Action Plan for Emerging Molecular Imaging Technologies

As a major element of its ongoing molecular imaging campaign, SNM convened a retreat on June 23 and 24, 2007, in Reston, VA, to address issues related to the utilization of current PET probes, to the development of the next generation of molecular imaging probes and technologies, and to their regulatory approval, clinical introduction, acceptance, and reimbursement. "Development Strategies for Imminently Emerging Technologies: An Action Planning Retreat" brought together SNM members and invited experts from government, academia, and industry to develop a strategic action plan through which SNM can play an active role in moving emerging molecular imaging technologies from bench to bedside. The group discussed the current status of PET and molecular imaging, focusing on barriers to product development, approval, reimbursement, and clinical acceptance and use by oncologists and other clinicians.

Among the critical issues identified by the group was the effect that the Deficit Reduction Act has had on current utilization patterns of FDG, as well as difficulties associated with expanding rates of utilization for current indications.

In order to identify actions required to ensure appropriate and timely approval, reimbursement, and acceptance of the next generation of PET tracers, the retreat focused on 3 areas of functional imaging in which the panelists felt the greatest clinical yield was most likely: cell proliferation imaging, hypoxia imaging, and amyloid imaging. Activities focusing on these 3 areas will serve as models for addressing issues related to U.S. Food and Drug Administration (FDA) policy, standardization of procedures, reimbursement, engagement of health care communities of practice, and intellectual property concerns.

Background: The Need for Accelerated Development of Emerging Molecular Imaging Technologies

Molecular imaging targets processes at a cellular level, enabling a more comprehensive interrogation of physiology and pathology. Advances in molecular imaging have the potential to improve risk assessment, prevention, early detection, diagnosis, prognosis, and treatment of a variety of diseases. Molecular imaging can help select and guide patients for individualized therapy in drug development, clinical trials, and clinical practice.

Molecular imaging can contribute to both translational research and clinical care by increasing biological understanding from molecules to organisms, assessing disease changes, and providing information for the development and assessment of therapies. Molecular imaging is thus a biomarker to characterize disease status and to demonstrate the effectiveness of a given therapeutic intervention.

It is clear that molecular imaging represents a potentially powerful addition to the diagnostics armamentarium. Several sophisticated molecular imaging agents and technologies are currently available for clinical use. Their utility and promise are evident in the substantial number that have been studied in clinical trials. None of these agents, however, is officially approved and reimbursed. In fact, only 2 new imaging agents have been approved by the FDA in more than 10 years. This is a reality and a challenge that the molecular imaging community must face as it prepares to introduce the next generation of imaging agents.

Many barriers contribute to the paucity of molecular imaging agents in clinical practice, and overcoming these barriers will require a coordinated effort by academic researchers, industry, patient advocacy groups, and regulators. These issues fall in 3 broad categories: clinical development, regulatory approval and reimbursement, and clinical acceptance.

To successfully bring molecular imaging as a biomarker into clinical practice, we will need to ensure that the imaging biomarkers are appropriately validated, are incorporated in the earliest stages of clinical trial design, and have a significant impact on patient management. Imaging methodologies and biomarkers must be discussed with regulators early in the development process and then appropriately validated for regulatory approval. Clinicians and scientists need to be trained in clinical study design, especially for biomarker-type studies. Collaboration and data sharing are essential among industry, academia, professional societies, patient advocacy groups, and government representatives.

Opportunities for Product Development in the Next 5 Years

Three groups of radiotracers typify the promise and potential of molecular imaging, are in fairly developed stages of clinical development, identify unique biologic processes of importance as biomarkers, and exemplify the issues related to imaging biomarker development: imaging agents that identify proliferation, hypoxia, and amyloid. The biomarkers are of critical importance in cancer (proliferation, hypoxia); cancer, infection, and cardiovascular events (hypoxia); and neurodegenerative disease (amyloid). An understanding of the development of these radiotracers will provide insight into imaging biomarker development.

Cell proliferation imaging is emerging as an important tool for the characterization of solid tumors and tracking responses to therapy. Measuring proliferation is based on

Key Issues in Emerging Molecular Imaging Technologies

1. Development and Clinical Introduction Issues

- Research funding
- Intellectual property and university/industry interface
- Clinical validation
- Market size
- Costs of development are high and still growing, but the return on investment for new molecular imaging agents is uncertain.
- The research and development infrastructure, in general, for imaging agents is a fraction of that available for development of therapeutic agents.
- The shortage of patients for some clinical trials leads to extended development time frames.

2. Regulatory Issues

- Cost and complexity
- Biochemical versus disease indication
- Indication fragmentation
- Clinical trial issues of radiopharmaceutical development
- Role of molecular imaging in clinical trials
- Imaging/surrogate biomarker issues
- Lack of definition by regulatory authorities on what is required to qualify or validate an imaging biomarker
- Regulators treat imaging agents as therapeutic drugs, applying therapeutic drug expectations in terms of efficacy and safety that may exceed what is reasonable or, at times, what is possible.

3. Issues Related to CMS Funding, Clinical Acceptance, and Expansion of Indications

- Many imaging studies have been inappropriately designed or powered.
- Endpoints derived from conventional imaging experience may appear to have limited validity and utility for future molecular imaging applications.
- No outcomes parameters are available for molecular imaging that are comparable to the Response Evaluation Criteria in Solid Tumors criteria for response to therapy in solid tumors.
- Technical issues/obstacles are abundant, particularly use of different platforms and less than comprehensive standardization of manufacturing, image acquisition, and image analysis.
- Clinicians are fixed on the idea of using imaging to detect a disease and reluctant to expand their vision to use imaging to characterize disease, including changes over the course of treatment.
- Many physicians are skeptical about the usefulness of molecular imaging data.

the incorporation of labeled thymidine into DNA. ^{18}F-labeled thymidine analogs, fluorothymidine (FLT and FMAU), have been evaluated as markers of proliferation. Initial studies in humans have shown the promise of these probes; however, a concerted effort is still needed to demonstrate their utility as biomarkers of cell growth and proliferation.

Hypoxia is a process that is relevant to evaluation of solid tumors and myocardial ischemia/infarction. In cancer, for example, imaging biomarkers of hypoxia may help deal with therapeutic challenges related to resistance or enhanced tumor progression. Labeled nitroimidazoles (^{18}F-AZA, ^{18}F-MISO) have been validated as biomarkers of hypoxic tissue, and further human studies are warranted to identify areas of clinical utility. Hypoxia agents may be valuable tools for identification and monitoring of patients who may respond to antihypoxia treatment.

β-amyloid plaques are considered to be hallmarks of Alzheimer's disease and possibly other forms of dementia. A number of plaque-avid tracers have emerged as potential agents for the detection of early disease, differential diagnosis of dementias, monitoring of disease progression, and development of new antiamyloid therapeutic agents.

Action Steps for SNM and Others

The 3 biomarker groups share the same approval, reimbursement, and acceptance challenges. Although each group is biologically unique, there was consensus that SNM could drive a new set of processes applicable to all 3 and generalizable for approval of molecular imaging agents. The following specific objectives were discussed.

Demonstrating Clinical Effectiveness of Molecular Imaging: SNM should conduct a health technology assessment (HTA) of imaging agents to serve as a model for evaluating their effectiveness. For example, detection of β-amyloid plaques with PET agents could be selected as a test case to conduct an HTA to establish the process. An HTA involves assessment of the clinical utility of medical interventions through systematic review of the literature and use of appropriate qualitative and quantitative methods of synthesizing data from multiple studies. Economic models for cost-effectiveness analysis incorporate, process, and analyze multiple datasets, allowing for a better understanding of the efficacy and comparative costs of competing diagnostic and therapeutic paradigms. Part of the HTA process is reaching consensus on the most appropriate economic model. The

basic idea is to articulate the value of detecting something (in this case, amyloid plaques) from the standpoint of clinicians who are responsible for patient management decisions. HTAs should be incorporated into plans for testing and disseminating each new technology.

Ensuring Reimbursement for Use of Molecular Imaging Agents: SNM will collaborate with the Centers for Medicare & Medicaid Services (CMS) to create a protocol for obtaining reimbursement for molecular imaging agents when used to image biochemistry (i.e., as biomarkers). For example, CMS should consider approval of FDG as a marker for glucose metabolism, rather than for disease-specific indications. We will focus on demonstrating that detection of a disease process by molecular imaging contributes to the economic and clinical aspects of patient care management, the main criteria upon which CMS is likely to focus. SNM will need to identify what precedents exist and may also have to help create new processes for this effort to be successful.

Obtaining FDA Approval Based on Validation Rather Than Clinical Results: Diagnostic agents for molecular imaging, especially radiopharmaceuticals, are fundamentally different from therapeutic drugs in that: (1) they are not intended to have a physiologic or pharmacodynamic effect; (2) they are given infrequently for any single patient and almost never more than a few doses; and (3) their efficacy as diagnostic agents is related to their ability to measure molecular processes, not to their ability to treat a particular disease. As such, the process for approval of diagnostic molecular imaging agents should be substantially different from that for therapeutic drugs. SNM should develop a rationale and proposal for a new regulatory process for new molecular imaging agents, with these points in mind.

A 2-step process for testing and approval is envisioned:

(1) The first level of approval would be related to the safety and efficacy of the molecular imaging agent as a tool for detecting and measuring molecular processes in patients. The safety criteria would involve confirmation that the agent does not cause toxicity and the estimation of radiation dose for radiopharmaceuticals. In this step, molecular imaging agent efficacy would entail validation against a reference or "gold standard." For example, the use of the PET imaging agent FLT to measure tumor proliferation could be validated against an established assay of tumor proliferation, such as the Ki-67 immunohistochemical index, performed on tumor biopsy material. This level of approval would enable use of the molecular imaging agent for specific molecular assay tasks and would facilitate clinical trials to determine clinical efficacy.

(2) The second level of approval would require demonstration of clinical utility and efficacy, not simply accuracy in measuring specific molecular processes. This would require phase II or III clinical trials to determine the utility and impact of the diagnostic molecular imaging for directing patient treatment and improving patient outcomes. The nature of the clinical trials would depend on whether the intended use was to detect disease, provide prognostic or predictive data, monitor response to therapy, or some combination of these goals. For example, a clinical trial of a novel molecular imaging agent might measure early response to cancer therapy, as compared with a gold standard, such as pathologic response, disease-free survival, or overall survival.

Although the suggested approach is consistent with some aspects of the FDA's current regulations for diagnostic imaging agents, the current system is cumbersome and not well suited to diagnostic molecular imaging agents. The current Radioactive Drug Research Committee (RDRC) legislation allows early testing of some radiopharmaceuticals, including biodistribution and radiation dosimetry measurements; however, it explicitly forbids clinical trials and tests of safety and efficacy of the radiopharmaceutical. Furthermore, only radiopharmaceuticals in which the nonradioactive chemical forms have been previously studied in humans can be used under RDRC authority. The RDRC mechanism cannot be used when testing a new imaging agent in conjunction with a clinical trial of a new therapeutic agent. Finally, the RDRC legislation is quite old and has been subject to periodic changes in interpretation. All of these considerations limit the applicability and utility of the RDRC mechanism for early molecular imaging testing, as envisioned in step 1 above.

Exploratory Investigational New Drug (IND) approvals have been proposed to facilitate early testing of low-risk agents, such as diagnostic molecular agents. However, this mechanism does not appear to be intended to allow more widespread use and large-scale clinical trials, nor is it tailored to molecular imaging agents.

There is a particular need to enable greater standardization and transparency in the legislation for testing and approval of diagnostic molecular imaging agents so we may more effectively and efficiently determine which imaging agents are valid and effective biomarkers. The proposed 2-step process is tailored to facilitate the appropriate testing and approval of diagnostic molecular imaging agents and, at the same time, provide a mechanism that will lead to well-designed clinical trials prior to widespread clinical use. SNM can bring together the clinical perspective, standardization of imaging, and manufacturing standards guidelines into a single package that will assist in these types of discussions with the FDA.

A new approval process for radiopharmaceuticals, expanding upon the exploratory IND process and mimicking the oncologic orphan drug process, would make it possible to test market drugs through combined phase III and phase IV trials. Legislative changes may be needed to make this possible. SNM can work with the FDA on the RDRC and exploratory IND guidances now to make them appropriate for step 1 of the proposed approval process and begin

discussions on how to adapt the existing IND framework to accomplish the goals of step 2 for new molecular imaging agents.

SNM is continuing its initiative to support the reinstitution of the Medical Imaging Drug Advisory Committee to support further development of investigational imaging agents. We also note that the agency is continuing to actively work with SNM and the imaging industry in general to increase the availability of investigational imaging agents for incorporation in multicenter clinical trials.

Standardization: As information becomes available on molecular imaging agents that provide the greatest value to clinical patient management, SNM will develop, in concert with its membership and/or the imaging community:

- Guidelines for image acquisition, processing, and quantitation so that multicenter trials can produce comparable results;
- Platform standards for PET tracers and a set of procedures to determine whether a product meets those standards across multiple sites for all types of imaging; and
- A system to develop protocols and validate outcome measures for oncologic and nononcologic (e.g., infection) indications, including appropriate phantoms and statistical designs.

Addressing Intellectual Property (IP) Issues: SNM should work with industry and like-minded academic groups, such as the Biomarkers Consortium, to identify important compounds and develop models for IP packaging.

Topics for Future SNM Discussions

- Review sections of the FDA Critical Path Initiative related to imaging to develop SNM proposals on regulation of molecular imaging probes;
- Communicate with the Institute of Medicine (IOM) to ensure that SNM proposals are aligned with IOM recommendations concerning nuclear medicine and the use of molecular biomarkers;
- Communicate with medical professional organizations to achieve understanding of how best to integrate molecular imaging into clinical practice;
- Broaden the scope of discussion to encompass molecular imaging in general rather than focusing on radiotracers;
- Ensure that the proposals are consistent with the recommendations of the recent National Academy of Sciences report, *Advancing Nuclear Medicine Through Innovation*;
- Engage 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.

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