Taking a Look at FDA’s Critical Path Initiative

Update on Progress and the Next Steps
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By the time this article appears in print, the FDA may well have announced its Critical Path Opportunities List, which will be the culmination of the first phase of the Critical Path Initiative announced on March 16, 2004.

The document serves as the roadmap for achieving near- and long-term progress in rectifying the perceived imbalance between the funding of biomedical research and the pace of delivery of new medical technologies to improve healthcare outcomes.

When it released its “Challenges and Opportunity on the Critical Path to New Medical Products” report in March, the FDA framed the challenge as the shortage of modern tools to enable effective and efficient assessment of the safety and efficacy of new medical products.

As a result of a series of public interactions, especially under the auspices of its Science Advisory Board, and an open docket for formal comments, the agency has expanded its conception of the opportunities for meeting this challenge to include both a redefinition of scientific research supporting the product development process and improved communication with product sponsors to apply existing evaluation tools and strategies more efficiently.

The meeting of the FDA Science Advisory Board on November 5 and a joint CDER-DIA webcast on December 3 have provided a detailed update on the progress made since March to gather and evaluate public comment on the purpose and direction of the initiative.

Improving Public Health

Federal investment in basic biomedical research is expected to lead to an overall improvement in public health. However, as observed and reported by the FDA in its March “Critical Path” report, the expectation is not being fulfilled.

Data, based on 10-year trends, show that, while there has been an increase in NIH spending and pharmaceutical company R&D investment, there has been a consistent decrease in major drug and biological product submissions to FDA.

FDA’s analysis of this “pipeline problem” in innovative medical products reaching patients led to the conclusion that the current medical product development path is becoming increasingly challenging, inefficient, and costly. To address this concern, FDA launched the initiative to identify the most pressing obstacles in this path.

The agency also wants to prioritize the steps that provide the greatest opportunities for rapid improvement in public health, concentrating on the important aspects of the product development (critical) path, i.e., assessment of safety and evaluation of medical utility.

Since March, FDA has worked together with all stakeholders (scientists, reviewers in FDA’s medical product centers, and the public and private sectors through the open docket, meetings, and workshops) to identify the most important challenges and to create the Critical Path Opportunities List as an outline of its strategy to overcome them.

FDA has collected information from within and outside the agency, and has worked with its medical product centers to prioritize problem areas, analyze comments received through the open docket, and identify issues seen as bottlenecks and needing attention.

Request for Recommendations

Results of the investigative phase of the initiative were presented to the FDA Science Advisory Board at its November 5 meeting along with a request for recommendations prioritizing the issues and identifying mechanisms to implement solutions.

From the approximately 120 comments transmitted to FDA via the docket by industry, societies, and patient advocacy groups, it has become clear that there is overwhelming support and concurrence with the Critical Path diagnosis.

There is also agreement on the need for research and science-based standards and collaborations, and recognition of the science infrastructure problem as well as FDA’s important role as the gatekeeper between the research enterprise and the patient's bedside.

As represented through docket submissions, the medical product

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industry, in general, supports collaborative efforts with academia and the agency, and agrees that new product development tools will improve predictability and efficiency by providing better information on the safety and effectiveness of investigational products at earlier stages in development.

Importantly, the initiative must not substitute for improvements in the review process. In addition, the regulatory pathway for certain types of products, such as combination and tissue-engineered products, must be clarified.

Common Themes

While a number of issues and opportunities were identified, FDA reported that certain common themes have emerged. The overriding concerns are clinical trials, biomarkers, and surrogate endpoints. There is a need to improve clinical trials and outcomes assessment, generally. Accelerating the development and regulatory acceptance of biomarkers will enable their use to characterize the product, as well as to measure outcome for both preclinical and clinical studies.

Post-market surveillance efforts will be important in assessing identification of the correct markers. As FDA indicated, today’s biomarkers are tomorrow’s diagnostics, and continued improvements in biomarker development will have widespread applicability from in vitro diagnostic products to therapeutic monitoring and assessment.

Key Considerations

To prioritize the concerns expressed and to develop the Opportunities List, FDA identified the following considerations:

- projects that promote collaboration within the agency and with outside groups;
- public health needs in at-risk populations;
- activities that provide benefits across product types, diseases, and industry sectors; and
- activities where standards/guidances can be provided.

The Science Advisory Board agreed with these considerations and with the identification of clinical trials, biomarkers, and surrogate endpoints as high-priority issues because of their cross-cutting potential in the agency as well as with specific concerns of individual Centers.

To implement projects, the board suggested the agency undertake a proactive outreach effort to develop collaborations with public and private groups, select projects that can

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readily demonstrate progress (while continuing to assess the utility of standards and guidelines), assess the balance and adequacy of pre- and post-market strategies, and establish realistic timelines so that activities can be monitored and progress maintained.

The board commended the agency on the considerable progress made since March when the initiative was announced.

Next Steps

As next steps, FDA indicated that the Opportunities List will be published in 2005. The initiative will continue as an ongoing effort with development of a formal process for continued input from all stakeholders.

Dialogue with outside groups will be continued and active collaboration for identified projects will be pursued. However, the agency has cautioned that a very real challenge will be the allocation of resources among short- and long-term projects.

Nevertheless, the agency announced that a few projects in the area of clinical trials and biomarker/surrogate marker development will be initiated in 2005 where consensus and resources exist. FDA also will look to collaborators to accomplish additional work.

These proposed projects, especially in the critical areas of clinical trials and biomarkers, may indicate priorities and goals to be announced in the Critical Path Opportunities List.

CLINICAL TRIALS: Attention to the overall clinical trials process and approaches to streamline data collection and analysis are essential.

Standardizing data collection and handling is an important first step. Accelerating development and acceptance of novel trial designs which, although widely discussed, have not seen widespread use because of concerns regarding regulatory acceptance. Demonstration projects or guidances, or both, are needed to move the field forward.

Other goals include developing scientific consensus on certain methodological/analytical issues such as treatment of multiple endpoints and treatment of missing data for shorter term trials; performing internal assessment of the clinical trials process through oversight of Bioequivalence Monitoring and IRB inspections in all phases of trials; developing pre- and post-market disease modeling and trial simulations for early drug development; and facilitating medical device development by improving pre- and post-market balance and leveraging outside expertise.

BIOMARKERS

Public discussion and consensus development on a general framework for investigating/accepting surrogate markers is needed.

Progress in pharmacogenomics as an example where sponsors can discuss data outside the review process, such as genomic data in concert with development of a particular drug, should be a goal.

Additional considerations include collaboration on specific biomarker projects, such as safety biomarkers, data mining projects, imaging as a potential biomarker, and evaluation of consortia in advancing the study of specific markers and surrogate endpoints. (As discussed at the November 3 public meeting of the Critical Path Subgroup of the FDA’s Pharmaceutical Science Advisory Committee).

Extensive materials describing the initiative and progress made to date can be found at the key “Critical Path” web links listed in the Table. The December 3 web-cast also provides insight into the agency’s thinking on related issues, including the importance of improved communication with product sponsors to ensure the application of current best practices and efficient integration of new assessment tools as they become available.

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Corrections

In the January 1, 2005, issue of GEN, the Legal Affairs column on page 8, entitled “Legal Uses of a Patented Invention in the U.S., should have been titled “Registration of Clinical Trials.”

In a brief in the Clinical Trials Update section of the December 2004 issue of GEN, it was noted that Rio-North American concluded a two-year Phase III clinical trial for rimonabant (Acomplia®). In fact, the Rio-North American trial was conducted by Sanofi-Synthelabo (New York City).

In the December 2004 issue of GEN, an article entitled “Drug Discovery Trends for the Next Decade” a quote by Christopher Ahlberg of Spotfire (Somerville, MA) was run incorrectly.

It should have read: “Today’s methods can feel like speeding down a dark road in a sports car without headlights, the engine is fast but you don’t know if you’ve passed something worthwhile or are about to hit a wall. New instrumentation, tools, and analysis software need to be developed in parallel, so researchers...”