of Investigational New Drugs" (10). For information on that tier testing approach, the reader is referred to that document.

In contrast to classic small molecule drugs, genotoxicity testing is not routinely required for biotechnology drugs. Nonetheless, as illustrated in the case studies presented later in this chapter, it is not uncommon to see the ICH recommended battery of genotoxicity studies conducted with biotechnology products. Carcinogenicity studies are also not generally performed on these biotechnology products, although the guidance does indicate circumstances where animal bioassays may be relevant. Similarly, reproductive toxicity testing is dependent on the biotechnology product and the intended clinical population. Again, the submission of such studies, or lack thereof, is illustrated in the case studies presented later in this chapter.

4. ADDITIONAL SAFETY TOPICS AND GUIDELINES

The preclinical toxicity testing of a drug was outlined in the previous section. Toxicity is one of the three major areas evaluated during preclinical development; the other two being pharmacology and pharmacokinetics (administration, adsorption, metabolism and elimination, hence the acronym ADME). For the purposes of completeness of the presentation of safety topics addressed by ICH, this section will briefly discuss the ICH guidelines to date in the realms of pharmacology and pharmacokinetics. The preclinical safety topics in these areas are provided in Table 10.

4.1. Note for Guidance on TK: the Assessment of Systemic Exposure in Toxicity Studies (ICH Topic S3A)

The demonstration of systemic exposures to the drug product in toxicity studies is extremely important, perhaps best illustrated by the fact that this topic was addressed early on in the ICH proceedings (21). The incorporation of blood sample collection in animals, either the actual study animals or separate satellite groups, provides an evaluation and correlation of systemic exposure with toxicity endpoints and can validate the relevant selection of the animal species in the toxicity study. The TK data collected in animals can provide vital comparisons with the clinical data, allowing for assessment of potential risk and possible margin of safety of the drug product in humans. This ICH guidance provides strategies for incorporation of pharmacokinetic data collection in toxicity studies, termed TK. Excellent real-life examples of how these data have been collected in the conduct of toxicity studies and how the data are used, especially to design subsequent toxicity studies, are provided in the section on Non-clinical Drug Development Programs (see Section 5).

ICH S3A provides some guidance for the collection of TK data as a part of the toxicity testing discussed above; that is, single- and repeat-dose