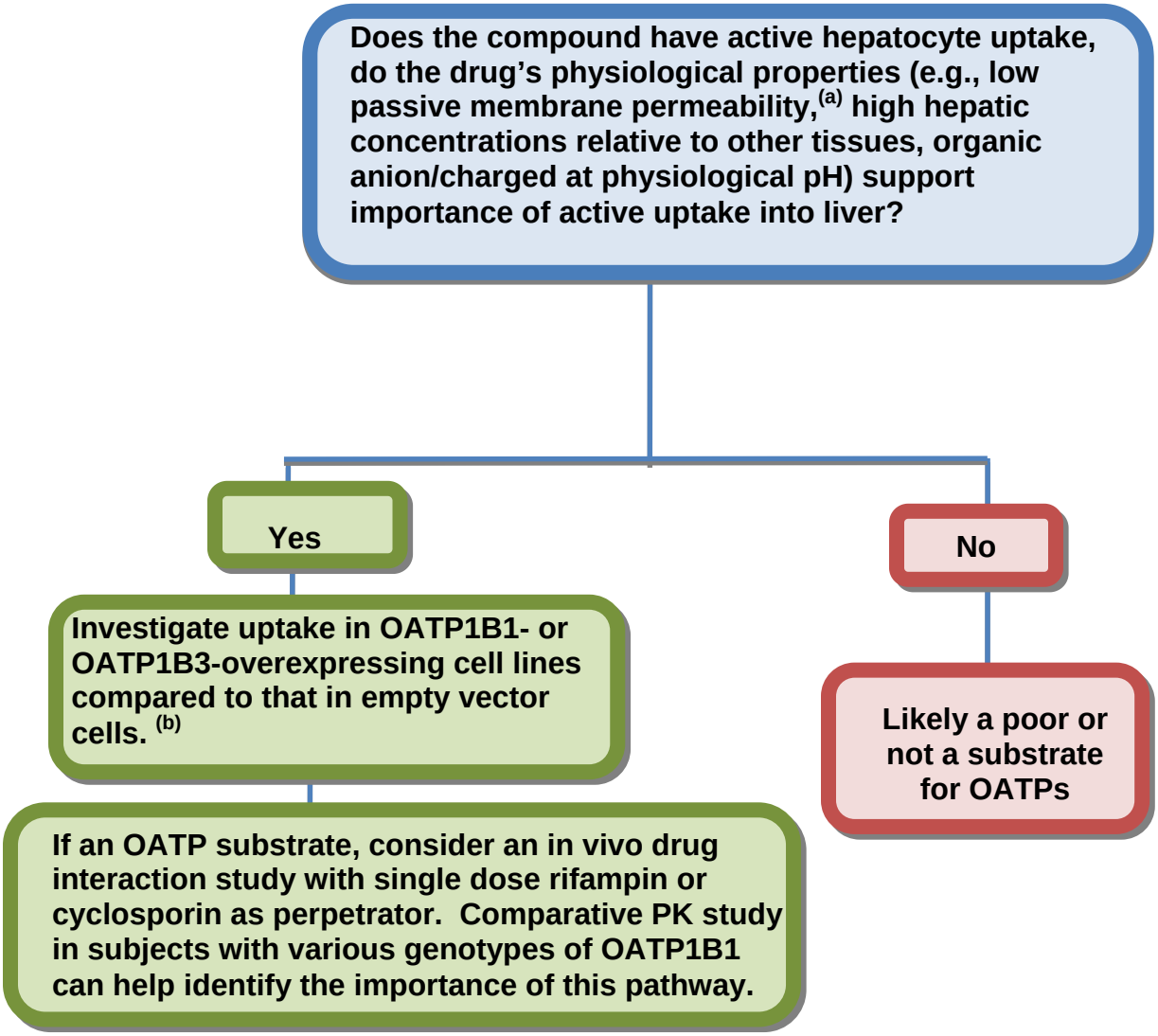
OATP1B1 and OATP1B3 (Liver uptake transporters):

Figure 8. Decision tree to determine whether an investigational drug is a substrate for 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) Low permeability needs to be defined by each lab based on standards, such as atenolol (a biopharmaceutics classification system (BCS) reference drug). A general guide would be that 10^{-6} cm/sec (10 nm/sec) or lower is classified as "low" permeability.

(b) The following criteria suggest the investigational drug is a substrate of OATP1B1 or OATP1B3: Uptake in OATP1B1- or OATP1B3-transfected cells greater than 2-fold of that in empty vector transfected cells and is inhibitable (e.g, >50% reduction to unity) by a known inhibitor (e.g., rifampin) at a concentration at least 10 times of its K_i. 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.