Vision and Status of the Critical Path Initiative

AN INTERVIEW WITH SHIEW-MEI HUANG, PhD

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The Food and Drug Administration's (FDA's) Critical Path Initiative is a broad effort to update and streamline the development, production, and evaluation of the products the agency regulates. Since the project's 2004 launch, the FDA has provided updates through the 2006 Critical Path Opportunities List and the Center for Drug Evaluation and Research (CDER) 2007 Update. As the Deputy Director of CDER's Office of Clinical Pharmacology, Shiew-Mei Huang, PhD, has participated in the agency's advance along the medical product improvement path.

Explaining the rationale for the initiative, Dr. Huang shares the FDA's concerns about the product pipeline: "the traditional inefficiency" in development, the small number and high cost of investigational new drugs (INDs) that reach the market, and the fact that a "drug that is entering Phase 1 now, in the 21st century, is not more likely [to succeed] than those that entered Phase 1, say, twenty-some years ago." The FDA has an essential role in the transformation of this landscape: for trials submitted and reviewed by the FDA, "we have seen all of the drug development process, and we [have information on] all the trials that failed and those that succeeded," she says.

Basic research does not automatically result in new products, so the FDA "would like to bridge the gap from basic research to translational science," says Dr. Huang. To do so, the agency must work in public-private partnerships with industry, healthcare providers, health management organizations, academics, and the National Institutes of Health (NIH) "to share data in a pre-competitive way in order to advance the technology and then use it in product development," she continues.

Although this collaboration represents a departure from past practice, Dr. Huang sees no conflict in the agency's roles of facilitator and regulator. Joining the FDA in 1996 after 15 years in industry, she has witnessed movement from a sometimes antagonistic relationship between the FDA and industry to a more open exchange. In her opinion, "it is [in] our best interest to share information." It is true that, "for a failed product, unless the sponsor discloses [the data], some of the details will not be available to the public," but the agency can provide the broader perspective. She adds, "if we have, across products . . . issues that we can share among the stakeholders, then I think we will be much more effective."

Those stakeholders have themselves come together to form pre-competitive consortia to share information. The Critical Path Institute (C-Path), an independent organization working with FDA on the initiative, is leading one such collaboration, the Predictive Safety Testing Consortium (PSTC). Dr. Huang observes that not all companies are willing to share their data, but those who do will

have access to information relevant to product development much earlier in the process. The FDA is not a member of consortia such as the PSTC and the Serious Adverse Events Consortium (SAEC), but the agency is involved in discussions with these groups and reviewing the data they produce to ensure the work has regulatory importance. Another avenue for information sharing is a voluntary submission program; sponsors can submit data to the FDA at an early stage of research in the genomic/biomarker areas without any regulatory impact, a process that allows for discussion that can move the development process forward.

Dr. Huang refers to the CDER 2007 Update as the authoritative document on the Critical Path Initiative's evolution. In clinical pharmacology, the initiative has made possible new ways to obtain external expertise and assemble expert teams. For example, Dr. Huang cites C-Path's hosting of the first summit to discuss the effect of pharmacogenetics on warfarin therapy. The summit helped

the National Heart, Lung, and Blood Institute design a clinical study scheduled for this fall, and contributed to the FDA's relabeling of warfarin in August 2007. Continuing to reap the benefits of the warfarin summit, which

allowed the agency to "receive feedback from experts in a very efficient way," the FDA is now "in the process of combining more specific dosing recommendations based on genotype," she says.

Dr. Huang's own projects at the FDA have included research into interactions between prescribed drugs and herbal and citrus products. Given the pervasive use of such products, she sets realistic expectations for the agency's efforts in this area; the agency does not want to send out "unnecessary warnings," but "what we can do is to label the drug." A draft guidance on the subject was published in 2006, more up-to-date information about interactions can be found on the Critical Path Web site, and an October 2008 workshop supported by initiative funds will yield further information.

To address intrinsic and extrinsic factors affecting medical treatment, Dr. Huang insists that "personalized medicine is really the key." The FDA is currently drafting a guidance to help sponsors

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As the Deputy Director of CDER's Office of Clinical Pharmacology, Shiew-Mei Huang, PhD, has participated in many of the agency's steps to advance along the path of medical product improvement.

SELECT Resources

1. Critical Path Initiative: www.fda.gov/oc/initiatives/criticalpath
2. March 2006 Critical Path Opportunities List: www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf
3. CDER 2007 Update: www.fda.gov/cder/reports/rtn/2007/default.htm
4. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products: www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf
5. Critical Path Institute: www.c-path.org

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In the affirmative, an NDA is then prepared and submitted, and if it meets all the technical requirements,³ it is “filed” (accepted for review) 45–60 days later. According to the Prescription Drug User Fee Act, the FDA then has 10 months to render a decision on approvability.⁴ If an NDA has limitations for definition of clinical benefit, the safety concerns of the new therapy are not well understood, or a clear unmet need is not defined, then an advisory committee composed of academic experts, statisticians, and representatives from appropriate patient advocacy and industry groups is asked to review the NDA and recommend a course of action to the FDA.⁵ Another reason to convene an advisory committee meeting would be when the NME represents a new therapeutic direction, where scientific interpretation or even ethical issues require expert, interactive opinion.^{6–7}

For devices, which include diagnostic tests, review and approval are handled by another branch of the FDA, the Center for Devices and Radiological Health (CDRH). At the CDRH, there are 2 routes of possible FDA approval for a diagnostic test that is linked by an algorithm to prognosis or selection of candidates for therapy: a 510(k) or a Premarket Approval (PMA). A PMA differs from a 510(k) in that clinical efficacy data are required. The discussion here will be confined to a genetic diagnostic test that is coupled to use of a drug (pharmacogenetic targeting), something that has generated a great deal of recent interest from investigators, pharmaceutical and biotechnology companies, and the FDA. As clinical data are required to demonstrate the utility of such a test, the regulatory submission would likely be a PMA.

Although different divisions of CDER may have different approaches, currently within the Division of Cardiovascular and Renal Products (DCRP) of CDER, a drug approval with labeling linked to a genetic biomarker to identify responsive versus unresponsive subpopulations is handled by CDER/DCRP performing the NDA evaluation, CDRH the PMA (with the clinical data in the NDA serving as the clinical component of the PMA) review, and the Office of Combination Products serving to organize and expedite the process. To facilitate communication, all initial submissions for the combined product approval are submitted through DCRP. An advantage to this construct is that each review group performs the function with which it is accustomed, using principles and precedents that are well established. The only novel aspects of the review are the interpretation of the pharmacogenetic data, for which the FDA has a recently established a specialty group that can provide assistance.⁸

It is fashionable to criticize the FDA for the decline that has recently occurred in NME approvals.^{9–11} However, it is our position that this decline has everything to do with deficiencies in drug development and little to do with the regulatory process. Academic investigators interested in developing and commercializing their discoveries should be encouraged to access the FDA for assistance, where they will likely be pleased by the experience. **CTS**

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appropriately collect, analyze, and store genetic information to explain the variable responses that occur in clinical trials. A priority for the next several years is pediatric care. To begin, the FDA has invited a number of experts on sabbatical at the FDA to research the relationship between human ontogeny and drug metabolism. Other projects include outreach efforts towards healthcare providers and device companies and the exploration of bioinformatics. Dr. Huang believes more needs to be done with “gene expression, either to select patients or to see . . . how patients are responding to drugs.”

The FDA is constantly identifying needs and opportunities in the area of medical product development; fortunately, its collaborators have proved quick to respond to the call. As an associate editor for *Clinical Pharmacology and Therapeutics* until April 2008, Dr. Huang saw many warfarin manuscripts that addressed the questions the FDA and the summit had posed. Other FDA appeals for warfarin research involving race or pediatrics have also been answered by multiple organizations.

Dr. Huang sees the research focus shifting from determining genetic importance to discussions of implementation. She predicts the next step is a conversation not just among researchers but also within a larger community to address questions of reimbursement for medical products. In this way, the FDA hopes to lead U.S. healthcare down the critical path from initial investigation of these products to safe, effective medical treatment. **CTS**