Session 1: Strategies to Engage Pharma

The imaging community was not particularly interested in the past in helping the pharmaceutical industry with imaging as biomarkers, because this is not our community's "product line"; that is, developing drugs is not our business. However, when it became clear that ^{18}F-FDG would be effective not only at diagnosis and staging of disease but also to monitor treatment benefits, we began to see a convergence between the ways in which imaging agents are used diagnostically for the clinical benefit of patients and the ways in which these same agents are applied in the research realm by the pharmaceutical industry. This escalates the potential for the development of products that are useful not only for diagnosis but for monitoring and quantifying treatment results. In drug development, this could translate into identifying and stratifying patients who are eligible candidates for a trial and then quantifying the results of treatment in using that same imaging agent longitudinally. The convergences of stratification and diagnosis, or quantification of treatment benefit in research and that in clinical treatment, for the purpose of portfolio management and patient care is an important new element that suggests that the imaging community and pharmaceutical industry have shared objectives with numerous areas for potential collaboration. This objective is shared also by the authorities as they consider data on safety and efficacy in allowing patients access to novel treatments and diagnostics.

Presentations

Participants in this panel and in the discussion sessions that followed outlined key challenges in satisfying the needs of pharmaceutical companies in molecular imaging, addressing, among other topics: clinical trials for biomarker validation, standards, ways to reach a consensus on and evaluate treatment response criteria, and streamlined approaches to approval mechanisms for biomarkers and diagnostic imaging agents. One question provided a foundation for discussions: "What does the pharmaceutical industry want and/or need from the imaging community?" We were fortunate to have participants who brought a range of academic, industry, and regulatory perspectives to these discussions.

Dah-Ren Hwang, PhD, Director of Imaging Services, Medical Sciences, at Amgen (Thousand Oak, CA), provided an overview of the ways in which the biopharmaceutical industry currently makes use of molecular imaging and discussed avenues that are likely to be pursued in the near future. Using examples from Amgen's collaboration with academicians and PET centers on new biomarkers, he provided specific areas in which industry looks to the imaging community for assistance and collaboration.

Dean Wong, MD, PhD, a professor of radiology, psychiatry, neuroscience, and environmental health sciences and director of the Section on High-Resolution Brain PET at the Johns Hopkins Medical Institutions (Baltimore, MD), described current molecular imaging successes and challenges in the preclinical and early clinical phases of drug discovery, using examples from neuroreceptor imaging. He also reported on a suggestion for the creation of a radiotracer clearinghouse that could serve as a new approach to sharing biomarkers across previously siloed industry and academic spaces.

Adrian Nunn, PhD, is Executive Director, International Area Head, Discovery Biology, Bracco Research USA, Inc. (Princeton, NJ). He provided another industry perspective, with special emphasis on the various viewpoints and values that the entire range of stakeholders brings to the imaging biomarker development and approval process. He addressed the need for greater clarity in guidance and proposed a 2-stage approval process that could offer distinct advantages in streamlining development, decreasing time and effort spent on nonpromising agents, and opening the way to faster approval of commercial imaging agents.

Wendy Sanhai, PhD, is Senior Scientific Advisor, Office of the Commissioner, at the U.S. Food and Drug Administration (FDA; Rockville, MD). She reviewed 3 areas of current activity in which the FDA is partnering with other groups to advance development of goals identified as part of the agency's Critical Path Initiative, including the Oncology Biomarker Qualification Initiative, the Cardiac Safety Research Consortium, and nanotechnology outreach efforts.

George Mills, MD, is Vice President of Medical Imaging Consulting for Perceptive Informatics (Gaithersburg, MD), a PAREXEL Company. He looked at the evolving "regulatory lexicon" for imaging biomarkers and emphasized the collaborative efforts in which industry must engage before reaching the qualification and approval stages. He pointed to the importance of integration of imaging and clinical assessment in driving the approval process.

The final presenter in the session was Daniel Sullivan, MD, a professor of radiology at the Duke University Medical Center (Durham, NC) and director of the Imaging Program in the Duke Comprehensive Cancer Center. He provided perspectives both from his current academic position and from his previous role as head of the Cancer Imaging Program at the National Cancer Institute. His presentation touched on the benefits of collaboration, the variables that

affect the accuracy of quantitative imaging biomarker data, and a range of potential collaborative solutions to the most pressing problems in molecular imaging agent development.

Challenges and Observations

The presenters and attendees at the breakout session that followed brought a focused and creative approach to the task of identifying strategies that SNM and the larger molecular imaging community should recognize in the pharmaceutical industry if we are to engage in mutually beneficial collaboration on hardware (image acquisition), software (image acquisition, reconstruction, coregistration, quantitation, and analysis), IT (image handling and cross-platform synthesis of data to information), and imaging agents. We followed an iterative process, first brainstorming a range of suggestions and ideas, editing these down to key recommendations, and then prioritizing the final items. In the process of these discussions, several key observations were made, including:

- The focus of these collaborations is likely to be much more on biomarkers than on approved diagnostic pharmaceuticals.
- It is important to recognize "segments" in the pharmaceutical industry. Not only do pharmaceutical companies differ in size and in scope of research, but the types of issues of most concern vary at different stages of the research and development process.
- Pharmaceutical companies are looking to the imaging community for 2 types of collaborative input: (1) to enrich the population of clinical trials with likely responders (and those at lower risk of adverse events); and (2) to quantify the effect of the drug (treatment benefit or safety) over time. Longitudinal quantitation is essential to substantiate the mechanism of the drug and is the area in which imaging is likely to provide the greatest value in the future. At the same time, it carries the greatest need for control in quality and variance.
- In a larger context, the pharmaceutical industry needs data on the clinical relevance of a specific tracer—this goes beyond simply quantifying a specific target to quantifying it in such a way that the resulting data have relevance to clinical and pathology data. This is particularly important when the biomarker is not yet approved for use as a diagnostic.
- Pharmaceutical companies also need assistance and cooperation in increasing the willingness of the FDA to accept imaging data as a component of the evidence for approval. Imaging data can be used in many ways in this context, but the highest value to the pharmaceutical industry will be as a surrogate endpoint.
- If an imaging agent works well as a biomarker that helps to substantiate use of a drug in treatment and ultimately quantify the benefits and refine the regimen, then similar utility as a biomarker might apply in the commercial space as a diagnostic. Therefore, the diagnostics industry may be interested in partnering to take that biomarker from the research and development space into the clinical space as a commercial diagnostic agent when it is included in the labeling for a drug.

Recommendations

The presenters and discussion participants honed their recommendations to 4 areas that addressed the challenges and areas of promise identified over the previous 2 days of the summit. SNM and the larger molecular imaging community should:

(1) **Develop certification of imaging:** Other efforts to do this have not progressed. SNM could develop standards and administer certification of imaging acquisition and analysis, using approaches based on successful National Institute of Standards and Technology models. Once certified (and with a regularly recurring recertification), core labs (facilities, procedures, and personnel) at universities or other settings could partner with the pharmaceutical industry to perform clinical trials in accordance with SNM certification standards that are already known to be acceptable to the FDA. This would provide a service model for the core labs and would save time and dollars spent by pharmaceutical companies defending and documenting imaging methodologies in each trial.

(2) **Provide data and advocacy to streamline toxicology and dosimetry studies as a refinement of the exploratory Investigational New Drug process.** Because tracer doses administered in development and clinical trials are quite small, one may have to prove only that they are subpharmacologic in order to understand that the requirements for therapeutic agents need not apply in their fullness. It would not be reasonable to propose a complete pass on safety checks, but these could be streamlined based on the scientific and clinical expertise of SNM and allied societies in this area.

(3) **Develop criteria for qualification of imaging biomarkers to inform FDA guidance:** SNM could take a lead role in convening the various stakeholders in a conference or other setting to determine the relevant qualifiers, to identify which elements can be generalized and which must be specific, and to come up with evidence-based documents that can inform FDA guidance on biomarker approval. An analogous process could inform the drafting of an Rx–Dx guidance.

(4) **Develop a business model around the 2-stage approval process,** based on value criteria rather than cost.

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