may be progressed into the drug development stage. Typically, multiple lead series are identified in both the lead discovery and lead optimization phases through iterative rounds of experimentation. In many cases, the lead discovery and lead optimization phases overlap, as a typical drug discovery program will produce multiple sets of related compounds with the potential for identification of candidates that might progress into drug development. This approach is required for success, as it is often difficult, if not impossible, to identify the lead series that will contain the final lead candidate in the early phases of the drug discovery process. Parallel operations of this type mitigate the risk of failure of any one series of compounds. The lead discovery phase typically concludes with the successful demonstration of *in vivo* efficacy in an appropriate animal model employing a compound that possess physical and chemical properties consistent with eventual clinical study in the drug development stage.

The second major stage, drug development, typically begins once a single compound has been identified, which is then progressed through various studies designed to support its approval for sale by the appropriate regulatory bodies. The first step in this process is the submission of an Investigational New Drug (IND) Application that requests permission to move a clinical candidate into human study. This document provides regulatory agencies with detailed preclinical data describing animal pharmacology and toxicology studies, chemical manufacturing information (including formulation, stability studies, and quality control measures), and, of course, detailed clinical protocols that describe how the clinical compounds will be studied in human populations if the studies are approved.

While clinical trial designs can vary substantially from one candidate to another, the general goals of phase I, II, III, and IV are the same. Chapter 9 will provide a more detailed review of clinical trials, but the basic tenants of clinical trials are as follows. In phase I clinical trials, safety and tolerability of an investigational new drug is examined in a small number of healthy individuals, typically 20 to 100 people, with the goal of determining if safety margins are suitable for further progression in the clinical trial process. Pharmacokinetic and pharmacodynamic aspects of the candidate are closely monitored, and the drug candidate is typically administered first in a single ascending dose (SAD) study, followed by a multiple ascending dose (MAD) study. In the SAD study, the drug is given to a group of subjects once and they are monitored to determine the impact of the drug. If there are no adverse effects, then a second group is treated with a single higher dose of the drug candidate and monitored as before. The cycle is repeated until intolerable side effects appear in order to determine the maximum tolerated dose (MTD). MAD studies are similar, but each group of subjects is provided with multiple low doses of a candidate compound over a set time. As in the SAD studies, the manifestation of clinically intolerable side effects defines the MTD for the MAD studies. The