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

be effectively incorporated in primary efficacy endpoints for registration clinical trials because of the lack of PET imaging experience in adequate and well-controlled clinical trials. Without such experience, the performance of PET imaging at clinical sites lacks the necessary standardization of imaging at the individual sites and has not demonstrated effective harmonization across a multicenter clinical trial. FDA is collaborating with NCI and the American College of Radiology Imaging Network on 2 adequate and well-controlled multicenter clinical trials for qualification of $^{18}$F-FDG PET as an imaging component of surrogate criteria for primary efficacy endpoints in phase 3 oncology clinical trials. These collaborations incorporate efforts to standardize the performance of $^{18}$F-FDG PET imaging in an adequate and well-controlled clinical trial protocol at each individual clinical site and the ability to harmonize across multiple clinical sites to allow independent confirmation of PET imaging results in multicenter trials.

## Imaging Biomarkers and Surrogates

Understanding the regulatory lexicon—the ways in which regulators describe imaging biomarkers—is helpful to the imaging community in crafting more successful collaborations to advance molecular imaging. Prebiomarkers, for example, lack 3 specific characteristics that are significant in proceeding to the acceptable status of qualified biomarkers:

(1) Standardization: Although reports on the efficacy and safety of specific prebiomarkers may be promising, these single-center reports are not standardized in multicenter clinical trials.
(2) Precision/harmonization: Reports on imaging prebiomarkers lack demonstration of the precision/harmonization needed to enable centralized, independent image interpretation in multicenter clinical trials.
(3) Safety evidence: Single-center reports on prebiomarkers lack a well-developed safety profile.

A qualified biomarker must have all of 3 of the characteristics that prebiomarkers typically lack. As such, an imaging biomarker must be established and standardized in multiple single centers to establish proof of:

(1) Reproducibility and standardization within, between, and among multiple institutions;
(2) Precision in interpretation in a multicenter clinical trial experience (i.e., the criteria for interpretation are well established and unambiguous); and
(3) An established safety profile.

If an imaging biomarker meets these criteria, it is available for multicenter imaging for therapeutic and/or diagnostic clinical trials. The question not answered for an imaging biomarker in this process is whether the imaging biomarker has "value added" for drugs or biologics development.

A qualified imaging surrogate is a qualified biomarker for which regulators have established utility for drug/biologic development. Documentation of utility for the regulators can come from the medical literature as well as from evidence gathered in clinical trials development. Several sets of imaging surrogate criteria have been used to drive efficacy and safety documentation. Examples include Cheson's International Working Group criteria for lymphoma response, Sharp's criteria (which are numerous), the Response Evaluation Criteria in Solid Tumors (RECIST), and the OLINDA software.

It is important to remember that imaging surrogates are constellations of integrated imaging findings and clinical data, designed to represent an effective monitoring of the response of disease to a therapeutic intervention. A licensed imaging surrogate is one in which imaging has proven to be a validated gatekeeper and has been incorporated in the approved label to assure or improve safety and/or efficacy. One example would be in whole-body imaging for altered biodistribution, as in the Zevalin and Bexxar regimens.

## Recommendations

The first recommendation is to continue to understand and to be aware of the evolving lexicon when making decisions about collaborative development. Another recommendation is to continue to focus on the required integration of imaging and therapeutic data to support the development and approval processes.

Additional recommendations include the need to:

(1) Develop new and/or modified imaging surrogates to support phase 3 clinical trials.
(2) Evaluate qualified imaging surrogates currently in phase 1/2 development to allow effective modification for phase 3; and
(3) Utilize phase 3 qualified imaging surrogates for design and use in phase 4. Throughout the pharmaceutical industry today a tremendous amount of discussion focuses on next steps after approval. Imaging biomarkers and surrogates are doubtless going to be of great value in follow-up studies.

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