Within the context of the modern pharmaceutical industry, a clinical trial can be defined as a biomedical or behavioral experiment conducted on population of humans that is designed to answer key questions about a potential therapeutic agent. (Medical device and medical procedure can also be the subject of clinical study, but for the remainder of this text, only drug therapies will be considered.) The studies are designed to generate safety and efficacy data that can be presented to the appropriate regulatory bodies in order to gain market approval. In general terms, clinical trials are divided into 4 phases (Phase I to Phase IV), each with its own purpose. Phase I studies define safety margins and the pharmacokinetic profile of a candidate compound. Phase II studies are pilot studies designed to provide an initial assessment of efficacy and safety in the target patient population. Phase III studies are broad efficacy and safety studies designed to determine the risk to benefit ratio of a candidate compound in the target population. Finally, phase IV studies, also referred to as post-approval studies, monitor a drug's efficacy and safety after it has gained marketing approval. Each of these phases and the associated trial designs will be examined in greater detail later in this chapter.[13] It is important to understand, however, that there are some important hurdles that must be crossed in between the identification of a potential clinical candidate and the initiation of clinical trials.

BEFORE THE CLINIC

The identification of a candidate compound that has the desired efficacy in an appropriate *in vivo* animal model and a sufficient safety window in two animal species (rodent and non-rodent) represents the final step in the majority of drug discovery programs. Moving a candidate compound into clinical study, however, requires a significant amount of additional work. There are a number of issues that must be addressed before human studies will be permitted by the various regulatory bodies. Compound manufacture (drug supply), dosing method, and formulation must be determined before an Investigational New Drug Application (IND) would be approved for execution. There are, of course, numerous other areas that must be explored, both scientific and economic, but for the purpose of exemplifying the difficulties associated with moving from discovery to clinical development, we will consider these three key issues.

DRUG SUPPLY

Production methods capable of generating pharmaceutical grade active pharmaceutical ingredient (API, the candidate compound) under good manufacturing practice (GMP) conditions must be established in order to initiate a clinical program. In an ideal world, this would simply be a matter of increasing the scale of the synthetic methods employed in the original preparation of the candidate compound. In practice, however, this is