RASAD Meeting

AD Biomarkers: Regulatory Science Path
March 29, 2012

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FDA’s 2004 Message: Find the “Critical Path”
Delivering on the FDA’s Critical Path Initiative

GOAL
Enhanced tools and collaborations to decrease uncertainty in medical product development

Consortia for Creating Consensus

Predictive Safety Testing Consortium
DRUG SAFETY

Patient-Reported Outcome Consortium
DRUG EFFECTIVENESS

Coalition Against Major Diseases
UNDERSTANDING DISEASES OF THE BRAIN

Polycystic Kidney Disease Consortium
NEW IMAGING TESTS

Critical Path to TB Drug Regimens
TESTING DRUG COMBINATIONS

- Biomarkers
- Patient Reported Outcomes
- Disease Progression Models
- Data Standards
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  - **Qualify** biomarkers (FDA Draft Guidance 2010)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
Members and Partners

Nonmember participants: Academic key opinion leaders, CROs
Biomarkers are being actively employed in AD therapeutic trials

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Pathogenic process</th>
<th>Position as theragnostic biomarker in trial type</th>
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<tr>
<td>Amyloid PET</td>
<td>Brain Aβ load</td>
<td>Aβ immunotherapy</td>
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<td>CSF Aβ42</td>
<td>γ-secretase-dependent APP and Aβ metabolism</td>
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<td>CSF Aβ40</td>
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<td>CSF sAPPβ</td>
<td>β-secretase-dependent APP and Aβ metabolism</td>
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<td>CSF BACE activity</td>
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<tr>
<td>CSF Aβ1-14, Aβ1-15, Aβ1-16</td>
<td>γ-secretase-independent APP and Aβ metabolism</td>
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<td>CSF sAPPα</td>
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<td>CSF Aβ oligomers</td>
<td>Aβ oligomerization</td>
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<tr>
<td>CSF total tau</td>
<td>Intensity of neuronal degeneration and brain atrophy rate</td>
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<td>MRI hippocampal volume</td>
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<tr>
<td>CSF phospho-tau</td>
<td>Tau phosphorylation and tangles</td>
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<tr>
<td>FDG PET</td>
<td>Brain glucose metabolism</td>
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Blennow, Nature Med 2010 16(11) 1218
AD Biomarkers for Patient Enrichment: Prognostic Biomarker Context of Use

**SLIDE 3**

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

Baseline hippocampal volume

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

**Clinical Factors**

<table>
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<tr>
<th>Episodic memory</th>
<th>ApoE4 status</th>
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<tr>
<td>Vascular risk factors</td>
<td>Structural imaging</td>
</tr>
<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.

**Baseline hippocampal volume**

*Hansson et al., 5(3):228, 2006*

*Feldman, CNS Spectr. 2008;13(3 Suppl 3):4-7*
Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: Cerebrospinal-fluid related biomarkers for drugs affecting amyloid burden — Regulatory considerations by European Medicines Agency focusing in improving benefit/risk in regulatory trials

Maria Isaac*, Spiros Vamvakas, Eric Abadie, Bertil Jonsson, Christine Gispen, Luca Pani
Qualification opinion of low hippocampal volume (atrophy) by MRI for use in regulatory clinical trials - in pre-dementia stage of Alzheimer’s disease

<table>
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<tr>
<th>Agreed by Scientific Advice Working Party</th>
<th>1 September 2011</th>
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<td>Adoption by CHMP for release for consultation</td>
<td>22 September 2011</td>
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<td>End of consultation (deadline for comments)</td>
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FDA Biomarker Qualification Process

Link to new website on FDA

Biomarker Qualification Program

The Biomarker Qualification Program was established to support CDER’s work with external scientists and clinicians in developing biomarkers. As an inter-Office collaborative endeavor within CDER, the Biomarker Qualification Program offers a formal process to guide submitters as they develop biomarkers and rigorously evaluate them for use in the regulatory process.

The goals of the CDER Biomarker Qualification Program are to:
- Provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development
- Facilitate integration of qualified biomarkers in the regulatory review process
- Encourage the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making
- Support outreach to relevant external stakeholders to foster biomarker development

Biomarkers being considered for qualification are conceptually independent of the specific test performing the measurement. A biomarker cannot become qualified without a reliable means to measure it. However, FDA clearance of a testing device for marketing does not imply that the biomarker it measures has been demonstrated to have a qualified use in drug development and evaluation. Additionally, qualification of a biomarker does not automatically imply that a specific test device used in the qualification process for a biomarker has been reviewed by FDA and cleared or approved for use in patient care.

The biomarker may also have potential value outside the boundaries of the qualified context of use. As data from additional studies are obtained over time, submitters of biomarkers will be able to continue working with the Biomarker Qualification Program to submit additional data and expand the qualified context of use.
Goal of Regulatory Qualification

- To bring novel methodologies and tools into regulated drug development studies that can be used with confidence to support decision making.

- FDA: “If we qualify a DDT, analytically validated measurements of it can be relied upon to have a specific use and interpretable meaning in drug development… to expedite development of successful marketing applications.

- Industry… and CDER can be confident in applying the DDT for the qualified use without the need to reconfirm the DDT’s utility.”
Consortia are the common mechanism for advancing biomarkers to the FDA

Current status of biomarker qualifications with the FDA

PSTC, safety biomarkers qualified for use in preclinical drug development

Review of Qualification Data for Biomarkers of Nephrotoxicity
Submitted by the Predictive Safety Testing Consortium

Biomarker Qualification Review Team

Melanie Blank
Albert De Felice
Federico Goodsaad
Patricia Harlow
Elizabeth Hausner
David Jacobson-Kram
William Taylor
Aliza Thompson
Douglas Throckmorton
Shen Xiao

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

February 21, 2008.

Nature Biotechnology, May 2010, vol 28 no 5
Biomarker Qualification
Review Process at CDER

Woodcock et al., 2011
Themes emphasized in BQRT review

- Context of Use
- Applications in Drug Development
- Measurement Science
- Evidentiary Standards and Research Plan
AD CSF Biomarker Team Members

Alliance for Aging Research—Daniel P. Perry
Alzheimer’s Association—William Thies, Maria Carrillo
A.J. Simon Enterprises—Adam J. Simon
ADx NeuroSciences—Hugo Vanderstichele
AstraZeneca—Kathleen Gans-Brangs, Pat Patterson, Chi Ming Lee
Bristol-Myers Squibb—Holly Soares, Thomas Kelleher, Robert Berman, Sue Behling, Howard Feldman*, Anthony Johnson
Critical Path Institute—Lynn Hudson, Diane Stephenson, Steven Angersbach, Denise Frank, Martha Brumfield, Christopher Davidson, Robin Shane, Elizabeth Walker, Marietta Anthony, Steven Broadbent
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, John Morris
Banyon Biomarkers—Andreas Jeromin
BARC Laboratories—Theresa Heath
University of Arizona—Erin Ashbeck
University of Antwerp—Sebastiaan Engelborghs
UCSD—Paul Aisen

* presently at UBC
Key FDA questions posed to AD CSF team

Selection of Patient Population
  Define level of cognitive impairment and how this relates to biomarker

Assay Performance and Biomarker Performance Characteristics
  precision based vs accuracy based assays
  cutoff values
  interlab variability, lot/reference standards variability

Data Analysis and Interpretation
  define and describe confirmatory datasets
  concern for bias

Define guidelines and SOPs to allow sponsors to use biomarker effectively for determining % enrichment
AD Imaging Biomarker
Team Members

Alliance for Aging Research—Daniel P. Perry
Alzheimer’s Association—William Thies, Maria Carrillo
AstraZeneca—Kathleen Gans-Brangs, Patricia Patterson
Bristol-Myers Squibb—Thomas Kelleher, Feng Luo, Wendy Hayes, Holly Soares, Sue Behling, Anthony Johnson, Howard Feldman*
Critical Path Institute—Lynn Hudson, Diane Stephenson, Steven Angersbach, Denise Frank, Martha Brumfield, Christopher Davidson, Robin Shane, Elizabeth Walker, Marietta Anthony, Steven Broadbent
Eli Lilly & Company—Peng Yu, Adam Schwarz, Richard Mohs
FDA—Marc Walton
Imagepace—Patricia E. Cole
Imperial College London—Robin Wolz
IRCCS-FBF—Giovanni Frisoni, Martina Bocchetta, Marina Boccardi
IXICO Ltd—Derek Hill, Paula Munday
Johnson & Johnson—Gerald Novak, Gary Romano
Mayo Clinic—Clifford R. Jack
Novartis—Richard Meibach, Paul Maguire
Pfizer—David Raunig**
Synarc, Inc—Joyce Suhy, Joonmi Oh
University of Arizona—Erin Ashbeck
University of California, UC Davis—Laurel Beckett, Huanli Wang
University of California, San Diego—James Brewer, Paul Aisen
University College London—Nick Fox
Kings College London—Andy Simmons, Simon Lovestone

*UBC
**Icon Medical Imaging
Selection of Patient Population
Define level of cognitive impairment and how this relates to biomarker specificity of the biomarker to AD

Assay Methodology and Biomarker Performance Characteristics
- test retest reliability (scanners, field strength)
- hippocampal volume cutoff values-how to define
- defining hippocampal boundaries
- image analysis approaches vs manual tracing of hippocampus

Data Analysis and Interpretation
- define and describe confirmatory datasets
- concern for bias

Define guidelines and SOPs to allow sponsors to use biomarker effectively for determining % enrichment
Next Steps for CAMD
AD Biomarker teams

• AD biomarker teams to provide written responses to FDA questions (2 months)

• Teams analyze confirmatory datasets and conduct validation studies and submit to FDA (6 months)

• Seek advice from FDA

• Prepare and submit qualification dossier
EMA vs FDA biomarker qualification processes

**EMA**
- Fees charged
- Accelerated review
- Seeks public opinion
- Evidentiary standards - primarily literature based
- Lacks medical device division

**FDA**
- Fees not charged
- Review is slower
- Does not seek public opinion
- Evidentiary standards - prefers de novo analysis of raw data
- CDRH input/advice
Summary

• Critical Path Institute was formed to align with Critical Path Initiative and Deliver on FDA’s mission to accelerate drug development tools across the industry

• Biomarker Qualification by Regulatory Authorities is a mechanism for accelerating drug development of any novel therapeutic agent

• Consortia approaches provide advantages in terms of sharing costs and risks

• EMA has qualified two AD biomarkers, CSF biochemical biomarkers and structural neuroimaging of the hippocampus for prognostic biomarker use in AD trials at the predementia stage

• Two AD biomarker teams are at the consultation phase with the FDA for qualification as prognostic biomarkers for patient enrichment in AD trials at the predementia stage
Back ups
• Seven companies remapped and pooled data from 22 trials for ~6100 patients: value = $400 Million

• Database open to >200 qualified research teams in 35 countries
## What Was Learned?
### ADAS-Cog Variability

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<th>Item 1</th>
<th>ADNI</th>
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