Preface

Some of the challenges the pharmaceutical industry faces in the current research and development processes are: (1) a lengthy process that takes, on average, approximately 11 years from target identification to the development of a new medicine; (2) an ever increasing costly process; (3) an inefficient process where too many drugs fail before they reach the market because of a lack of efficacy or unacceptable toxicity, as well as postmarketing withdrawal due to rare serious adverse events; (4) drug--drug interactions or toxicity is not uncommon; (5) the increasing difficulty in identifying novel drug targets; and (6) the mode of action for many compounds is often unknown. This is a depressing reality. Where are the improvements in both quality and efficiency often claimed in the drug development process? Why haven't the advances in science and technology made a greater impact? How can improvements in the process reduce the already high cost of drug development generally?

To address some of these issues, the pharmaceutical industry is actively exploring the relationships between human genetics and drug responsiveness, susceptibility to disease, and disease severity. While research approaches and emphases may vary from company to company, the overarching goal of the industry is largely consistent: to discover and develop new medicines based on an improved understanding of patient response to drugs (positive or negative) and of diseases etiology. Pharmacogenomic (PGx) methods are aimed at determining the contribution of genetic differences in ADME, drug target, and disease genes to drug response, thereby improving the safety and efficacy of drug therapy through use of genetically guided treatments, an approach called *personalized medicine. Personalized medicine* is both one of the newest disciplines of medicine currently being used and very much an ongoing work in progress. Many drug companies have incorporated genetic research, such as the collection of genetic samples, into their drug development programs. And while only a few examples of true success stories have emerged during the past few years of research, it is clear that the current landscape is driving us toward a more widespread acceptance of personalized medicine. Currently many questions arise regarding the appropriate implementation of this technology: how can the industry go about delivering true business value while recognizing that the ability to address patients' demand for safer and more efficient novel drugs might be met by engaging this technology more fully. There are

concerns within the pharmaceutical industry about generating data that might be difficult to interpret in a regulated environment. There is also a growing appreciation for the challenges in translating this new information into clinical utility, including scientific, commercial, ethical, and policy challenges.

Pharmacogenomics and Personalized Medicine, which is part of the *Methods in Pharmacology and Toxicology* series, comprises chapters on selected aspects of pharmacogenomics and personalized medicine. Our overall intent is to assist both novice and experienced investigators in understanding the current scientific challenges in applying PGx to discovery and clinical development and in making appropriate decisions to engage in and interpret PGx research. Designed to share the experiences of leading experts in the field, the book is a useful guide for conducting PGx research--from discovery to the market, but we also aim to present a realistic perspective on the challenges, practicalities, and obstacles in applying pharmacogenomics. Generally, the book avoids statements such as "Pharmacogenomics is going to revolutionize the practice of medicine," which are neither realistic nor particularly useful to anyone.

The book presents an industry perspective on the implementation of PGx in research and development, in drug discovery, and in clinical trials, including recommendations for a systematic approach for assessing the feasibility and added value of PGx studies in clinical trials. It also provides guidance on the key logistical issues required to prepare the pharmacogenomics protocol and an informed consent form for sample collection and analysis, the strategies and resources for SNP marker selection, and genotyping in genetic association studies, and the study design and statistical methodologies for data analysis in PGx research. We have included an interesting view of the effect of genetic variation, as well as a description of recent PGx applications in drug metabolism, adverse drug reactions, and in a few selected therapeutic areas (epilepsy, Alzheimer's disease, psychiatry, oncology, HIV, cardiovascular diseases). Additional key topics,s such as the current regulatory environment and drug label implications, biomarker qualification and trial design, the co-development of drugs and diagnostics, and the translation of genomics biomarkers into clinical utility, are also covered. Furthermore, two chapters describe the current state of knowledge of PGx in rare and monogenic disorders and in children, which are currently less well covered in the published literature but deserve attention.

Pharmacogenomics and Personalized Medicine focuses on DNA data and associated analytical methodologies that are currently the more mature components of the evolving constellation of genomic sciences. However, complementary RNA-based studies are also being considered in some chapters. It is important to also acknowledge that remarkable progress is being made in complementary methodological areas such as *proteomics*, *metabolomics,* and *imaging*. Given the layered complexities of biological regulation, it is likely that reliable markers will be hybrids that will cross methodological disciplines. A program of persistent innovation is being required from the industry to balance near-term profit with the need to accommodate the increasingly competitive and changing landscape. Education and cooperation among experts from the scientific community, industry, and government are recognized as integral to greater success in personalized medicine. It is my hope

that the knowledge we share here regarding DNA information may be leveraged to create a useful foundation for further progress in personalized medicine, using other approaches that will benefit the pharmaceutical industry overall, and most importantly the patients.

Experts from the pharmaceutical industry, scientific community, and government have been invited to contribute their experience to this book. I would like to express my gratitude to all contributors for their enthusiasm to this work. Without their time and energy, *Pharmacogenomics and Personalized Medicine* would not have been possible.

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