Working Together to Enhance the Efficiency of Medical Product Development

In our current environment of ever-shrinking budgets, limited staff, and diminishing resources, added to the sometimes unreasonable expectations of having to produce more with less and under shorter timelines, joining forces with mutual goals in mind is an extremely attractive option. In fact, working together to leverage resources and expertise is almost a necessity if we hope to expeditiously bring new medical products to the market. In the context of fast-tracking technology development and the transfer of these technologies into the hands of clinicians, patients, and consumers, it is unusual (if not impossible) for a single entity to possess all the needed tools, resources, and expertise to bring technologies and safe and effective medical products to patients in a cost-efficient and timely manner. Our only hope, it seems, for fast-tracking medical product development is for stakeholders to work synergistically and for regulators to set clear expectations and develop unambiguous and transparent pathways that regulated entities can follow. It is also necessary for regulators and regulated entities to have open and regular communication so that all parties can stay up to date on developments, inform future steps, and come to consensus on challenges.

The FDA Mission and Introduction of the CPI

The U.S. Food and Drug Administration (FDA) is "responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation." The FDA is also responsible for "advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health." As part of this mission, the Critical Path Initiative (CPI), launched in 2004, is the agency's effort to stimulate and facilitate a national effort to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured. *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, the report released at the CPI launch, looked at the scientific reasons for recent decreases in the numbers of innovative medical products submitted for approval. The report noted with concern the rising difficulty and unpredictability of medical product development and called for a national effort to identify specific critical activities that, if carried out, would help modernize these efforts.

The FDA is now overseeing a range of CPI activities and, with considerable input from industry, academia, and the public, has identified priorities that seem most promising for collaboration. Among these are: better evaluation tools, especially in biomarkers and imaging; streamlining of clinical trials; harnessing the power of bioinformatics; moving product manufacturing into the 21st century; developing products to address urgent public health needs; and targeting specific at-risk populations (e.g., children). In March 2006, the agency released its Critical Path Opportunities List, which provided 76 concrete opportunities that, if taken on, could facilitate a pathway for more efficient medical product development.

Basic Steps in Collaborating with the FDA

It is impossible to summarize in a single short presentation the various mechanisms available through the FDA or the ways in which stakeholders can work with the agency. For the purposes of introduction, however, certain steps (neither consecutive nor comprehensive) can be broken out as essential in the process. These include the following needs: (1) Start with an evidence-based public health need, including the necessary scientific base to define the need. (2) Identify priorities for multiple stakeholders. (3) Identify both gaps in existing knowledge and possible duplications of effort; that is, determine what already exists to meet this need and what work is currently underway. One strategy is to hold expert scientific workshops. (4) Develop a plan for leveraging resources and expertise to maximize returns on investment. (5) Identify partners and convey to these partners a clear understanding of roles and responsibilities and final goals. This should include a well-defined strategic plan. (6) With these partners, codevelop highly specific proposals, budgets, and timelines. (7) Implement joint proof-of-concept projects. (8) Share data in the public domain as quickly as appropriate.

It is important to remember that a prerequisite for working with the FDA, the National Institutes of Health (NIH), and other government agencies is that outcomes of such collaborative efforts be placed in the public domain for the benefit of public health. All of these steps, therefore, exist in the precompetitive domain—which might more appropriately be called the procompetitive domain. By participating in such a collaborative manner with the FDA—sharing data, leveraging expertise and limited resources—

stakeholders may develop predictive and evaluative tools that may benefit all, thereby stimulating competition and even facilitating growing their businesses in other ways. All groups benefit from this collaborative process. Private partners gain know-how, predictive tools, and input in project selection and, in doing so, have a stake in the product development. The FDA gains valuable information that can be used in developing guidance, standards, and evaluative tools for scientific review. Data are accrued that can be used to support best practices and evidence-based science and techniques. And, of course, the most important stakeholder, the patient, should ultimately benefit from the quick transition of safer and less costly medical products from basic research to clinical use.

Models for Collaboration

This presentation discusses several strategies used by the FDA to successfully engage pharmaceutical companies and other stakeholders in attempting to solve major problems in the interest of public health.

Changing Approaches to Warfarin Dosing

The first example is that of the drug warfarin and is a story that highlights the growing importance of genetics and personalized medicine in FDA activities. In 2006, more than 43,000 individuals were seen in U.S. emergency departments with problems associated with warfarin. About one-third of individuals have a genetic predisposition that causes them to metabolize warfarin differently. These genetic variants result in the need for a different dose, may cause some individuals to take longer to stabilize the dose, and may even be the cause of greater risks of bleeding. The FDA asked whether a prospective study could be created that would determine the appropriate approach and whether it was possible to use the resulting data to develop a genetic algorithm for dosing.

With support from Congress, FDA partnered with the Critical Path Institute (C-Path; Tucson, AZ), an independent nonprofit research and education institute, and researchers at the University of Utah (the COUMAGEN study) to develop a dosing algorithm for warfarin. Information coming out of this research was analyzed, statistical analyses were performed, and the results were submitted to the FDA. Together with these and other data, FDA was able to modify warfarin labeling based on evidence-based clinical data. This will undoubtedly benefit many patients who previously would have experienced adverse reactions and empower doctors to prescribe warfarin with more assurance.

The Predictive Safety Testing Consortium

The second model of an effective collaborative strategy is that of the Predictive Safety Testing Consortium (PSTC). The consortium was formed as a result of cumulative frustrations arising from the siloed nature of industry toxicologic research. Most major pharmaceutical companies have developed animal genomic markers to evaluate organ toxicity, but such outcomes remain siloed, because they are considered proprietary. As a result, similar studies are sometimes needlessly repeated to yield analogous data. Through the PSTC, under the auspices of C-Path, companies contributed their research-grade assays and were encouraged to validate other companies' contributed assays. In a process that has been compared to a "bake-off," the 16 current corporate members of the consortium shared internally developed preclinical information and know-how. Several FDA scientists participated as advisors, along with more than 120 industry and academic scientists, and C-Path served as the "neutral third party," collecting and summarizing the data and facilitating the entire process. The European equivalent of the FDA, the European Medicines Evaluation Agency (EMEA), has agreed to appoint observers to work with the PSTC. The United Kingdom Academy of Medical Sciences has also asked to be kept informed of the progress and offered to share the results of a similar UK initiative that is modeled after the PSTC.

The goals of the PSTC are to: identify early indicators of human safety in clinical drug development and postmarketing surveillance; employ the combined resources, sample sets, compounds, and expertise of member companies; and generate biomarker data that may inform regulatory decisions at FDA and EMEA (the first dataset from PSTC was shared with FDA in June 2007).

The consortium is a model in which FDA can work effectively to leverage the power of stakeholders' cooperation to realize benefits for all involved. The process has not been without its challenges, among them working out the legal framework on which interactions may occur. Company scientists work under a consortium agreement that covers antitrust, intellectual property, confidentiality, and information-sharing issues. The FDA staff are involved as they provide scientific and regulatory input into the process. Areas of focus under PSTC include nephrotoxicity, hepatotoxicity, vascular injury, carcinogenicity, and myopathy.

Molecular Assays and Targeted Therapies Consortium

A third model of collaboration resulted from a shared goal by the FDA, the National Cancer Institute (NCI), the Centers for Medicare and Medicaid Services, and others to develop tests that could identify tumors with a high probability of response to a given drug. A memorandum of understanding (MOU) was executed for a larger effort called the Oncology Biomarker Qualification Initiative (OBQI), under which this consortium's activities are coordinated. The participants of this effort began to work together to identify potential targets and establish protocols and standards for assay validation. An initial project has focused on epidermal growth factor receptor diagnostic tests, with a number of companies involved in an "assay bake-off." A number of early milestones have been met in these and other collaborations, and the FDA is hopeful that the outcomes will provide best practices and know-how for industry, academia, and government agencies.

Collaborative Business Models

A number of successful creative business models for cooperation are available for study and emulation, including but not limited to: SEMATECH, Product Quality Research Institute, SNP Consortium, Biomarker Consortium, C-Path, OBQI, NCI's Nano Alliance in Cancer, and others.

FDA Resources and Mechanisms

One useful resource in collaborating with the FDA is a document originally intended for agency staff: *The Leveraging Handbook: An Agency Resource for Effective Collaborations* (available at: www.fda.gov/oc/leveraging/handbook.html). The handbook sets out all of the mechanisms that staff can draw upon, including but not limited to information on: confidentiality disclosure agreements, MOUs, cooperative research and development agreements, cosponsorship agreements, material transfer agreements, contracts, grants, interagency agreements, and licenses.

The FDA has a unique role, with scientists involved in all aspects of review through the entire course of medical product development. We have seen successes, failures, and missed opportunities. We use both our experience and state-of-the-art information available to evolve and inform our regulatory processes and decisions. New guidances, which are prepared by FDA staff for applicants, sponsors, and the public, contain recommendations that are not binding and represent current thinking on a regulatory issues. New guidances may include information on design, production, labeling, promotion, inspection, enforcement, manufacturing, processing, and testing of regulated products.

The CPI has special importance for molecular imaging, because it may provide a transparent path from basic research through regulatory submission: providing tools to inform the entire spectrum of medical product development. The FDA welcomes inquiries from whomever and from wherever the inquirer may be along that path and even beyond product approval.

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The Exploratory IND

In its March 2004 *Critical Path Report*, the U.S. Food and Drug Administration (FDA) explained that to reduce the time and resources expended on candidate products that are unlikely to succeed, new tools were needed to distinguish earlier in the process those candidates that hold promise from those that do not. The point, of course, was to develop processes and mechanisms that would speed up the process of candidate development, particularly in crossing from preclinical to phase 1 applications—a crucial point in the development pipeline.

The applicable exploratory Investigational New Drug (eIND) guidance was issued in January 2006. This guidance described "early phase 1 exploratory approaches that are consistent with regulatory requirements while maintaining needed human subject protection, but that involve fewer resources than is customary, enabling sponsors to move ahead more efficiently with the development of promising candidates." The mechanism is designed to allow more flexibility in the IND process and is ideally positioned to open the pipeline for imaging development and reduce barriers at key transitioning thresholds. The guidance defined an eIND study as a clinical trial that is conducted early in phase 1, involves very limited human exposure, and has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies).

Understanding the Exploratory IND

Among other potential advantages to developers, the eIND mechanism facilitates first-in-human clinical trials. Radioactive Drug Research Committee requirements associated with traditional INDs prohibit first-in-human trials. The eIND allows the researcher to bring these efforts in earlier to be able to differentiate promising from not-so-promising agents. Another part of the underlying structure of the new mechanism reduces the threshold on how much pharmacologic and toxicologic (pharm/tox) testing must be completed before entering into an eIND. If the agent turns out to be promising during the eIND process, then the pharm/tox assessments can be completed; if not, then these never have to be done. The result is a remarkable reduction in cost in preclinical efforts, as well as economies that allow researchers to focus on those agents with the greatest chances for success. This aids every developer in maintaining a more focused portfolio. It is noteworthy that even in the mid-1990s many companies were evaluating new agents with a process much like that at work in eINDs, and today both pharmaceutical and biopharmaceutical companies are actively embracing the eIND approach and using it to evaluate their portfolios.

Some of the language in the original guidance may cause confusion ("microdose," "without therapeutic intent," etc.), but all stakeholders should know that the FDA staff is available to clarify these issues and provide assistance. In planning for an eIND, it is helpful to know that the focus and associated questions should be quite specific and designed to provide data that support a specific proof of concept. It is for this reason that the eIND mechanism is ideal for targeted assessment questions that can be answered with a definitive