Collaborative Business Models

A number of successful creative business models for cooperation are available for study and emulation, including but not limited to: SEMATECH, Product Quality Research Institute, SNP Consortium, Biomarker Consortium, C-Path, OBQI, NCI's Nano Alliance in Cancer, and others.

FDA Resources and Mechanisms

One useful resource in collaborating with the FDA is a document originally intended for agency staff: *The Leveraging Handbook: An Agency Resource for Effective Collaborations* (available at: www.fda.gov/oc/leveraging/handbook.html). The handbook sets out all of the mechanisms that staff can draw upon, including but not limited to information on: confidentiality disclosure agreements, MOUs, cooperative research and development agreements, cosponsorship agreements, material transfer agreements, contracts, grants, interagency agreements, and licenses.

The FDA has a unique role, with scientists involved in all aspects of review through the entire course of medical product development. We have seen successes, failures, and missed opportunities. We use both our experience and state-of-the-art information available to evolve and inform our regulatory processes and decisions. New guidances, which are prepared by FDA staff for applicants, sponsors, and the public, contain recommendations that are not binding and represent current thinking on a regulatory issues. New guidances may include information on design, production, labeling, promotion, inspection, enforcement, manufacturing, processing, and testing of regulated products.

The CPI has special importance for molecular imaging, because it may provide a transparent path from basic research through regulatory submission: providing tools to inform the entire spectrum of medical product development. The FDA welcomes inquiries from whomever and from wherever the inquirer may be along that path and even beyond product approval.

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The Exploratory IND

In its March 2004 *Critical Path Report*, the U.S. Food and Drug Administration (FDA) explained that to reduce the time and resources expended on candidate products that are unlikely to succeed, new tools were needed to distinguish earlier in the process those candidates that hold promise from those that do not. The point, of course, was to develop processes and mechanisms that would speed up the process of candidate development, particularly in crossing from preclinical to phase 1 applications—a crucial point in the development pipeline.

The applicable exploratory Investigational New Drug (eIND) guidance was issued in January 2006. This guidance described "early phase 1 exploratory approaches that are consistent with regulatory requirements while maintaining needed human subject protection, but that involve fewer resources than is customary, enabling sponsors to move ahead more efficiently with the development of promising candidates." The mechanism is designed to allow more flexibility in the IND process and is ideally positioned to open the pipeline for imaging development and reduce barriers at key transitioning thresholds. The guidance defined an eIND study as a clinical trial that is conducted early in phase 1, involves very limited human exposure, and has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies).

Understanding the Exploratory IND

Among other potential advantages to developers, the eIND mechanism facilitates first-in-human clinical trials. Radioactive Drug Research Committee requirements associated with traditional INDs prohibit first-in-human trials. The eIND allows the researcher to bring these efforts in earlier to be able to differentiate promising from not-so-promising agents. Another part of the underlying structure of the new mechanism reduces the threshold on how much pharmacologic and toxicologic (pharm/tox) testing must be completed before entering into an eIND. If the agent turns out to be promising during the eIND process, then the pharm/tox assessments can be completed; if not, then these never have to be done. The result is a remarkable reduction in cost in preclinical efforts, as well as economies that allow researchers to focus on those agents with the greatest chances for success. This aids every developer in maintaining a more focused portfolio. It is noteworthy that even in the mid-1990s many companies were evaluating new agents with a process much like that at work in eINDs, and today both pharmaceutical and biopharmaceutical companies are actively embracing the eIND approach and using it to evaluate their portfolios.

Some of the language in the original guidance may cause confusion ("microdose," "without therapeutic intent," etc.), but all stakeholders should know that the FDA staff is available to clarify these issues and provide assistance. In planning for an eIND, it is helpful to know that the focus and associated questions should be quite specific and designed to provide data that support a specific proof of concept. It is for this reason that the eIND mechanism is ideal for targeted assessment questions that can be answered with a definitive

yes or no in the proposed study. Such questions would support efficacy schema assessing selection, localization, and retention (Does the agent target the tumor? Does it target the abscess? Does it cross a specific barrier? If so, how long is it retained beyond the barrier?) and safety schema. Even with a standard IND open on a therapeutic agent, a developer may open an eIND on the same agent for targeting solely to demonstrate safety and efficacy in terms of imaging. In the past year we have seen both pharmaceutical and biopharmaceutical companies opening up eINDs based on imaging development related to safety. These eINDs focus on areas such as nontarget and unexpected organ localization, rates and routes of clearance, and radiation dosimetry.

Development and Cost Advantages

The eIND process offers advantages for both promising and not-so-promising drugs and biologics. If early eIND assessment indicates that a drug is promising, the exploratory eIND can be closed and the applicant can prepare to proceed to a standard phase 1 study, completing development and pharm/tox. It is noteworthy, however, that many eINDs for promising drugs will not be closed, because the developers will want to come back and use the eIND to perform targeted evaluations as definitions of optimal populations are refined. One of the most frequent complaints when I first came into this field was about the costs of pharm/tox studies. The eIND addresses this very specifically. Ironically one of the biggest challenges has been getting this message out to pharmaceutical and biopharmaceutical companies, many of whom still want to do all of the pharm/tox before the IND stage because it has been done this way in the past. Part of the essential intent of the eIND mechanism is to ensure that costs are lowered by allowing developers to come in and distinguish promising from not-so-promising products at an earlier stage. When not-so-promising drugs and biologics are identified, developers can shift their focus to other agents, limiting pharm/tox costs, reducing overall development costs, and abridging development time. In this way, the most promising drugs and biologics can move across from preclinical to phase 1 studies more rapidly and cost effectively.

Another competitive and comparative advantage of the eIND is the ability to perform portfolio analysis through whole-body biodistribution studies. One approach to comparative biodistribution trials assessment can be called "horizontal" portfolio analysis. If a developer has 4 compounds, these can be put together in a single eIND to do comparative biodistribution studies and identify the most promising agents. This is a very effective methodology, regardless of performance, when developers want the full information on agents. This approach would be most effective for the "big dollar" performers and is costly but rapid.

A second approach, which could be termed "vertical" portfolio analysis, is more suitable for the small developer. In this "top-down" approach, the developer works sequentially, from top to bottom, to find the limits sought—and then stops. The first agent to perform within those limits "wins." As noted previously, it is important to precisely define questions and understand what answers are sought with eINDs, and this kind of specificity drives vertical portfolio analysis. The goal of both approaches is to use the eIND to find the pathway to take a backroom set of preclinically developed products and evaluate them rapidly to determine which should progress in the pipeline.

Investigational Agent Analysis with an eIND

The process of investigational agent analysis can be broken down into 2 key components. The first is the identification and testing of effective labeling (quite often radiolabeling) techniques that are nondestructive to the drug or biologic and in which the radiolabel demonstrates in vivo stability. It is important to bear in mind that the point of imaging is to focus on the agent that is labeled, not the radiolabel itself.

The second is verification of comparative whole-body biodistribution imaging over time. Time is a key factor in providing evidence that the agent is nondestructive to the underlying biological, chemical, and nanostructures. This process allows developers to ask well-defined questions. In the last several months alone, I have seen eIND-associated questions that focus on pharmacokinetics/pharmacodynamics (e.g., nontarget organ localization and retention, routes and rates of clearance, and final retention in body, organs, and tissues), efficacy in selection and localization (e.g., tumor targeting, abscess localization), and safety selection (e.g., unexpected organ localization and retention).

Without imaging, answering any of these questions is extraordinarily time consuming and costly. Imaging not only makes this easier but is providing new kinds of information that, in turn, may help to create economies of time and cost as well as more timely benefits for patients. One of these areas comes from the ability to track labeled agents over time with relatively simple labeling approaches. PET and SPECT radiolabels, for example, that allow monitoring of organ localization or tumor localization from timepoint 1 to timepoint 2 to timepoint 3 provide significant information in an area in which the traditional approach was to follow patients over long periods of time, collecting urine and blood samples. This is an area in which the silo of diagnostic work in molecular imaging is connecting most effectively with the therapeutic developers.

Challenges and Summary

The challenge for all of us is to establish ways of putting all this new knowledge to work in support of advances in molecular imaging. A number of questions must be answered. How, for example, do we integrate "imaging signals" into long-term biologic and drug development? If we achieve the expected imaging of a radiolabeled therapeutic in a tumor, does that equal efficacy? If the radiolabeled therapeutic localizes unexpectedly in an organ, does this always represent a safety issue?

In summary, several points have emerged with early experience in utilizing eINDs and have been outlined here.

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