indicated receptor occupancy. However, this was followed by repeated demonstrations of lack of efficacy at higher and higher doses. Although tremendous industry investment went into this effort, doubt now currently surrounds the idea that these compounds may become effective antidepressants. One of the challenges, then, is that we cannot know ahead of time what level of occupancy is needed for efficacy.

Other important cautions in thinking about potential imaging biomarkers include the fact that some radiotracers used for disease progression (for example, in Alzheimer's disease and Huntingdon's disease) may be better for initial diagnosis than for monitoring disease with or without therapy. ^{11}C-PiB, for example, may be sensitive in Alzheimer's disease at baseline, but ^{18}F-FDG may provide a clearer assessment of changes over time. In addition, the concern is that many of these amyloid imaging compounds may be useful in cross-sectional diagnoses but the information gained in these diagnoses may not be valuable in changing either the natural history or treatment.

The Radiotracer Clearinghouse: A New Approach for Sharing Biomarkers

A final area of challenge is in intellectual property and sharing of tracers. Too much duplication of effort (e.g., toxicology and dosimetry studies) is devoted to the same limited number of successful radiotracers. Individuals from the American College of Neuropsychopharmacology and Society for Non-Invasive Imaging in Drug Development initiated a concept of sharing in a trusted environment. This is a proposal to create a novel way to share PET radiotracers among academic and industry scientists even before full public disclosure, because of concerns about trade secrets or even under the FDA research exemption to use patented or publicly known radiotracers. This grew out of discussions between industry research and development leaders and academic PET investigators in the CNS area.

This clearinghouse would: (1) provide a central database of companies, academic centers, and radiotracers; (2) provide a neutral and confidential intermediary model to encourage collaboration among companies and between companies and academic PET centers; (3) establish a tier-based annual fee system of membership and tiered charges for involvement by clearinghouse staff; (4) meet the requirements of 4 case examples developed by the planners and follow templates developed for other technological development efforts; and (5) provide a mechanism to share radiotracers globally across any academic or government PET center and industry, with the capability to facilitate public disclosure as well as confidential interactions for all targets and therapeutic areas. Many of us believe that these clearinghouse principles are critical to the development of new research tools and in the application of imaging technology to drug development. They can be implemented within a standalone nonprofit enterprise or incorporated into another entity. This interaction can be global and is not dependent on specific countries or regions but remains respectful of local cultures and regulations.

Dean F. Wong, MD, PhD
Johns Hopkins Medical Institutions
Baltimore, MD

Imaging Biomarkers, An Industry Perspective

The imaging industry, pharmaceutical companies, the U.S. Food and Drug Administration (FDA) and other government agencies, and payers all look to imaging as critical to personalized medicine, but each from a different and sometimes mutually exclusive viewpoint. An emphasis on drug development and qualified biomarkers obscures the need of the imaging industry to obtain new validated (commercial) products. Clearly both are needed, but the current regulatory architecture is not well described and presents unnecessary risk. This presentation describes some of the issues that qualified and validated imaging biomarkers face and suggests a new architecture that may meet the needs of all parties.

The FDA recognizes 2 classes of biomarkers: those that predict the presence of disease or characterize disease and those that predict response to therapy. A qualified imaging biomarker is one that is established for some aspects of drug development providing data on safety or efficacy but that does not have specific labeling as an approved drug. Examples are unsealed sources for radiation dosimetry or the Response Evaluation Criteria in Solid Tumors (RECIST)/World Health Organization criteria for tumor response. A validated imaging biomarker is an approved drug with the corresponding indication to assure or improve safety and/or efficacy. An example is whole-body biodistribution assessment in Zevalin and Bexxar. It is important to note that commercialization is tied to validation.

Every group involved in drug or agent development has different goals and different ways of meeting these goals. Companies who develop imaging (diagnostic agents) want faster, cheaper successful clinical trials, as do companies who develop therapeutic agents. Diagnostic imaging companies would like to get from the validation side through to commercialization as quickly as possible, whereas the

therapeutic companies want to have qualified imaging agents that they can use to prove their success in drug development. FDG is an example of a commercial imaging agent that is neither qualified nor validated and therefore not as useful as a biomarker as it might be.

The government wants to reduce health care spending increases, obtain better responses to treatment, and ensure optimal uses for drugs. Payers demand evidence of the clinical value of a drug and cost effectiveness. Patients and physicians are demanding more personalized medicine and better outcomes. Validated imaging biomarkers have the potential to satisfy many of these criteria.

Biomarkers can also be categorized as general and specific. General biomarkers target processes that may accompany a variety of diseases or physical states. Among the most well-known general biomarkers and the processes they target are FDG and glycolysis, fluorothymidine (FLT) and proliferation, fluorocholine and lipids, annexin-V and apoptosis, and dynamic contrast-enhanced MR imaging or dynamic contrast-enhanced ultrasound as nonmolecular markers of microvessel density. Specific markers target processes that are associated with specific diseases or illnesses. Among the most well-known specific biomarkers and their targets are octreotide and neuroendocrine tumors; Dopascan injection for Parkinson's disease; Pittsburgh Compound B (PiB), FDDNP, and IMPY for Alzheimer's disease; and metaiodobenzylguanidine for heart failure. To move forward in molecular imaging, both types of biomarkers must be validated and qualified.

Numerous protein targets in oncology have been successfully addressed using targeted drugs and imaging agents that observe such systems and are at various stages in the development and approval process. A few of these include trastuzumab for epidermal growth factor receptor 2 (EGFR2); cetuximab, erlotinib, and gefitinib for EGFR1; lapatinib for EGFR1/2; sorafenib for vascular endothelial growth factor receptor 2 (VEGFR2) and platelet-derived growth factor receptor (PDGFR); bevacizumab for VEGF/VEGFR2; sunitinib and imatinib for PDGFR; and bortezomib for proteasomes.

Heterogeneity in Cancer

One of the challenges in developing new biomarkers and in imaging potential treatments is the essential heterogeneity of tumors. Examples from the literature demonstrate the complexities posed by this heterogeneity.

In a study by Shah and colleagues (*Cancer Res.* 2004; 64:9209–9216) from the University of Michigan School of Medicine (Ann Arbor, MI), 103 metastases were obtained by rapid autopsy from 30 patients with hormone-refractory prostate cancer (HRPC). The researchers concluded that metastatic HRPC has a heterogeneous morphology, immunophenotype, and genotype, indicating that "metastatic disease" is a group of diseases even within the same patient. They concluded that "an appreciation of this heterogeneity is critical to evaluating diagnostic and prognostic biomarkers as well as to designing therapeutic targets for advanced disease."

In a study by Torres and colleagues (*Breast Cancer Res Treat*. 2007;102:134–155) from the Portuguese Oncology Institute (Porto, Portugal), genomic hybridization was performed on 122 tissue samples from 60 patients with breast cancer, including 34 tumor samples obtained from different quadrants of 9 breast carcinomas as well as paired primary metastatic samples from 12 patients. The researchers concluded that "primary breast carcinomas may be composed of several genetically heterogeneous and spatially separated cell populations and that paired primary breast tumors and lymph node metastases often present with divergent clonal evolution."

"Personalized" medicine in oncology, then, is even more complex than "the right agent for the right patient." Right now, targeted oncology drugs are used in patients who have been demonstrated to have the target in excised tumor tissue. In fact, a requirement for documented presence of the target has been included in product labeling of about 70% of targeted oncology drugs approved by the FDA in recent years. However, this has not necessarily translated into greater efficacy. One example can be found in breast cancer with Herceptin, which in the 30% of breast cancer patients who are human EGFR2 (HER2)-positive is effective in only 30% (resulting in a 9% response among all patients with breast cancer). This relatively low response rate is compounded by significant rates of cardiotoxicity (18%). However, the FDA has approved Herceptin for neoadjuvant therapy, meaning that many more patients, including younger patients, could be treated with no response but life-threatening cardiotoxicity and sequelae. Other examples include Avastin and Erbitux, with 10% and 11%–14% response rates, respectively, in patients with metastatic colon cancer.

In these cases there is no doubt that the therapeutic agents are good for the minority who respond, but what about the others? If all patients are different and cancers can be different even within the same patient, then molecular imaging is the only route to characterizing these differences and providing truly personalized medicine. The reasons that molecular imaging is needed in drug development, then, include certain givens: (1) the presence of target is necessary but not sufficient; (2) variable responses from metastases may be noted in the same patient; (3) targeted drugs will not control every metastasis, because not every metastasis (even in the same patient) is the same; (4) each metastasis has a different propensity for killing the patient; (5) serum analyses provide only an average signal of output from all lesions; and (6) biopsies characterize only the tissues that were biopsied.

The Cost of Molecular Imaging

One of the questions that is often asked is how the high costs of molecular imaging can be justified. An example is the case of 3 targeted drugs: Erbitux, Herceptin, and Avastin, each of which in 2007 had sales of about $2 billion. Given

a quite generous estimate of an average 20% response rate for these agents, then a total of ~$2 billion per drug × 3 × 0.8, or ~$4.8 billion in potential savings, are wasted each year because we are not treating the right patients—for these 3 drugs alone. The therapeutic drug companies recognize that there is a potential for lost sales if better patient selection is achieved. However, if imaging can be used to more accurately identify those patients who will respond and those patients who will not, then the savings can be redistributed in ways that are better for patients and, ultimately, better for all parties with an interest in health care.

A Quest for Clarity

In order to move forward in more accurate molecular imaging development, specific challenges must be addressed. In June 2004, the FDA issued guidance for industry in developing medical imaging. The areas in which the agency believed imaging would be most useful were:

(1) Structure delineation: a topic that is beyond the scope of this presentation.
(2) Disease or pathology detection or assessment: the process of monitoring and assessing the extent, rate of progression, or other aspects of a specific disease in patients previously diagnosed with that disease. One example would be a radioloabeled monoclonal antibody that can attach to a unique tumor antigen to detect the presence or extent of a mass with this tumor antigen (e.g., breast cancer). This is very much in line with molecular imaging agent development.
(3) Functional, physiological, or biochemical assessment: the process by which a radiopharmaceutical assesses metabolism of a substrate where the normal pattern of metabolism in that organ or tissue is well known. This is somewhat challenging in tumors, but molecular imaging developers can find ways to address this.
(4) Diagnostic or therapeutic patient management: The ability to provide information (such as the presence of a certain receptor in a specific type of cancer patient) that can predict survival or patient response to a specific type of therapeutic drug.

The way seems open, then, for the development and approval of molecular imaging agents of varying types. The problem, however, is that the biomarker approval process is unclear. Even the FDA admits this. In the 2006 Critical Path Opportunities List, the FDA noted: "The process and criteria for qualifying biomarkers for use in product development should be mapped." That is a euphemism; they are actually saying the process is broken. The FDA went on to ask the following questions: How can biomarkers be used most effectively to evaluate dose response in later trials? What biomarker evidence is appropriate to guide selection of patients for clinical testing? What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy? (Note here that the FDA was referring to a qualified biomarker, not even a validated biomarker.) The fact that these questions remain unanswered has enormous implications for companies contemplating imaging biomarker development. We currently have no fixed target at which we can aim. It is essential that the risks associated with this development be clarified.

Looking to existing approved molecular imaging agents for examples and guidance provides little insight. ^{18}F-FDG was approved to assess glycolysis for the brain (1994), in cardiac applications (1999), and in oncology (1999). Attempts to secure specific information on exactly which data were used to establish FDG in that approval have not been successful. FDG, in fact, was approved only after a literature review. The other approved agent is ^{111}In-pentetreotide (Octresoscan), which was approved in 1994 for localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors. Both of these agents were approved far too long ago to provide significant insight into today's approval pathways.

The approved indications for ^{18}F-FDG PET sound very much like the general types of indications that are currently targeted by developers of other molecular imaging agents. The ^{18}F-FDG indications include: (1) identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures; (2) assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer; and (3) in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function.

We are all facing the challenges posed by cost versus value considerations in imaging agent development. Therapeutic agents are distinguished mainly by efficacy (value); if the value is high, a higher cost is deemed more acceptable by payers. Diagnostics, however, usually are distinguished by cost as well as efficacy. At least right now, the perception is that imaging agents have low value but a high price. This perception must change if we are to realize the full potential of personalized medicine.

Proposed: A 2-Stage Approval Process

A list of radiolabeled imaging agents currently in development includes 3 agents in preclinical trials and 7 in phase 1/2 trials on the NIH site, as well as 11 phase 1/2 and 1 phase 3 agent under commercial development. The earliest approval date for any of these is 2010, a timeline that is more likely to slip until after 2012. The extent to which each of these agents can be "personalized" depends on the indications for which they are approved.

Academia, government, industry, and payers all have slightly different interests. A possible strategy of 2-stage approval may provide a way not only to streamline the

approval process but to satisfy to some extent the demands of all stakeholders. Using this approach, more imaging agents could be qualified more quickly, pharmaceutical companies would have more tools to speed up development, and early qualification of an imaging agent could lead to cleaner, faster trials and approval of commercial imaging agents.

The proposed 2-stage approval process is not a panacea; in fact, with each positive aspect of this solution potential problems can be identified that must be addressed. In general, the 2-stage approval process would include:

(1) Early conditional approval of all molecular imaging agents with the Coverage under Evidence Development mechanism (1 example of such an approach is the current National Oncologic PET Registry). This conditional approval would be for broad initial indications. Safety would be established to secure this approval, but no rigorous proof of benefit to the patient would have been established in controlled clinical trials in the numbers now required for full approval. The implication would be that such a benefit exists and that patient management might be changed on the basis of imaging. One obvious question would be about the financial implications of such conditional approval for imaging companies.
(2) These initial approval studies would be followed by studies to further define appropriate uses (perhaps coupled with a sunset provision). Narrower indications with proof of efficacy would be submitted for full approval, which could also lead to increased reimbursement.

Conditional approval would yield a validated diagnostic biomarker for use by pharmaceutical companies in clinical trials to measure biochemistry. To be worthwhile to an imaging company, the entirety of this 2-stage program would have to represent significant advantages. Many challenges would have to be met before such a system could be implemented.

The Gold Standard Challenge

One of the challenges in developing a molecular imaging agent is the requirement that safety and efficacy for detecting and measuring molecular processes in patients must be validated against a reference or "gold standard." Current FDA guidance states, "If no standard of truth applies to the proposed use of a medical imaging agent for functional, physiological, or biochemical assessment, we recommend that a clinical trial be conducted to determine that the findings are clinically useful." What is being asked for here is an outcomes trial, which fits nicely with the idea of the second stage of a 2-stage approval process.

But significant questions remain about the standards against which molecular imaging agents can and should validate their safety and efficacy. The ability of FLT, for example, to assess tumor proliferation may be validated against an established (and we must, of course, ask by whom) assay, such as the Ki-67 immunohistochemistry index in tumor biopsy material. This might work in some cases, but how can we validate FDG assessment of glycolosis in patients? In animals this is easy, but it presents a major problem in humans. And even when biopsy is possible, validating ligand binding by immunochemistry against a target presents potential difficulties. In addition to possible discordance between the detection of protein presence and actual function, questions remain about who validates antibodies for these tests, how this is done, and how many are likely to be validated in the future.

The nature of the standards in biopsies adds additional levels of difficulty. The RECIST standards include up to 5 measurable lesions per involved organ (10 in total) as target lesions. Bone and many other types of lesions are categorized as nontarget lesions and, therefore, are considered unmeasurable. What happens, however, when attempting to assess a patient with hormone-refractory prostate cancer using these criteria? And if more than 5 measurable lesions are detected in an involved organ or more than 10 in total, which ones are to be used as target lesions? Molecular imaging, of course, would be the answer, but that would be putting the metaphorical cart before the horse if we are looking to RECIST to validate imaging.

An example from the literature illustrates this difficulty. Morris et al. (*Urology.* 2002;59:913–918) correlated abnormalities on CT, MR imaging, and bone scans with results from ^{18}F-FDG PET in 17 patients with progressive metastatic prostate cancer. On PET and/or bone scan, 134 osseous lesions were identified (95 lesions [71%] on both; 31 [23%] on bone scan alone—of which 30 were stable; 8 [6%] on PET alone—all of which were active). The authors concluded that ^{18}F-FDG PET can discriminate active osseous disease from scintigraphically quiescent metastatic lesions in these patients. The authors did not do biopsies in this study; instead they compared the index scan to previous and subsequent scans to track changes in the lesions.

Looking Ahead

If some therapeutic drugs have surrogate marker approval, why cannot imaging drugs? How might this be achieved? A possible answer would be to define clinical imaging parameters for a target molecular imaging agent correlated with limited (biopsy) data in the same patient. This might then be correlated against historical biopsy data obtained during therapeutic clinical trials for which outcomes are already known. This approach might work for a retrospective imaging agent developed for an already marketed targeted drug.

We must remember that every stakeholder in drug development has different goals. Therapeutic companies might support the development of a qualified biomarker, but the company making the diagnostic must believe that it can then go on to validate/commercialize that biomarker. Other-

wise, they have no reason to be involved in the development process. Tradeoffs would be needed on all sides.

Significant questions remain unanswered: How can an imaging company get reimbursed for use of a drug as a qualified biomarker? Is biochemical assessment of lesser value than patient management? What if an imaging agent is available both as a validated biomarker (commercial imaging agent with narrow labeling) and as a qualified biomarker (noncommercial imaging agent used under a broad biochemical indication)? What if an agent is a good qualified biomarker but is subsequently found to be not commercially viable and thus is not developed or supported by the imaging agent company? Does that mean that the qualified biomarker is then unavailable for further studies?

Adrian Nunn, PhD
Bracco Research USA Inc.
Princeton, NJ

Strategies to Engage Industry

The purpose of this presentation is to share some of the processes that we at the U.S. Food and Drug Administration (FDA) are using to reach out to our many and varied stakeholders to address health issues. These efforts are happening under the framework of the agency's Critical Path Initiative (CPI). The CPI is the FDA's effort to stimulate and facilitate a national process to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured. The initiative was launched in March 2004 with the release of the report *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf). The report diagnosed the scientific reasons for the recent decrease in the number of innovative medical products submitted for approval and noted with concern the rising difficulty and unpredictability of medical product development. The resulting goals were designed to reap the anticipated public health benefits from the promises of the biomedical advances of the 21st century.

In March 2006, the FDA announced the release of the *Critical Path Opportunities List* (www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf). This priorities list, which was developed with extensive public input, described the areas of greatest opportunity for improvement in the product development sciences and provided 76 concrete examples of ways in which new scientific discoveries—in fields such as genomics and proteomics, imaging, and bioinformatics—could be applied during medical product development to improve the accuracy of tests used to predict safety and efficacy of investigational medical products. The CPI priorities, each of which contains numerous opportunities that are ripe for collaboration, include: (1) better evaluation tools; (2) streamlining clinical trials; (3) harnessing bioinformatics; (4) moving manufacturing into the 21st century; (5) developing products to address urgent public health needs; and (6) addressing the needs of specific at-risk populations.

This presentation looks at only a small percentage of the first of these priorities: better evaluation tools, which includes areas of importance for molecular imaging such as biomarkers and predictive and evaluative tools. Three case examples of current activities will demonstrate the diverse ways in which the FDA is partnering with other groups to advance development in these areas.

Oncology Biomarker Qualification Initiative

In 2005, the FDA partnered with the Centers for Medicare and Medicaid Services (CMS) and the National Cancer Institute (NCI) to address the extensive cross-sector and multidisciplinary efforts needed to understand and develop the clinical utility of a new generation of biomarker technologies to be used for detection, diagnostic, and clinical assessment tools in cancer research. Each group had a stake in this collaborative effort. Such new biomarker technologies, if proven effective in assessing therapeutic response in clinical trials and thereby "qualified," have the potential to be adopted by the FDA as assessment tools for use in guidance on cancer drug development. CMS is interested in the development of evidence to inform reimbursement decision making about existing or new treatment regimens. NCI is interested in eliminating suffering and death as a result of cancer and seeks to develop technologies to improve the detection, diagnosis, treatment, and prevention of cancer. Earlier, in 2003, the FDA and NCI had formed an Interagency Oncology Task Force that served as a convening body and the source of concepts for a memorandum of understanding (MOU) among the FDA, NCI, and CMS to support collaborations on oncology-related issues, including development and qualification of biomarkers and predictive tools for clinical benefit, and standardization of approaches for evaluating biomarkers and tools in diagnosing, staging, and assessing therapeutic response in cancer clinical trials. This MOU was signed in January 2006, formally launching the Oncology Biomarker Qualification Initiative (OBQI).

The group identified mutual priorities and agreed to codevelop concept papers and justification for scientific projects. From the beginning it was realized that many of these projects and collaborations would go beyond NCI/FDA/CMS intramural collaborations to public/private partnerships involving multiple partners. Four priorities