Clearing the critical path

The FDA is advancing a new initiative to bring 21st-century tools to medical product development.

BY DAVID FILMORE

Spinal cord tissue engineering, systems biology, microelectromechanical systems, the need for new antibiotics, and the dangers of poorly designed clinical trials were just a few of the topics presented at an FDA Science Board meeting held in April at the agency's Maryland headquarters. To a casual observer, the four hours of discussion and presentations might have seemed simply a hodgepodge update from outside advisors on broad scientific themes affecting the agency. But, in fact, a more specific and ambitious goal framed the meeting. The topic at hand was the FDA's "critical path" initiative.

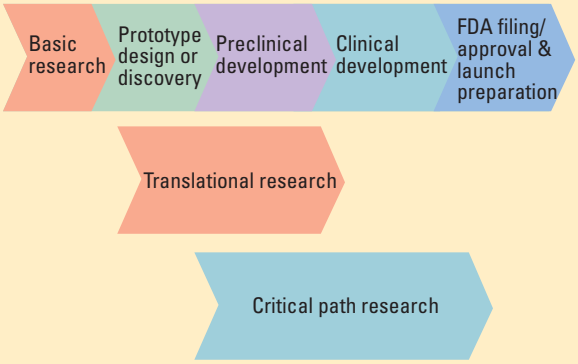
This endeavor, introduced in a white paper released in March (*www.fda.gov/oc/initiatives/criticalpath*), seeks nothing less than to comprehensively overhaul the tools and methods of drug and medical device development.

Whereas basic biomedical research has exploded over the last decade, "not enough scientific effort is being put into improving the product development process itself," says Janet Woodcock, who is spearheading the initiative as the FDA's acting deputy commissioner for operations. "This is one of the root causes," she tells *Modern Drug Discovery*, behind the trend of fewer novel treatments reaching patients.

R&D investment by the NIH and the pharmaceutical industry approximately doubled from 1995 to 2003, with much to show for it in terms of high-tech innovations, sequenced genomes, and early-stage drug candidates.

However, over the same period, the number of applications for novel therapeutics—small molecules and biologics—received by the FDA declined from more than 80 in 1995 to the mid-30s in 2003 (with a mostly steady decrease in between). The FDA cites data in its white paper that a new medicinal compound entering Phase I testing has only an 8% chance of reaching the market.

Removing the disconnect between society making large investments and successfully improving basic research but failing to accelerate new product development is at the heart of the critical path initiative.



Pick a path. "Translational" research, the focus of several initiatives including the NIH Roadmap (*http://nihroadmap.nih.gov*), is directed at moving basic discoveries from concept to clinical evaluation. The main concern of critical path research, on the other hand, is making it easier to develop approvable products. (Adapted from *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products;* U.S. FDA, 2004.)

The critical path starts "somewhere in the middle of the prototype design or discovery phase and [moves] all the way through to getting the product onto the market," Woodcock explained to the panel of scientists from industry, academia, and consumer groups in April. This pathway, she said, is not working as it should.

The reason for this, the March report contends, is that drug developers are often stuck using "the tools of the last century to evaluate this century's advances."

The FDA's proposed solution is to establish extensive cooperation between government, industry, and academia to create a new toolkit that will increase efficiency, lower cost, and generally make the critical path a more predictable one to tread. The white paper and Science Board meeting signaled the launch of this broad effort.

"We didn't know when we wrote the report and put it out if people would agree," Woodcock tells *Modern Drug Discovery*. But, in subsequent discussions with industry and others, "we have not had one group that has disagreed with us," she adds. "After they think about what we describe as the cause, usually the reaction is, 'We never thought about this before.' "

A toolkit for the future

An improved toolkit, as proposed by the FDA, needs to attend to three distinct "dimensions" of product development: ensuring safety, demonstrating efficacy, and industrialization (i.e., taking a laboratory concept to mass production). Tools envisioned for the first two categories are predominantly focused on improving the success and efficiency of the clinical trials process.

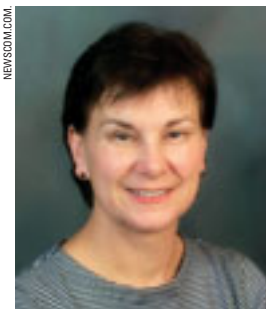
Robert Califf, director of the Duke Clinical Research Institute, warned the Science Board of the dire need in this area. "There seems to be a myth—and I don't know where it came from—that the industry has figured out how to do clinical trials efficiently. This is not the case."

Although there isn't agreement on what precisely needs to be done, the agency has made several suggestions for removing some of the guesswork from clinical research. The suggestions include the use of biomarkers to predict a drug's efficacy, computer models to assess toxicity, and clinical outcome measures to better reflect patient needs.

"Nobody is studying how to [improve clinical trials]," Califf said. "And trying to get the industry to talk about it is almost impos-

sible because they are scared to death that, if the question comes up that it might be imperfect, it will hold up an application."

Woodcock says the FDA strongly agrees with the need to study this problem and provide a greater "science base" to clinical trials. "We need standardized trial designs," she said at the meeting, so that it is clear that "if you do the trial design and you run your compound through it, you have addressed the question to the degree that you need to."



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"Not enough scientific effort is being put into improving the development process," says Janet Woodcock, acting deputy commissioner for operations at the FDA.

The agency understands it is in a unique position to play a central role in advancing technologies to a point where they can actually improve and speed up clinical development. Its access to proprietary data is unprecedented—agency files purportedly constitute the world's largest repository of in vitro and animal results linked to human outcomes.

Woodcock clarified the vital function the agency could perform using the specific context of developing biomarkers as validated surrogate end points in clinical trials. Typically, a disease marker is discovered in one laboratory, published, and then used by other laboratories, she explained. If it's promising, before long it will be incorporated into home-brew, non-FDA-approved tests and then measured as part of clinical trials.

"Then publicly, and in scientific journals, there are calls for us to use this biomarker because everybody has gotten used to it," she continued. "But then we get stuck as a society. What happens next? We have had biomarkers that have been in this status for 20 years."

"Who is going to pool all the data and analyze it—not just published summary data but the primary data? Who is going to identify the gaps?"

Woodcock suggests the FDA is best situated to identify the gaps and guide a collaborative process of filling them. The agency has taken this responsibility in the past on a limited basis—for instance, in facilitating the adoption of CD4 cell counts and, subsequently, new measures of viral load to cut the time-to-market for anti-HIV drugs in the 1990s. The new initiative envisions this on a broader scale for biomarkers as well as other tools, including ones that aid the evaluation of manufacturing processes or the clinical development of pioneering technologies, such as bioengineered tissues and novel drug delivery systems.

A cooperative effort

Cooperation is a key component of this proposal. "The thing I like best about the critical path initiative is the realization that there is a lot of synergy between research in the public and private sectors that is relevant to drug discovery and development," said Gail Cassell, vice president of scientific affairs at Eli Lilly, at the Science Board meeting. "We should admit that and figure out how we can better have these two sectors working together."

The concept of public–private partnerships is prevalent in the white paper, Woodcock tells *Modern Drug Discovery*, "because some of this is what you would call 'bigger science.' It isn't something you accomplish in a single laboratory. You have to go across treatments, maybe across populations, to find out the answers, so there has to be a lot of collaboration."

Some companies are already taking this message to heart. California-based Iconix Pharmaceuticals, for instance, announced in March that it plans to provide public access to a set of its proprietary genomic biomarkers for research and validation by the scientific community. In doing so, the company specifically referred to the FDA initiative. "We are pleased to be the first company to make our proprietary genomic biomarkers available, and to be supporting the FDA in its call for a creation of a 'new product development toolkit,' " Iconix CEO Jim Neal says.

Woodcock says the agency is exploring various models to encourage and focus collaboration. A public–private endeavor the NIH has undertaken for osteoarthritis research (*www.niams.nih.gov/ne/oi*) and the FDA's own Orphan Products program that provides target grants and market exclusivity for pursuing development for rare diseases are two examples that she cites. "We can use targeted programs like this," she explains, for critical-path-related research, to encourage "specific outputs or outcomes, not just nebulous projects."

A matrix of opportunities

In this early stage, however, many components of the new initiative are still nebulous. "We are in validation and information-collection mode," Woodcock tells *Modern Drug Discovery*. "We have described a problem and proposed a path forward and are seeking input."

The agency has requested detailed responses from industry, patient groups, and other parties to identify pressing product-development hurdles, potential solutions, and suggestions on the best role for the FDA to play. It plans to incorporate these comments, together with other issues it identifies, into a Critical Path Opportunities List it hopes to make available this fall.

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Woodcock is not sure precisely how the list will be organized, but she envisions "a matrix that goes across diseases and tools in rows and columns. Some of those tools cross-cut everything, and others are specific to a single disease."

The next step after the list is compiled, she acknowledges, is very much an open question. "We are going to publish our list and then see what people think about how these things could be accomplished."

One thing she does seem sure about, however, is the momentum in the drug discovery community for moving forward with the plan. Because the agency considers the critical path issue to be a huge topic, it wasn't looking for specific advice from the Science Board at the brief April meeting. Still, Woodcock says she took away one clear message from the diverse agenda—namely, "Full steam ahead." ■