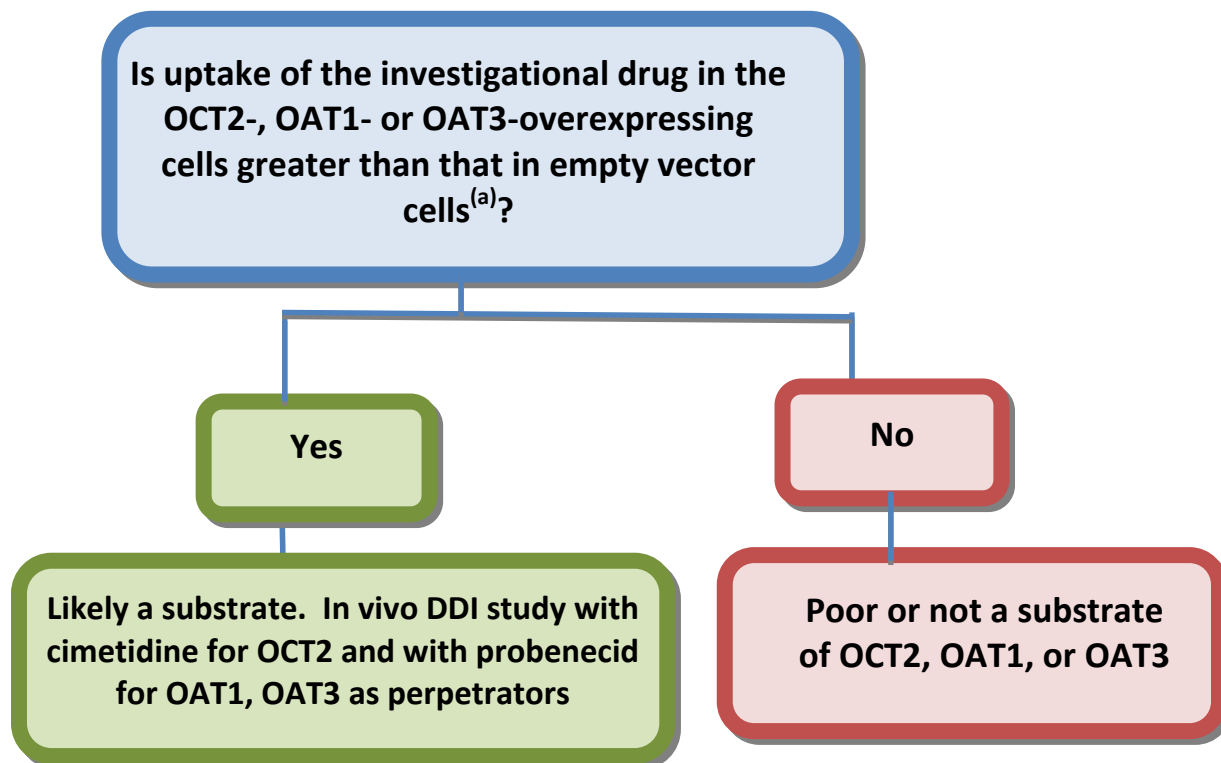


OCT2, OAT1, and OAT3 (renal transporters):

Figure 10. Decision tree to determine whether an investigational drug is a substrate for OCT2, OAT1, or OAT3 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) The ratio of the investigational drug uptake in the cells expressing the transporter versus the control (or empty vector) cells should be greater than 2. It is important that uptake into the transfected cells be significantly greater than background in a control cell line and be inhibited by a known inhibitor of the transporter. Michaelis–Menten studies may be conducted in the transfected cells to determine the kinetic parameters of the investigational drug. A positive control should be included. In an acceptable cell system, the positive control should show a ≥ 2 fold increase in uptake compared to vector-transfected cells. An uptake ratio (transporter transfected vs. empty vector transfected cells) other than 2 may be used if a ratio of 2 is deemed non-discriminative as supported by prior experience with the cell system used.