

Introduction — Drug Development: Who Knows Where the Time Goes?

In June 1996 FDLI, the Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER), and the Center for Drug Development Science at Georgetown University cosponsored a conference designed to explore all facets of contemporary new drug development. This meeting was held in the Leavey Conference Center at Georgetown University, and is referred to as the "Georgetown Conference." The motivation for the program was the widely-held belief that the time and expense requirements for the development of new medicines in the United States are greater than they need to be. A broad range of topics was addressed by speakers from FDA, academia, and the pharmaceutical industry. This report summarizes some of the key points made during the meeting and its conclusions.

The focus of interest in the Georgetown Conference was the activities involved in the new drug development process, from the filing of an investigational new drug (IND) exemption to the filing of a new drug application (NDA) with the FDA. Improvements in the review times for NDAs were acknowledged. An underlying assumption in the presentations, however, was that all parties (FDA, academia, and industry) play a critical role in determining the length of time and resource requirements for new drug development. Thus, scientific factors, as well as the impact of policy and management practices in all sectors were examined critically.

That the process of taking a new chemical entity from discovery to a marketed drug takes significantly longer and costs, in relative terms, a great deal more today than in the past was not disputed by any of the Conference participants. Data presented from the Center for the Study of Drug Development at Tufts University indicated that the length of time from synthesis of a new compound to marketing of a new drug consumed, on average, eight years in the 1960s, fourteen years in the 1980s, and fifteen years in the 1990s. This was not explainable on the basis of a global shift in therapeutic classes to those that typically take longer than others. Clinical development time alone was reported to have increased by seventy-seven percent from the 1960s to the 1970s, twenty-eight percent from the 1970s to the 1980s, and an additional six percent from the 1980s to the 1990s. The average time from IND filing to NDA filing has doubled from a little less than three years in the 1960s to six years in the 1990s.

Detailed data on the cost of new drug development were not presented. Figures ranging from \$200,000,000 to \$500,000,000 dollars have been presented, and sometimes disputed, elsewhere. The striking increase in time required to complete the process, however, would be expected to generate at least a proportional increase in cost, possibly accelerated by the inflation of technology during the same period. The observation was made that there has been a significant increase in the size of the NDA database as a consequence of growing expectations and policy about documentation and standards of evidence. Whether these changes alone are responsible for the longer time and greater cost of new drug development is not clear. The impact of policy changes and less formal expectations (i.e., guidelines) on the duration and cost of the process has not been studied rigorously.

Greater interaction between industry and FDA during the drug development process is a characteristic that distinguishes current practice from the past. There is a common belief that such interaction is facilitative; it is encouraged by FDA and often sought and embraced by the industry. FDA speakers observed, however, that it is not certain

that such interaction is the norm. Examples cited in support of a close ongoing interaction usually involve drugs for which there are many external motivations for accelerated development. It is also possible that such interaction may generate a proliferation of studies to fulfill individual expectations that are not central to the evaluation of a new drug's safety and effectiveness. In response to this interaction, industry may overreact to casually-expressed interests by FDA, leading to larger numbers of studies and expanded data collection within studies. A striking proliferation of drug-drug interaction studies as a component of the drug development process was offered as an example of ritualistic behavior in response to perceived expectations that may have little or no basis in fact.

Among the most significant changes in the technology of clinical development during the past two decades has been the recognition of drug dosage as a determinant of therapeutic response and safety. Dose-response trials have come to be expected in many therapeutic areas, and are believed to have produced an improved, more rational drug development paradigm. In addition, dose-response trials have contributed to the magnitude of time and costs involved in drug development. While the impact on time and cost has not been analyzed in a quantitative way, examples of very costly errors resulting from inadequate attention to dose-response have been cited compellingly as justification for this change.

As encouraged by FDA, employed by industry, and often promulgated by significant forces in academia, the methodology for elucidating dose-response in the clinical development of new drugs may not be optimal. It is usually empirical and based on statistical hypothesis testing, a procedure that often necessitates large numbers of patients. An approach that employs more intense application of preclinical data and thorough evaluation in smaller focused clinical pharmacology studies, perhaps with surrogate measures of activity, was advocated by some Conference speakers. The distinction was characterized as an "empirical" versus a "mechanistic" strategy for clinical drug development. While the topic generated interesting discussion, it was noted that there are no rigorous studies to establish the greater efficiency of the latter paradigm. The critical need for such data was acknowledged.

The efficiency of the process of drug development as practiced in the pharmaceutical industry was a key topic of the Georgetown Conference. A preliminary study at the Center for Drug Development Science of twelve NDAs approved in 1994 and 1995 showed a strikingly broad range of numbers of studies and patients that could not be explained solely on the basis of differences in therapeutic class or targets. The smallest NDAs in this survey contained fewer than twenty-five studies and 1000 patients, and the largest contained more than 100 studies and 10,000 patients. It is unlikely that all, or even most, of the studies included in many of these NDAs are required to meet regulatory requirements for approval. Some may be generated for other reasons, such as marketing approval, pricing outside the United States, or establishing competitive advantages. There is a strong impression, however, that many also failed to have or achieve clear scientific or regulatory objectives. Also acknowledged at the Georgetown Conference was the need for a more detailed analysis of drug development practice as reflected by the content of NDAs.

Benchmarking studies of industry practice reveal a broad range of performance in many aspects of clinical drug development, from protocol design to generation of final reports. A report from Barnett Associates noted that companies differ greatly in their performance of the same tasks, with a range of two-to-three-fold between the best and worst in many cases. The time required to complete certain tasks, such as enrollment,

appears to be related to resource allocation. Some differences, such as data management, may be a function of technological sophistication, but some of the findings (e.g., the time required to complete a simple phase I report versus a complex phase III report, the difference in which was surprisingly small) suggest that suboptimal management systems are common.

The culture and management practices of research and development organizations in the pharmaceutical industry have not been studied to the same extent as other research-dependent industries. A recent and ongoing study, the Project on the Pharmaceutical Industry conducted by the Sloan School of Management at MIT, suggests that important principles learned over the past several decades about management effectiveness in research and technology have not been adopted widely by the pharmaceutical industry. Despite an intense need for crossfunctional integration pharmaceutical research, organizations tend to be fragmented and hierarchical. Project management often is relatively weak in contrast to the power and influence of individual functional areas within the organization. This characteristic may be responsible for breakdowns in coordination and delays in the completion of the highly complex process of new drug development. Data in this area, too, were acknowledged to be sparse.

The pharmaceutical industry in recent years has experienced a number of changes that have posed significant challenges to its research and development effort. The first is globalization of the clinical development process, made possible by increased coordination across regulatory bodies through the International Conference on Harmonization. Another is the consolidation of resources occasioned by acquisitions and mergers, which have affected a significant segment of the industry. These changes have created stress on the cultural environment of many companies and the management structures within their research and development organizations. The increasingly competitive marketplace for new drugs, a product of global healthcare reform movements, has prompted many of these changes and has created time pressures that also are a challenge to effective management. The need to meet expectations of third-party payers and formulary managers has led to a marked increase in comparative drug trials, which has contributed substantially to the volume of data generated during the drug development process. While such studies may not be required for marketing approval in the United States, the heightened postpatent competition occasioned by the Waxman-Hatch Act has caused sponsors to begin these “market-oriented” clinical trials during the presubmission development process. Of necessity, these trials become part of the NDA submission and contribute to the overall costs. Senior pharmaceutical executives at the Georgetown Conference highlighted the importance and impact of these changes on the process of new drug development.

It became apparent during the various Conference presentations and discussions that the problems that have led to a dramatic proliferation in the time and costs associated with developing new drugs are multifactorial and will, therefore, require crossfunctional solutions. The roles of government (legislative as well as regulatory), academia, and industry are related in a very complex web that cannot be untangled effectively by any one group or party. This realization prompted consideration of a new collaboration aimed at addressing the problems in an integrated fashion. The goals of this collaboration were articulated as follows:

- (1) Establish an effective “Theory of Drug Development.”
- (2) Optimize clinical trials with respect to number and design.
- (3) Improve the process of science (project and portfolio) management.

- (4) Optimize the process of data management and flow.
- (5) Review effectiveness of organizational cultures and leadership.
- (6) Review regulatory standards, requirements, and practices.

A commitment to support this collaboration was expressed by those senior representatives of the pharmaceutical industry and of FDA who attended the Georgetown Conference. A strong interest in participating in the process also was expressed by representatives of a few academic institutions.

Transcripts of presentations included in this issue of the *Food and Drug Law Journal* were selected because they represented the various perspectives expressed at the meeting. Others, not included, reflected similar perspectives and provided a broad range of relevant opinion. All speakers agreed that there are insufficient data on the process of drug development as a whole to make firm recommendations for major improvements. The need for research on the process and how it can be improved was clear. It is hoped that the collaborative effort growing out of the Georgetown Conference will generate meaningful data upon which decisions can be made to generate significant improvements in efficiency. The status quo is unsatisfactory for everyone, especially the sick, who may be the ultimate beneficiaries of a successful collaboration.