FDA Webinar
Early Alzheimer's Disease
Draft Guidance

March 28, 2013

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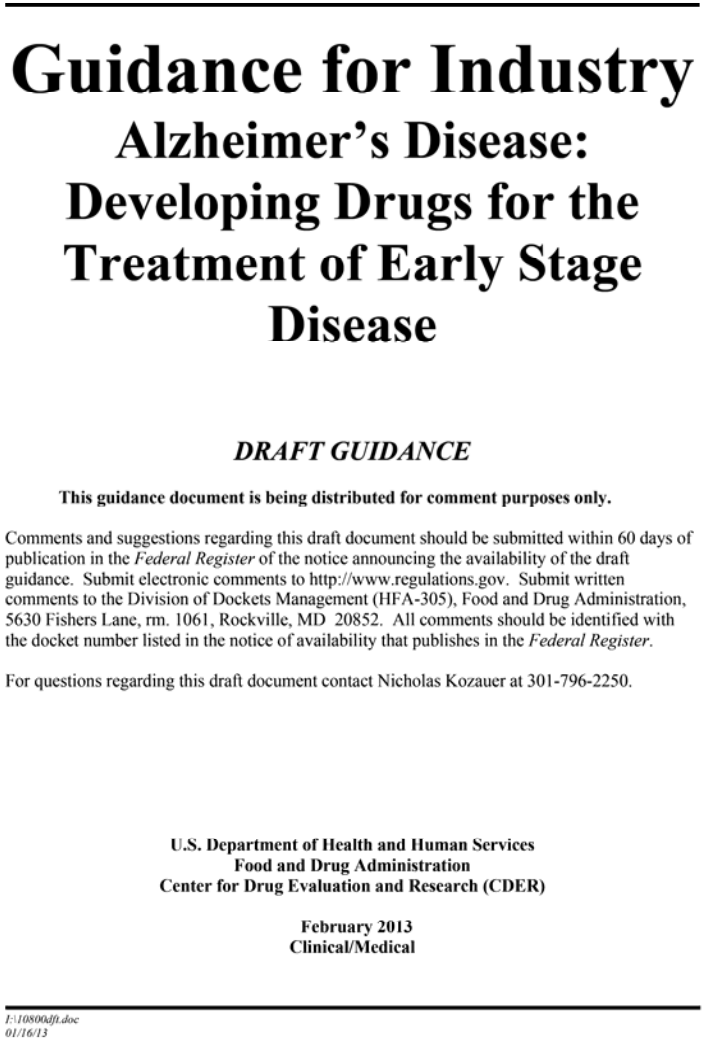
Center for Drug Evaluation and Research (CDER)

Outline

- Background
- Diagnostic Criteria
- Clinical Endpoints
- Biomarkers/Disease Modification
- Summary



Guidance for Industry

Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Nicholas Kozauer at 301-796-2250.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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- Released – February 7th
- Comments until – April 9th

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AD Progression Model

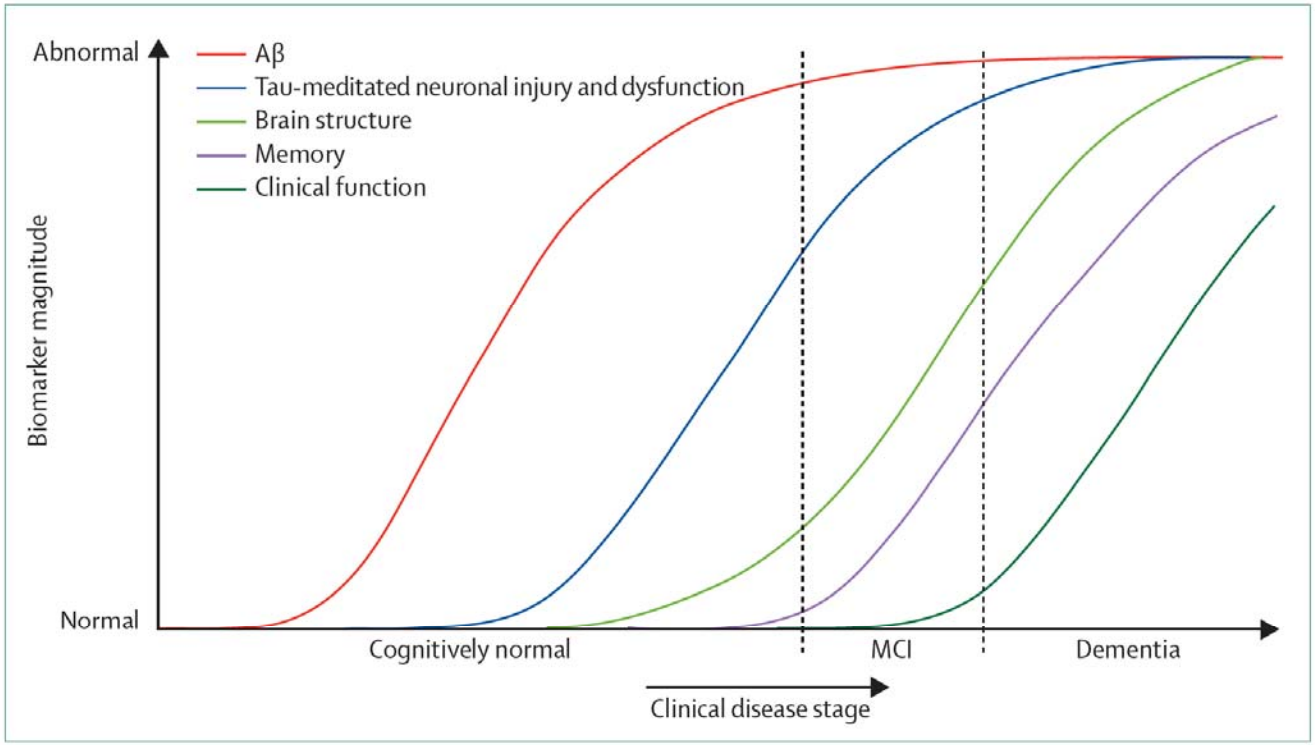

Figure 2: **Dynamic biomarkers of the Alzheimer's pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

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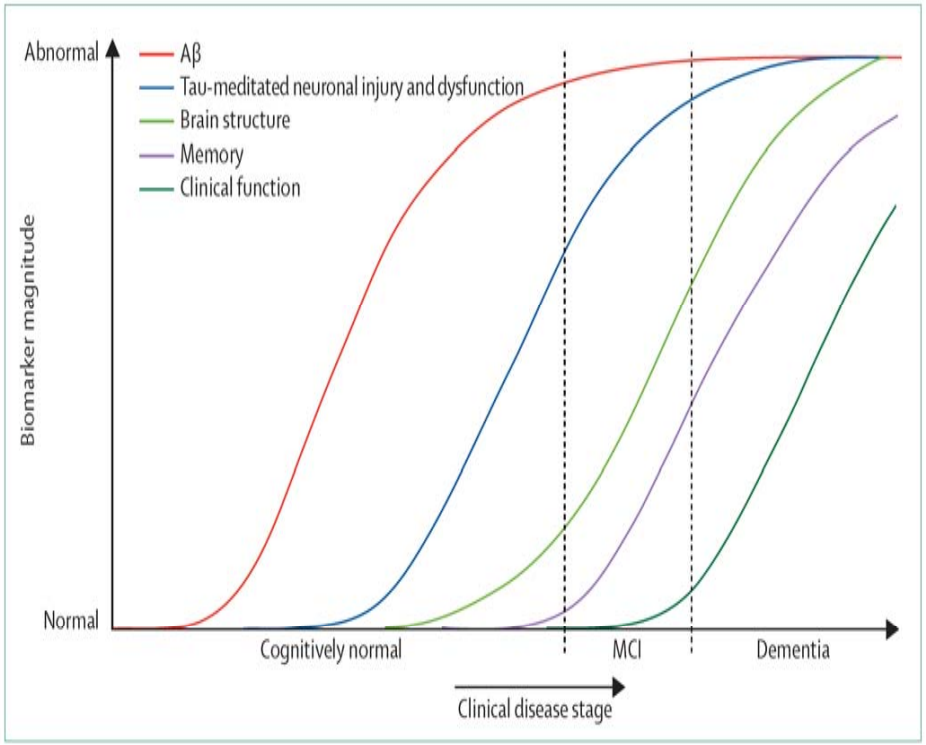

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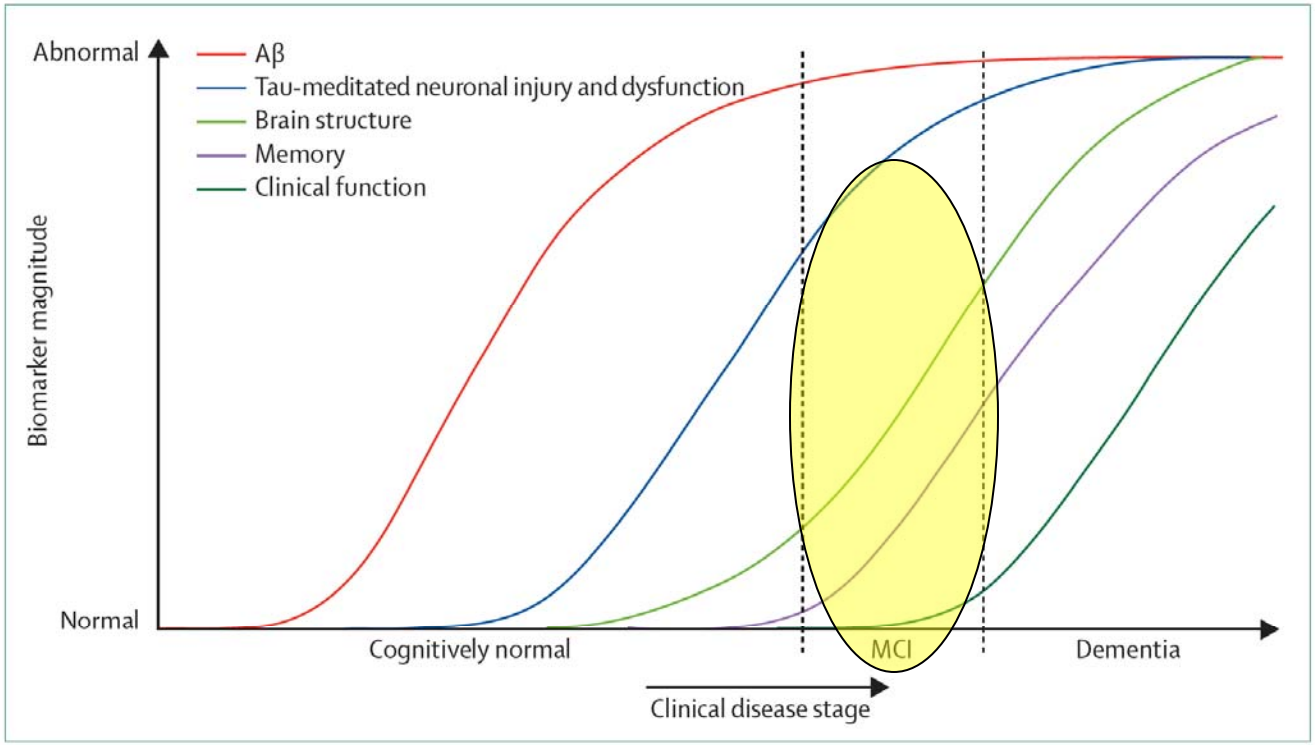
- AD Dementia trials disappointing
- Move to Early AD trials
- Novel regulatory framework required

AD Progression Model



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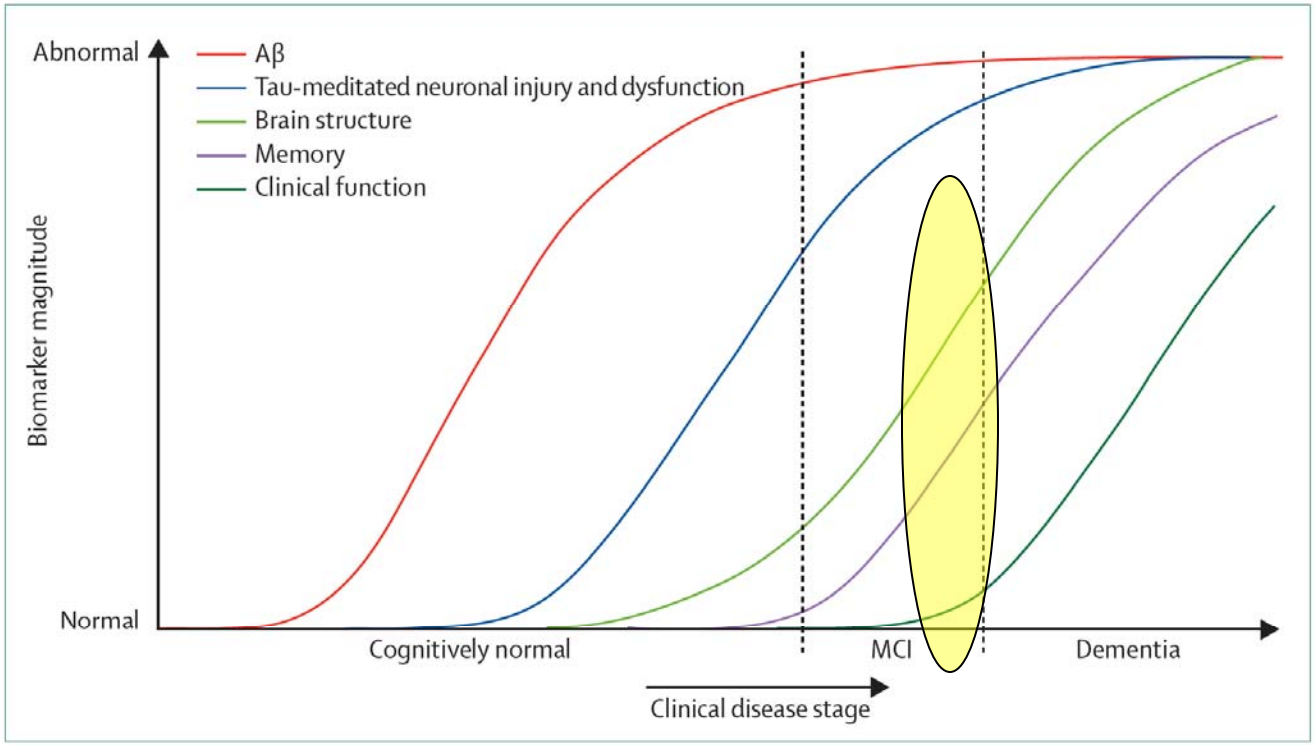

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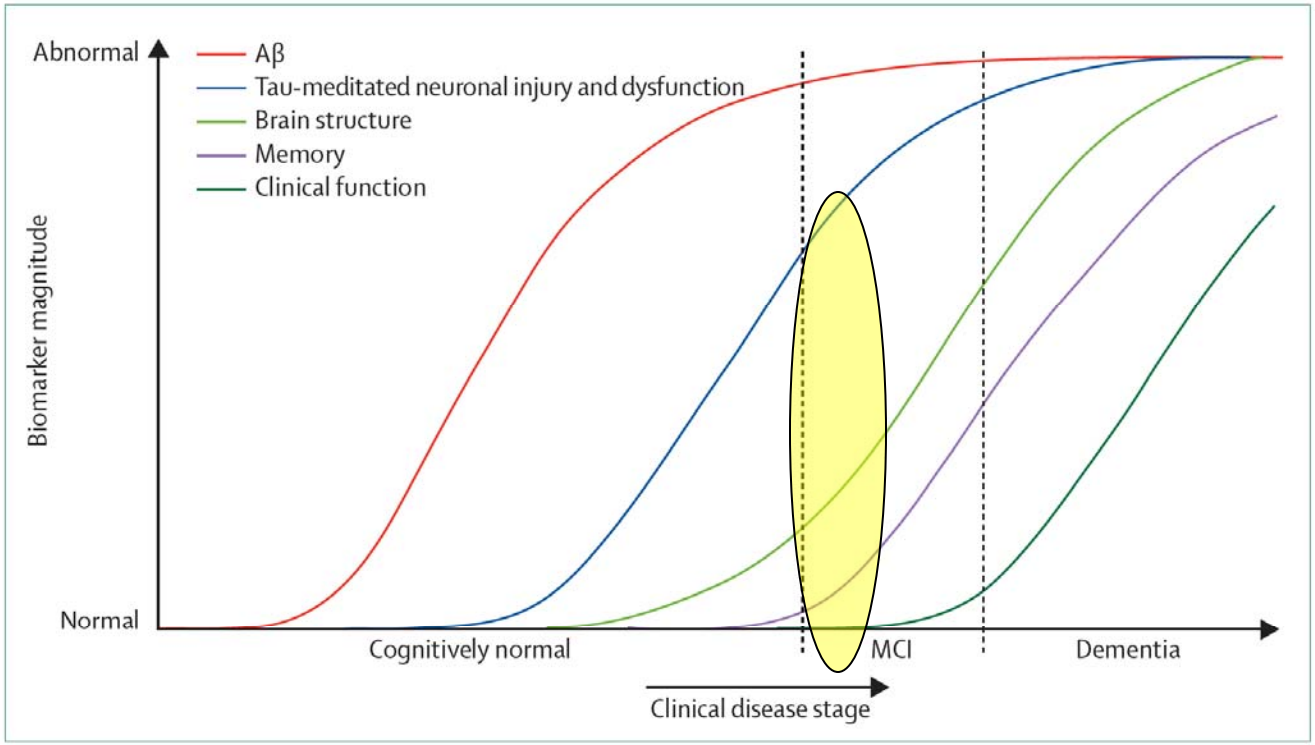

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Goals

- Provide a framework for how drugs might be studied in Early AD trials

- Focus for continued discussion

Early AD Diagnosis

- Criteria under development:
  - National Institute on Aging – Alzheimer's Association (NIA-AA)
  - International Working Group for New Research Criteria for the Diagnosis of AD
- Combine clinical/biomarker findings
  - Amyloid – PET
  - CSF levels of amyloid and/or tau
  - Brain volume (vMRI)

Early AD Diagnosis

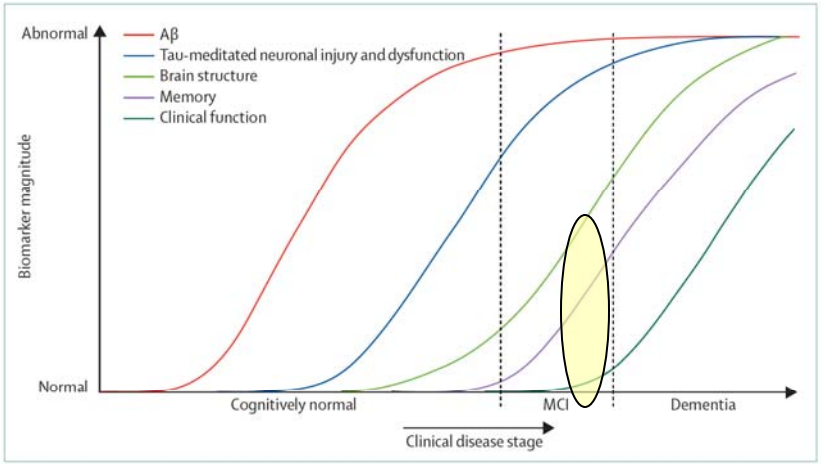
- Guidance position:
  - Support trial enrichment
  - Respective criteria yet to be validated, Agency unable to formally endorse
- Critical point is that correct patients are identified

Clinical Endpoints

- Dementia Trials
  - Co-primary outcome measures
    - Cognition
    - Function or Global Rating
- Early AD Trials
  - Co-primary approach impractical
  - Should still apply in principle

Clinical Endpoints

- Closer to dementia
  - Detectable functional impairment
  - No well-validated functional scales



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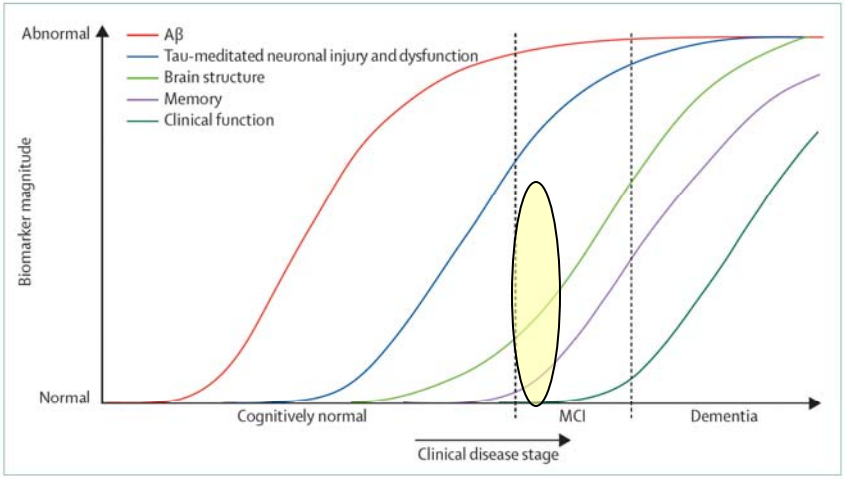
Clinical Endpoints

- Single primary outcome measure
  - Assesses both cognition and function
  - *Example:* Clinical Dementia Rating – Sum of Boxes (CDR-SB)
  - Open to other such scales

Clinical Endpoints

- Earliest Symptoms
  - Subtle cognitive deficits
  - No detectable functional impairment



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Clinical Endpoints

- Most to gain (potentially)
- Isolated cognitive measure
  - Several scales under development
  - Small effect sizes
  - Hard to interpret clinical meaningfulness

Clinical Endpoints

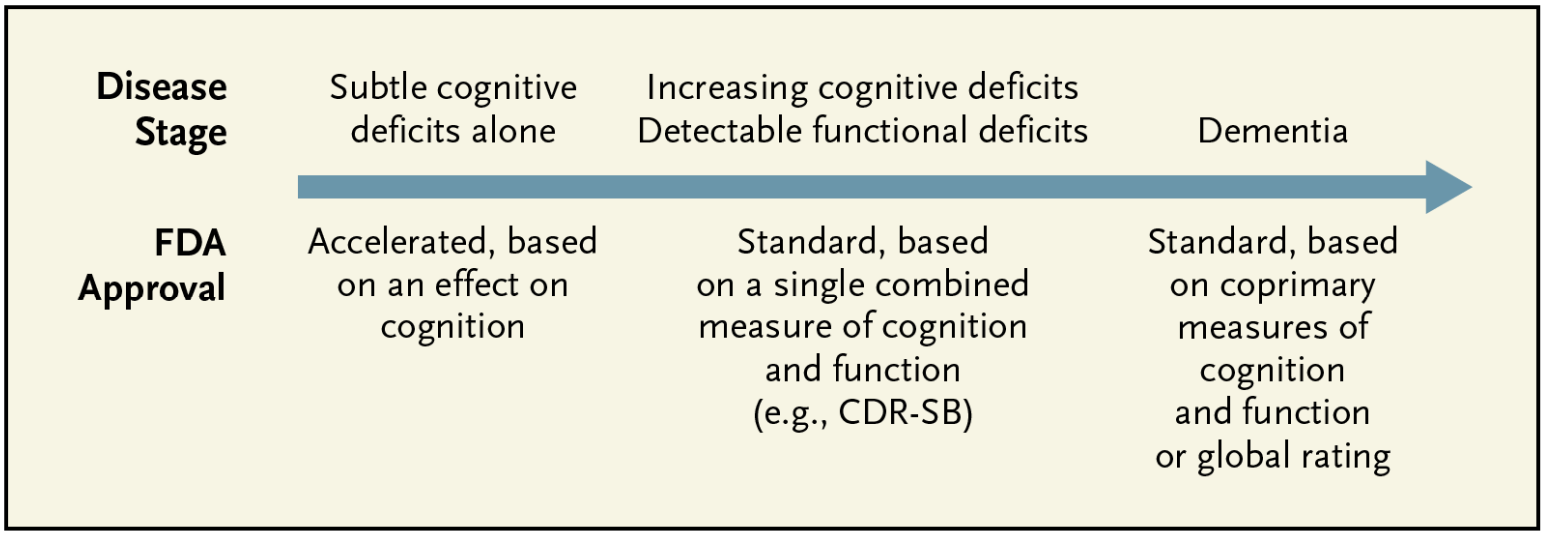
- Accelerated Approval (21 CFR 314.510)
  - Associated with an effect on a surrogate endpoint (*e.g.* viral load in HIV)
  - Effect on an intermediate clinical endpoint that is reasonably likely to predict ultimate clinical benefit (*i.e.,* irreversible morbidity)
  - Requires further post-marketing evaluation to ensure the ultimate relationship to the ultimate clinical outcome

Clinical Endpoints

- Requires accurate identification of patients

- State of the science will be critical
  - *e.g.*, Alzheimer's Disease Neuroimaging Initiative (ADNI)

Clinical Endpoints



Potential Regulatory Pathways in Early Alzheimer's Disease.

Biomarkers/Disease Modification

- Relates primarily to product labeling
- Desirable claim
- Divergence of slopes is problematic

Biomarkers/Disease Modification

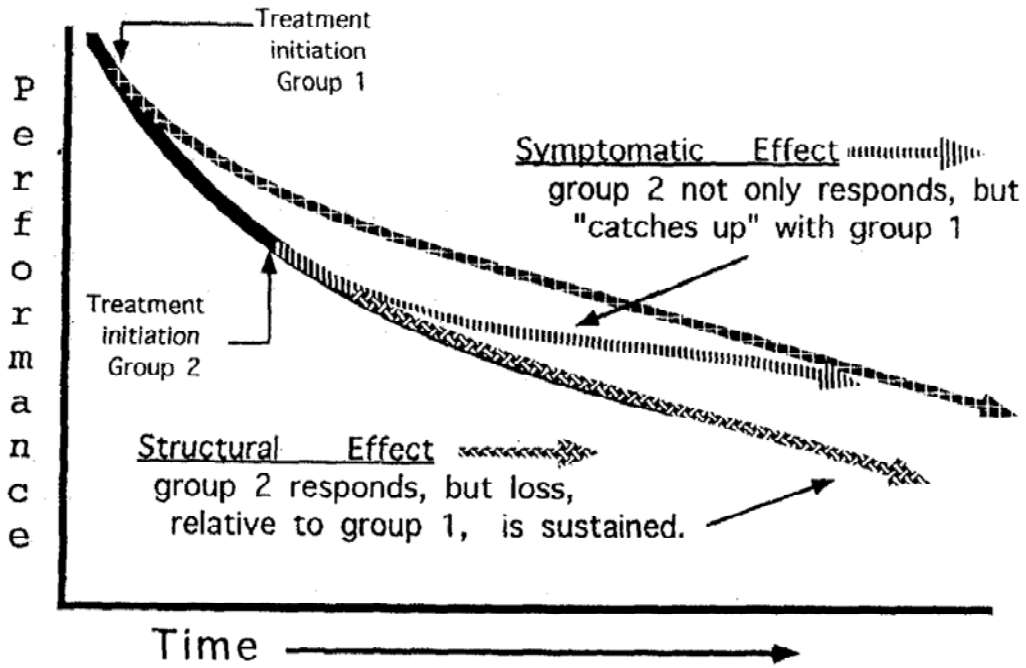
- Correlation between AD biomarkers and clinical effect quite unclear
- Insufficient as single primary outcome measures (*i.e., surrogates for Accelerated Approval)*

Biomarkers/Disease Modification

- Potentially supportive of a disease modification claim
  - Combined with clinical endpoint
- Requires widespread evidence-based agreement

Alternative Trial Designs

RANDOMIZED START DESIGN (Leber, 1997)



Summary

- AD is devastating and elusive
- Field moving to earlier trials
- Novel regulatory challenges
- Draft Guidance attempts to suggest pathways forward