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?

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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

were identified: cancer imaging, molecular assays and targeted therapies, clinical trials, and data mining.

The initial step within the Department of Health and Human Services infrastructure was to establish working groups and steering committees that focused on science and the public within well-specified parameters. The idea was to identify specific projects and then secure input from public/private partners on developing protocols, elements of the protocols, and pathways for implementation and funding. The ultimate goal for all of these projects and of the OBQI itself is to put the resulting data in the public domain—a process from which all stakeholders will benefit. Private partners (who are mainly industry but can be professional organizations as well) will get the know-how they need, access to innovative evaluative tools, and input into the process. The FDA can use the data to inform guidance development and standards setting and can bring more evaluative tools back to our reviewers at the agency to assist in reviewing new products. NCI can use these data to evolve best practices and expand on clinical data. CMS uses these data as evidence-based information on which to base reimbursement decisions.

Two ^{18}F-FDG PET Projects

Two imaging biomarker qualification demonstration projects were developed under the OBQI, involving ^{18}F-FDG PET to assess response to therapy in non–small cell lung cancer (NSCLC) and in non-Hodgkin's lymphoma (NHL). Data coming from these studies could ideally provide a new surrogate endpoint to be used by the FDA. As part of the process of developing the blueprint for solving the problem of clinically qualifying ^{18}F-FDG PET as a biomarker in response to therapy, it was important to remember that the resulting information would be shared—developed by stakeholders and shared with stakeholders. The economic justification for these public/private partnerships was clear to both industry and the agencies involved. If private entities perform these types of studies separately and alone, then any resulting data are siloed. And public entities do not have sufficient resources to pursue all of the potential projects identified. From the industry drug development viewpoint, biomarker qualification efforts also promised to provide a significant "bang for the buck."

The Lymphoma and Leukemia Society sponsored the first protocol planning meeting for the NHL study—an example of additional stakeholder participation in these efforts. In looking at ways to implement and fund this study, we determined that an NCI Cancer and Leukemia Group B (CALGB) study, already ongoing, on which patients with NHL were on standard therapy, provided a setting in which the utility of ^{18}F-FDG PET to assess response to therapy could be incorporated. The OBQI study was activated in May 2007, and, as of January 2007, 4 CALGB sites had qualified, with 12 additional sites in the process of qualification and 10 additional CALGB sites contacted. The Imaging Review Charter template is being developed by the Pharmaceutical Research and Manufacturers of America (PhRMA) and the FDA. Data from this study will determine whether the addition of ^{18}F-FDG PET imaging leads to earlier identification of responders and nonresponders, with accompanying benefits in patient management and decision making.

The OBQI ^{18}F-FDG PET NSCLC Study was activated in March 2007, with 17 sites qualified as of January 2008 and 13 additional sites expressing interest. The Imaging Review Charter was produced by PhRMA and the FDA.

As noted previously, these kinds of studies will yield data that provide value to all stakeholders. The NCI, as well as patients and academicians, will have better clinical data about ^{18}F-FDG PET in these disease settings to support more effective treatment and management. FDA will have additional information for evidence-based regulatory decisions. Pharmaceutical companies can look to a more efficient drug development and approval path and for better early response criteria that can inform go/no-go development decisions. The medical device industry will benefit from these types of data by ultimately having a larger market for PET, PET/CT, and PET/MR imaging instruments. CMS will have the clinical evidence it demands to define reasonableness and need in expanding indications for approval of ^{18}F-FDG PET imaging indications.

Assessing Cardiac Safety

The needs addressed in a recent partnership to assess cardiac safety have many parallels with those of molecular imaging, and the project as a whole provides an excellent example of ways in which the FDA has partnered with other agencies and entities to solve major problems in public health. To develop meaningful study data on cardiac safety (and also to develop such data in large-scale imaging studies), we need to: enter and manipulate large volumes of digital data; retain raw digital data and integrate these with clinical data; develop standard methods of collection, archiving, and annotating; develop standard lexicons/vocabularies; and develop relational databases, including subject and study demographics, multiple interpretations, and multiple study populations.

The FDA focused on the health problems (as well as the economic issues) associated with the number of drugs pulled off the market between 1998 and 2004 because of cardiac safety issues. Among these were rofecoxib, cisapride, grepafloxacin, astemizole, sertindole, and terfenadine. The challenge was to identify a way to come together to solve some of these cardiac safety problems. One resource for algorithm development and associated research was the ECG Warehouse. After the establishment of an ECG waveform and annotation standard, the FDA partnered with Mortara Instrument Inc. to develop a digital ECG warehouse to support the storage and review of the submitted data. The ECG Warehouse contains anonymized ECGs included as part of submissions to the agency, separated from any personal patient information. We have

a large database of ECGs, as well as ways to integrate clinical data and develop new algorithms to look, for example, at genetic factors that make a patient more prone to specific types of cardiac disease or to identify subtle indicators of cardiac risk.

In 2006, the FDA and the Duke Clinical Research Institute signed an MOU to launch the Cardiac Safety Research Consortium. The consortium was designed to include members of academia, patient advocacy groups, other government and nonprofit organizations, and industry to coordinate and support a variety of research projects involving data from the ECG Warehouse database. The purpose of the consortium's work is to identify gaps in cardiac biomarkers and prioritize projects based on those needs. The mission is "To advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the FDA's Critical Path Initiative as well as other public health priorities." Molecular imaging can look to these kinds of consortia in identifying ways to build its own collaborative efforts.

Addressing the Challenges of Nanotechnologies

The FDA recognizes that nanotechnologies have tremendous promise in addressing a number of major health issues but that many uncertainties accompany the development process. We would like to create a virtual "yellow brick road" for nanotechnology leading to the FDA. Imaging should be in the forefront of those on this road, because it promises to be 1 of the best tools for nanoparticle tracking and monitoring.

The FDA foresees that every single product—including cosmetics—will be benefited by nanotechnology, and we want to work together with stakeholders in a proactive way. Among the products expected to be affected by nanotechnology in the near future are: combination products (e.g., drug delivery systems), drugs (new molecular entities, including imaging agents), medical devices (e.g., dental fillers, nanoelectrical systems), tissue engineering and biologic products (e.g., DNA-based constructs), and vaccines (e.g., nanoengineered virus-like particles).

We also recognize and are finding ways to address the significant scientific and technological challenges that nanotechnology brings to our existing development and approval paradigms. Among these are the lack of physical and chemical characterization methods and tools (a problem on which the FDA is working with NCI, the International Organization for Standardization, ASTM International, and others); scientific gaps in (reproducible) control of stability of NP (and resulting lack of predictability in medical products, as well as potential adverse environmental issues); lack of standards and reference materials; difficulties in determining bioavailability and biodistribution (the point at which molecular imaging will undoubtedly play a key role); lack of toxicologic and biocompatibility data; and challenges in bridging the preclinical–clinical gap.

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Imaging Biomarkers and Surrogates: The Evolving Regulatory Lexicon

The Critical Path Initiative (CPI) of the U.S. Food and Drug Administration (FDA), initiated in 2004 and updated with a list of opportunities and guidelines, has 2 key premises: (1) imaging is a key technology for assessing, accelerating the development of, and guiding the use of new therapeutic options; and (2) synergy between current drug/biologics development programs and current imaging techniques can be created for drug/biologics development to work in a more cost-effective manner.

Given these premises, CPI efforts are directed at 2 types of priorities: (1) identifying better imaging evaluation resources, including imaging biomarkers and imaging evaluation/prognostic surrogates; and (2) facilitating more streamlined clinical trials, a process that has been augmented by the creation of exploratory Investigational New Drug guidance for imaging.

To address these priorities, the CPI has identified "enabling mechanisms," including: (1) the support of cost-effective developmental imaging, efforts toward which have included encouragement of stakeholder collaborations among the FDA, National Cancer Institute (NCI), drug and biologic developers, the imaging industry, academics, and payers; and (2) the promotion of inclusion and integration of biomarkers in ongoing clinical trials and in routine clinical care.

Examples of these efforts can be seen in the current status of ^{18}F-FDG PET and PET imaging in general. Neither ^{18}F-FDG nor any other PET imaging biomarker can