NAPA Scientific Advisory Council
FDA Update

February 3, 2014

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U.S. Food and Drug Administration
Protecting and Promoting Public Health
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Introduction

- **Commitment to AD Drug Development**
  - Drug Development Tool Qualification
  - Expedited regulatory mechanisms
  - External engagement
- **Draft Guidance: *Developing Drugs for Early AD***
  - Response to paradigm shift in AD drug development (uncharted territory)
  - Published February 2013

Introduction

- **Drug Development Tool (DDT) - Qualification Process**
  - Development of publically available drug development tools that can be widely employed
    - Biomarkers, clinical outcome assessments (COAs), and animal models
  - Facilitate work in the pre-competitive space
  - Several submissions by the Coalition Against Major Diseases (CAMD) are ongoing
    - Biomarkers
    - Prodromal AD clinical assessment scale

Introduction

- **Endorsed AD Clinical Trial Simulation Tool**

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

FOR IMMEDIATE RELEASE

Contact:
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U.S. Food and Drug Administration and European Medicines Agency Reach Landmark Decisions on Critical Path Institute's Clinical Trial Simulation Tool for Alzheimer's Disease

Tucson, Arizona, July 10, 2013 –

In a big step forward for Alzheimer's disease (AD) therapy development, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have independently reached favorable decisions on the value of Critical Path Institute's new disease simulation tool

Introduction

- **Expedited Regulatory Mechanisms for Serious Diseases**
  - **Fast Track Designation**
    - Frequent interactions with FDA
  - **Breakthrough Therapy Designation**
    - New with FDASIA (2012)
    - Fast Track plus…
  - **Accelerated Approval**
    - Surrogate endpoint or intermediate clinical endpoint
    - FDASIA clarified (very relevant to AD Guidance)

Introduction

- **External engagement**
  - **Meetings/conferences**
    - Industry
    - Academia
    - Advocacy Groups
  - **Public/private partnerships**
    - Coalition Against Major Diseases (CAMD)
    - Accelerating Medicines Partnership (AMP)

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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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AD Progression Model

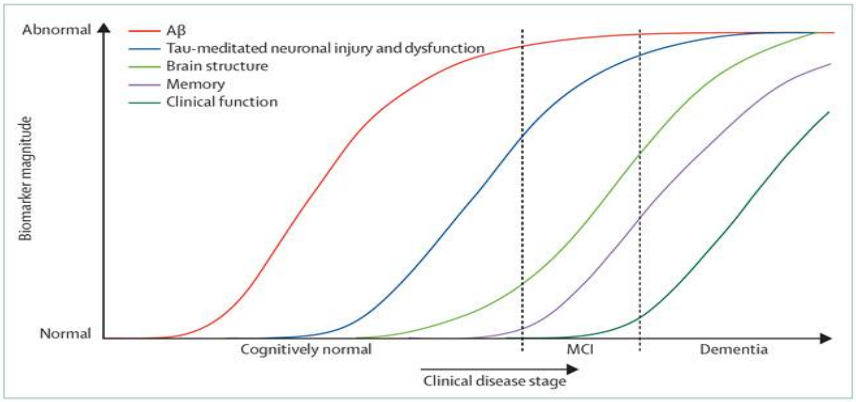
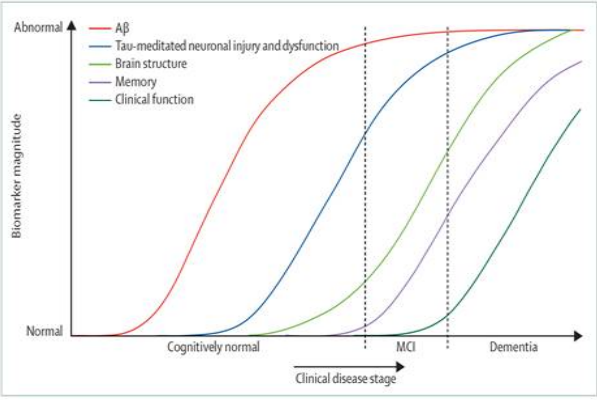


Figure 2: **Dynamic biomarkers of the Alzheimer's pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild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

AD Progression Model



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

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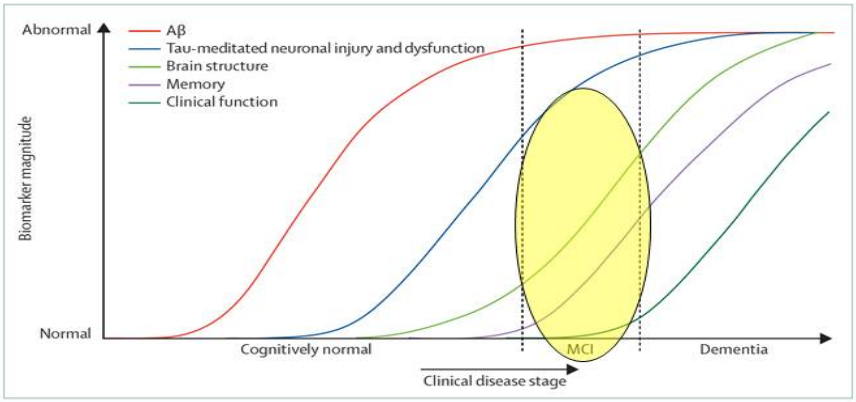

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Draft Guidance: Early AD

- Early AD defined as symptomatic but pre-dementia

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Early AD Diagnosis

- **Diagnostic 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)
- **Guidance supports enrichment**

Clinical Endpoints

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

Clinical Endpoints

- **Closest to overt dementia**
  - Some detectable functional impairment
  - Single endpoint that integrates cognition/function (e.g., Clinical Dementia Rating – Sum of Boxes)
- **Earliest symptoms**
  - No detectable functional impairment
  - Most to gain (potentially)
  - Isolated cognitive measure

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

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Clinical Endpoints

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

Surrogate Biomarkers

- Data do not yet support use of a biomarker as a single primary outcome measures
- Potentially support a disease modification claim along with a clinical endpoint

Summary

- AD drug development has proven extremely challenging
- FDA is committed to AD on several fronts
- Field is moving to early-stage trials that pose novel regulatory challenges
- Draft Guidance attempts to suggest pathways forward