Table 4 Predictive Value of Animal Models

Findings in		Predictive value	
Animal[a]	Human[b]	Efficacy	Toxicity
Found	Found	Yes	Yes
Not found	Not found	Yes	Yes
Not found	Found	No	No
Found	Not found	No	?

[a]Multiple of human dose.
[b]Human effective dose.
Source: Ref. 73.

in humans, because no agents have been shown to provide anything other than symptomatic relief in human OA (80).

Of course, if the efficacy of a drug was seen in animal models, but not found in humans, the drug would fail to show proof of concept in humans, and is likely to be dropped from further development. The most difficult decision, however, has to be made when toxicity, found in an animal model, is not necessarily seen in humans, after which the predictive value of this animal model may be questioned. In this case, drug developers must carefully plan and design clinical studies to adequately address safety issues raised in animal models, and the preclinical database can give them meaningful insight into potential safety concerns, as exemplified in the case of pioglitazone (51,55,56).

Physiologically based pharmacokinetic (PBPK) modeling, although not widely used in drug development because of its technical complexity, may be useful for internal decision making to assess the predictive value of the preclinical database for clinical drug development (81–83). Because PBPK approaches help drug developers link toxicity data from animal species to expected clinical observations using the exposure–response (i.e. toxicokinetic–safety) relationship, PBPK modeling can serve as a valuable tool for understanding what preclinical PK, safety, and efficacy results ultimately mean in humans (84).

6. CONCLUSIONS

Although there are some limitations of preclinical studies, they provide the sole source of data upon which the assessments of drug efficacy and safety are to be made before human data become available (73). Therefore, if utilized adequately, coupled with more physiological models that account for the biological inter- and intra-species diversity, and variability based on