# Session 2: Strategies for Fast-Track Technological Development and Regulatory Issues

The number of submissions for new imaging agents over the previous decade decreased significantly—an ironic fact given the number of academic, industry, and government investigators focusing on these agents and the multitude of new applications and technologies in which they can be used. More astonishing is that only 2 radiopharmaceutical approvals have been issued since 1995. A large number of radiotracers are now "on the cusp" of approval. Not all are economically viable, but it is vitally important to find ways to make as many of these as possible available to researchers. This challenge has been recognized by all those involved in the development and approval process, and addressing this challenge was the focus of this summit session.

Participants in this panel and in the discussion sessions that followed outlined key challenges in the current need to accelerate technological development from initial preclinical investigations to clinical use. This focus was part of an ongoing series of workshops and retreats on both emerging instrumentation and radiopharmaceutical technologies. In June 2007 SNM convened "Development Strategies for Imminently Emerging Technologies: An Action Planning Retreat," which brought together SNM members and invited experts from government, academia, and industry to develop an action plan through which SNM can play an active role in moving molecular imaging innovations from bench to bedside. A white paper summarizing the action plan was published in an earlier issue of Newsline (2008;49[2]:37N–40N).

Among the specific actions identified at the retreat for future consideration were to:

- Review sections of the U.S. Food and Drug Administration (FDA) Critical Path Initiative (CPI) related to imaging to develop SNM proposals on regulation of molecular imaging probes;
- Engage the Centers for Medicare and Medicaid Services (CMS) to develop a mechanism for reimbursement of new molecular imaging agents; and
- Initiate discussions with FDA to define new approval pathways for molecular imaging probes.

These and other strategies informed the selection of topics and expert panelists for the session at the 2008 Molecular Imaging Summit highlighted here and in the following 5 presentation summaries. Because of time constraints and the decision to focus in depth on radiopharmaceutical and drug development, instrumentation was not included in this session—but remains a vital element in considering ways to accelerate development in our field.

## Presentations

At the summit session, Barbara Croft, PhD, Program Director in the Cancer Imaging Program (CIP), Division of Cancer Treatment and Diagnosis, at the National Cancer Institute (NCI; Bethesda, MD), provided an overview of the activities of the NCI CIP in areas that affect molecular imaging. She summarized recent reviews, renewals, and reissuances of grant initiatives and discussed CIP programs in imaging drug development. Her talk also highlighted new facilities in support of molecular imaging through NCI as well as information technology initiatives aimed at aggregating, archiving, and making available for investigation the large amount of imaging data now coming in from preclinical and clinical trials.

Wendy Sanhai, PhD, is Senior Scientific Advisor, Office of the Commissioner, at the FDA (Rockville, MD). She detailed effective strategies used by the FDA in "fast tracking" the development of several regulated projects and reviewed successful collaborative partnerships between industry, academia, and the agency. Many of these efforts to streamline drug development were based on guidance issued as part of the FDA's CPI.

George Mills, MD, is Vice President of Medical Imaging Consulting for Perceptive Informatics (Gaithersburg, MD), a PAREXEL Company. He described the advantages that both small and large drug and biologic developers can leverage through the use of the FDA's exploratory Investigational New Drug (eIND) mechanism. The eIND can be used to speed development and lower costs by allowing fast identification of "promising" from "not-so-promising" agents.

Daniel Skovronsky, MD, PhD, founded Avid Radiopharmaceuticals (Philadelphia, PA) in 2004 and is the company president and CEO. His presentation provided insight from the industry and developer viewpoint on the use of eINDs for evaluation of multiple promising imaging agents, in this case for PET imaging of amyloid plaque in investigations of Alzheimer's disease.

The final presenter in the session was David Lee, PhD, Senior Director of Health Economics and Outcomes Research at GE Healthcare (Waukesha, WI). He provided a primer on the role of health economics in drug and biologic development, outlining the tools that health economists use to assist in decision making in the commercialization of new medical technologies.

## Challenges and Trends

In discussions immediately after the presentations and in a wrap-up session, the presenters and attendees identified several challenges and trends and, within each, discussed key issues and potential solutions. A brief outline of these issues is included here, and these topics were used as starting points in creating action items and recommendations for SNM and the larger molecular imaging community. Among the key challenges identified were:

(1) **Making imaging agents available to multiple centers for trials:** Among the topics discussed was the possibility that companies may be willing to assist in making a study tracer available to multiple centers, perhaps through mechanisms that NCI has developed for contracts with companies for distribution of agents for clinical trials. Sources of funding for such distribution remain problematic.

(2) **Complex standardization issues.** Among the needs identified were: a mechanism for generating systematic protocols for clinical trials; enhanced solutions to standardization among centers; resolution of wide variations in image acquisition; and development of training centers that prepare researchers to perform clinical trials, including biomarker studies and clinical trials investigating new tracers. Other standardization issues include agent preparation and chemical manufacturing controls for agents to be distributed to multiple centers, a challenge best addressed by commercial entities. The group cited the need for guidelines that can direct trials and provide a resource for multidisciplinary preclinical and clinical investigation in molecular imaging.

(3) **Difficulty in securing approval for new agents.** Developers find it challenging to prove and document benefits to patients, including integration of imaging data with pathology and documented changes in management and outcomes. Demonstrating clinical utility is also problematic when no effective therapies are available for the disease targeted by the new agents (e.g., in Alzheimer's disease).

(4) **Bringing a new agent to market.** Participants emphasized repeatedly the need to come to the FDA with specifics, not generalities, especially when using the eIND mechanism. The example of Alzheimer's disease was used to indicate that specific questions must be answered about reasonable expectation of clinical utility and that the answers to these questions must be supported by evidence that the agent binds to the targeted receptor, that uptake and binding correlate to other biomarkers, and, ideally, that imaging positively affects clinical outcomes. The need for a call-down list for FDA advice on imaging was cited, as was the need to develop concrete examples of tracer development pipeline activities. Workgroups could be created to develop proposals, examples, and documentation in support of agents with specific types of targets (e.g., hypoxia, proliferation, amyloid plaques, etc.).

The group also identified several "important to remember" items. Chief among these was the importance of open communication channels between academia, industry, and the FDA. In these efforts the FDA's mission is to work with developers to bring the best agents to optimal applications as rapidly as possible. In fact, CMS presents much higher hurdles to development. The group also emphasized the key roles of technologists in the successful implementation of many drug and biologic development efforts.

## Recommendations

The presenters and attendees created a brief list of recommendations that, if implemented, might provide significant short- and long-term advantages in encouraging more rapid development and approval of beneficial molecular imaging agents. The group recommended that:

- SNM should develop a compendium of guidelines and principles of clinical trials;
- SNM should encourage commercial suppliers to put together a library of Drug Master Files;
- Specific examples (e.g., $^{18}$F-fluorothymidine) should be made generally available;
- Academia and industry should work with the NCI CIP to take agents from single-center to multicenter trials;
- Specialists in other disciplines outside of SNM should be engaged and invited to participate in SNM activities and strategy sessions;
- Representatives from CMS should be invited to SNM meetings to participate in discussions on these issues; and
- Other professional societies with congruent interests should also be involved in these efforts.

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