4. UTILIZING THE PRECLINICAL DATABASE TO DESIGN IN VIVO METABOLIC DRUG–DRUG INTERACTION STUDIES

Hepatic metabolism and renal excretion are the two main elimination routes of a non-protein drug or its metabolites (57). Many metabolic pathways, including the hepatic cytochrome P450 enzymes (CYP), can be inhibited, activated, or induced by the administration of a concomitant drug. More and more, preclinical in vitro studies using suitable probes and appropriately validated experimental methods, [e.g., human liver microsomes (58,59) or recombinant cytochrome P450 (59,60)] can be used as screening mechanisms to rule out a possible metabolic pathway and drug–drug interactions that could occur via this pathway. In many cases, negative findings from early in vitro studies, if coupled with similar results from early clinical studies, can eliminate the need for later in vivo clinical investigations (61,62).

On the other hand, when positive findings are seen in in vitro metabolic studies, in vivo clinical studies are recommended. The clinical importance of the potential drug–drug interaction should be quantitatively estimated for safe and efficient use in patient populations that were not necessarily tested in clinical development, for which the interaction may be sufficiently large to necessitate dosage adjustment or therapeutic monitoring of the drug itself or concomitant medications (61). For example, a potent CYP3A4 inhibitor, ketoconazole, inhibited 85% of in vitro pioglitazone metabolism at equimolar concentrations, suggesting that pioglitazone may be a substrate for the CYP3A4 metabolic pathway (63). However, the sponsor did not conduct any in vivo drug–drug interaction studies based on these preclinical results; instead, they conducted in vivo drug–drug interaction studies of pioglitazone with digoxin, glipizide, warfarin, and metformin, in which no significant changes in PK parameters were found. The sponsor's approach to address possible drug–drug interactions focused mainly on a specific group of drugs that were likely to be coadministered with pioglitazone (digoxin, hydrochlorothiazide) or for which the clinical consequences of potential interactions were of concern.

Additionally, troglitazone, another thiazolidinedione, was known to potentially induce CYP3A4 (64), but pioglitazone was not tested for this potential, neither in vitro nor in vivo. The clinical pharmacology and biopharmaceutics reviewer at the FDA discussed that the drug interaction potentials of pioglitazone were not investigated using the understanding of the metabolic pathways of related agents; instead, the sponsor's approach made it hard to draw conclusions for general drug–drug interaction profiles (62,63). As a result, the FDA requested that the sponsor conduct two drug–drug interaction studies as the phase IV commitments for regulatory approval of pioglitazone: a two-way crossover drug interaction study of single-dose pioglitazone and single-dose ketoconazole (i.e., pioglitazone as a