The FDA's Critical Path Initiative

Advances in biomedical research, especially the sequencing of the human genome, have substantially raised expectations that the pharmaceutical industry will generate increasing numbers of safe and effective therapies. However, there are warning signs of serious limitations in the industry's ability to effectively translate biomedical research into new therapies. The doubling of the failure rate during clinical drug development,[1,2] and recent high profile withdrawals of drugs due to safety problems are signs that the current drug development process needs improvement. After billions of dollars in research and development and years of clinical use, the public was shocked that rofecoxib, a drug that effectively treats inflammatory disease and may prevent some forms of cancer,[3] was removed from the market and is no longer available to the patients who could be helped. When so many drugs are being removed from the market, many believe we must address the "safety problem." While true, we must consider that medical product development is analogous to a "listing ship" and that any effort to change its course could well pull it under. The inherent flaws of the current system must be righted before we can resume a forward course and effectively navigate these waters.

A Wake-Up Call

In March of 2004, the FDA released a report entitled: *Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products.*[4] This Critical Path Report rang an alarm on the state of drug development. The rising cost of drug development was already recognized. What was not widely known was that there had been a 50% decline in new product submissions to the FDA for review over the previous decade[4] (**Figure 1**) despite, a 250% increase in research and development expenditures. The report also noted the increasing failure rate of drugs during clinical development, especially in phases II and III(1;2). The billions of dollars invested in basic biomedical research and clinical development of new medical products are resulting in fewer innovative products that reach the market. A long, expensive development process has become a major impediment and is a disincentive for new product development. The report concluded that the major contributor to the inefficiency in development was the absence of innovative new methods for preclinical and clinical testing of drugs, "Often, developers are forced to use the tools of the last century to evaluate this century's advances."

As action items, the FDA released the Critical Path Opportunities List of 76 projects that they believe will increase efficiency and productivity in the development of new medical products.[5] The projects fall into six general topic areas:

1. Biomarker development
2. Streamlining clinical trials
3. Bioinformatics
4. Manufacturing
5. Antibiotics and countermeasures to combat infection and bioterrorism
6. Developing therapies for children and adolescents

Are the longer development times and higher costs the natural progression of science?

Some say that 'easy' drugs, the low hanging fruit, have already been developed and now the difficult ones remain. An alternative view that we prefer, is we are now better able to understand the diseases and drug reactions because of the sophistication of our scientific tools.[6] For example, many of the episodes of syncope seen with certain drugs, previously discounted as "idiosyncratic reactions", are now recognized as an unacceptable adverse drug reaction caused by drugs that block hERG channels and result in *torsades de pointes* ventricular arrhythmia.[7]

Furthermore, the experience with AIDS drug development demonstrates that innovations can speed the availability of life-savings drugs without sacrificing safety. The average drug for AIDS was developed in three years because the FDA and sponsors agreed to use biomarkers such as "viral load" as a measure of probable clinical benefit with later confirmation of a

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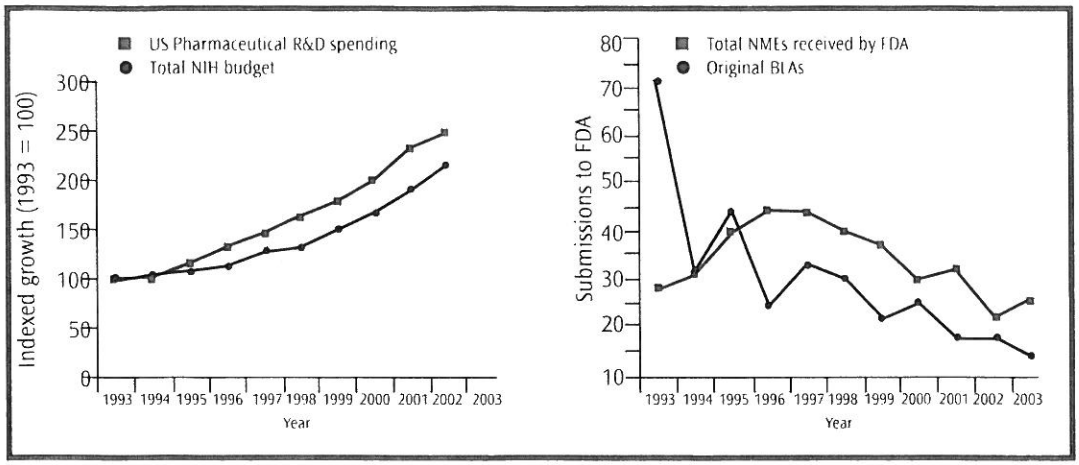

Figure 1. A: Biomedical Research Spending, B: Productivity of Medical Innovations[4]

mortality benefit.[8] We need to examine why this was successful and why the same has not happened for other lethal diseases such as heart failure, cancer and malaria.

The FDA's Critical Path Opportunity List also includes the need to create "virtual control groups" or natural history databases to facilitate the planning of clinical trials and reduce the risk of failure. The report called for a new national infrastructure to support and continually improve the Critical Path and new ways to collaborate and share data to accomplish common goals. The FDA correctly notes that no single company, university, or government agency will be successful with these tasks and that collaboration will be essential.

Did anyone hear the wake-up call?

The FDA has been "overwhelmed by the positive reactions" to the Critical Path Initiative (CPI). Most large pharmaceutical companies have developed internal working groups or task forces to study the CPI and plan for any future changes from the FDA. Many universities have created programs to work with the FDA on the CPI and eleven have formed a coalition to focus on the manufacturing changes called for in the CPI (http://www.purdue.edu/dp/nipte/index.php). However, for the most part, there is no immediate or obvious funding for these programs. One entity based in Arizona and funded by the community, The Critical Path Institute (C-Path), was created solely to work with the FDA on the CPI.[9]

Without specific funding to support the CPI, only a small fraction of the 76 projects are underway. A newly formed advocacy group, the FDA Alliance, is supporting increased FDA appropriations that will be essential.[10] Until the FDA has full and adequate funding for execution of its entire public health mission AND new funds for the CPI, progress will be slow. As important as the CPI is, the FDA cannot divert significant resources from its other responsibilities.

Collaborators and Consortia are working on the CPI

In response to the FDA's call to action, the FDA, the National Cancer Institute (NCI) and the Center for Medicare and Medicaid Services (CMS) have formed a coalition, the Oncology Biomarker Qualification Initiative (OBQI). Two projects are underway under the OBQI. One is to validate fluoro-deoxyglucose positron emission tomography (FDG-PET) as a tool (biomarker) to measure the clinical response of non-Hodgkins lymphoma to chemotherapy. Once validated, FDG-PET could greatly accelerate the development of drugs for solid tumors. The project is being supported by a coalition of companies and government agencies through the Foundation for the National Institutes of Health (FNIH). Another OBQI project, coordinated by C-Path, has brought together diagnostic and drug companies in a collaboration to evaluate the predictive power of assays for therapies that target the epidermal growth factor receptor (EGFR). The goal is to create the framework for future co-development of drugs and diagnostic tests for personalized medicine employing targeted therapies.

The National Heart Blood and Lung Institute (NHLBI), the FDA and C-Path are also working

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with the University of Utah, several other academic centers and industry to plan prospective projects to validate genetic tests that could guide the selection of the optimal dose of warfarin for individual patients.[11] Suboptimal dosing of warfarin is a major public health problem.[11] Although warfarin provides a net medical and economic benefit, adverse events due to the wrong dose of warfarin, such as bleeding, embolism and stroke, which are estimated to cost an average of $800/patient/year.[12] Extrapolated to a national economic loss, this would exceed $1 Billion per year. Retrospective studies have shown the influence of genetic polymorphisms in determining the final dosage of warfarin.[13,14] Yet, the absence of prospective data to support a validated genetic test has prevented the broad clinical application of individualized dosage selection. The broader goal of the project is to define a pathway for development and approval of tests that better predict individual clinical response to drugs, i.e. personalized medicine.

One of the areas called for in the CPI Opportunities List[5] is improved preclinical testing of drugs. Methods have not substantially changed for decades and often fail to accurately predict the safety of drugs in humans. Many drugs expected to be safe, fail because of toxicity in phase III or, worse, after reaching the market. Pharmaceutical companies have invested millions of dollars to develop better tests but these are not independently validated and the FDA is often unclear about which of the many methods to accept. With encouragement from FDA and industry scientists, C-Path has created a consortium that includes fifteen of the largest pharmaceutical companies (the Predictive Safety Test Consortium) who are sharing their methods with each other and FDA scientists.[15] Also, they have agreed to cross validate methods, i.e. test one another's methods, and submit the data for all to review. The ultimate goal of this project is to develop data that will enable the FDA to write guidance documents that recommend tests which have greater predictive accuracy and to identify tests that should no longer be performed. This unprecedented collaboration should make it possible for companies to accelerate the entry of drugs into human testing with greater confidence in their safety and reduce the failure rate during development.

Several other biomarker consortia address points along the discovery/development pipeline. The development of biomarkers for early cancer detection is the goal of the National Cancer Institute's Early Detection Research Network (EDRN), the University of Washington's Cancer Consortium and the Friends of Cancer Research Biomarker Consortium.[16] The Foundation for the National Institutes of Health Biomarker Consortium was formed for discovery and validation of biomarkers, to monitor the success of cancer therapy. An industry-financed consortium has been created to identify genetic biomarkers associated with serious adverse drug reactions. Imaging biomarkers are the focus of the Harvard-MIT Center for Biomarkers in Imaging and European Molecular Imaging Laboratories. Duke University, the FDA and Mortara Instument have a collaboration to establish an "ECG Warehouse" where pharmaceutical companies can contribute electrocardiograms from clinical trials.[17] The project leaders expect that the Warehouse will make it possible to identify predictors for QT interval prolongation, usually considered to be a biomarker for drug toxicity.

Global Aspects of CPI

The declining productivity in medical products is not restricted to the US. Today pharmaceutical companies are global in scope and their diminished productivity affects many other nations and, especially, parts of the world where health care gaps are greatest. Improvements in the medical product development and approval process through CPI would have a favorable ripple effect worldwide, including in those countries which depend on effective medical products developed elsewhere.

Conclusions

The global effort to improve health requires advances in biomedical technologies. However, too little attention has been given to the need for modernization of the processes for developing safe new products. The FDA's Critical Path Initiative and the European Union's Innovative Medicines Initiative (IMI or Innomed),[18] have clearly defined the problem and laid out the path to correct the deficiencies. New and sustained collaborations will be essential to identify the methods that ensure that innovative new therapies are both safe and effective. To succeed, we must foster and reward work that is vital for the process improvement needed to solve the critical unmet medical challenges of man.

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