the future of Alzheimer's disease treatment lies in combination therapy, and we would encourage the FDA, as part of its reflections on clinical meaningfulness, to articulate an approval standard that encourages, rather than discourages, development of individual agents that might contribute to a safe and effective combination therapy.

Finally, we would note that even if the FDA may be open to approving a safe and well-tolerated drug that demonstrates efficacy on a single primary endpoint of cognition *or* function,²² the agency might naturally wait for such a drug to be presented to the agency before articulating this

¹⁸ Hong Liu-Seifert et al., "Function and clinical meaningfulness of treatments for mild Alzheimer's disease," *Alzheimers Dement (Amst)*, March 2016, p. 105–112, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879645/> (internal footnote omitted).

¹⁹ Michael T. Ropacki et al., "Clinically Meaningful Outcomes in Early Alzheimer Disease: A Consortia-Driven Approach to Identifying What Matters to Patients," *Therapeutic Innovation & Regulatory Science*, January 2017, p. 1-11, <http://journals.sagepub.com/doi/abs/10.1177/2168479016689712>

²⁰ Pub. L. 114-255.

²¹ There is an argument that the practice of classifying endpoints in terms of cognition and function is itself in need of conceptual re-examination. To a patient, a memory loss (cognition) that prevents normal social engagement or reading comprehension (function) could be viewed as either or both a cognitive endpoint or a functional endpoint. Regarding function as meaningful and cognition as not meaningful doesn't make sense from a patient's perspective. From a patient's perspective, the critical inquiry is whether a drug candidate has a truly 'clinically meaningful' impact on an endpoint that matters to him or her, whether classified as cognition or function. A full explication of this argument is beyond the scope of this paper.

²² We recognize that with advances in our understanding of Alzheimer's disease and other dementias, the categories of "cognition" and "function" have become less rigid and more confusing, as it has become increasingly clear that cognition is a surrogate for function, although not a substitute for it.

position. We would strongly disagree with such an approach. If the FDA were to state that meaningful efficacy on a single endpoint is sufficient for approval, we believe that it would impact prospective investments in this therapeutic area as well as clinical trial design, including considerations of power and sample size, and possibly even reducing the costs and burden of trials to some degree.

From our perspective as medical researchers and patient advocates, it is critical that the FDA articulate a modernized standard for drug approval in Alzheimer's disease *sua sponte*. As clinicians, we fear that the failure of drugs like solanezumab in late-stage clinical trials may have a chilling effect on further research in Alzheimer's disease therapies. Even more devastating than the failure of EXPEDITION3 would have been an FDA rejection of solanezumab following a successful phase 3 study achieving its single primary outcome. At present, the uncertainty surrounding approval standards looms large over the field, potentially deterring investment in Alzheimer's drug development in favor of other disease areas where the FDA has articulated with greater clarity the regulatory path to market (i.e., patients) for innovative medicines.

This chilling effect is not just theoretical. A 2016 analysis by several leading Alzheimer's disease researchers found that in 2014-2015, there were 135 ongoing interventional Alzheimer's disease clinical trials as compared to 4976 ongoing interventional oncology trials.²³ We believe a clarified and modernized FDA approval standard for Alzheimer's disease would catalyze renewed investment in the discovery and development of new medical advances for Alzheimer's disease, particularly in early stage companies and for venture investment.

The main obstacle in our field remains elusive: new chemical entities with demonstrated therapeutic benefit in patients suffering from or at risk for Alzheimer's disease. Like all researchers, we are striving actively to discover and develop these compounds. In the meantime, we appeal to regulators to do their part in heralding this much-needed breakthrough by modernizing standards for primary outcomes in Alzheimer's clinical trials, and by so doing, providing greater clarity for measures of success to the field.

²³ Jeffrey Cummings et al., "Alzheimer's Drug Development Pipeline: 2016," *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 2016, p. 222-232, [http://www.trci.alzdem.com/article/S2352-8737\(16\)30019-1/pdf](http://www.trci.alzdem.com/article/S2352-8737(16)30019-1/pdf)