CAMD FDA Qualification Update

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MAJOR GOAL
Accelerate the Drug Discovery Path to Advance Effective Treatments for Alzheimer’s and Parkinson’s Disease

- Advance drug development – “Tools”
  - Develop common data standards
  - Create public databases of pooled clinical trial data
  - Qualify biomarkers (FDA Draft Guidance 2010)
  - Develop “Accepted for use” quantitative disease models
Nonmember participants: Academic, key opinion leaders, CROs
Multidisciplinary Global Initiatives for AD CSF Biomarkers

Kang, Vanderstichele, Trojanowski, Shaw
Methods 56 (2012) 484–493
Why Qualify a Biomarker?

**Historic route for regulatory acceptance of biomarkers poses challenges**

- Case by case. Context of use is always drug dependent
  - Original individual drug submissions (NDA)
  - Labeling updates

- Accepted over time

- Co-development of Drug and Test

**Qualification:** A regulatory conclusion that, within a specific context of use, the results of biomarker assessments can be relied on to have a specific interpretation and application in drug development.
FDA Biomarker Qualification Process

Link to website on FDA
AD Biomarkers for Patient Enrichment

**SLIDE 3**

*Conceptual Model Depicting the Approach to Earlier Alzheimer’s Disease Diagnosis*

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Biomarkers</th>
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<tr>
<td>Episodic memory</td>
<td>ApoE4 status</td>
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<tr>
<td>Vascular risk factors</td>
<td>Structural imaging</td>
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<tr>
<td>Depression</td>
<td>CSF Aβ/tau/phosphotau</td>
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<td>Functional imaging</td>
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MCI=mild cognitive impairment; AD=Alzheimer’s disease; ApoE4=apolipoprotein E4; CSF=cerebrospinal fluid; Aβ=amyloid β.

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**Baseline hippocampal volume**

*Jack et al, Brain 33:3336-48, 2010*

**CSF biomarkers**

*Feldman, CNS Spectr. 2008;13(3 Suppl 3):4-7*

*Hansson et al., Lancet Neurol 5(3):228, 2006*
AD CSF Biomarker Team Members

Alliance for Aging Research—Daniel P. Perry, Cynthia Bens
Alzheimer’s Association—William Thies, Maria Carrillo, Dean Hartley
A.J. Simon Enterprises—Adam J. Simon
ADx NeuroSciences—Hugo Vanderstichele
AstraZeneca—Pat Patterson, Chi Ming Lee
Bristol-Myers Squibb—Holly Soares, Thomas Kelleher, Robert Berman, Sue Behling, Leah Burns, Howard Feldman*, Leah Burns
Critical Path Institute—Lynn Hudson, Diane Stephenson, Steven Angersbach, Martha Brumfield, Chris Davidson, Robin Shane, Elizabeth Walker, Steve Broadbent, Klaus Romero
Eli Lilly & Company—Robert Dean, Janice Hitchcock, Peng Yu, Richard Mohs
FDA—Marc Walton
Johnson & Johnson—Gary Romano, Allitia DiBernardo, Jerry Novak
Novartis—Richard Meibach
University of California, UC Davis—Laurel Beckett, Huanli Wang
University of Gothenburg—Kaj Blennow
University of Pennsylvania—Leslie M. Shaw
Washington University—David Holtzman, Anne Fagan, John Morris
NextGen Sciences—Andreas Jeromin
BARC Laboratories—Theresa Heath

* presently at UBC
Key Topics Discussed with the FDA: AD CSF Biomarker Team

**Selection of Patient Population**
Define level of cognitive impairment and how this relates to the biomarker concentrations.

**Assay Performance and Biomarker Performance Characteristics**
- ‘Precision-based’ vs ‘Accuracy-based’ assays
- Cut-off value determination
- Inter-lab variability, lot consistency

**Data Analysis and Interpretation**
Define and describe confirmatory datasets, Statistical Analysis Plan
Considerations for bias

**Aim:** Define guidelines and SOPs to allow sponsors to use biomarker effectively to determine what % enrichment to expect
Comparable clinical accuracy when same product is used in independent studies, notwithstanding differences in absolute concentrations for the analytes.

Kang et al., Methods 56 (2012) 484–493
Key Factors in Advancing CSF Assays to Qualification

FDA feedback following advice meeting, Feb 27, 2012:

CAMD should look into the possibility of obtaining the data from companies who have conducted relevant trials. If at least the placebo group data could be obtained it may both strengthen the evidence regarding the biomarkers and address the concern about potential differences in patients in a natural history study vs. drug-intervention trials.
• Biomarker Qualification by Regulatory Authorities is a mechanism for accelerating drug development of any novel therapeutic agent

• AD CSF biomarker team is at the consultation phase with the FDA for qualification as prognostic biomarkers for patient enrichment in AD trials at the pre dementia stage

• Success of CAMD’s qualification efforts is critically dependent on multidisciplinary approaches and successful collaborations