

in vitro criteria, demonstrate efficacy in the appropriate animal model, and have PK properties consistent with the desired dosing regimen.

Safety and side-effect profiles are also major concerns, and there are a number of *in vitro* and *in vivo* screens that can be used to assess the risks associated with a compound (e.g., *in vitro* hERG screening,⁸⁸ Ames mutagenicity screening,⁸⁹ dog cardiovascular safety assessment⁹⁰). The nature and scope of safety studies is well beyond the scope of this text, but should always be a major concern in the minds of drug discovery scientist as any project moves forward. It is also important to realize that the side-effect profiles for a potential clinical candidate are somewhat dependent on the intended use. For example, compounds used to prevent life-threatening illness, such as cancer, AIDS, and ALS, may be given more latitude with their side-effect profiles, given the severity of the illness. On the other hand, treatments designed for chronic use or non-life-threatening conditions, such as osteoarthritis or neuropathic pain, must be scrutinized for possible safety issues or side effects. The concern for safety bridges through all aspects of discovery and development of novel therapeutics. It is impossible to guarantee that compounds entering clinical development will be safe, but compounds with “red flags” in safety screens are generally not pursued as drugs.

Finally, the ability to identify patentable compounds will also gate the progress of any drug discovery program. As mentioned earlier, drug discovery and development is an exceptionally expensive endeavor. Market exclusivity through patent protection provides the necessary financial incentive required for companies to invest in new drug development. Compounds and compound classes that cannot be protected through the issuance of patents are unlikely to be pursued by private organizations, as recouping the significant investments required to move a compound into clinical use becomes challenging. Further information regarding the importance of patent protection in the pharmaceutical industry is provided in Chapter 12.

Drug discovery scientists walk on the edge of several precarious slopes in attempting to identify potential new therapeutic entities. Balancing the needs of potency, selectivity, solubility, stability, pharmacokinetics, safety, and novelty is critical to the success of any project, and failure to deliver in any one of these areas can terminate the forward progression of a test compound.

QUESTIONS

1. What are the three major phases of drug discovery?
2. What are the four major phases of drug development?
3. Describe the lead optimization cycle.
4. What is a screening cascade (also referred to as a screening tree)?
5. Why is compound selectivity an important aspect of drug discovery?