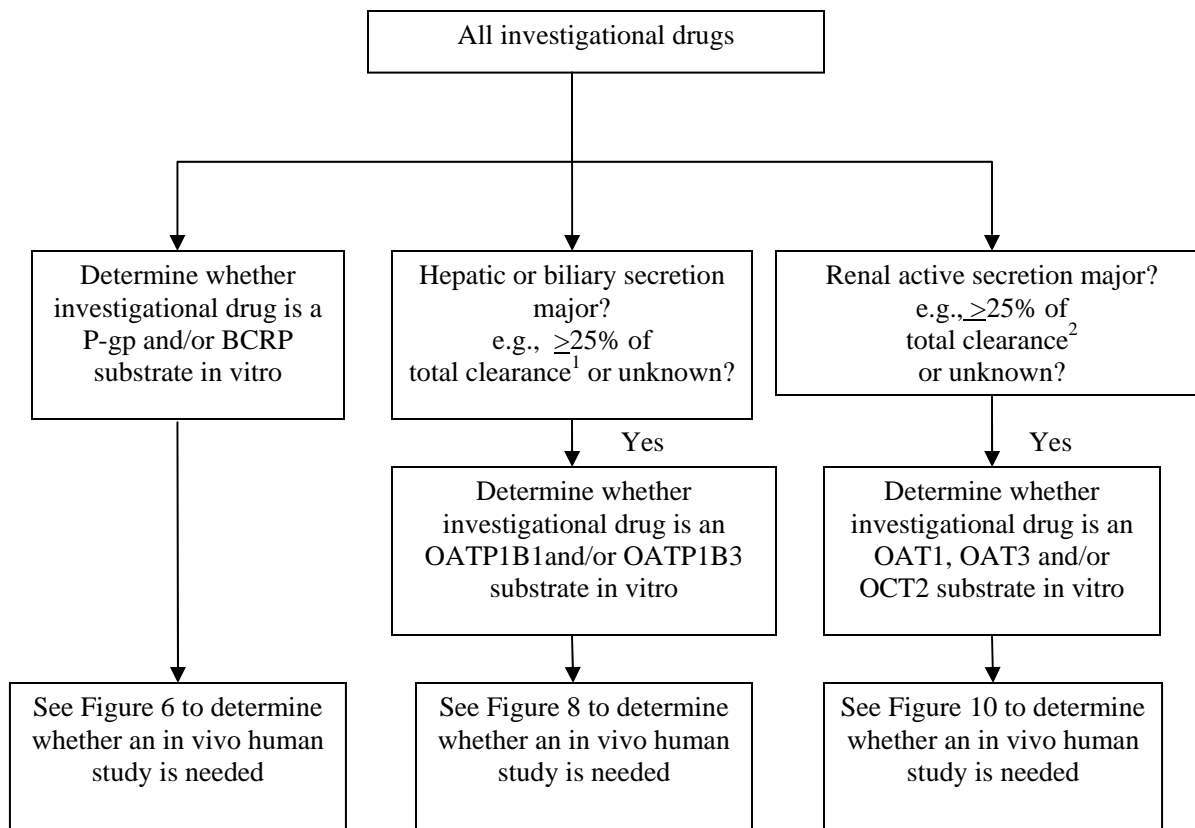**Possible Model for Decision Making: Transporter-Based Drug-Drug Interaction Studies (Figure 5)**

Figure 5. Evaluation of Investigational Drugs as Substrates for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 Transporters.

```
                        ┌─────────────────────────┐
                        │ All investigational drugs │
                        └─────────────────────────┘
                                    │
        ┌───────────────────────────┼───────────────────────────┐
        ▼                           ▼                           ▼
┌──────────────────┐  ┌──────────────────────┐  ┌──────────────────────┐
│ Determine whether│  │ Hepatic or biliary   │  │ Renal active         │
│ investigational  │  │ secretion major?     │  │ secretion major?     │
│ drug is a P-gp   │  │ e.g., ≥25% of total  │  │ e.g., ≥25% of total  │
│ and/or BCRP      │  │ clearance¹ or        │  │ clearance² or        │
│ substrate in     │  │ unknown?             │  │ unknown?             │
│ vitro            │  │                      │  │                      │
└──────────────────┘  └──────────────────────┘  └──────────────────────┘
        │                    │ Yes                     │ Yes
        │                    ▼                         ▼
        │         ┌──────────────────────┐  ┌──────────────────────┐
        │         │ Determine whether    │  │ Determine whether    │
        │         │ investigational drug │  │ investigational drug │
        │         │ is an OATP1B1 and/or │  │ is an OAT1, OAT3      │
        │         │ OATP1B3 substrate in │  │ and/or OCT2          │
        │         │ vitro                │  │ substrate in vitro   │
        │         └──────────────────────┘  └──────────────────────┘
        ▼                    ▼                         ▼
┌──────────────────┐  ┌──────────────────────┐  ┌──────────────────────┐
│ See Figure 6 to  │  │ See Figure 8 to      │  │ See Figure 10 to     │
│ determine whether│  │ determine whether an │  │ determine whether an │
│ an in vivo human │  │ in vivo human study  │  │ in vivo human study  │
│ study is needed  │  │ is needed            │  │ is needed            │
└──────────────────┘  └──────────────────────┘  └──────────────────────┘
```

[1] Biliary secretion can be estimated from preclinical data, in vitro heptocyte uptake data or radiolabeled ADME data, and nonrenal clearance data.

[2] Percent (%) active renal secretion was estimated from $(CL_r - fu*GFR)/CL_{Total}$; fu is the unbound fraction in plasma.