substrate of the CYP3A4 pathway), and a two-way crossover drug interaction study of steady-state pioglitazone and single-dose midazolam (i.e., pioglitazone as a possible *inducer* of the CYP3A4 pathway) (56).

Again, this pioglitazone drug interaction study exemplifies why it is so important for clinical drug development to be guided by information and knowledge obtained from preclinical studies.

5. LIMITATIONS AND PREDICTIVE VALUE OF THE PRECLINICAL DATABASE

As presented in the previous sections, the preclinical database can play a significant role in clinical drug development by providing supportive, sometimes critical, information on the safety and/or efficacy of the drug in humans for the purposes of regulatory approval. Although new in vitro techniques have reduced the need for animal studies, these conventional studies still have been the primary method to understand the in vivo pharmacology, toxicology, efficacy, and safety of a drug for clinical development.

However, toxicity testing using animals carries ethical liability, is time consuming and expensive [for example, a monkey can cost $3500–$5000 (65)], which together may restrict the breadth of the preclinical database for clinical drug development (66). Additionally, there are some inherent limitations of preclinical studies, which may render a naïve empirical extrapolation from animals to humans less useful or even meaningless for the purposes of an informed decision during clinical drug development (67). For example, the variability between human individuals can be overestimated due to extrapolation across different animal species; diversity even exists within inbred strains of homogenously derived and maintained laboratory animals (68,69). Furthermore, there are few animal models or animal-based in vitro or ex vivo systems that can duplicate the structure or function of humans, and drug developers must validate the animal systems as models for human systems at all levels (70–72).

Therefore, the value of animal models in predicting the efficacy and toxicity of a drug in humans can be realized only in cases where findings are congruent in both animal models and humans (73,74), i.e., efficacy/toxicity found (75–77), or not found (78), in both animals and humans (Table 4). When animal models failed to define a drug's efficacy and toxicity, seen later in humans (third row of Table 4), these animal models had no predictive value (79); in practice, the drug could have dropped from further clinical development at preclinical stage. But, the failure to find efficacy in animal models does not necessarily preclude further clinical development. For example, none of animal models of osteoarthritis (OA), including mouse and guinea pig spontaneous OA, meniscectomy and ligament transection in guinea pigs, meniscectomy in rabbits, and meniscectomy and cruciate transection in dogs, have been used with success to predict drug efficacy