

Executive Summary

The unsustainable rising costs and low productivity of pharmaceutical R&D is the central issue in the pharmaceutical/biotechnology industry today. Pharmaceutical companies are attempting to deal with the fallout from this problem by large-scale mergers, restructurings, and outsourcing R&D to China and India. However, unless companies can successfully address the R&D productivity problem, all of these measures are, at best, short-term solutions.

Central to the R&D productivity problem is the issue of drug attrition during development, especially Phase II attrition. Industry experts have proposed solutions to the developmental attrition problem, based on the discipline of translational medicine. Most pharmaceutical companies and many biotechnology companies have adopted this approach.

Translational medicine studies are aimed at obtaining evidence that can help clinical researchers predict outcomes of treatment with experimental agents in early development. This especially involves obtaining proof-of-concept (POC) that a drug is likely to be safe and efficacious early in development by carrying out clinical trials that are designed to determine POC rapidly and at relatively low cost. Biomarkers for determining pharmacodynamic, efficacy, and safety parameters are central to these clinical studies. Biomarkers that can be used to give an indication of likely efficacy much more quickly than clinical endpoints that are accepted by regulatory agencies for drug registration are especially important.

A large part of the reason for developmental attrition is that companies have been increasingly addressing complex diseases with high unmet medical needs. Addressing these complex diseases involves addressing unprecedented targets. However, drugs that address unprecedented

targets are much more likely to fail in Phase II (by a factor of 2–4-fold) than drugs that address precedented targets. The most common reason for this attrition is failure to demonstrate clinical efficacy.

In this report, we discuss strategies to reduce the risk in Phase II due to addressing unprecedented targets. These strategies are designed to 1) identify those targets that have the best chance of success in the discovery phase, and 2) employ early stage POC clinical trials to weed out drugs and targets that do not achieve POC. The general strategy proposed in this report thus involves both improving the drug discovery and preclinical phases, and improving early development.

Strategies for improving drug discovery (Chapter 2) focus on sets of methods for moving beyond the target validation paradigm (*e.g.*, addressing multiple targets, addressing whole pathways, biology-driven drug discovery, and systems biology-based methods). Developing improved animal models that more closely model human pathways and/or diseases and are thus more predictive (Chapter 3) is important in both discovery and in the preclinical phase.

In Chapter 4, we provide an overview of translational medicine and its use in drug development. In this chapter, we discuss the questions that need to be answered in translational studies, and the use of biomarkers in these studies. We also discuss how translational medicine is changing early drug development to emphasize learning enough about a drug to determine if it is likely to provide substantial patient benefit and survive full-scale clinical trials. The goal of late-stage clinical trials then becomes to confirm that the drug is indeed safe and efficacious, and to enable the drug's registration and commercialization.

In Chapter 5, we discuss biomarkers and their use in translational studies in more detail. Biomarkers constitute a young discipline, and there is a need to identify more biomarkers and to qualify and validate them for use in POC trials and other types of early clinical studies. The FDA's Critical Path Initiative emphasizes biomarker development and use in drug development. Such research consortia as the Biomarkers Consortium, the Alzheimer's Disease Neuroimaging Initiative, and the High-Risk Plaque Initiative are attempting to improve the state of biomarker science and technology via collaborative, precompetitive studies. However, the vast majority of biomarker identification, qualification, and validation studies take place in individual academic laboratories and companies.

In Chapter 6, we discuss new strategies for early-stage clinical trial design, including Phase 0 human clinical studies using microdosing, and adaptive clinical trials. We also summarize discussions of POC clinical trials from earlier chapters. Designing a POC clinical trial usually involves using a biomarker in lieu of a clinical endpoint, and testing an investigational drug in a small number of patients using that biomarker in order to get a relatively rapid determination of efficacy.

We conclude that the ability of researchers to successfully identify and validate biomarkers, and to design and carry out POC clinical trials, depends to a large extent on an understanding of disease biology and disease pathways. Thus, biology-driven strategies of drug discovery carry over to the new paradigm of early drug development. Our discussions thus indicate that both drug discovery and early drug development will need to become more biology-driven in order to weed out drugs that are likely to fail in development, and to increase the success rates of drugs that are taken into full clinical development.

The report also includes the results of a survey of researchers and executives in corporate and academic organizations who work in drug development. The survey results include information regarding respondents' involvement in drug development, as well as their views on the Phase II attrition problem, the use of translational medicine approaches, and POC, Phase 0, and adaptive clinical trials in early development.

Finally, the Appendix includes expert interviews with five industry leaders: Charles Gombar, PhD and Evan Loh, MD (Wyeth), Peter Lassota, PhD (Caliper Life Sciences), Bruce H. Littman, MD (Translational Medicine Associates), and Daniel M. Skovronsky, MD, PhD (Avid Radiopharmaceuticals).

