

RASAD Meeting

AD Biomarkers: Regulatory Science Path

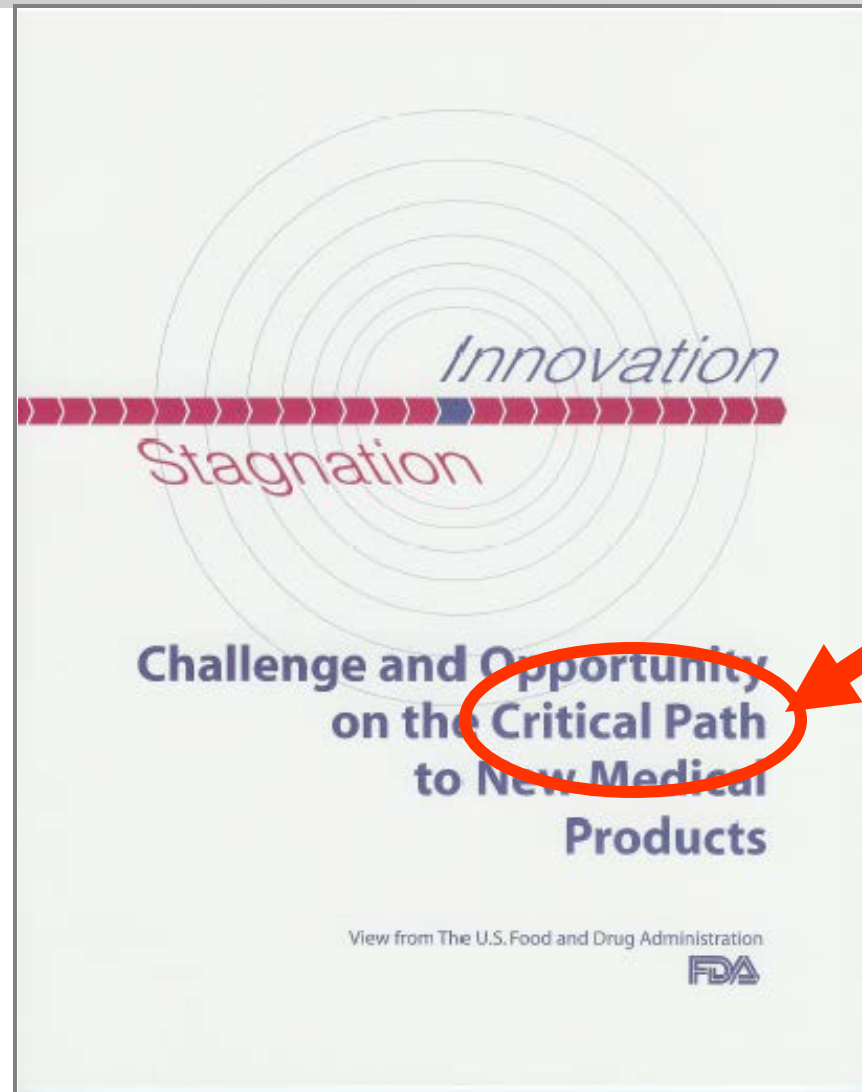
March 29, 2012

Diane Stephenson

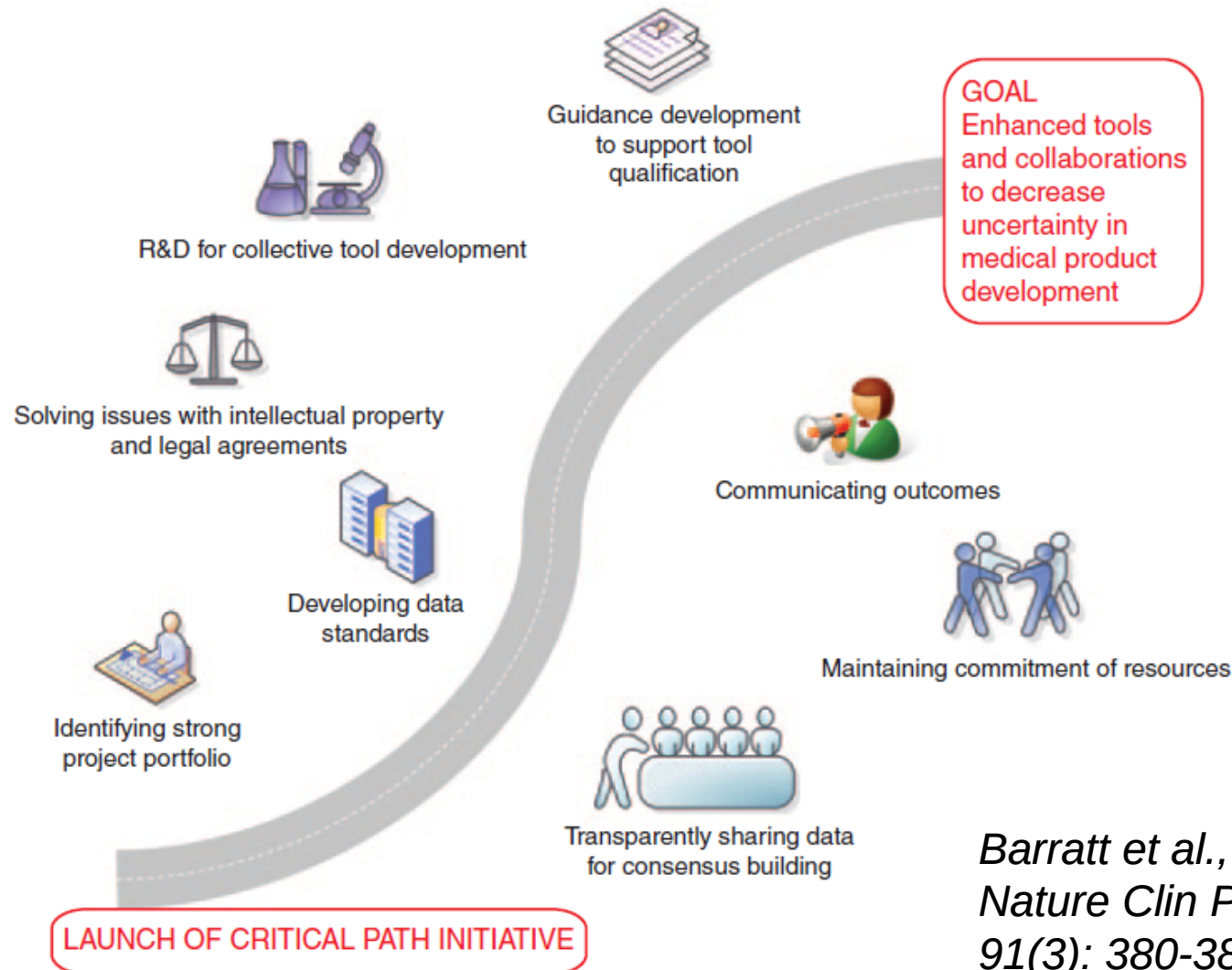
Associate Director, CAMD

DStephenson@c-path.org

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



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***



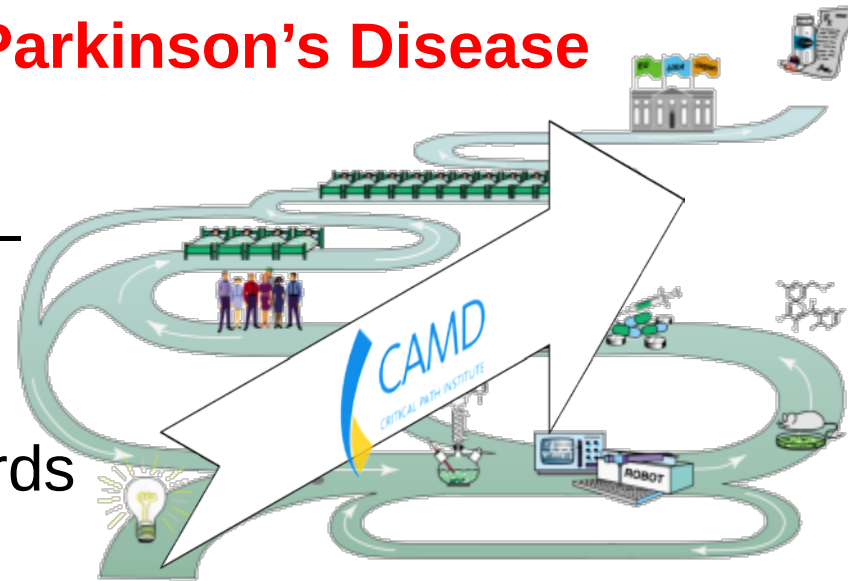
Coalition Against Major Diseases (CAMD)



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- **Qualify** biomarkers (FDA Draft Guidance 2010)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



Government/Regulatory participants



National Institute
on Aging ■ ♦ ★ ✱



Industry members



GE Healthcare

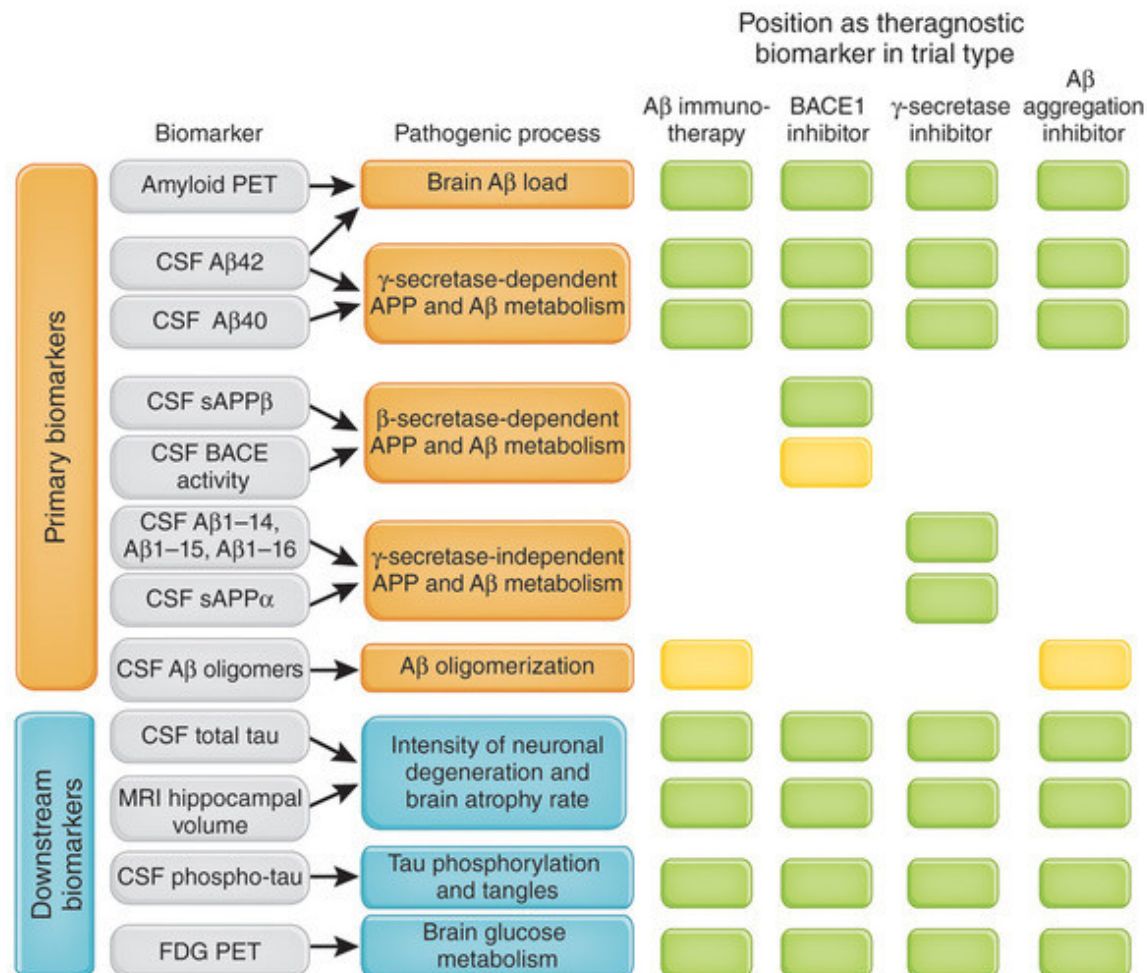


Non-profit research members



Nonmember participants: Academic key opinion leaders, CROs

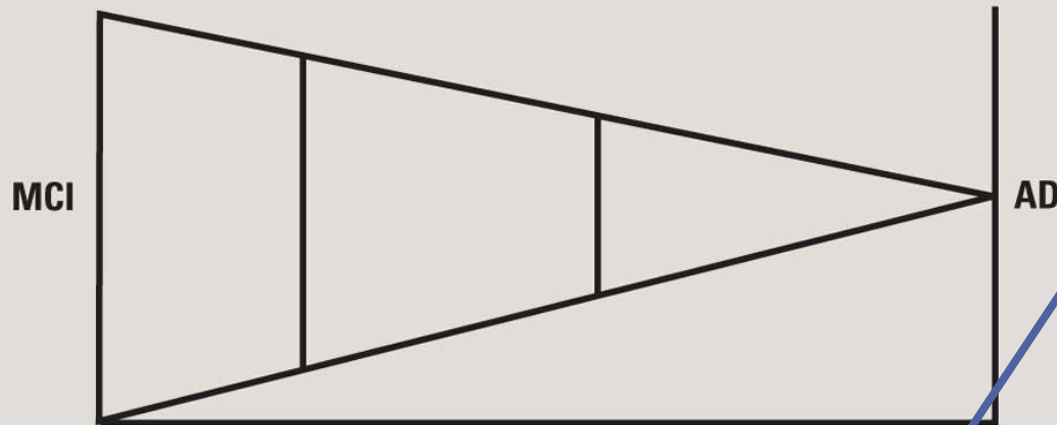
Biomarkers are being actively employed in AD therapeutic trials



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

Episodic memory
Vascular risk factors
Depression

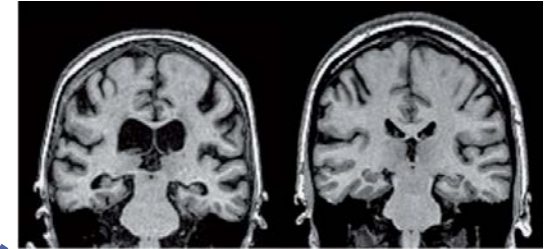
Biomarkers

ApoE4 status
Structural imaging
CSF A β /tau/phosphotau
Functional imaging

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

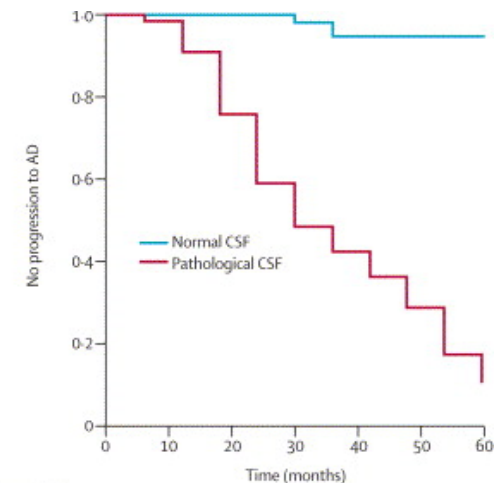
Feldman, CNS Spectr. 2008;13(3 Suppl 3):4-7

Baseline hippocampal volume



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

CSF biomarkers



Numbers at risk		134	131	111	87	74	55	31
Total		134	131	111	87	74	55	31
Normal CSF		67	66	62	56	47	40	28
Pathological CSF		67	65	49	31	27	15	3

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

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



European Neuropsychopharmacology (2011) 21, 781–788



www.elsevier.com/locate/euroneuro



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

MRI as a Drug Development Tool for Patient Enrichment



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 10 October 2011
2 EMA/CHMP/SAWP/809208/2011
3 Committee for Medicinal Products for Human Use (CHMP)

4 Qualification opinion of low hippocampal volume
5 (atrophy) by MRI for use in regulatory clinical trials - in
6 pre-dementia stage of Alzheimer's disease
7

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>

The screenshot shows the FDA website's navigation bar with the FDA logo and the text "U.S. Food and Drug Administration Protecting and Promoting Your Health". It includes links for "A to Z Index", "Follow FDA", and "Subscribe to Emails", along with a search bar and a "SEARCH" button. Below the navigation bar is a horizontal menu with tabs for "Home", "Food", "Drugs", "Medical Devices", "Vaccines, Blood & Biologics", "Animal & Veterinary", "Cosmetics", "Radiation-Emitting Products", and "Tobacco Products". The "Drugs" tab is selected, leading to a page titled "Drugs". The breadcrumb trail reads: "Home > Drugs > Development & Approval Process (Drugs) > Drug Development Tools Qualification Program". On the left is a sidebar with a "Development & Approval Process (Drugs)" section containing links to "Drug Development Tools Qualification Program", "Animal Model Qualification Program", "Biomarker Qualification Program", and "Clinical Outcome Assessment Qualification Program". Below this is a "Resources for You" section with links to "Biomarker Qualification Context of Use", "Biomarker Qualification Process", and "Biomarker Qualification FAQ". The main content area is titled "Biomarker Qualification Program" and contains the following text: "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." It then lists the goals of the program: "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." This is followed by a paragraph explaining that biomarkers being considered for qualification are conceptually independent of the specific test performing the measurement, and that 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. Finally, it states that the biomarker may also have potential value outside the boundaries of the qualified context of use, and that 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.

U.S. Food and Drug Administration
Protecting and Promoting *Your Health*

A to Z Index | Follow FDA | Subscribe to Emails

SEARCH

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

Drugs

Home > Drugs > Development & Approval Process (Drugs) > Drug Development Tools Qualification Program

Development & Approval Process (Drugs)

- Drug Development Tools Qualification Program
- Animal Model Qualification Program
- Biomarker Qualification Program
- Clinical Outcome Assessment Qualification Program

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.

Resources for You

- Biomarker Qualification Context of Use
- Biomarker Qualification Process
- Biomarker Qualification FAQ

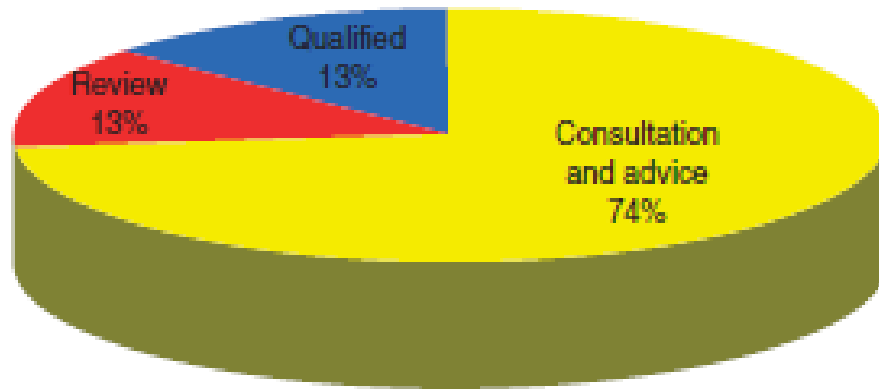
Goal of Regulatory Qualification



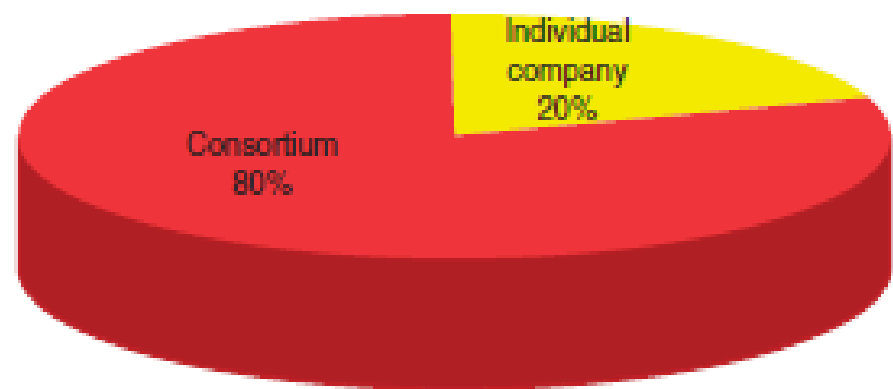
- To bring novel methodologies and tools into regulated drug development studies that can be used with confidence to support decision making
- FDA: “If we qualify a DDT, analytically validated measurements of it can be relied upon to have a specific use and interpretable meaning in drug development... 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

A.



B.



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

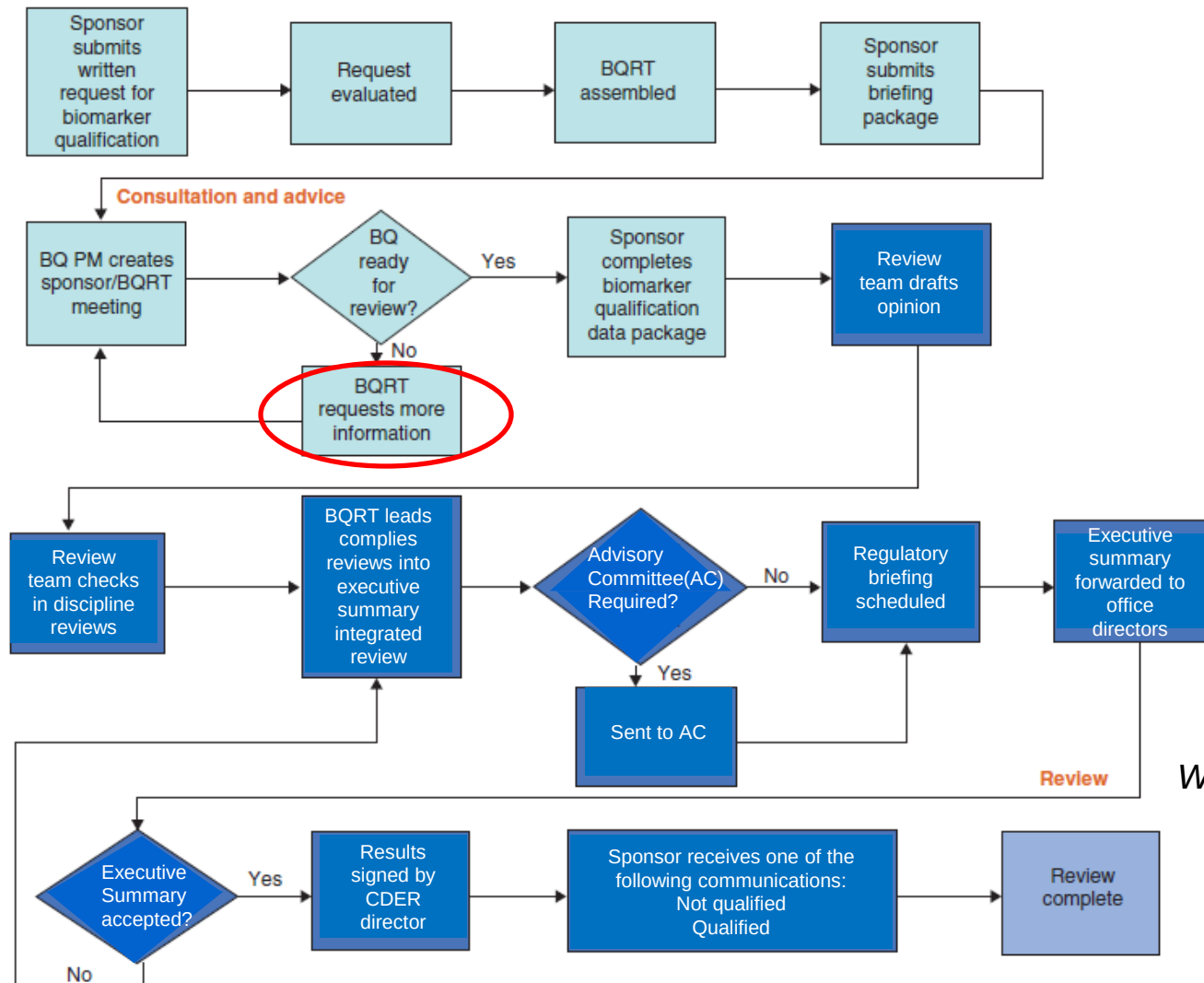
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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

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		