

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Update of FDA's Critical Path Initiative

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H&O What is FDA's Critical Path Initiative and what are the challenges it is trying to address?

SK The Critical Path Initiative was introduced by the US Food and Drug Administration (FDA) because of the challenges that currently exist in drug development. It aims to stimulate and facilitate a national effort to modernize the scientific process through which a drug is developed from a discovery into a medical product. One of the problems that face drug development today is the tremendously long time it takes to develop an agent from phases of early discovery to clinical trials, and ultimately to mass production. Of the many investigational drugs studied in trials, very few actually proceed to the market. At present, a drug may take anywhere from 8 to 12 years to go through this process. Drug development is also extremely expensive, in part because of the way clinical trials are designed. Within oncology, researchers are using approaches that were designed almost 50 years ago when conducting clinical trials. Current randomized trials study a large number of patients who have a similar type and stage of cancer regardless of other characteristics. They then observe how many patients did and did not respond to treatment and based on the findings, they determine the progress of development and evaluate whether to continue studying the drug. New cancer drug development programs, however, should focus on targeted medicine. Controlling against the bias and the impact of "random" variability is really the antithesis of personalized medicine because in personalized medicine, it is necessary to select patients with a genetic makeup that fits with the particular treatment. Not every patient is similar; hence the treatment works in 10% or 20% of patients and does not

work in 80% or 90%. Thus, the question is who are those patients that respond to treatment. If we can determine ways to enrich trials for responders, we can design clinical trials that require much fewer patients, that are less expensive, and take a shorter period of time, with even better safety and efficacy. These are some of the issues that the Critical Path Initiative is working with currently.

The Critical Path addresses 6 issues. The first and most crucial factor is the need for better evaluation tools such as biomarkers; these are necessary in order to determine which patients respond to treatment or to forecast outcome. The second issue is determining how we can have better clinical trial designs that utilize the biologic tools that are currently available (ie, biomarkers). The third issue is related to utilizing the revolution of bioinformatics to advance the whole development process. There are multiple ways of doing this; one involves unifying data annotation and another consists of identifying and interpreting specific biomarkers, such as multigene profiling. The fourth deals with the manufacturing process of the drugs. The last 2 issues that the Critical Path addresses deal with urgent public health needs and specific populations (eg, pediatric). Accordingly, the Critical Path's efforts primarily lie in improving the scientific and regulatory process of drug development. We are trying to put forth specific guidance to help advance the process of clinical trial design and drug development. At the present time, the guidelines are in various phases of completion.

H&O What are some of the main projects related to the Critical Path Initiative that are ongoing in cancer?

SK There are few national efforts that are currently underway, one such project is the Cancer Biomarkers Collaborative (CBC) between the American Association

for Cancer Research, the FDA, and the National Cancer Institute. The mission of this collaboration, made up of academia, government, industry, and patient advocacy groups, is to define a set of best practices for effectively developing and incorporating predictive biomarkers into oncology trials. The CBC deals with different issues related to hurdles in the development of biomarkers and covers 4 areas: biospecimens, bioinformatics, assay validation, and information sharing. The CBC's efforts related to biospecimens cover issues related to collection and handling, quality assurance, annotation, and unification of documentation. One of the methods proposed for biospecimen collection is to identify a national biospecimen reference source where one can help in defining the quality of specific biospecimens to the reference biospecimen. Another area involves biomarker assays validation, which is the process of demonstrating that an assay is reliable and meets experimental objectives in a reproducible and comparable fashion. The challenge here is to ascertain what kind of process needs to be implemented to incorporate these assays into clinical trials for the purpose of clinical qualification of the specific biomarker. The last area that the CBC addresses is information sharing—what kind of environment is needed to encourage researchers and developers to share data earlier in the process of development in the pre-competitive space without jeopardizing intellectual property or with substituting incentives.

The CBC has been active for the past 2 years, with approximately 130 experts nationwide who are involved in this work. The group has started to put together white papers of best practices reflecting the experts' opinion on relevant issues and how they can be implemented.

The International Society of Biological Therapy of Cancer (iSBTc) and the FDA have joined to create iSBTc-FDA Taskforce on Immunotherapy Biomarkers. This taskforce focuses on the issues related to immunologic monitoring assays. They also address the standardization and validation of assays and evaluate the clinical

utility of new technologies and the incorporation of these technologies into clinical trials.

H&O Can you discuss any work that has been done to improve clinical trials?

SK There is a collaboration between the American Society of Clinical Oncology and the FDA called ASCO/FDA Alternative Clinical Design Working Group, which has been working for the past year and a half on alternative clinical trial designs and how they can enhance the development of drugs, while taking into account advancement and biomarker integration. The white paper for this is currently being written.

H&O What is the anticipated effect of these projects on the drug development process?

SK With these projects we hope to create new scientific tools that add to the understanding of drug development and hopefully make it shorter and less costly. This may also help pharmaceutical companies to redirect resources to the development of other potential drugs if needed, which in turn would increase the availability of new drugs coming to the market. Also, with the proposed approaches of bioinformatics, genomics, and biomarkers, researchers will be able to create targeted, safer, and more effective drugs.

Suggested Readings

Pitts P. FDA and the critical path to twenty-first-century medicine. *J Med Philos.* 2008;35:515-523.

Woodcock J, Woosley R. The FDA critical path initiative and its influence on new drug development. *Annu Rev Med.* 2008;59:1-12.

"Innovation Stagnation: Challenge and opportunity on the critical path to new medical products." US Department of Health and Human Services, Food and Drug Administration, 2004. Available at <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>