PRECLINICAL SAFETY EVALUATION OF BIOPHARMACEUTICALS

A SCIENCE-BASED APPROACH TO FACILITATING CLINICAL TRIALS

Edited by

Joy A. Cavagnaro
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Biopharmaceutical research represents the use of various biotechnology techniques to discover and manufacture potential new medicines, to test their safety, and to prove their value in treating or preventing disease in humans and animals. It employs the skills and hard work of discovery and development scientists, pharmacologists, immunologists, toxicologists, pharmacokineticists, pharmacists and manufacturers, clinical scientists, and clinical research organizations representing the public interest, healthy and patient volunteers, ethics committees, and regulatory agencies.

The public, venture capitalists, media, and even novelists have looked to biotechnology for health care solutions with high expectations. Bringing the safest possible new medicines into public use is critical for society as a whole, from human and veterinary medical and economic perspectives, and also to maintain public trust in the industry. However, no drug can ever be “100% safe.” Drugs are developed and approved because they show benefits that outweigh foreseeable risks for specific indications in specific populations. Once marketed, a drug can be less safe if it is used in a way that decreases foreseeable benefits, or that increases risks if the actual risks are greater than or differ from the predicted risks. What then are the most appropriate and reasonable ways to answer the essential questions about possible risks versus benefits during the lengthy process of developing a new drug? What can be predicted from preclinical studies and of what value are the predictions?

Before testing new medicines in humans, various in vitro and in vivo preclinical studies are performed in selecting the lead candidate for clinical development. In particular, studies are designed to support a first in human (FIH) dose for phase 1 clinical trials. Phase 1 trials are principally designed to examine safety of single and sometimes several doses in about 20 to 80 study subjects, usually healthy volunteers. Phase 2 trials are designed to confirm safety, determine clinical activity, and help define an optimal dose, usually following one- to three-month dosing, for the subsequent phase 3 trials. Phase 2 are controlled studies of approximately 100 to 300 volunteer subjects with disease. Phase 3 trials are designed to prove efficacy and safety of the drug. These trials are double-blinded and placebo-controlled involving hundreds to
thousands of research subjects with the intended disease in clinics and hospitals. The duration of dosing for drugs administered chronically can last six months or longer. Each phase is supported by in vivo animal studies based on consideration of the population being tested and the duration of the clinical trial. Following the completion of all three phases of clinical trials, the sponsor of the trial analyzes all the data and files a marketing application with one or more regulatory authorities. Once approved, the new medicines become available for physicians to prescribe. For some drugs the process from discovery to approval can take as long as 10 years or more. Sponsors are also required to submit periodic reports, including any cases of adverse reactions and appropriate quality control records even after a product is approved. The phase 4 or postmarketing study commitments, which may involve additional preclinical as well as clinical studies, are for evaluation of long-term effects as well as detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors.

A pre-approved capitalized cost estimate for development of a new biopharmaceutical has recently been estimated at over $1 billion (US dollars) with $615 million estimated for all R&D costs, including basic research and preclinical development prior to initiation of clinical testing and $626 million for clinical testing [1]. These estimates take into account the significant attrition rates over the course of clinical development.

In order to facilitate clinical development, it is important to define risk and benefit in the most reasonable and appropriate way. Preclinical studies are the foundation for the initial and ongoing assessment of potential risks and as such should be designed in order to realize their maximum value. The primary objective of preclinical safety evaluation studies is to provide data that clinical investigators can use to better predict adverse effects in study subjects and to help researchers design clinical studies that will minimize their occurrence. The same information will also help to guide research toward new, less toxic drugs and, if harmful effects cannot be entirely avoided, to suggest means to lessen or alleviate the adverse actions.

In this context the term “nonclinical” is often used interchangeably with “preclinical,” particularly to define the preclinical studies performed after a product has advanced into the clinic (and thus is no longer in the preclinical development phase). Diverse studies are performed at different times to answer specific questions that only become relevant during particular phases of clinical development; for example, carcinogenicity studies are done to answer questions that ultimately arise at the end of lifetime administration to patients. Based on the explicit objective of safety studies to reveal or exclude potential adverse effects before they occur in healthy subjects or patients, the term “preclinical” will be used throughout this book to highlight the importance of the data to be derived prior to the specific clinical phase they are designed to support.

The expanding role of preclinical safety evaluation has changed the discovery/development interface for conventional small-molecule pharmaceuticals
as well as large-molecule biopharmaceuticals. A larger proportion of scientific staff and resources are required to support research and screening efforts. There has been an increasing emphasis on mechanistic studies, exploratory research, and a systems biology approach to detect and investigate an expanding range of predictable and unexpected harmful effects, always with the intention of improving the predictive value of the positive and negative information obtained.

Major technological advances in platform technologies have had a major impact on the pathways and timelines of pharmaceutical development. These include high-throughput assays for profiling and probing new molecules: “omics” technologies, exposure technologies, delivery technologies, and “informatics” technologies. A number of strategies have evolved to improve the predictive value and increase the safety knowledge based including the validation and acceptance of alternative methods, in vitro cellular models, in silico techniques and animal-based simulation models, use of nontraditional animal models and animal models of disease including humanized transgenic mice, development of noninvasive and minimally invasive technologies, and increased efforts in computational toxicology and data mining have also evolved to improve predictive value and increase the safety knowledge base and provide feedback from failed and successful development programs. A practical challenge has been the prioritization and validation of these innovative technologies.

Integration and optimization of results from early evaluation models have been essential components in improving the predictive value of preclinical studies. Programs have been accelerated through innovative study designs that can incorporate efficacy, pharmacokinetics, and safety/toxicity endpoints in the same model, thus speeding the delivery of safer therapeutic and prophylactic medicines. Lead candidate selection has been advanced by the clinical exploration and acceptance of microdosing and exploratory investigational new drug application (IND) regulatory mechanisms that support early investigation of new drugs in humans based on the results of focused preclinical information sufficient to exclude unacceptable risks and obtained with limited but proportionate expenditure of time and resources. Such strategies meet the goal of hastening development without increasing risks to the subjects involved.

Conventional FIH studies designed to determine the maximum safe dosage while ensuring the greatest possible safety in healthy volunteers may not always suffice to meet clinical needs and development and financial timelines. For accelerated development plans, FIH studies should be designed not only to identify development-limiting adverse effects but to establish proof of concept or initial effectiveness, ideally this may mean studying in an index population (i.e., a disease population). Accordingly preclinical development strategies need to be designed to support early treatment of patients and seamless progress into full clinical development.

Sometimes a product will be shown not to be ready for the widespread use and must go back for refinement. It is, however, very difficult from preclinical