Industry Watch

Medical Imaging in Drug Discovery, Part I

While economic, scientific and regulatory questions still need to be answered, imaging technologies have the potential to increase efficiencies in many areas of drug research. This first of a three-part series examines initial applications in clinical trials and industry's growing interest in monitoring biomarkers throughout discovery and development.

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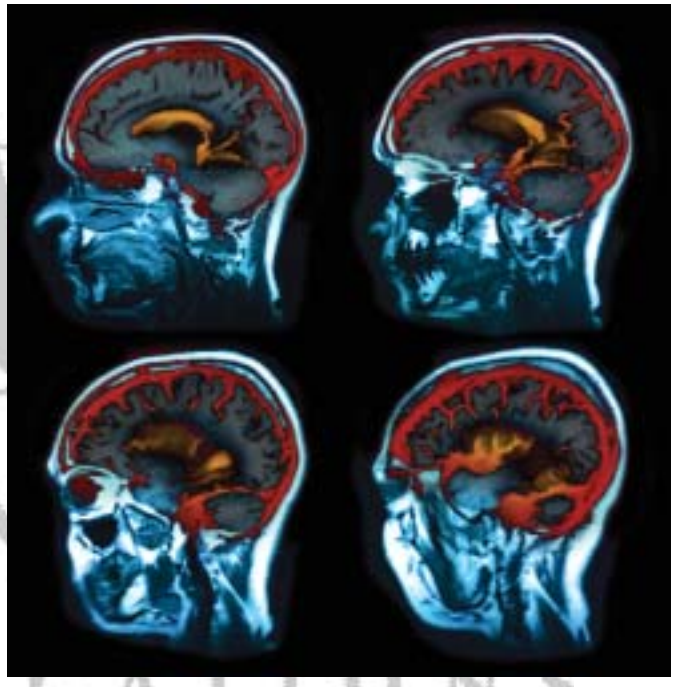
A couple of Christmas seasons ago, a series of radio advertisements were running on some of the Boston area's "oldies" stations. The announcer encouraged listeners to "give the gift of peace of mind." He suggested that the gift was the perfect stocking stuffer for loved ones. What could be better, he asked, than to help your beloved family members sleep more easily, knowing that they are healthy. What was being pitched? A gift certificate for an MRI.

Most readers will agree that giving the "gift" of a magnetic resonance imaging (MRI) scan is a bit ghoulish. But it does point to just how ubiquitous medical imaging has become in our society. That's not without reason. In a 2001 survey, physicians ranked MRI and computed tomography (CT) — two high-tech scanning devices used as diagnostic tools — as the most important innovations of the last quarter-century (1).

All sorts of medical imaging tools are used to make diagnoses. The typical hospital radiology department has at its disposal MRI and CT scans, as we've already mentioned. There also is the positron emission tomography — or PET — scan, which produces pictures of metabolism that cannot be obtained with CT, MRI or conventional X-rays (although it's not as widely available as the others). Then, there are ultrasounds, which use sound waves to obtain a medical image or picture of various organs and tissues in the body. There also are specialized techniques for specific purposes, such as mammography; another newer tool, called virtual colonoscopy, allows physicians to examine the large bowel or colon to detect polyps and cancers.



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Researchers are exploring the possibilities of using medical images, such as MRIs, to facilitate development of marketable pharmaceutical products.

For the most part, imaging technologies have been used to help make diagnoses in individual patients in order to guide therapeutic decisions. But for almost a decade, and especially in the past couple of years, there has been a shift to a broader-than-diagnostic view of the value these technologies have. More researchers are looking at how medical imaging can be used to facilitate development of marketable pharmaceutical products. That's the focus of this column, the first of a three-part series on the application of medical imaging in drug discovery and development.

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Imaging's Growing Importance

Dare we say that MRI has become, and will continue to remain, indispensable to the pharmaceutical and biotech industries? That's what BioInformatics LLC (Arlington, Virginia, USA) concluded in a 2002 report (2). The report explains, "structural data is critical in determining how a potential drug will bind with a target molecule. Nuclear magnetic resonance (chemists refer to the technology as NMR, while the medical community prefers MRI) screening of multiple targets and the rational design of high-affinity ligands now are a main focus of drug discovery efforts… Adaptations of current NMR methods, along with improvements to instrumentation, currently are being developed, as scientists implement high-throughput automated approaches to accelerate the drug discovery process. Such approaches are necessary in order to fully characterize the large number of proteins currently being generated by structural genomics research."

PET, too, is playing an increasingly important role in drug development. In clinical trials, the technology evaluates whether a drug has had a biological effect, how the effect compared with other agents, whether the drug reached the target organ and whether it did so at an effective concentration.

At the center of much of this research are biomarkers. A biomarker is "a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes on a clinically meaningful endpoint" (3). Massachusetts General Hospital (Boston, Massachusetts, USA), in conjunction with the Harvard-MIT Division of Health Sciences and Technology (Cambridge, Massachusetts, USA), has established a Center for Biomarkers in Imaging (Boston, Massachusetts, USA) to advance this research.

Beginning to Consider Biomarkers

Why is the study of biomarkers important? The Center for Biomarkers in Imaging web site (www.biomarkers.org) offers perspectives in three areas: academia, government and industry. From the academic perspective, the center considers that "imaging with advanced modalities such as magnetic resonance and PET allows identification and quantification of physiological processes — such as brain function — with MR spectroscopy. These same modalities, together with experimental methods such as molecular imaging, provide insight into the pathophysiology of disease, as seen with nuclear and optical imaging methods that demonstrate tumor metabolism and tumor-associated angiogenesis." Further, "imaging biomarkers also could assist academic researchers and scientists to more efficiently assess promising new therapies" (4).

From the industry's perspective, "appropriate application of imaging biomarkers in both clinical trials and clin-

ical use is yet another promising area. Imaging offers the potential for more timely and quantitative data than traditional trial endpoints of morbidity and mortality." Importantly, the center says, "biomarkers in imaging hold the promise of more efficient and accurate medical product evaluation, decreasing both the time and cost involved in successfully bringing new products to market" (4).

FDA certainly is ready to consider biomarkers. FDA Commissioner Mark McClellan, looking to speed up drug approvals, asked rhetorically in a telephone interview with a *Boston Globe* reporter last summer, "Are there valid biomarkers, valid indicators, that we could observe early on, that are highly predictive of clinical benefits that could take years to observe" (5)? And as we write this column, the agency has announced that it is "commencing an initiative to encourage use of imaging technologies to develop surrogate endpoints for drug submissions" (6).

The FDA initiative (which we'll discuss in more detail in our next column) is good news for the pharmaceutical industry, which despite continued profitability, is reeling from the 15 years it takes — and the $800 to $900 million that must be invested — to get a new drug to market. Given that only one in approximately every 5000 of the targeted molecules being generated by genomics, proteomics and high-throughput screening techniques ultimately will be approved as a new drug, one easily can understand why the pharmaceutical industry would embrace any technology that appears to offer efficiency improvements.

As the Center for Biomarkers in Imaging explains, "biomarkers in imaging, appropriately and knowledgeably applied, offer the potential of increased efficiency throughout the research and development spectrum. In pre-clinical and early clinical tests, imaging biomarkers have delineated compounds that perform as anticipated, and others that are clear failures, allowing resources to be directed to the most promising applications far earlier than would otherwise be possible" (4). There are several examples of imaging biomarkers being used in Phase 2 and Phase 3 clinical trials. Genentech Inc. (South San Francisco, California, USA) used tumor volume, as measured by CT scan, in the approval of Herceptin for metastatic breast cancer. Berlex Laboratories (Montville, New Jersey, USA) employed lesion volume by MRI in the successful application of its treatment for multiple sclerosis, Betaseron. And the uses are not limited to drugs; imaging biomarkers can be used for testing devices, too. Luminal diameter by angiography has been used as a secondary endpoint in the evaluation of cardiac stents, and FDA officials have indicated a willingness to consider this as a primary endpoint. "In all these cases, imaging biomarkers almost certainly made possible considerable savings in both time and resources" (4).

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Big Players Getting Involved

Greg Sorensen, the Center for Biomedical Imaging's director, makes the point for the industry even more directly in his slide presentation, *Imaging and Biomarkers*, which was presented at the fall planning workshop at Harvard–MIT's division of health sciences and technology. "Imaging in drug development," he writes, is "not about science, but about dollars" (3). He estimates savings of from $10 to $30 million per project thanks to the application of advanced imaging technologies.

It should come as no surprise, then, that leading companies are jumping on the medical imaging bandwagon. Companies such as General Electric, through its GE Medical Systems (Waukesha, Wisconsin, USA) subsidiary, are investing heavily. In November 2003, GE Medical Systems announced an agreement with Suinsa Medical Systems (Madrid, Spain) to be the exclusive worldwide distributor for that company's small-animal PET scanners. Here's how GE Medical Systems explains its business: the company "brings molecular imaging expertise with multi-modality, preclinical and clinical imaging offerings, providing a bridge between novel drug discovery and today's clinical needs" (7).

An exclusive distribution agreement, though, is small potatoes compared to GE Medical Systems' announced purchase of Amersham Plc (Little Chalfont, Buckinghamshire, United Kingdom) a month earlier. When completed, this will be a $9.5 billion transaction. Amersham is considered to be a world leader in diagnostic imaging agents. The merger probably will be completed by the end of this year; Jeffrey R. Immelt, GE's chairman and CEO, says the deal "will allow GE to accelerate the development of molecular imaging and personalized medicine to where it will be possible to predict and treat disease with therapies tailored to the individual" (8).

GE Medical Systems is positioning itself to be a device and service provider to the pharmaceutical industry, where the imaging of biomarkers is taking off. The Center for Biomarkers in Imaging cites Pfizer (New York, New York, USA) and Novartis (Basel, Switzerland) as two firms already using the technology. Of course, this is only the tip of the iceberg.

A Long Way to Go

There's a long way to go with this emerging use of a now familiar technology. Regulatory issues need to be addressed, but we're interested in the economics and the science. In our next two columns, we aim to expand the discussion of medical

imaging in drug discovery and development and to explore the use of the technology at the molecular and single-cell levels. Our discussion will be guided by the view that solving the pharmaceutical industry's efficiency problems has direct benefits for society. After all, if we can get effective drugs to market faster and at less cost, everyone should stand to benefit.

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The stakes are high, as has been the case with all the new developments in science and technology we've been discussing during the past two years of this column. The amount of dollars involved is substantial. The potential impact on the development of personalized medicine cannot be understated. Following this unfolding story, we think, will be an exciting ride.

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