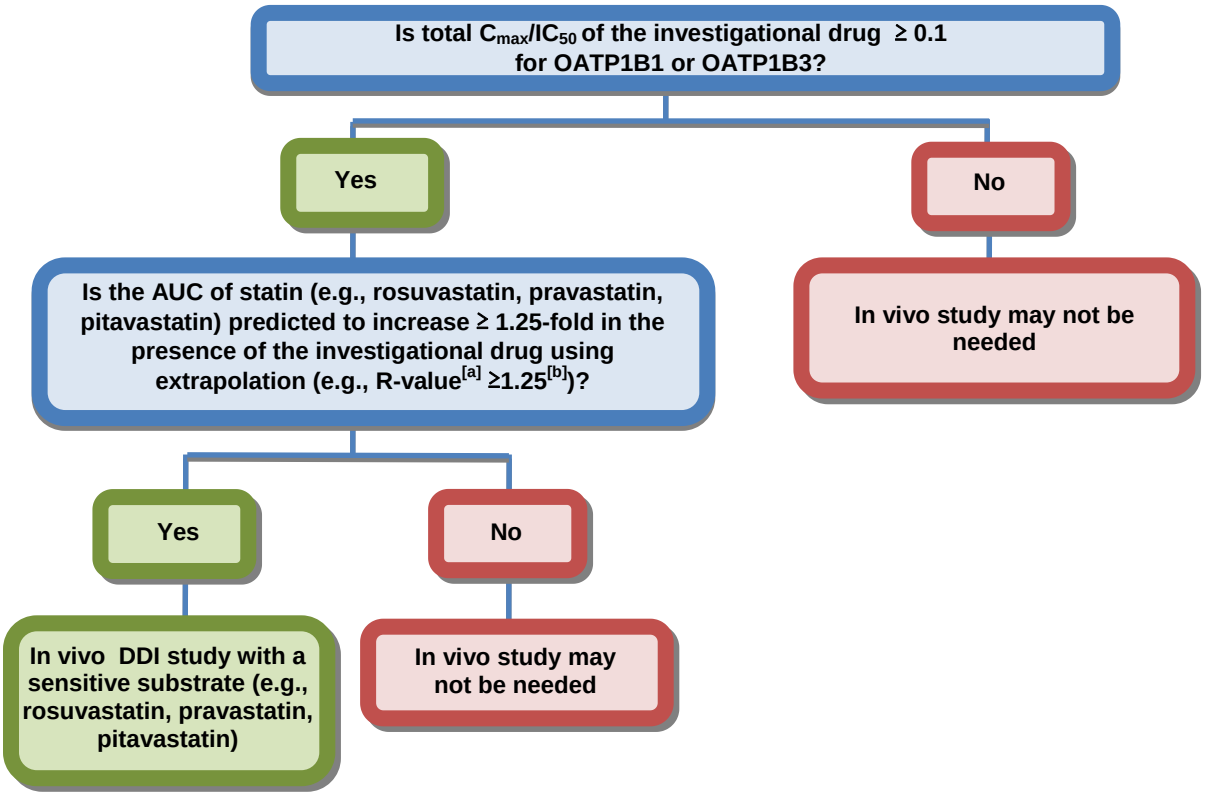
Figure 9. Decision tree to determine whether an investigational drug is an inhibitor of OATP1B1 or OATP1B3 and when an in vivo clinical study is needed —(Modified From Figures in Giacomini KM, *et al*, Nat. Rev Drug Discov. 9: 215-236, 2010)



[a] R-value = 1+ (fu x $I_{in,max}/IC_{50}$), where, $I_{in,max}$ is the estimated maximum inhibitor concentration at the inlet to the liver and is equal to: C_{max} + (k_a x Dose x F_a F_g/Qh). C_{max} is the maximum systemic plasma concentration of inhibitor; Dose is the inhibitor dose; F_aF_g is the fraction of the dose of inhibitor which is absorbed; k_a is the absorption rate constant of the inhibitor and Qh is the estimated hepatic blood flow (e.g., 1500 mL/min). If Fa Fg values and ka values are unknown, use 1 and 0.1 min^{-1} (Ito et al. *Pharmacol Rev.* 50 (3): 387-412, 1998) for FaFg and ka, respectively because the use of theoretically maximum value can avoid false-negative prediction. For drugs whose fu values are less than 0.01 or fu cannot be accurately determined due to high protein-binding, then assume fu = 0.01, to err on the conservative side to avoid false negative predictions.

[b] These are the suggested values according to the upper limit of equivalence range. We are open to discussion based on sponsors' interpretation.