Harmonizing Regulatory Requirements to Benefit Alzheimer’s Disease Patients: Lessons learned from Critical Path Institute

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Critical Path Institute Consortia

Six global consortia collaborating with 1,000+ scientists and 41 companies

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<th>Consortium</th>
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<td>PSTC</td>
<td>Predictive Safety Testing Consortium</td>
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<td>PRO</td>
<td>Patient-Reported Outcome Consortium</td>
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<td>ePRO</td>
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<td>CAMD</td>
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<td>PKD</td>
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<td>Critical Path to TB Drug Regimens</td>
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- Biomarkers
- Patient Reported Outcome Instruments
- Disease Progression Models
- Data Standards
Regulatory Qualification Programs introduced by EMA, FDA and PMDA
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.
Regulatory Paths for Biomarker Qualification

• FDA Draft Guidance for Industry entitled “Drug Development Tool Qualification”, 2010

• EMA’s “Evaluation of novel methodologies for use in drug development”, 2009

• PMDA official notification regarding a special Consultation on Pharmacogenomics/Biomarkers, 2012
• Renal biomarkers acceptable for detection of acute drug-induced renal toxicity in non-clinical drug development¹

• Consortium collaboration:
  >60 studies, >50 compounds – cost savings: >$4million²

2. Sistare F et al. Nature Biotech May 2010 28(10) 446-454
CAMD: Tools to Advance Effective Treatments for Alzheimer’s and Parkinson’s Disease

- Qualify biomarkers (FDA Draft Guidance 2010)
- Develop common data standards
- Create integrated databases of clinical trial data
- Develop quantitative drug-disease-trial models

Nonmember participants: Academic key opinion leaders, CROs
CAMD: Building on Data Standards

- Nine member companies agreed to share data from 22 trials
- The data were not in a common format
- The data needed to be combined in a consistent manner
- All data were remapped to the CDISC standard and pooled

Result

- A new *in silico* modeling tool was created through the application of data standards and is under review by the FDA
First imaging biomarker for trial enrichment qualified by the EMA (Alzheimer’s disease)

First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard

First and largest open database of CDISC aggregated clinical trial data for Alzheimer’s disease

First drug-disease-trial model under review by the FDA
How do we identify patients with MCI due to AD?

Baseline hippocampal volume

CSF biomarkers

MCI = mild cognitive impairment; AD = Alzheimer’s disease; ApoE4 = apolipoprotein E4; CSF = cerebrospinal fluid; Aβ = amyloid β.

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

Hansson et al., Lancet Neurol 5(3):228, 2006
2011: AD Three Top Tier Biomarkers Identified

- Cerebrospinal Fluid biomarkers
  - Amyloid, tau, phosphotau
- Structural Neuroimaging
  - Volumetric MRI
- Molecular Neuroimaging
  - Amyloid PET


EMA, 2011. Qualification opinion of Alzheimer’s disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment for use in predementia AD clinical trials. 
EMA vs FDA Biomarker Qualification Processes

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

- Fees not charged
- Review is slower
- Does not seek public opinion
- Evidentiary standards - prefers de novo analysis of raw data
- CDRH input/advice
Qualification of Biomarkers to enable clinical trials in Alzheimer’s disease
Ways to Accelerate the Path Forward

- Increased visibility and attention to regulatory harmonization

INTERNATIONAL REGULATORY HARMONIZATION AMID GLOBALIZATION OF BIOMEDICAL RESEARCH & MEDICAL PRODUCT DEVELOPMENT: A WORKSHOP

February 13-14, 2013 – Washington, D.C.

- Expanding the precompetitive space with sharing of clinical trial data

- Foster and expand venues for Regulatory Agencies to work together in AD drug development
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