invading organism. If, however, the goal is to develop a new surgical anesthetic, metabolic stability may be less of an issue, as it may be desirable for drug efficacy to fade rapidly upon termination of dosing regimens.

In a related sense, compounds that have chemical stability issues may be problematic as drugs. Special packaging systems, some as simple as amber bottles for light-sensitive compounds or cold storage, may be required in order for the drug to be available commercially when a patient is in need. While these kinds of issues are not insurmountable, generally speaking, more chemically stable compounds are preferred.

It is also important to consider how candidate compounds may impact the normal metabolic processes, potentially altering the metabolism of drug products used in tandem with the candidate compound. Inhibition of key metabolic enzymes in the liver, such as Cyp3A4, Cyp2D6, and Cyp2C9, members of the cytochrome P450 (Cyp450) family of metabolic enzymes, are often studied using *in vitro* screening methods (liver microsomes) in order to determine the risk of drug–drug interactions.[86] A compound that meets all other *in vitro* criteria and demonstrates efficacy, may still fail as a drug candidate if it is determined that there is significant risk of drug–drug interactions. The withdrawal of Seldane[61,87] from market is a classic example of the risks associated with unintended inhibition of the normal metabolic processes, and is discussed in greater detail in Chapter 13.

Positive results through the *in vitro* screening portion of a discovery program represent a significant accomplishment, but are still not necessarily indicative of success. The pharmacokinetic properties (PK) of a candidate compound must be determined in order to answer key questions about the *in vivo* fate of the potential drug candidate. For example, if the candidate compound is dosed orally, what percentage of the oral dose actually reaches the systemic circulation? How rapidly is the candidate compound excreted or metabolized? Does the compound reach systemic concentrations high enough to suggest that *in vivo* efficacy should be expected in an animal model? Is the compound freely distributed through the body, or does it concentrate in a particular organ or tissue type? The answer to these and a number of similar questions will have a significant impact on the ability of any given compound to provide the desired *in vivo* efficacy in a given animal model. Irrespective of the positive results of *in vitro* screening, compounds with poor PK profiles are not likely to be successful drugs.

Compounds found to possess suitable PK profiles must, of course, demonstrate activity in key animal efficacy trials before they can be considered for clinical study. The type of efficacy studies required is based on the desired biological endpoint (disease state), and a full discussion of *in vivo* efficacy models is well beyond the scope of this text. Some examples are given in chapter 7, but it should be clear that the ultimate goal of a discovery program is to identify compounds that meet all of the aforementioned