where systemic exposures are anticipated to be minimal. Studies with cytotoxic drugs in cancer are usually excluded from any safety pharmacology testing. Biotechnology products with highly specific targets and mechanisms of action may also be exempt from safety pharmacology testing, although biotechnology products with less-specific targeting or unknown mechanisms of action should have the core battery assessment of testing. With regards to timing, safety pharmacology testing in the core battery of systems should be completed prior to administration of the drug in the clinical setting.

4.4. Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (ICH Topic S7B)

The high profile for the cardiovascular system in the assessment of safety pharmacology is emphasized with this ICH guidance extending the guidance discussed in ICH Topic S7B to specifically identify and assess the risk of potential cardiovascular effects, specifically effects on the QT interval (24).

ICH S7B provides general recommendations for the testing strategy to evaluate risk of a drug product to cause a prolongation of the QT interval in man. The guidance calls for evaluation in four particular areas. Number 1 is the evaluation of the pharmacological class to which the drug product belongs and whether this class is known to possess cardiovascular effects. Number 2 is an evaluation of the drug effects in an ionic current assay in vitro (e.g., isolated animal or human myocytes, cultured cardiac cell lines). Number 3 is an evaluation of action potential parameters in isolated cardiac preparations or alternatively, the measurement of specific electrophysiological parameters indicative of action potential duration in animals. Number 4 is an in vivo QT assessment. This assessment should be a component of the core battery cardiovascular study conducted as part of the safety pharmacology evaluation described in ICH S7A. An investigator can expand the scope of the in vivo QT assessment to include regional information relating to ventricular repolarization, and thereby satisfy testing in area Number 3. Each of these evaluations should be complete prior to initiation of clinical trials.

ICH topic S7B also provides extensive guidance and protocol elements of investigational test systems to address drug effects in each of the areas, numbers 2, 3, and 4, described above. A discussion of each of the test systems in the ICH guidance is beyond the scope of this chapter and the reader is referred to the ICH S7B guidance document (24).

5. NON-CLINICAL DEVELOPMENT PROGRAMS

This section presents some case studies of drug development programs that have been reviewed by the regulatory authorities in the United States and/or in Europe and approved to support the marketing approval of the pro-