Coalition Against Major Diseases and FDA 2015 Annual Scientific Workshop -Meeting Notes

Date:	October 15, 2015
Time:	8:30 am to 4:45 pm Eastern (US)

Attendees

ORGANIZATION	NAME
AbbVie	Maurizio Facheris
AFFiRiS	Achim Schneeberger
Alliance for Aging Research	Cynthia Bens
Alzheimer's Association	Maria Carillo
Alzheimer's Association	Jim Hendrix
American Association of Colleges of Pharmacy	Joan Lakoski
Biogen Idec	Jesse Cedarbaum
Biogen	Melanie Leitner
Biogen Idec	Alvydas Mikulskis
Biogen	Kristin Van Goor
Boehringer Ingelheim	Mark Gordon
Bristol-Myers Squibb	Nancy Kribbs
CHDI Foundation	Cheryl Fitzer-Attas
C-Path	Steve Arnerić
C-Path	Klaus Romero
C-Path	Diane Stephenson
C-Path	Volker Kern
C-Path	Lindsay Lehmann
C-Path	Anne Robbins
C-Path	Jenny Sabol
C-Path	Steve Broadbent
Cetics	Larry Koz
Cogstate Inc.	Paul Maruff
DS Government Solutions	Dan Callahan
EMA	Maria Isaac
EMA	Manuel Haas
Eisai, Inc.	Johan Luthman
Eli Lilly	Bob Dean
EUROMMUN US, Inc.	Michael Locke
FDA	Deepak Aggarwal

FDA	Shashi Amur
FDA	Eric Bastings
FDA	ShaAvhrée Buckman-Garner
FDA	Teresa Buracchio
FDA	Meghana Chalasani
FDA	Peter Como
FDA	Billy Dunn
FDA	Victor Crentsil
FDA	Robert Guidos
FDA	Jim Kaiser
FDA	Allison Kuman
FDA	Sandra Kweder
FDA	Chris Leptak
FDA	Jinzhong Liu
FDA	John Marler
FDA	Michael Pacanowski
FDA	Gerald Podskalny
FDA	Salina Prasad
FDA	Anne Rowzee
FDA	Vikram Sinha
FDA	Marian Strazzeri
Faster Cures	Ekemini Riley
Georgetown University	Jennifer Purks
Georgetown University	Ira Shoulson
inventive Health Clinical	David Hewitt
Ixico	Derek Hill
Janssen	Gerald Novak
Kyowa Hakko Kirin Pharma, Inc.	Yao Want
Lundbeck	Gary Tong
Merck	Lisa Gold
Merck	Sreeraj Macha
Merck	Julie Stone
Michael J. Fox Foundation	Mark Frasier
Molecular Imaging, LLC	Ken Marek
National Center for Health Research	Nick Jury
National Center for Health Research	Tracy Rupp
NIA	Neil Buckholtz
Novartis	Richard Meibach
Otsuka Pharmaceutical Development & Commercialization	Joan Amatniek
PMDA	Keiju Motohashi
PMDA	Takaaki Suzuki
Parkinson's UK	Steve Ford

Parkinson's UK	Arthur Roach
Pfizer, Inc.	Brian Corrigan
Pfizer, Inc.	Monique Carter
Pfizer, Inc.	Kaori Ito
Pfizer, Inc.	Dan Karlin
Pfizer, Inc.	Rachel Schindler
PhRMA	Gabriela Lavezzari
Sanofi	Peter Loupos
Takeda	Pat Cole
Takeda	Ferenc Martenyi
Teva	Igor Grachev
Thomson Reuters	Sean McCreery
UCB	Pierandrea Muglia
	Marc Cantillon
	Natasha Hamblet
	C. Grace Whiting
Medical Writer	Lisa Bain

Agenda Highlights & Summary

Welcome (Martha Brumfield, Janet Woodcock, Diane Stephenson, Stephen Arnerić)

Dr. Martha Brumfield welcomed everyone to the meeting on behalf of C-Path, noting that there are now 12 consortia, with plans to expand further into other neurologic diseases. Dr. Steve Arnerić will now be the executive director for CAMD and Dr. Diane Stephenson will be executive director for the new consortium, Critical Path for Parkinson's (CPP). Dr. Klaus Romero will support both along with new staff in the modeling and simulation group.

Dr. Janet Woodcock congratulated C-Path on its 10th anniversary and recalled the successful journey that C-Path has taken with FDA to get more recognition for drug development tools. This led to the qualification process, which has also been instituted by EMA. She noted that to develop interventions more quickly for AD and neurodegenerative diseases, scientific gaps will need to be filled with a new generation of biomarkers and improved models such as the AD clinical trial disease progression model. Data sharing and standardization are critical to these efforts, and the FDA will continue to work with CAMD to build these essential tools. FDA also is interested in validating instruments to enable capture of day-to-day measures.

Diane Stephenson reflected back on CAMD's progress over the past four years since she joined C-Path. Key achievements in the past year include gaining access to the first AD biomarker data contributed from Novartis, receiving three letters of support from FDA, and making CAMD's first regulatory submission on Parkinson's Disease to EMA. A briefing document on hippocampal volume as an enrichment biomarker for AD will be submitted soon to the FDA. CAMD has also played a major role in the launch of new C-Path consortia focused on PD, Duchenne Muscular Dystrophy with additional interest in Traumatic Brain Injury, and Huntington's disease. Major challenges that will be addressed in the coming year include patient consent issues, and gaining access to anonymized patient level clinical trial and a

corresponding biomarker data to enable the critical work required to support the qualification process.

Steve Arnerić looked to the future of CAMD, citing four major areas of focus: 1) collecting and sharing of data; 2) continuing to develop the modeling and simulation tool and expanding it into early disease stages; 3) establishing foundational standards to enable the potential integration of digital biomarker technologies as Drug Development Tools, and 4) leveraging learnings between AD and PD, working together to build a foundation that will extend across all neurodegenerative diseases.

Keynote Address (Manuel Haas)

In his keynote address, Manuel Haas, Head of Central Nervous System Office, Evaluation Division at the EMA, noted that EMA and CAMD share the focus on dementia as evidenced by the large number of scientific advice requests related to AD and other CNS diseases in both 2013 and 2014. Since introducing their qualification procedure in 2008, EMA has issued 16 qualification advices focused on AD, including two submitted by CAMD: the AD disease progression model and the hippocampal volume qualification opinion as an enrichment biomarker for AD. Like CAMD, EMA also places strong emphasis on data sharing and fostering of regulatory efficiency through collaboration with international partners. Dr. Haas emphasized EMA's support for the launch of the new fully dedicated international Parkinson's consortium, CPP.

Regulatory Perspectives (ShaAvhrée Buckman-Garner)

Dr. Buckman-Garner described the journey taken by FDA since 2004 in the area of biomarker development and qualification (BQ). In the last year, they have focused on streamlining the steps for BQ, increasing a focus on communication between submitters and staff, harmonizing the letter of intent requirements with EMA, and initiating the letter of support (LOS) and critical path innovation meetings (CPIM). Along with C-Path and the Maryland Center for Excellence in Regulatory Science and Innovation (M-CERSI), FDA also held the first in a series of meetings on evidentiary considerations in August. Moving forward, FDA will continue to focus on communicating issues focused on evidentiary standards and enhancing data sharing, particularly in disease areas where biomarkers could advance drug development and satisfy unmet needs.

Developments in CAMD Working Groups

Meeting the Needs of the Parkinson's Community. Steve Ford, CEO Parkinson's UK, described the priorities of Parkinson's UK and their increasing focus partnerships that aim to speeding up the process of developing new treatments. Parkinson's UK, the largest charity funder for Parkinson's, is working at all stages to accelerate delivery of new treatments**.** It was announced that Parkinson's UK will join the Critical Path Institute to lead a consortium of industry, academic researchers and regulators to share the data and learnings from previous clinical studies to make clinical trials faster, more efficient and robust. The regulatory goals of this new fully dedicated global consortium, Critical Path for Parkinson's (CPP), will follow along the goals of the successes of CAMD in the area of Alzheimer's disease.

Computational Modeling for AD. Dr. Klaus Romero described the development of the existing clinical trial simulation tool for AD and plans for the future. Next year, plans are to expand the CAMD AD database with studies that include biomarker data, move into earlier stages of the

disease, and build a disease progression component into the model to define entry criteria and balance power, sample size, and trial duration given varying effect sizes. Dr. Julie Stone from Merck provided additional background on quantitative systems pharmacology and mechanistic ways to represent and model the biology of AD. She described the utilization of model-based integration of data taken from three biomarker studies to predict dose response and select doses to test in Merck's clinical studies. Models also help answer other drug development questions and inform go/no-go decisions. Expertise, data, and tools brought together in pre-competitive space are critical to enhancing these models.

AD Hippocampal Volume Team. Dr. Derek Hill, IXICO, summarized recent developments on the need for enrichment, and particularly the usefulness of hippocampal volume (HV) as a marker of disease progression. It is acknowledged that a single biomarker for AD trials has limitations and that combinatorial biomarker strategies are ongoing and likely needed for the future. The team plans to assess the enrichment performance on the InDDEx (Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon) data from Novartis and explore the value of combining HV with CSF amyloid as a tool for assessing disease progression. A data analysis plan for the InDDEx data will be presented to the FDA to support the qualification effort.

AD CSF Biomarkers Team. Dr. Bob Dean, Eli Lilly, described efforts by the CSF biomarker team to advance qualification of CSF biomarkers as a prognostic biomarker for enrichment of AD clinical trials. A major challenge continues to be access to data beyond ADNI, and the team has focused on gaining access to data from the BMS Avagacestat study. The FDA issued a Letter of Support in March 2015, encouraging more data sharing, collaboration, and use of AD CDISC standards to enable the path for future qualification of CSF biomarkers.

Regulatory Panel Discussion. Richard Meibach, Novartis, moderated a regulatory panel with participants from the FDA, EMA, and PMDA. The panel discussed how to move forward with advancement of quantitative models of disease progression targeting the early stages of AD (MCI). It was suggested that instead of trying to develop a model with everything included, it might be better to focus on those biomarkers or endpoints that would be helpful in enriching trials for the most high priority targets under development, identify the best quantitative tools to assess those biomarkers, and build models that characterize disease progression using those markers. Historical data may be useful. Access to data, particularly patient-level data, continues to be a barrier to success. Issues related to informed consent are often difficult to overcome.

CAMD Annual Recognition Awards

Dr. Richard Meibach, Dr. Johan Luthman, and Dr. Mark Gordon received individual awards. The team award was presented to the Hippocampal Volume team. A member award was presented to Novartis. Parkinson's UK received the non-profit organization award. A special recognition award was presented to Dr. Diane Stephenson for her service as Executive Director of CAMD.

Strategies for Successful Implementation of Biomarkers in Clinical Trials – CAMD Data Sharing and Integration… Looking to the Future

Data sharing – what can be learned from ALS? Dr. Melanie Leitner, Biogen, discussed efforts by Prize4Life, in collaboration with Neurological Clinical Research Institute (NCRI) and the Northeast ALS (NEALS) consortium to build the Pooled Resource Open-Access Clinical Trials (PRO-ACT) database, which was launched in December 2012. The database currently contains 8500+ de-identified patient data records from 17 completed clinical trials and expects to acquire 2400 new records from 6 additional trials later this year. These data have led to a rich understanding of the natural history of the disease and provided a large biomarker resource. This has enabled modeling and simulation of clinical trials; modeling of stratification theories, impact of medication use, and base rates of adverse events; and identification of disease predictors. It has also attracted quantitative experts to the field.

The ALS prediction prize was established to promote efforts to translate big data into health. Thirty-seven unique solutions were submitted, leading to three $50K awards for three different prediction algorithms. One was developed into a new prediction tool to reduce the size of clinical trials. A number of minimally invasive, low cost, and rapidly translatable predictors were identified. An unexpected outcome was the impactful efforts of Origent Data Sciences, which is developing predictive models using advanced machine learning techniques.

PPMI paving the way for defining prodromal PD. Dr. Ken Marek, Molecular NeuroImaging (MNI), described the efforts of PPMI to define prodromal PD as a step towards preventing disease onset, elucidating and testing therapeutic targets, and enabling precision medicine approaches. The original study included 423 *de novo* PD patients plus 96 age- and gender-matched controls and 64 SWEDD patients. Subsequently, 67 prodromal, olfactory/REM Behavioral Disorder (RBD) subjects as well as subjects with known genetic risk factors were added. Data collected include clinical assessments, biomarkers (including imaging and CSF), and genetic data. These data have been used for risk profiling and to provide cohorts for characterizing prodromal and genetic studies.

Transforming AD therapies through collaboration. Dr. Jim Hendrix, Alzheimer's Association, described the Association as a connector/convener. Among the many public private partnerships in which they are involved are several in association with CAMD related to biomarkers and data sharing. A main current focus is the IDEAS (Imaging Dementia – Evidence for Amyloid Scanning) initiative, a four-year study to gather evidence on the benefits of amyloid PET scanning. The aim is to identify clinically meaningful aspects of early diagnosis, such as the potential for reduced hospitalization and use of medication if patients have an accurate diagnosis. CAMD partnerships include GAAIN (Global Alzheimer's Association Interactive Network) alliance and the Global Standardization Biomarkers Consortium aimed at standardization of CSF biomarkers.

C-Path Multiple Sclerosis Outcome Assessment Consortium (MSOAC). Dr. Jesse Cedarbaum, Biogen, presented information about the MS Outcomes Assessment Consortium on behalf of Dr. Richard Ruddick, industry co-director. MSOAC has worked with CDISC to create therapeutic area data standards for MS; version 2 is underway. Data acquisition, remapping, and creation of an online database have been very successful with >14,000 individual subject-level data from active treatment and placebo data from MS trials now integrated into an MS C-Path online data repository. The consortium aims to gain widespread acceptance of a new

performance outcome measure (PerfO) and advance it to regulators as a primary endpoint for use in MS clinical trials.

Panel discussion on Prospective Directions for CAMD…Focus on Data. Many topics were touched on in the panel discussion, including the relative value of clinical data vs. biomarkers for prediction and the challenge of integrating data as the tools for collecting data are being updated. Many challenges were discussed related to open data access. Ken Marek, MNI, stated that some journal editors have expressed concern about publishing multiple studies using the same data that come to different conclusions. Dr. Neil Buckholtz, National Institute on Aging, replied that this was raised as a concern with ADNI, but their experience is that there is power in having data reanalyzed from independent groups. Data theft was raised as an additional concern, pointing to the need for better tools to manage and protect data. Jim Hendrix commented that, from a patient advocacy perspective, patients would be horrified to learn that their samples are destroyed and data made inaccessible when a trial ends, so there is a need to rethink how to share samples more effectively.

Integrated Focus Sessions:

Modeling. Dr. Brian Corrigan (Pfizer), Dr. Kaori Ito (Pfizer), and Dr. Klaus Romero (C-Path) described the process that led to regulatory endorsement of the clinical trial simulation model. The total journey took 1317 days with much learning along the way. Lessons learned included the value of an integrated dataset and partnerships. Success is a function of time and patience. Future plans include taking what was learned in mild and moderate AD to expand the CAMD database with more contemporary studies and extending the model into earlier stages of AD. Dr. Vikram Sinha (FDA) commented that FDA also learned a lot through this journey with CAMD – the first of its kind for FDA. The most important aspect, from the agency's perspective, is getting the context-of-use (COU) right and then determining what kind of data and what level of evidence is needed.

Klaus Romero commented that standard operating procedures on how to clean, remap and anonymize data were created, so future efforts should have built-in efficiency. Moving forward, it needs to be made sure that the steps taken are achievable, that the questions we want to answer have been clarified, and it is made sure we have the data needed to answer those questions.

Digital Biomarker Technologies. Dr. Jesse Cedarbaum, Biogen, discussed the potential power of digital biomarkers, e.g., from wearable devices and smartphones, to inform drug development. Progress will require defining the COU, developing a common language with regulators, gaining user acceptance, making data available, ensuring mechanical computational reliability of devices and transparency of the measurement method, and developing interfaces between devices and sponsor data systems. Important clinimetric properties include part 11 compliance and development of CDISC standards. Peter Como (FDA) noted that these devices are regulated by CDRH (Center for Devices and Radiological Health) and he outlined the different regulatory pathways compared to CDER (Center for Drug Evaluation and Research). One rather novel regulatory mechanism in CDRH is the MDDT (Medical Device Development Tools) pathway. Other issues raised by CAMD members included the reliability of chain of custody, and the possible need for combination pathways using multiple devices.

Summary & Key Recommendations for moving forward

CAMD continues to advance regulatory science and make progress in collaborative strategies that are key to filling gaps in drug development for AD. The launch of a fully dedicated consortium focused on Parkinson's disease (CPP) will facilitate more rapid progress on each disease. Shared learnings will continue to be fostered across the CNS diseases that C-Path is focusing on. Key core competencies for the future include expanded data standards, database expansion and integration (C-Path Online Data Repository, CODR), model-based drug development, and development of digital biomarker technologies for use as novel Drug Development Tools.