PRESENTATIONS

How the Biopharmaceutical Industry Uses Molecular Imaging

Over the past decade, biomarkers have been recognized as a critical element needed to improve predictability and efficiency in the process of developing more effective, more affordable, and safer therapeutics for patients. Biomarkers can provide information critical to both internal decision making (e.g., establish presence of target, evaluate biological/clinical populations, select dosages for later-phase trials, stratify study populations, and conduct interim analysis of efficacy and/or safety) and establishing efficacy and safety data for regulatory approval as a substitute for a clinical characteristic or variable reflecting patient feeling, function, or survival (i.e., as a surrogate endpoint). This presentation reviews the ways in which the pharmaceutical industry uses imaging as a biomarker, including what is needed from the molecular imaging community.

The drug discovery and development process is more challenging today than ever before. Only a small fraction of agents pass successfully through the evaluation processes, and an even smaller fraction make it through the approval process and eventually to clinical applications. Of 10,000 compounds screened, only 100 are evaluated in animals, only 10–14 advance to studies in humans, and only 1 is likely to be marketed. This entire process can take 10–18 y and cost $800 million or more. The biggest needs in drug discovery today directly address the complexity and cost involved in the current pipeline. We need to find ways to shorten the overall timeline, reduce attrition, and decrease the cost.

The U.S. Food and Drug Administration (FDA) addressed 1 approach to this triple need in documentation issued in 2004 on its Critical Path Initiative: "A new product development toolkit—containing powerful new scientific and technical methods such as. . .biomarkers for safety and effectiveness. . .—is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product." The FDA Critical Path language went on to describe the content of this toolkit: "The new tools will match and move forward new scientific innovations and will build on knowledge delivered by recent advances in science, such as bioinformatics, genomics, imaging technologies, and materials science."

Before discussing the ways in which the biopharmaceutical industry is approaching the development of biomarkers for medical imaging, it is important to define the terms we use. In a rapidly developing field, technical terms sometimes take on a life of their own and become laden with shorthand that is specific to a single field or interest group. The key terms for this discussion as defined in 2001 by the Biomarkers Definition Working Group are:

- Biological marker (biomarker): Objectively measured indicator of biological/pathobiological process or pharmacologic response to treatment;
- Clinical endpoint: Characteristic or variable that reflects patient feeling, function, or survival; and
- Surrogate endpoint: Biomarker intended to substitute for a clinical endpoint (predict benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Molecular imaging can be treated as a biomarker in many applications and can be used to answer many questions, including but not limited to: Does the drug reach/cover the target? Does the drug affect the hypothesized biologic pathway, and if so, at what exposure, magnitude, and duration? Does the observed biologic effect lead to the desired clinical effect? This last question is difficult, in that it is not yet clear whether imaging biomarkers can provide satisfactory answers.

Biomarkers have an increasing number of applications in early development of drugs. Among the preclinical uses are in vivo confirmation of activity (a critical step), exploration of exposure/response relationships, and informing selection of candidates for clinical testing. In exploratory clinical uses, biomarkers can be used to establish the presence of the agent in a target, establish the extent of target coverage, stratify study populations, evaluate activity (biologic/clinical) and safety issues, assist in dose selection, and provide valuable data supporting the go/no-go decision to continue development.

Later-phase biomarker uses include applications in registrational clinical studies, where they can be used to stratify study populations, conduct interim analyses of efficacy and/or safety, and supply information that supports documentation for regulatory approval. For drugs already in commercial use or clinical practice, biomarkers can differentiate responders from nonresponders, identify new indications, confirm diagnoses, assess safety, and monitor response to provide prognostic indices.

Imaging as a Biomarker

Imaging can be used as a biomarker in 2 ways that are characterized by the functions they serve. Clinical imaging biomarkers support imaging interpretation and provide differential diagnoses, new ways to identify lesions/disease, and a means of monitoring response to therapy. Quantitative imaging biomarkers are much more critical to the pharmaceutical industry and are, in fact, the focus of much of the excitement about molecular imaging in the drug development process. Quantitative imaging biomarkers can provide

objective measures of tissue characteristics, computer analyses and scaled evaluations, and numeric output. Moreover, these biomarkers can be incorporated into hypothesis testing.

I should note that out of all biomarkers, imaging biomarkers make up only a small (but growing) portion. Surrogate imaging endpoints make up only the tiniest subset of imaging biomarkers, but much interest is centered on new investigations in this area.

Industry and the Molecular Imaging Community

One of the questions that we hear most frequently is: how can academia work most productively with industry to advance new imaging agents into clinical use? Two examples from Amgen's work will help to highlight what the biopharmaceutical industry needs from the molecular imaging community.

In the first example, Amgen wanted to identify and develop a biomarker for a novel central nervous system (CNS) target. Among the specific parameters and practical considerations for this process were: (1) no adequate pharmacodynamic biomarker or tracer for the target was publicly available, and new tracers had to be identified; (2) target coverage would have to be established to advance the molecule in the pipeline, and the tracer would have to be ready when the candidate therapeutic went into the clinic; (3) guidance on doses for phase 2 studies was needed, especially in defining target coverage; (4) imaging studies would need to be conducted at a single institution, so that a relationship with a capable PET center was important; (5) patients and normal volunteers would be recruited, and the ability to recruit patients would be a critical asset in partnering with an institution; and (6) the ability to evaluate therapeutic candidates in preclinical models would be helpful, so that the sooner the tracer could be available, the better.

These parameters point to a range of the types of support we seek from molecular imaging collaborators. Among these (and collated to the numbered items in the previous paragraph) are: (1) the ability to identify new tracers, a process that depends on previous experience and internal capabilities; (2) the ability to meet aggressive timelines to ensure that the tracer is ready when the candidate therapeutic enters the clinic; (3) the ability to define and document the required target coverage, a process that most often requires preclinical facilities and staff; (4) demonstration of expertise and capabilities in a PET center, including interested and skilled staff, rigorous attention to scientific and procedural detail, flexibility, and documented compliance with current Good Clinical Practice and Good Manufacturing Practice standards; (5) the existence of collegial relationships with appropriate specialists to ensure adequate patient recruitment; and (6) the ability to help us speed along the development of the tracer—the ability to perform miracles, is, of course, always welcome.

In the second example from Amgen's experience, we wanted to identify a biomarker for tumor apoptosis that could provide strong support for a broad range of cancer studies. Among the specific parameters and practical considerations, several of which were similar to those for the CNS agent, were: (1) no reliable biomarker was available, and potential tracers would have to be evaluated; (2) the pharmacodynamic effect would have to be established to advance the molecule in the pipeline to be ready for first-in-human studies and approvals; (3) guidance for doses on phase 2 studies was needed, specifically in defining relevant levels of apoptosis; (4) imaging studies would be conducted at 2–3 institutions involved in first-in-human studies, which would require ensuring that the tracer and its synthesis were "portable" across sites (i.e., common protocols and centralized quality assurance/quality control would be needed); (5) the biomarker should also be useful for assessing treatment effect for future molecules, a requirement that calls for robust synthesis as well as standardized protocols and analysis procedures that can be readily translated to nonspecialist sites; and (6) the biomarker might be useful in clinical practice, in which case the tracer would need to be commercialized.

The types of support we would look for from molecular imaging collaborators (again collated with the numbers in the preceding paragraph) are: (1) active and willing collaboration in identifying and evaluating potential tracers; (2) readiness and capability for first-in-human studies, including the ability to help define the hypothesis, establish reproducibility, and meet aggressive timelines, including phase 0 (test/retest) studies; (3) the ability to define the relevant level of apoptosis, a process that most often requires preclinical facilities and staff; (4) demonstration of expertise and capabilities in a PET center, including experience with multisite issues, especially those relevant to assessing the same tracer at multiple institutions; (5) ability to call on the services of a central radiopharmacy and the capabilities of a core lab; and (6) commitment, interest, and ability to successfully partner in pursuing regulatory approval.

Conclusion

Biomarkers are clearly a key element in future drug development, and molecular imaging is already having beneficial effects in early drug development. If we are to expand on developing biomarkers and see them through from the initial discovery phase through clinical applications, cooperation among industry, academia, and regulatory agencies is needed. Strong partnerships between the molecular imaging community and biopharmaceutical companies provide 1 of the most promising pathways for accelerating commercialization of new tracers.

Dah-Ren Hwang, PhD
Jeff Evelhoch, PhD
Amgen
Thousand Oaks, CA