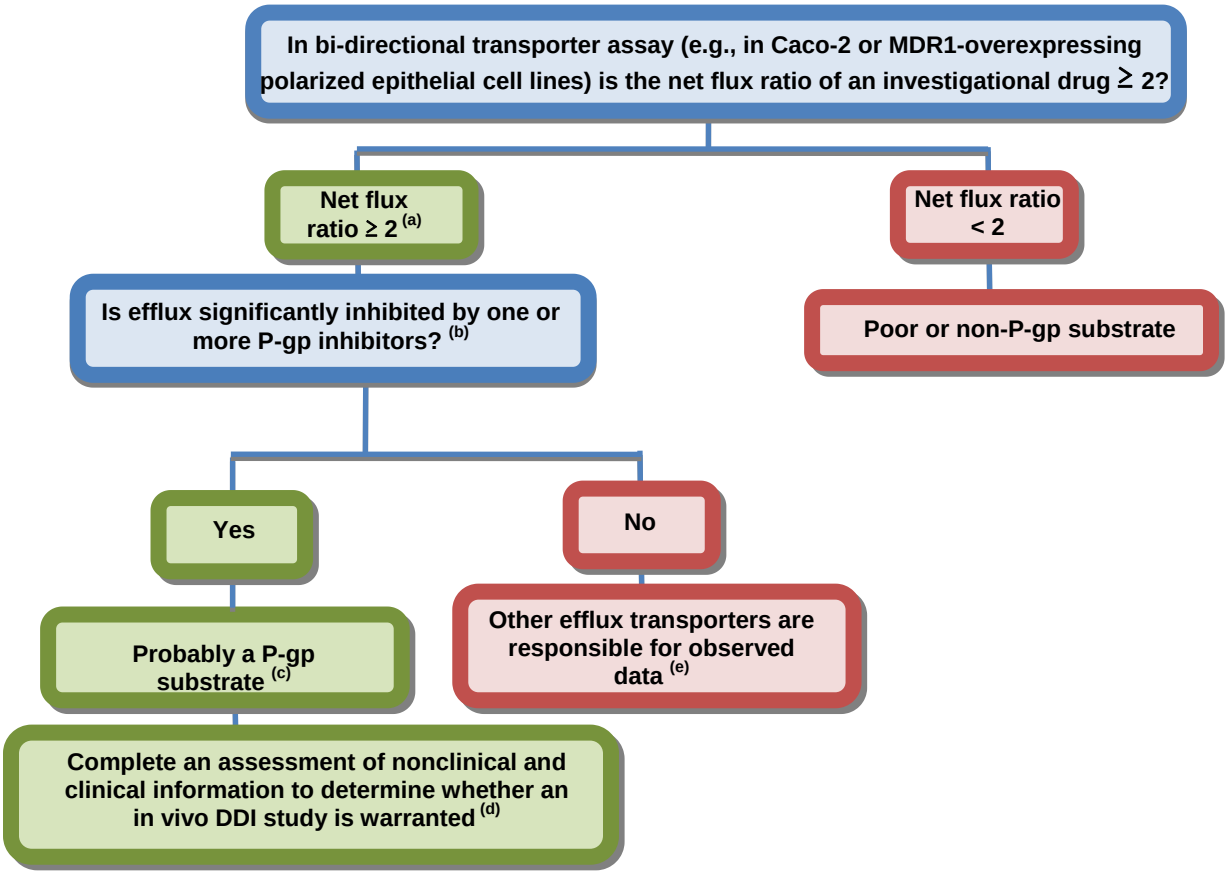
P-gp and BCRP:

Figure 6. Decision tree to determine whether an investigational drug is a substrate for P-gp and when an in vivo clinical study is needed. A similar model can be applied to a BCRP substrate —(Modified From Figures in Giacomini KM, *et al*, Nat. Rev Drug Discov. 9: 215-236, 2010).



(a) An acceptable system produces net flux ratios of probe substrates similar to the literature values. A net flux ratio ≥ 2 for the investigational drug is a positive signal for further evaluation. A net flux ratio "cutoff" higher than 2 or a relative ratio to positive controls may be used to avoid false positives if a ratio of 2 is deemed non-discriminative as supported by prior experience with the cell system used.
(b) Reduction of the flux ratio significantly (> 50%) or to unity.
(c) Additional data are needed to establish clinical relevance of the in vitro data. In particular, the relative contribution of the transporter-mediated pathway to the overall clearance of the drug is the primary determinant of whether an inhibitor will have a major effect on the disposition of the investigational new drug.
(d) Selection of inhibitors could be based on likelihood of co-administration and/or its inhibition potency on P-gp. Strong P-gp inhibitors (e.g., itraconazole, verapmil) provide the most sensitive assessment and should generally be tested first. If the drug is also a substrate for CYP3A, then inhibitors for both CYP3A and P-gp should be selected (Table 14).
(e) Based on existing knowledge of the compound class, further studies may be warranted to determine which efflux transporters are involved. Determining whether the drug is a BCRP substrate may be explored. A similar decision model may be used for a BCRP substrate; however, clinical studies would differ.