RASAD Meeting

AD Biomarkers: Regulatory Science Path

March 29, 2012

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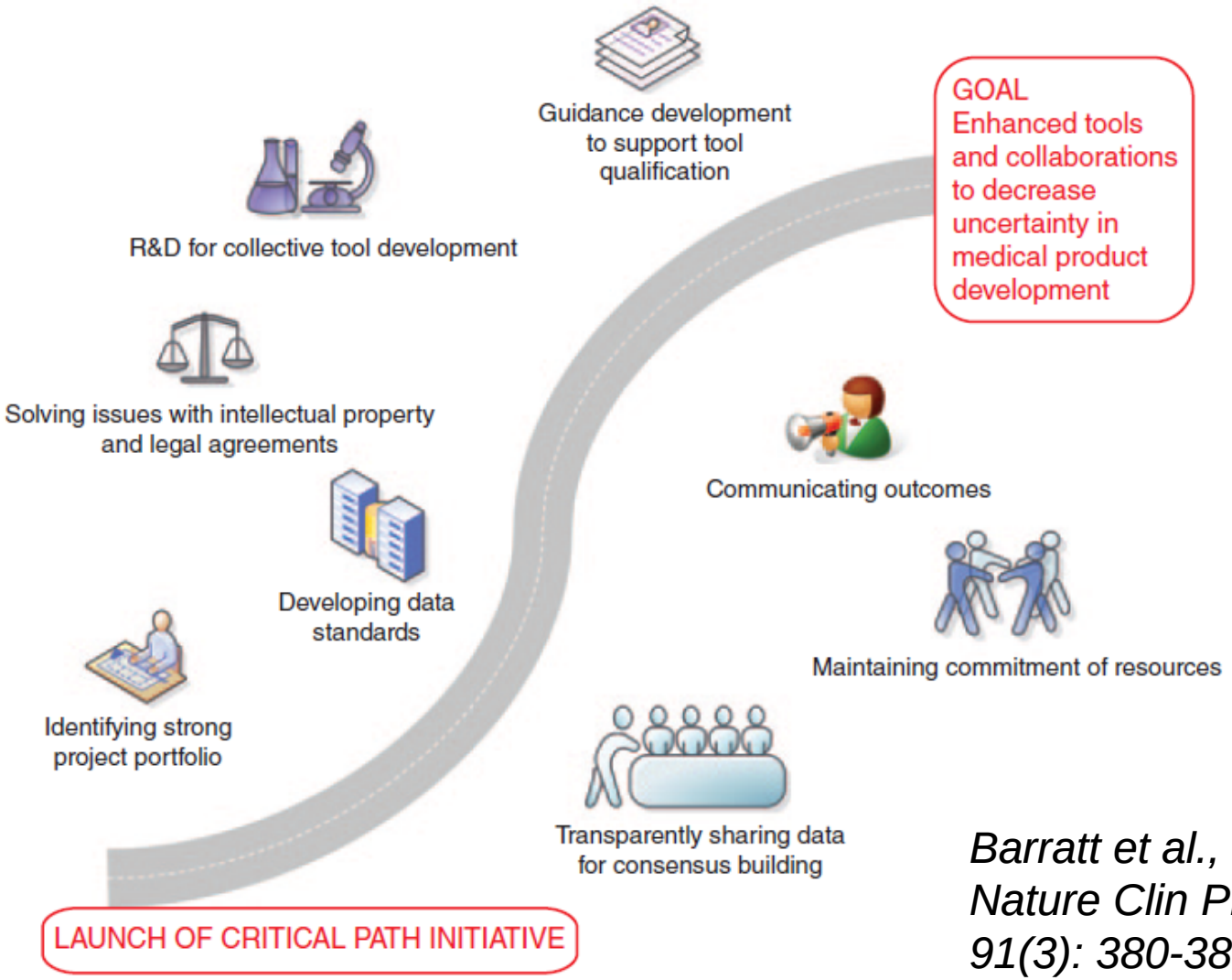
FDA's 2004 Message: Find the "Critical Path"

Delivering on the FDA's Critical Path Initiative



Barratt et al.,
Nature Clin Pharm Therap
91(3): 380-383, 2012

Consortia for Creating Consensus

CRITICAL PATH INSTITUTE

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

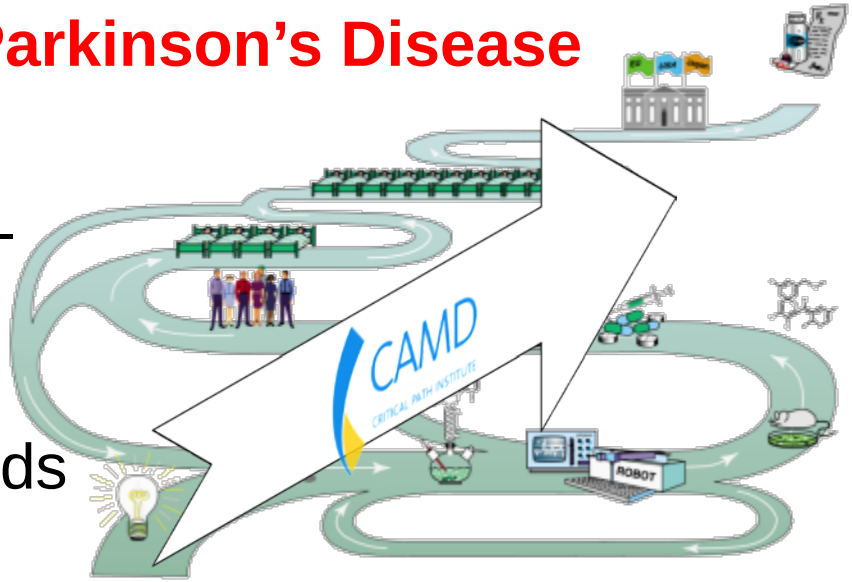
FDA

- ❑ *Biomarkers*
- ❑ *Patient Reported Outcomes*
- ❑ *Disease Progression Models*
- ❑ *Data Standards*

CDISC

Coalition Against Major Diseases (CAMD)

Accelerate the Drug Discovery Path to Advance Effective Treatments for Alzheimer's and Parkinson's Disease

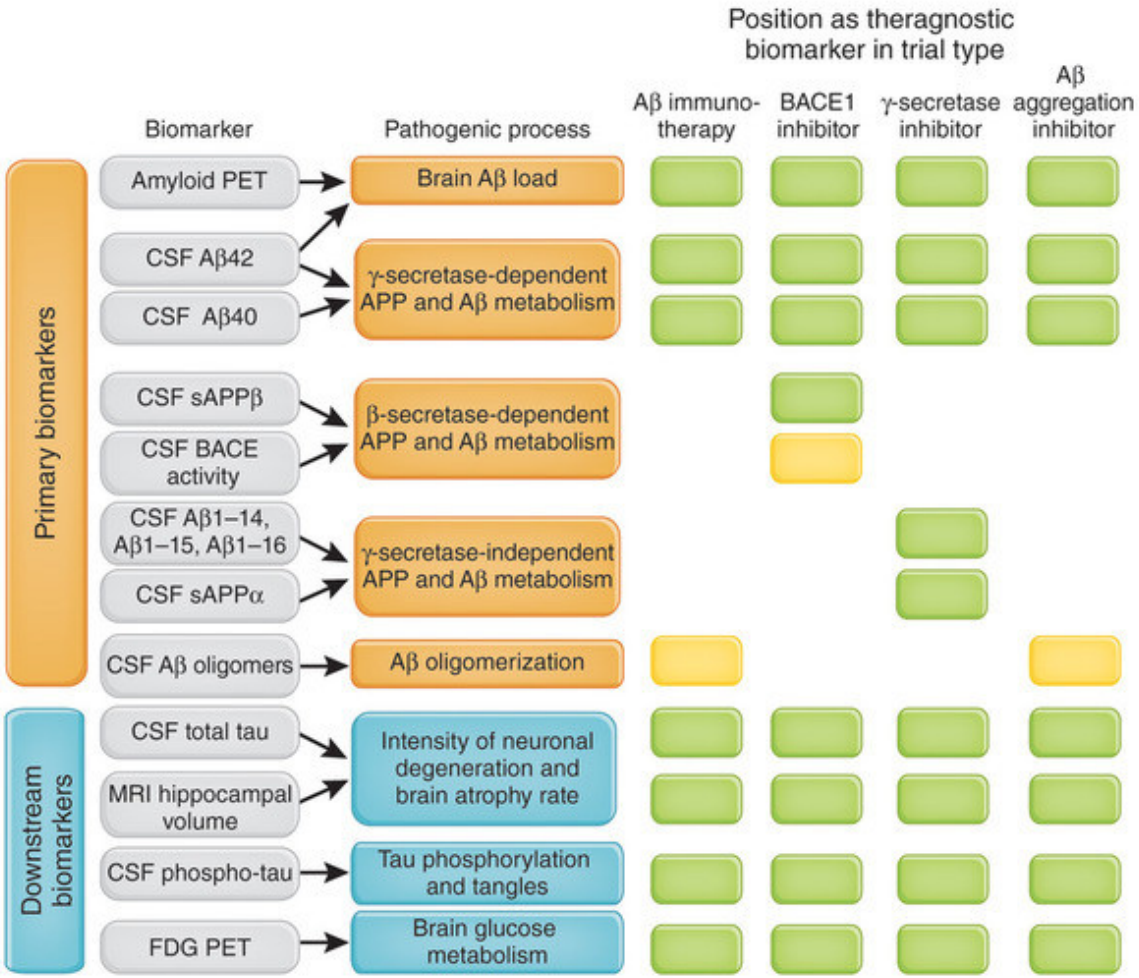


- **Advance** drug development – "Tools"
  - **Develop** common data standards
  - **Create** public databases of pooled clinical trial data
  - **Qualify** biomarkers (FDA Draft Guidance 2010)
  - **Develop** "Accepted for use" quantitative disease models

Members and Partners

Nonmember participants: Academic key opinion leaders, CROs

Biomarkers are being actively employed in AD therapeutic trials

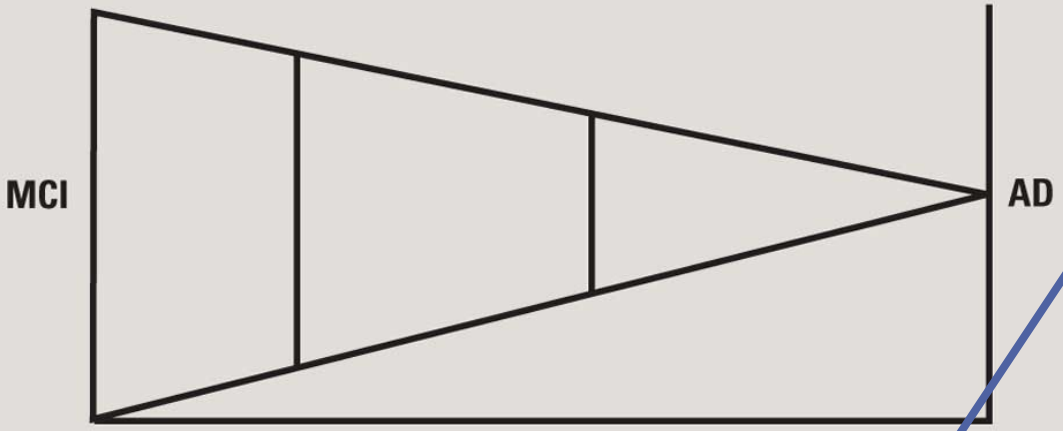


Blennow, Nature Med 2010 16(11) 1218

AD Biomarkers for Patient Enrichment: Prognostic Biomarker Context of Use

SLIDE 3

Conceptual Model Depicting the Approach to Earlier Alzheimer's Disease Diagnosis

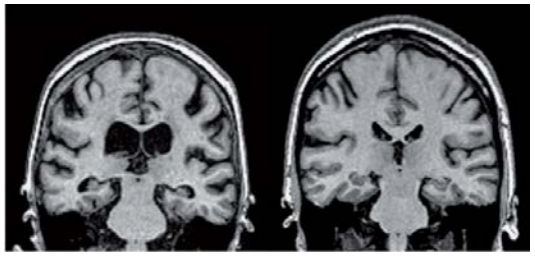


Clinical Factors	Biomarkers
Episodic memory	ApoE4 status
Vascular risk factors	Structural imaging
Depression	CSF Aβ/tau/phosphotau
	Functional imaging

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

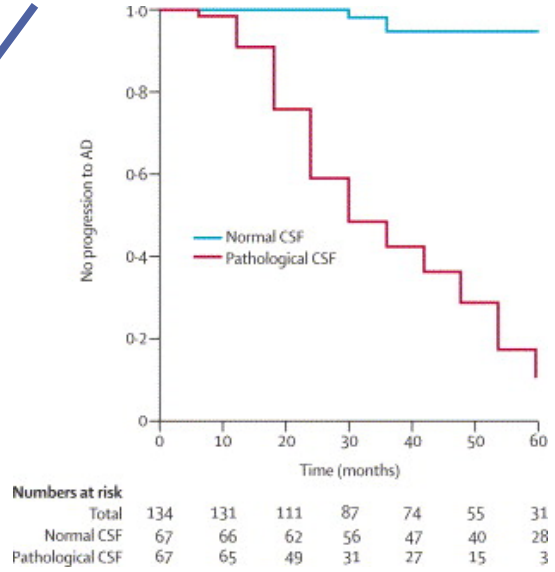
Feldman, CNS Spectr. 2008;13(3 Suppl 3):4-7

Baseline hippocampal volume



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

CSF biomarkers



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

EMA Qualifies AD CSF Biomarkers for Alzheimer's Disease Predementia Trials

European Neuropsychopharmacology (2011) 21, 781–788

ELSEVIER

www.elsevier.com/locate/euroneuro

Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: Cerebro-spinal-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

MRI as a Drug Development Tool for Patient Enrichment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 October 2011
EMA/CHMP/SAWP/809208/2011
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion of low hippocampal volume (atrophy) by MRI for use in regulatory clinical trials - in pre-dementia stage of Alzheimer's disease

Agreed by Scientific Advice Working Party	1 September 2011
Adoption by CHMP for release for consultation	22 September 2011
End of consultation (deadline for comments)	1 November 2011

FDA Biomarker Qualification Process

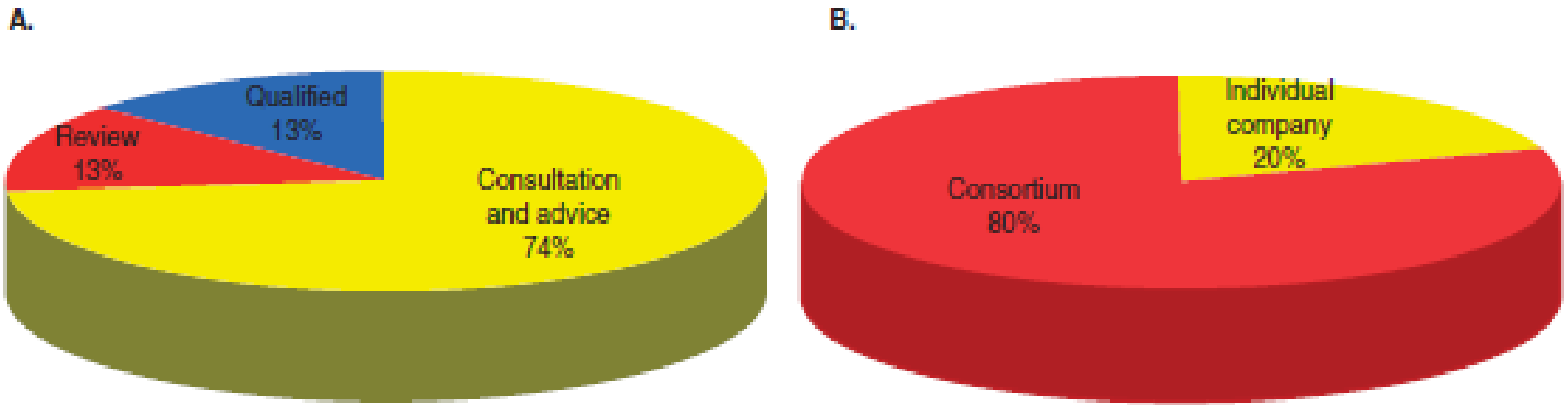
Link to new website on FDA
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

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

Woodcock et al., Qualifying Biomarkers for use in drug development: A US Food and Drug Administration Overview. Expert Opin Med Diag 5(5): 369-72, 2011

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

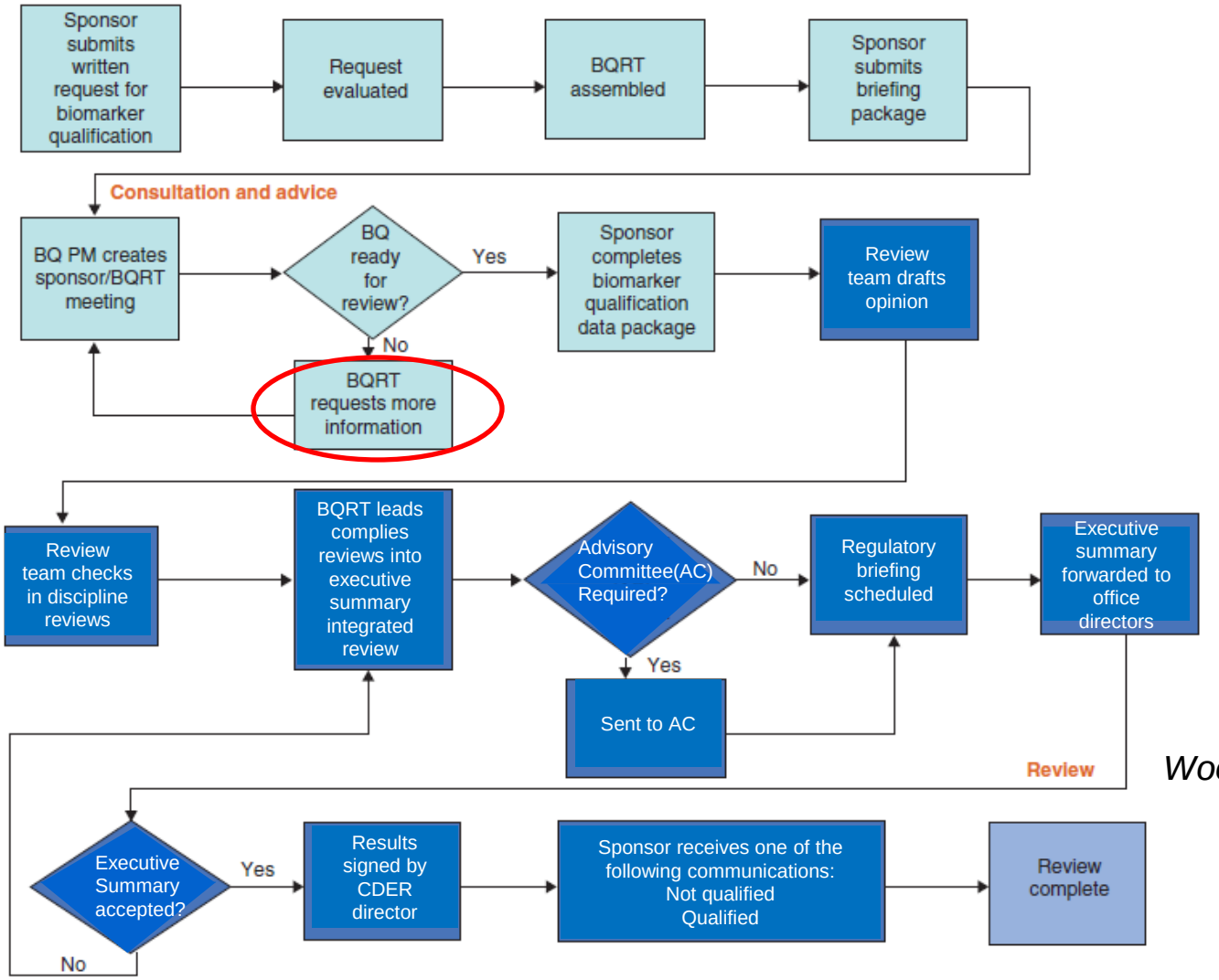
Melanie Blank
Albert De Felice
Federico Goodsaid
Patricia Harlow
Elizabeth Hausner
David Jacobson-Kram
William Taylor
Aliza Thompson
Douglas Throckmorton
Shen Xiao

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

presently at
*UBC
**Icon Medical Imaging

Key questions posed by FDA to AD imaging team

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

C-Path's Data Repository for Alzheimer's Disease

- **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

	ADNI	J&J	Wyeth	Sanofi	Pfizer	AstraZeneca	Abbott
Item 1	Word Recall	Word Recall	Word Recall	Word Recall	Word Recall	Word Recall	Word Recall
Item 2	Commands	Name Obj/fing.	Name Obj/fing.	Commands	Name Obj/fing.	Name Obj/fing.	Name Obj/fing.
Item 3	Constr. Praxis	Delayed recall	Commands	Constr. Praxis	Commands	Commands	Commands
Item 4	Delayed recall	Commands	Constr. Praxis	Delayed recall	Delayed recall	Constr. Praxis	Constr. Praxis
Item 5	Naming Obj/fing.	Constr. Praxis	Idea Praxis	Name Obj/fing.	Constr. Praxis	Idea. Praxis	Idea. Praxis
Item 6	Idea. Praxis	Idea Praxis	Orientation	Idea. Praxis	Idea. Praxis	Orientation	Orientation
Item 7	Orientation	Orientation	Word Recog	Orientation	Orientation	Word Recog	Word Recog
Item 8	Word Recog.	Word Recog.	Remem. Instr.	Word Recog	Word Recog	Remem. Instr.	Spoken Lang Abil.
Item 9	Remem Instr.	Remem Instr.	Spoken Lang. Abil.	Remem. Instr.	Remem. Instr.	Spoken Lang. Abil.	Comprehension
Item 10	Comprehension	Spoken Lang. Abil.	Word Finding Dif.	Spoken Lang Abil.	Spoken Lang Abil.	Word Finding Dif.	Word Finding Dif.
Item 11	Word Finding Dif.	Word Finding Dif.	Comprehension	Diff. Spont. Speech	Word Finding Dif.	Comprehension	Remem. Instr.
Item 12	Spoken Lang. Abil.	Comprehension	Concentration	Comprehension	Comprehension	Concentration	
Item 13	Number cancel.	Concentration		Concentration	Concentration		