Answers to Questions in Textbook by Chapter

CHAPTER 1

1. The three major phases of drug discovery are (1) target discovery, (2) lead discovery, and (3) lead optimization. (See Figure 7.)
2. The four major phases of drug development are (1) preclinical, (2) proof of concept, (3) full development, and (4) registration and launch. (See Figure 7.)
3. The lead optimization cycle begins with the identification of a lead structure ("hit") in a relevant biological assay. New analogs with structural modifications are prepared and screened in the biological assay. If the assay results improve, then the changes are kept and the cycle is repeated. If the changes are detrimental, then they are discarded and the cycle is repeated. This process continues until a candidate compound with the desired properties is identified. (See Figure 16.)
4. A screening cascade, also referred to as a screening tree, is a series of experiments designed to decrease the number of candidate compounds as a discovery program proceeds toward a clinical candidate. At each stage of the cascade, criteria, also referred to as "gates," are established that determine whether or not a test compound proceeds to the next level of screening. In principle, the number of compounds that pass through each gate will decrease toward the bottom of the screening tree, limiting the number of compounds that need to be studied in more complex, time-consuming, and costly experiments designed to identify in vivo active, safe candidate compounds. (See Figure 18.)
5. Compound selectivity is an important aspect of drug discovery because there is often substantial overlap between the macromolecular target of interest and many other biomolecules. In cases where sufficient selectivity is not achieved between the targeted macromolecule and structurally related biomolecules, a biochemical response may be elicited from the interaction with both the desired target and unintended targets. These unintended interactions have the potential to create unwanted side effects that could hamper future development of a candidate compound.