Among the important aspects of the eIND with which both academic and industrial developers should be familiar are the potential uses of this mechanism:

- To assess investigational drugs, biologics, and nanoparticles for proof of concept, that is, to distinguish promising from not-so-promising, in a process that is effective and fast.
- To assess investigational nanoparticles with biodistribution imaging to determine the relationships of "class-size barriers." The FDA has actually been approving compounds that have technically been "nano" for many years, but new questions around safety, localization, and retention that are being brought up around these compounds today will need to be answered.
- For "horizontal" simultaneous competitive portfolio analysis. Only 2 years ago, many large pharmaceutical companies did not think the eIND mechanism had much to offer them. Today they are recognizing that it offers a method for quick triage.
- For "vertical" first-to-win competitive portfolio analysis, a process that carries advantages for small developers.

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Use of eINDs for Evaluation of Multiple Related PET Amyloid Plaque Imaging Agents

U.S. Food and Drug Administration (FDA) exploratory Investigational New Drug (eIND) approaches are ideal for conducting human proof of mechanism trials on novel radiopharmaceuticals. At Avid Radiopharmaceuticals (Philadelphia, PA), we have employed eINDs to efficiently conduct clinical trials on a large number of novel radiopharmaceuticals, including 4 related novel ^{18}F-labeled PET amyloid imaging agents. The eIND was a rapid and efficient mechanism for generating first-in-human efficacy data (amyloid binding), kinetics, and dosimetry, with significant advantages over other possible approaches (foreign trials, traditional corporate INDs, and physician-sponsored INDs).

Speeding Development with the eIND Mechanism

Alzheimer's disease (AD) is defined by the presence of all of the following: (1) clinically diagnosed dementia (defined by clinical and neuropsychological examination) with progressive cognitive impairment in 2 or more areas, including memory; (2) pathology findings of abundant neuritic amyloid plaques; and (3) pathology findings of abundant neurofibrillary tangles. Avid's clinical imaging program focuses on amyloid plaque, 1 of the key diagnostic criteria required to make a definitive diagnosis of AD.

Several challenges confront the development of an effective amyloid imaging agent. Among these are the facts that preclinical assays do not fully predict human results and that no ideal animal model is available for testing compounds (mouse models show significant differences from human AD, and no primate model for AD is available). In addition, the traditional IND mechanism presents relatively high barriers to generating initial human proof of mechanism data.

The eIND process allows development of multiple compounds in parallel. In our effort to develop an effective amyloid imaging agent, we began with the synthesis of more than 1,000 compounds for testing. Several hundred of the most promising of these compounds were radiolabeled for mouse biodistribution and section labeling studies. More than 25 of the most promising compounds were then advanced to primate imaging studies to assess brain targeting and clearance. Thirteen compounds were selected for Good Laboratory Practices pharmacology and toxicology studies and were then tested in phase 1 clinical trials to assess safety and dosimetry, metabolism, and brain imaging in humans. At the end of this process, a single compound was selected to advance to phase 2 trials. This approach provided a process to identify the best agents quickly while minimizing time and effort on compounds that were unlikely to prove useful.

Transitioning from an eIND to a Traditional IND

FDA guidance requires withdrawal of the eIND and opening of a new traditional IND in order to continue clinical development. A pre-IND meeting can occur in parallel while the eIND studies are being completed. Additional pharmacologic and toxicologic studies—including repeating dose toxicity studies in 2 species, a full battery of genotoxicity studies, safety pharmacology studies, and cardiovascular

safety studies—are required. This transition, although complex, can be accomplished quickly, and at Avid we required only 6 wk from the last patient out in the eIND studies until the IND submission.

Challenges Ahead

The eIND worked quite well for achieving the first step in clinical development of an amyloid imaging compound, and the transition to traditional IND was achieved efficiently. Our phase 2 development goals are relatively straightforward. What is needed now is a clear path toward commercialization. Among the specific challenges we face are:

- How do we demonstrate efficacy for imaging amyloid plaques when the gold standard requires biopsy or autopsy?
- How can clinical utility for an innovative imaging agent be proven without prohibitively long prospective trials based on clinical endpoints?
- What is the optimal path for working collaboratively with therapeutic drug developers to ensure approval of both a novel therapy and a novel imaging biomarker?

Questions for the Future

Amyloid imaging agents are not intended to supplant the fundamental criteria by which Alzheimer's disease is diagnosed. Instead, we recognize the importance of integrating knowledge about pathology (gained from imaging data) into the existing framework for clinical diagnosis. By focusing on the potential imaging to provide valuable pathology data in support of clinical data, we might find it easier to advance molecular imaging through the development pipeline. For example, a 2-step approval process has been proposed for novel molecular imaging agents. In the first step, approval is based on establishing safety and dosimetry in clinical trials, demonstrating efficacy in imaging a particular known target, and providing data that will support a reasonable expectation that imaging this target will be clinically useful in a defined patient population. Approval based on this first step could provide a label claim limited to imaging pathology. The second step would involve demonstration of utility in prospective clinical trials. Successful completion of this step could lead to a label claim that would be broadened to include diagnostic/prognostic uses.

Among the big questions that the molecular imaging community will need to address proactively in the near future are:

- Should a molecular imaging agent be eligible for approval if it is proven to be safe and effective for imaging a defined pathologic target?
- What criteria do we use to determine whether a particular target presents a potentially approvable indication for imaging agents? The literature may provide sufficient supporting documentation for some targets but not others.
- How do we prove that an agent is effective for imaging the pathologic target?

The future is bright for molecular imaging in general and, in our work, for amyloid imaging. The most significant challenge remains uncertainty, and continued open communication among industry, academia, and the FDA is the key to resolving this uncertainty and moving forward.

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Health Economics in Technology Development: Is It Worth It?

Health economics is a broad discipline that incorporates a wide range of tools and techniques. As a result, it is often misunderstood, and its role in health technology development can be difficult to comprehend. For example, a survey of the 22 largest payers in the United States yielded 22 very different definitions for health economics, ranging from the somewhat nebulous "the impact of the agent on the total costs to the health care system" to the more detailed "clinical and economic outcomes for our health plan members measured using internal drug, medical, and laboratory data (claims and other data) and analyzed to reflect alternative drug, medical education, and other health care interventions."

This brief review offers a primer on health economics and an insider's view of the ways in which tools in the health economist's toolkit can be used to assist in the development and commercialization of new medical technologies. Health economics is important in any health care product de-