Drug Development and the FDA's Critical Path Initiative

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Advances in biomedical research over recent decades 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 marketed new therapies. Clinical pharmacologists should be aware of these signals and their potential impact. Here, we discuss a strategy, where clinical pharmacology can play an important role to improve the process of drug development.

EVOLUTION OF DRUG DEVELOPMENT

In recent decades, the Food and Drug Administration (FDA) has increased its requirements for drug testing. To reach the market today, a new drug requires an average of 15 years and approaching a billion dollars in research and development.[1] Unfortunately, much of the expense is lost on drugs that never reach the market. Only one in 10 drugs that enter clinical testing receives eventual FDA approval, in spite of millions of dollars spent on preclinical testing.[2] Alarmingly, for drugs in phase III that have shown evidence of effectiveness in phase II, the failure rate has increased to 50%.[3]

HOW DID THIS HAPPEN?

Scientists have become increasingly mechanistic in their approach to drug development.[4] The recent ability to identify genetic mutations and altered protein expression make possible a deeper understanding of the mechanisms of disease and therapies that are genuinely targeted. Clinical pharmacologists have found that genetic polymorphisms influence the sensitivity of drug targets,[5] drug metabolism,[6] drug distribution,[7] and the risk of adverse effects.[8]

With a better understanding of the factors influencing response to drugs comes an increased demand for additional testing during new drug development. It is now routine practice to conduct *in vitro* testing with human liver microsomes in order to predict the subsequent metabolism of drugs in humans. Clinical studies examine the importance of CYP450 gene polymorphisms or the potential for drug interactions.[9] Studies of the human *ether-à-go-go-related gene* potassium channel and a "thorough QT" clinical study are now expected of developers.[10] All of this new development work, while extremely important, has added to the time and expense of drug development.

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 that, we are now better able to understand the diseases and drug reactions because of the sophistication of our tools.[4] For example, many of the syncopal events, previously discounted as "idiosyncratic reactions", are now recognized as a predictable adverse drug reaction caused by drugs that block human *ether-a-go-go*-related gene channels and result in *torsades de pointes* ventricular arrhythmia.[11]

Furthermore, the experience with AIDS drug development demonstrates that innovations can speed the availability of life-saving 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 mortality benefit.[12] 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.

Recent high-profile withdrawals of drugs due to safety problems are another sign that the current drug development process needs improvement. After billions of dollars in research and development and years of clinical use, the community was shocked that rofecoxib, a drug that effectively treats inflammatory disease and may prevent some forms of cancer,[13] was removed from the market and is no longer available to the patients who could be helped. When so many drugs are removed from the market, many believe we must address the "safety problem". On the other hand,

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consider that medical product development is analogous to a "listing ship" and that any effort to change its course will simply pull it under. We believe that we must first address the inherent flaws of the current system before we can resume a forward course and effectively navigate the waters.

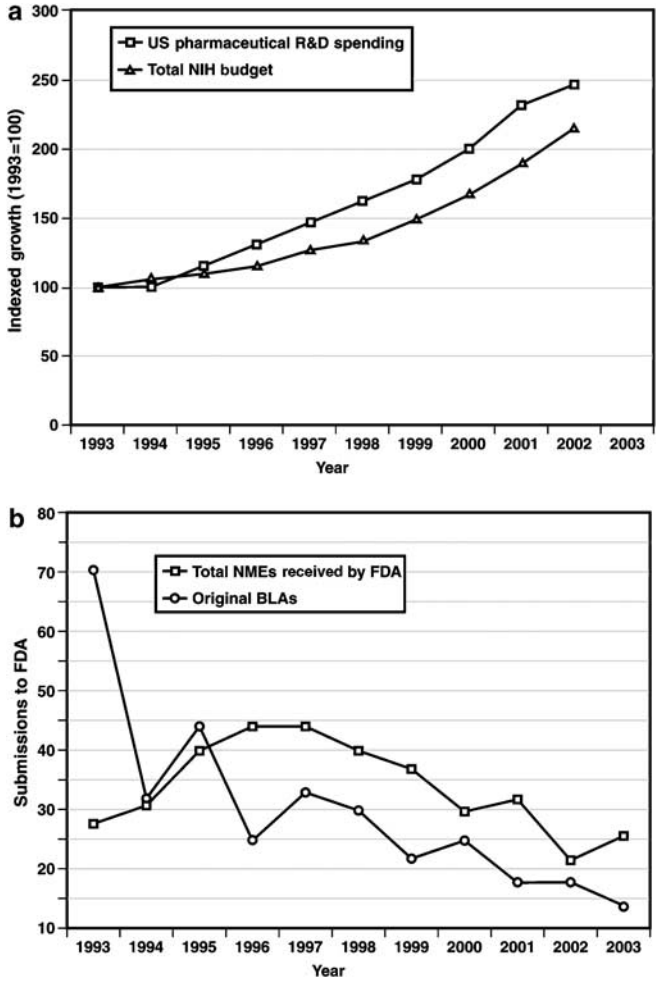

Figure 1 (**a**) 10 year trends in biomedical research spending as reflected by the NIH budget and by pharmaceutical companies' research and development. (**b**) Number of submissions of new molecular entities (NMEs) – drugs with a novel chemical structure – and the number of biologics license applications (BLAs) submissions to the FDA over a 10-year period.[14]

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*.[14] This Critical Path Report rang an alarm on the state of drug development. The rising cost of drug development was already appreciated. What was not widely known was a 50% decline in new product submissions to the FDA for review over the previous decade (**Figure 1**)[14] 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[2,3] (**Figure 2**).[3] The billions of dollars invested in basic biomedical research and clinical development of new medical products are yielding 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.[15,16] 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

Many of these projects will require the expertise of trained clinical pharmacologists, especially validation or qualification

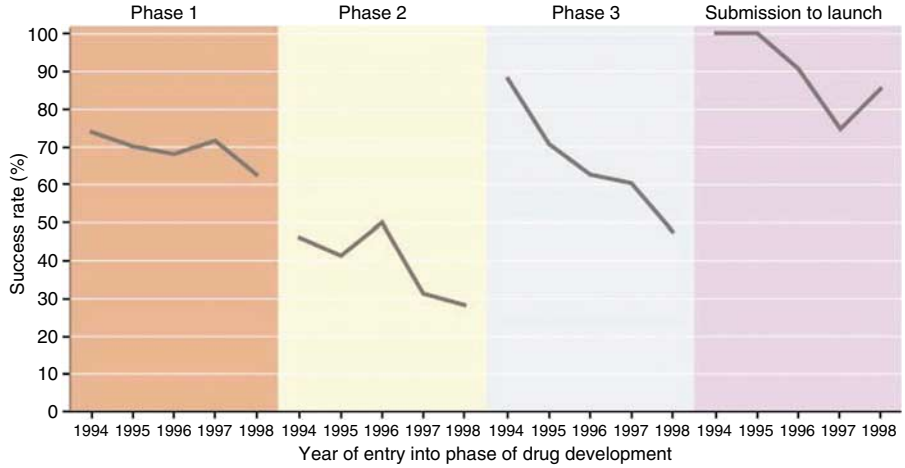

Figure 2 The success rate in drug development is declining in all phases of drug development.[3]

of biomarkers. An area often overlooked is the application of biomarkers to answer some of the basic questions important to drug development. For example, qualified biomarkers could be used to demonstrate the distribution of drugs to their site of action, the impact of receptor and metabolic polymorphisms, or to establish the bioequivalence of new formulations and dosage forms. Once qualified, biomarkers could be used to enrich trials with patients who are more likely to have a favorable response or to exclude patients at risk of being harmed. These are all areas in which clinical pharmacologists have conducted exploratory research on predictive biomarkers. Research to qualify such biomarkers for regulatory decision-making would be a logical area for clinical pharmacologists to apply their skills.

The CPI 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. Clinical pharmacologists have the expertise to identify clinical end points and define the standard data elements for such databases.

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 12 have formed a coalition to focus solely on the manufacturing changes called for in the CPI. 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, was created solely to work with the FDA on the CPI.[17]

Without specific funding to support the CPI, only a few of the 76 projects have begun. Two newly formed advocacy groups, the FDA Alliance and the Coalition for a Stronger FDA, are supporting increased FDA appropriations.[18,19] We have a long way to go: the entire FDA budget is less than the annual budget for the public school system in Montgomery County Maryland, the geographic home of the FDA and National institutes of Health. The President's budget for FY2007 includes a request for approximately $6 million for the FDA to support the CPI, but other cuts included in the FDA's budget could limit the impact of CPI funding. The trade organizations and many patient advocacy groups are publicly supporting congressional appropriations for the FDA's CPI. 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 and the Center for Medicare and Medicaid Services have formed a coalition, the Oncology Biomarker Qualification Initiative. Two projects are underway under the Oncology Biomarker Qualification Initiative. One is to validate fluoro-deoxyglucose positron emission tomography as a tool (biomarker) to measure the clinical response of non-Hodgkin's lymphoma to chemotherapy. Once validated, fluoro-deoxyglucose-positron emission tomography 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. Another Oncology Biomarker Qualification Initiative project, coordinated by the Critical Path Institute, 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. The goal is to create the framework for future co-development of drugs and diagnostic tests for personalized medicine using targeted therapies.

The National Heart Blood and Lung Institute, the FDA, and Critical Path Institute are also working 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.[20] Inaccurate dosing of warfarin is a major public health problem.[20] Although warfarin provides a net medical and economic benefit, adverse events due to warfarin dosing errors, such as bleeding, embolism, and stroke, which are estimated to cost an average of $800/patient/year[21] or, extrapolated as a national economic loss, exceeds $1 billion per year. Retrospective studies have shown the influence of genetic polymorphisms in determining the final dosage of warfarin.[5,6] 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[15] is improved preclinical testing of drugs. Methods have not substantially changed for decades and often fail to predict accurately 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, Critical Path Institute has created a consortium of 15 of the largest

pharmaceutical companies (the Predictive Safety Test Consortium), which are sharing their methods with each other and FDA scientists.[22] 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 generate 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, the University of Washington's Cancer Consortium, and the Friends of Cancer Research Biomarker Consortium.[23] 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. 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 Instrument, Inc. have a collaboration to establish an "ECG Warehouse," where pharmaceutical companies can contribute electrocardiograms from clinical trials.[24] The project leaders hope 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 Pharmaceutical companies that are global in scope, and their diminished productivity affects many other, if not all, 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, arguably, have a favorable ripple effect worldwide, including in those countries that depend on effective medical products developed elsewhere. In parallel to CPI, the European Union's European Commission has launched the Innovative Medicines Initiative (IMI or Innomed),[25] as a public–private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. The goal is to accelerate the development of safe and more effective medicines by addressing safety, efficacy, knowledge management, and education and training. The Innovative Medicines Initiative seeks to raise €450 million from government and industry and begin its programs in 2007.

LESSONS FROM OTHER TECHNOLOGIES

Competition fosters innovation, but it can also result in stalemates and stagnation. Industries need a way to agree on standards and a way to develop core technologies for process improvement. In the 1980s, the semiconductor industry was facing a crisis due to computer chip failure and aggressive competition from Asia. SEMATECH, a public–private partnership, created by the US government and 14 chip manufacturers, has been credited with bringing the US industry back into international competitiveness.[26] The cable industry created CableLabs to develop standards and conduct precompetitive development work.[27] The food industry created the Center for Food Safety Technology as a partnership between the FDA, academia, and industry to develop new methods to ensure the safety of foods.[28] Like the food industry, the pharmaceutical industry cannot set standards or validate methods without the input and participation of the FDA that approves and regulates its products. In order to perform the 76 projects on the CPI Opportunities List and others to be identified in the future, a mechanism is needed to enable FDA scientists to engage with the industry scientists and academic community in developing improved testing methods. It should be a shared undertaking, neutral with respect to commercial products. Neutrality can also be achieved by having balanced funding and shared leadership by the public and the industry. Clinical pharmacologists are logical participants in the planning and conduct of the work because of their training and expertise that bridges basic pharmacology and medical research.

CONCLUSION

The global effort to improve health demands advances in biomedical technologies. However, too little attention has been given to the need for modernization of the *processes* for developing new products. The FDA's CPI and the EU's Innovative Medicines Initiative have clearly defined the problem and laid out the path to correct the deficiencies. New and sustained collaborations will be essential. To succeed, we must foster and reward work that is vital for the process improvement needed to efficiently develop new medical products.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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