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December 29, 2011

Dr. Richard J. Hodes
Director, NIA
Building 31, Room 5C35, MSC 2292
31 Center Drive
Bethesda, MD 20814

RE: Input on the National Plan for Alzheimer's Disease

Dear Dr. Hodes,

Presently there are no approved treatments to slow the progression of Alzheimer's disease (AD) or cure this devastating disease. Filling the AD drug pipeline will require facilitating translation of basic research discoveries and increasing collaboration with the FDA and international regulatory agencies. The Critical Path Institute, working in a public-private partnership with the FDA, created the Coalition Against Major Diseases (CAMD) to identify improved methods and tools that accelerate drug development in neurodegenerative conditions such as Alzheimer's disease. NIA contributes to the consensus science for AD drug development tools in CAMD, as do our 16 member companies and other key stakeholders.

The goal of improving the drug development process for Alzheimer's disease can be addressed by incorporating the following actions into the National Plan for Alzheimer's Disease:

1) Widespread adoption and use of the AD data standards developed by the Clinical Data Interchange Standards Consortium (CDISC) to facilitate data sharing. These CDISC AD data standards should be used in all new and ongoing federally-funded and industry-sponsored AD clinical trials. While the FDA currently encourages sponsors to use CDISC standards when submitting data, the ability for the FDA to require such standards in applications should be considered. The AD data standards should be frequently updated and expanded to cover any new measures.
2) Construction of a comprehensive AD clinical natural history database that could be mined by qualified investigators. This database should contain both control and active intervention arms of clinical trials and include trials of failed drugs. For optimal data mining, the data should be deposited in CDISC format with legacy data remapped to the AD data standards. Such a database, whether constructed by a foundation or a public-private partnership, would need to address privacy and informed consent concerns as well as liability issues. Moreover, a mechanism to protect proprietary, confidential data would need to be built in. Incentives for pharmaceutical companies to submit deidentified and appropriately coded treatment arm data include immediate access to a rich source of pooled data. Data mining of the AD clinical database should provide information on which

biomarkers accurately track disease progression and response or non-response to treatment. This aggregated mega-database should also offer valuable insights for repurposing drugs.

3) Regulatory qualification of biomarkers that can be applied to testing new AD drugs. Progress in developing AD drugs has been hampered by the lack of biomarkers qualified by regulatory agencies for testing efficacy, particularly in the earliest stages of the disease. While AD researchers have identified some tantalizing candidates, providing the level of evidence needed for FDA qualification typically requires additional evidence and analysis. Such efforts are beyond the scope and resources of individual companies or academic researchers, and are best carried out through a public-private partnership/consortium model (e.g. ADNI, CAMD).
4) Development of analytic standards and reliable methods for measuring AD biomarkers. The lack of standardization for imaging modalities and/or assays of CSF analytes can prevent the FDA from accepting a biomarker for use in AD clinical trials. Standardization of analytic methods, together with establishing a resource of appropriate reference samples, should be a national priority.
5) Development of quantitative disease progression models to inform the design of AD clinical trials and evaluate new medicines. Mathematical models offer ways to differentiate between symptomatic and disease-modifying drug effects, determine the optimal sample sizes and sampling times, identify subpopulations with unique characteristics, assess the impact of baseline disease severity on drug response, and more. In short, models can prevent a good drug from failing, and keep bad drugs off the market. Modeling and simulation tools can be built using the clinical data of a large AD database, such as the one constructed by CAMD that contains ~ 6000 AD patients enrolled in the control arm of clinical trials. Even larger databases with cognitively normal controls and patients at the earliest stages of the disease, along with richer sources of biomarker information on these patients, should be constructed to facilitate the decision-making process in prevention trials as well as AD clinical trials. These quantitative disease models need to be evaluated by the FDA and accepted as "fit for use" so that the pharmaceutical companies can better design AD clinical trials.

Each of these drug development tools fall within the "precompetitive space", where the knowledge gained and time saved can benefit individual company efforts to bring new drugs to the market. The National Plan for Alzheimer's Disease would benefit by incorporating these action items to spur the development of safe and effective medicines for the prevention and treatment of Alzheimer's disease.

Thank you for the opportunity to provide input on the National Plan for Alzheimer's Disease.

Sincerely,

Lynn Hudson

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