Regulatory Challenges Across Dementia Subtypes

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• The content of this talk is my own and is not intended to reflect the official position of the FDA

• All information discussed is publicly available
Outline

• Draft Early AD Guidance
• Population definitions
• Endpoints
  – Clinical
    • Dementia, prodromal, “at risk” populations
  – Biomarkers/Disease modification
Dementia Subtypes

Common Types of Dementia

- Alzheimer's Disease
- Vascular Symptoms
- Huntington's Disease
- Normal Pressure Hydrocephalus
- Creutzfeldt-Jakob Disease
- Mixed Dementia
- Frontotemporal Lobar Degeneration
- FTD Behavioral Variant
- Primary Progressive Aphasia
- FTD Movement Disorders

Symptoms:
- Memory
- Disorientation
- Behavior Changes
- Difficulty Speaking
- Urinary Incontinence
- Memory Loss
- Agitation
- Severe Decline
- Involuntary Movements
- Depression
- Walking Difficulties
- Memory Problems
- Impaired Judgment
- Severe Memory Problems

Information Sources:
- www.alz.org
- Alzheimer's Association
- US National Institutes of Health (NIH)
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DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance.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.

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Clinical/Medical
**Figure 2: Dynamic biomarkers of the Alzheimer’s pathological cascade**

Aβ is identified by CSF Aβ$_{42}$ 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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Defining Populations

• AD diagnostic criteria
  – NIA-AA/IWG guidelines
  – Core clinical diagnosis + biomarker(s)

• Similar trends in other dementias
  – Biomarkers ↑ focus of attention
  – DLB: low dopamine transporter uptake (suggestive)
Defining Populations

• FDA does not need to endorse a specific set of diagnostic criteria for a given dementia type

• We will rely on evolving evidence-based guidance from the research community
Defining Populations

• Are mechanism claims possible? E.g. a tauopathy indication?
  – Challenging pathway
  – Key will be the scientific basis for such a claim
Clinical Endpoints

• Dementia Trials
  – Co-primary outcome measures
    • Cognition
    • Function or Global Rating

• Early Disease Trials
  – Co-primary approach more challenging
  – Should still apply in principle
Clinical Endpoints

- Closer to dementia

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Clinical Endpoints

• Generally accepted that these patients have some functional deficits

• FDA mandate: Approve drugs that affect how a patient feels, functions, or survives

• No well-established functional measures in pre-dementia patients
Clinical Endpoints

• CDR - sum of boxes
  – Proposed to us as an appropriate single endpoint
  – Appeal is function captured in cognition
  – Named as an example in the draft guidance
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)
Biomarkers

• Insufficient as the sole basis for an approval (i.e., surrogate endpoint)

• Could support a claim of disease modification
  – Alternative trial designs are also potentially appropriate