In reviewing new-drug applications for the treatment of Alzheimer’s disease, the Food and Drug Administration (FDA) has maintained that claims of improved cognition should be accompanied by evidence of improvement in function. However, the premise that effective cognitive improvement will be manifested in the functional assessment of patients is untenable in the case of early-stage Alzheimer’s disease, which is increasingly the target of drug-development efforts. We simply do not yet have drug-development tools that are validated to provide measures of function in patients with Alzheimer’s disease before the onset of overt dementia. Improvement in function, moreover, could lag substantially behind cognitive improvement mediated by pharmacologic agents early in the course of the disease. In view of the devastating effects of this disease on patients and their families, along with its growing prevalence, innovative approaches to trial design and end-point selection are urgently needed, especially as the drug-development community turns its sights on early stages of the disease.

The current landscape of research and drug development in Alzheimer’s disease offers a study in contrasts. On the positive side, numerous discoveries over the past decade have begun to unmask complex pathophysiological processes that underlie disease progression. Such advances have, in part, resulted from large, well-organized observational studies, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI), that have elucidated various disease biomarkers that reflect, or even predict, the progression of disease. On the negative side, drug discovery has been disappointing. Despite all best efforts to translate mechanistic insights concerning Alzheimer’s disease into new drug products, several candidate agents have failed to demonstrate efficacy in large, well-designed, phase 3 clinical trials of late-stage disease.

The hallmark pathological feature of Alzheimer’s disease is the presence of brain plaques, consisting primarily of β-amyloid peptide aggregates. Accordingly, the abnormal production and aggregation of β-amyloid peptide, associated particularly with late-stage disease, has been the principal target of many drug-development efforts, including the recent phase 3 efforts that failed to result in new drug products. To account for these disappointing results of trials involving patients with overt
dementia, a leading theory posits that the attempts at intervention may have been made too late in the progression of disease, at a stage when neuronal damage had become too widespread. According to some models, levels of β-amyloid peptide in the brain reach a plateau before the earliest symptoms of Alzheimer’s disease are apparent. A further hurdle to interpreting clinical failures is our limited understanding of how β-amyloid production may contribute to the pathophysiology of the disease. Because the biologic role of β-amyloid peptides is uncertain, researchers are also investigating alternative targets of intervention at various stages of progression.

The focus of drug development in Alzheimer’s disease has increasingly been earlier disease stages, before overt dementia. This refinement of focus, however, raises important new challenges because the subtleties of cognitive impairment in patients with early-stage Alzheimer’s can be difficult to assess. Moreover, the range of focus must extend to healthy people who are merely at risk for the disease but could benefit from preventive therapies. In recognition of these shifting challenges, the FDA has developed guidance for the design and execution of clinical trials involving patients who do not present with dementia.

One aspect of the FDA guidance covers the selection of patients for trials in early-stage Alzheimer’s disease. In particular, we have acknowledged the consensus emerging within the Alzheimer’s research community that clinical diagnosis of early cognitive impairment might be paired productively with appropriate biomarkers of disease — criteria that have been delineated and are being validated by various working groups. Such biomarkers might include brain amyloid load (e.g., as measured by positron-emission tomography) and cerebrospinal fluid levels of β-amyloid and tau proteins. Ongoing efforts by the research community to qualify biomarkers in clinical trial designs and methods for enriching study populations with patients with early-stage Alzheimer’s disease reflect important FDA priorities.

A specific suggestion that is also offered in the agency’s guidance for trials focusing on patients in whom overt dementia seems imminent is the use of a single scale that combines assessment of both cognition and function, such as the score on the Clinical Dementia Rating Sum of Boxes (CDR-SB), which rates patients on a series of six domains covering various aspects of cognition and daily functioning. For patients whose disease is at an even earlier clinical stage, so that functional impairment would be more difficult to assess, it might be feasible to approve a drug through the FDA’s accelerated approval pathway on the basis of assessment of cognitive outcome alone. The accelerated-approval mechanism allows drugs that address an unmet medical need to be approved on the basis of a surrogate end point or an intermediate clinical end point (e.g., a sensitive cognitive measure), with the stipulation that postapproval studies will be conducted to verify the clinical benefit. Such a regulatory process may hold promise for facilitating the approval of treatments that appear to be effective in early Alzheimer’s disease, when patients might be expected to derive the greatest benefit (see figure).

Despite our growing understanding of the relationship between various disease-based biomarkers and the clinical course of Alzheimer’s disease, it remains unclear whether the effect of a drug on one or more such biomarkers can actually predict a meaningful clinical benefit. This concern was reinforced by the recent phase 3 trials of amyloid-lowering agents that failed to improve cognition despite appearing to interact with putative targets in the brain. It remains possible that an effect of an intervention on one or more biomarkers could someday be accepted as predictive of a clinical benefit, but further research will clearly be needed before the effect of an intervention on a single biomarker alone could be considered an adequate surrogate measure for the purposes of accelerated approval of a
As the focus of drug development has shifted to earlier stages of Alzheimer's disease, many new and challenging scientific questions have emerged, and the regulatory framework under which such therapies are evaluated should evolve accordingly. The FDA remains committed to innovative approaches to the evaluation of drugs that are in clinical development. Effective treatments for the devastating disorder that is Alzheimer's disease are urgently needed, as the world's population continues to age.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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