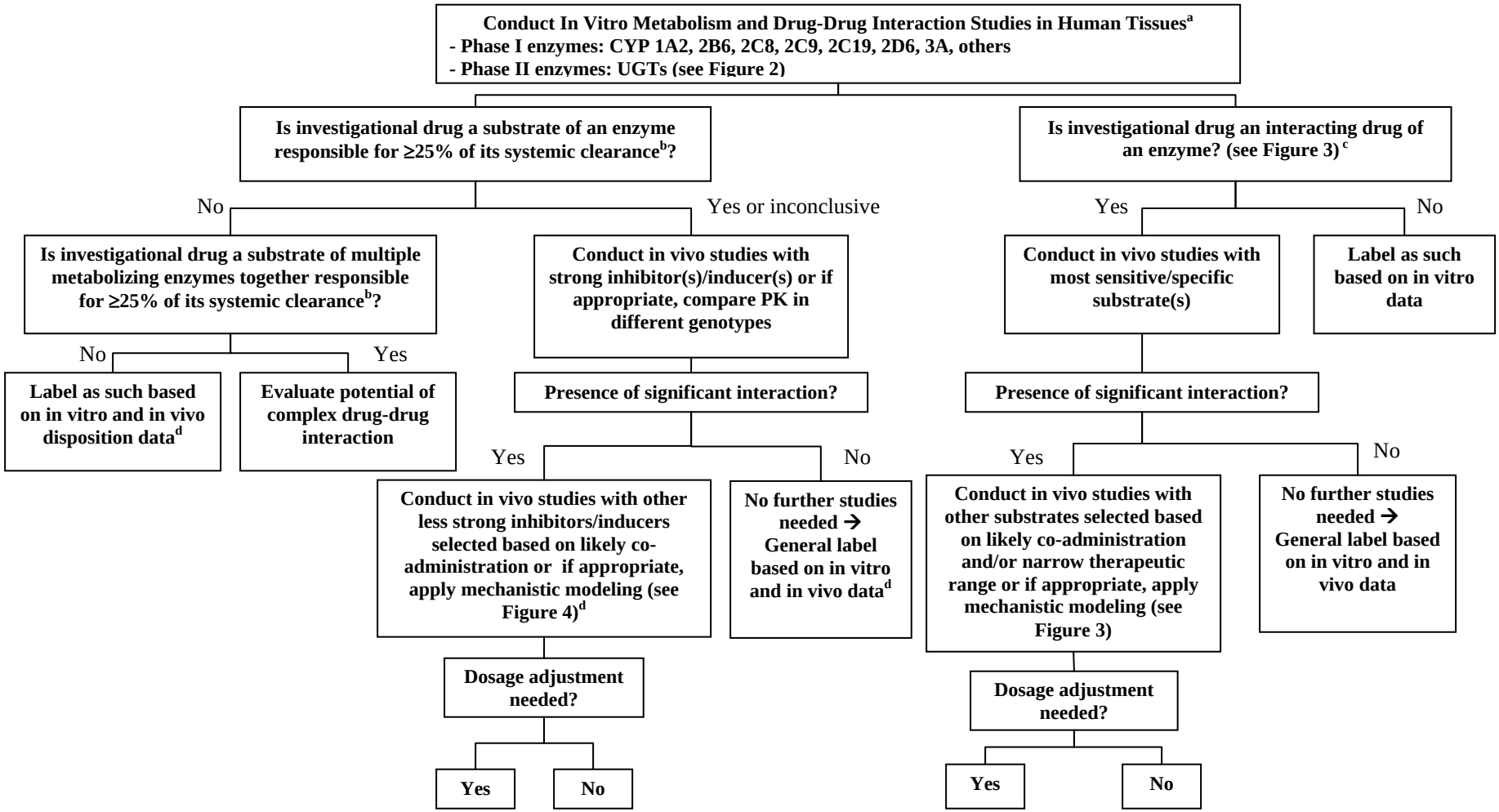
Figure 1. Metabolism-Based Drug-Drug Interaction Studies — Decision Tree



[a] Other Phase I enzymes (CYP and non-CYP) such as CYP2A6, CYP2J2, CYP4F2, CYP2E1, MAO, FMO, XO, or alcohol/aldehyde dehydrogenase.
[b] Results from in vitro enzyme phenotyping experiments, human pharmacokinetic studies such as an intravenous study, a mass-balance study, and pharmacokinetic studies in which renal/biliary clearances are determined can be evaluated together to determine the percent contribution of enzyme to overall in vivo drug elimination in humans.
[c] See Figure 3 for calculation of R values and cutoff values. Sponsor may conduct an in vivo cocktail study in humans (Reference: *Clinical Pharmacology and Therapeutics*, 81: 298-304, 2007).
[d] Additional population pharmacokinetic analysis may assist the overall evaluation of the investigational new drug as a substrate.