agents that target at specific receptors, it will be desirable to use animals carrying the corresponding human receptors for preclinical evaluation. For instance, a human cytokine-expressing vector should be tested in animals that carry the corresponding human cytokine receptor in appropriate tissues. To meet such a need, the gene for human cytokine receptor will be expressed in transgenic animals. To introduce changes into either somatic tissues or germ cells, all three types of genetic changes described earlier (i.e., random DNA integration, gene-targeting and inducible gene-targeting) can be applied. The challenge is the selection of appropriate expression vectors and regulatory sequences, obtaining appropriate cell types (in the case of somatic changes) for manipulation and the delivery methods. This remains an active research area and requires further exploration. These novel therapeutic agents/methods utilize cellular products or ex vivo manipulation of cells followed by reintroduction of these cells into humans. Specific concerns in the use of these types of therapeutic agents may vary from agent to agent; however, general concerns such as cell types, gene products, and vector systems are common to this type of genetic manipulation. Although many remain at the experimental stages, it can be predicted that the number of preclinical studies will grow rapidly, and the demand for animal models will increase dramatically. New guidelines for these types of therapeutic agents/methods are available at the Web site of FDA "http://www.fda.gov.cber.guidelines.htm."

3. APPLICATIONS IN PRECLINICAL DRUG DEVELOPMENT

Essentially, all studies in preclinical drug development involve animals. Two major goals in animal studies of preclinical drug development are to confirm the pharmacological effects of the drug and to determine and explore its potential toxicity in the context of animal physiology before a human trial is launched. The most elegant application of transgenic animals to evaluate the pharmacological effects of drugs is to create suitable disease models. The therapeutic value of the agent and its metabolism can be determined in these genetically altered animals that are relevant to human conditions. In preclinical studies of drug toxicity, transgenic animals are generated for screening general toxic effects and mutagenic/chronic effects. Additionally, transgenic animals can be generated in which a specific human condition associated with the therapy can be simulated in the animals. The pharmacokinetics and pharmacodynamics of these drugs in these types of patients can be assessed first in these animals. In the following, the application of transgenic animals in preclinical drug development is discussed with respect to biological activity, drug metabolism, and toxicity/carcinogenicity.