U.S. FOOD & DRUG ADMINISTRATION

Therapies in Alzheimer's Disease – The Approval Process and Implementing Scientific Discoveries and Advances into Patient Health

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Approval pathways

- Traditional Approval
  - Substantial evidence of effectiveness demonstrated on a clinically meaningful endpoint (e.g., how a patient feels, functions, or survives) or validated surrogate
  - Drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling

Approval pathways

- Accelerated Approval
  - May be considered for serious or life-threatening diseases with an unmet need
  - Substantial evidence of effectiveness demonstrated on an endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict that clinical benefit (e.g., surrogate or intermediate clinical endpoint)
  - Subsequent confirmation of clinical benefit is required
  - AA accepts some uncertainty with the use of a "reasonably likely" surrogate endpoint; however, substantial evidence of effectiveness for the surrogate or intermediate endpoint is required with a determination of adequate safety

Surrogate Endpoints

- An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives.
  - ***Validated surrogate endpoint*** **-** An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a clinical benefit. Therefore, it can be used to support traditional approval without the need for additional efficacy information. (e.g., blood pressure, HgbA1C)
  - ***Reasonably likely surrogate endpoint*** **-** An endpoint supported by clear mechanistic and/or epidemiologic rationale but insufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints can be used for accelerated approval for drugs or expedited access for medical devices.

Source: BEST (Biomarkers, Endpoints, and other Tools) Resource

Regulatory standards for effectiveness

- *Substantial evidence of effectiveness* is the legal standard to establish the effectiveness of a drug for approval
- Refers to both quantity and quality of the data
- *Substantial evidence* is defined in section 505(d) of the Food, Drug and Cosmetic Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Regulatory standards for effectiveness

- Substantial evidence of effectiveness has generally been interpreted as at least two adequate and well-controlled (AWC) studies, each convincing on its own, to establish effectiveness
  - Reflects the need for independent substantiation of experimental results protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective
- However, the Agency may also consider a single AWC study with clinically meaningful, statistically robust and very persuasive effects
- Under certain circumstances, FDA can also conclude that one AWC study plus confirmatory evidence is sufficient to establish effectiveness

Regulatory Flexibility

Substantial evidence of effectiveness is required for all diseases; however, our regulations allow for the application of regulatory flexibility in life-threatening and severely-debilitating illnesses with unmet need

- "recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated."

  21 CFR 312.80 Subpart E Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

- "…in certain settings, a somewhat greater risk (…) of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy, (…) for an unmet medical need."

  2019 FDA Draft Guidance, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products"

Unmet Medical Need in AD

- A serious and disabling disease with substantial unmet need
- A condition whose treatment is not addressed adequately by available therapy
  - Although there are approved therapies, AD remains a progressive disease
- FDA recognizes the urgent need for safe and effective therapies for AD

Aducanumab

- Approved via the accelerated approval pathway on June 7, 2021, based on reduction of amyloid beta plaques on amyloid PET imaging
- Clinical trial to confirm clinical benefit has been initiated

Lecanemab

- Approved via the accelerated approval pathway on January 6, 2023, based on reduction of amyloid beta plaques on amyloid PET imaging
- Phase 3 trial to verify clinical benefit is completed and has been submitted to the Agency for review
  - Advisory committee is scheduled for June 9, 2023 to discuss the ability of the study results to verify clinical benefit

https://www.federalregister.gov/d/2023-07526

Incorporating Scientific Advances into Regulatory Review

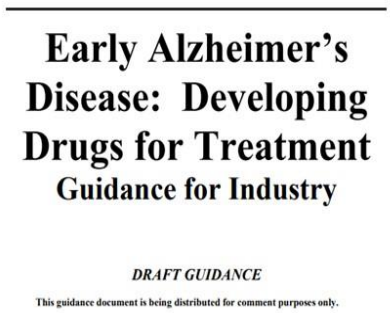
- Engagement with stakeholders
  - Scientific meetings
  - Working Groups
  - Public-Private Partnerships
  - Research Roundtables
  - Patient-focused drug development meetings
- Precompetitive Initiatives
  - Data sharing initiatives
  - Clinical trial simulation tools

Leveraging Ongoing FDA Regulatory Science Efforts

- Complex Innovative Trial Design Meeting Program
- Critical Path Innovation Meetings (CPIM)
- Fit-for-Purpose Initiative
- Model-Informed Drug Development Program
- Real World Evidence Program

Implementation of Scientific Advances into Regulatory Review

- Formal advice meetings with sponsors during development
- Review of submissions to INDs (e.g., protocols, statistical analysis plans)
- Review of NDAs/BLAs
- Qualification of biomarkers and clinical outcome assessments
- Published Guidances


Early Alzheimer's Disease: Developing Drugs for Treatment
Guidance for Industry

DRAFT GUIDANCE

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