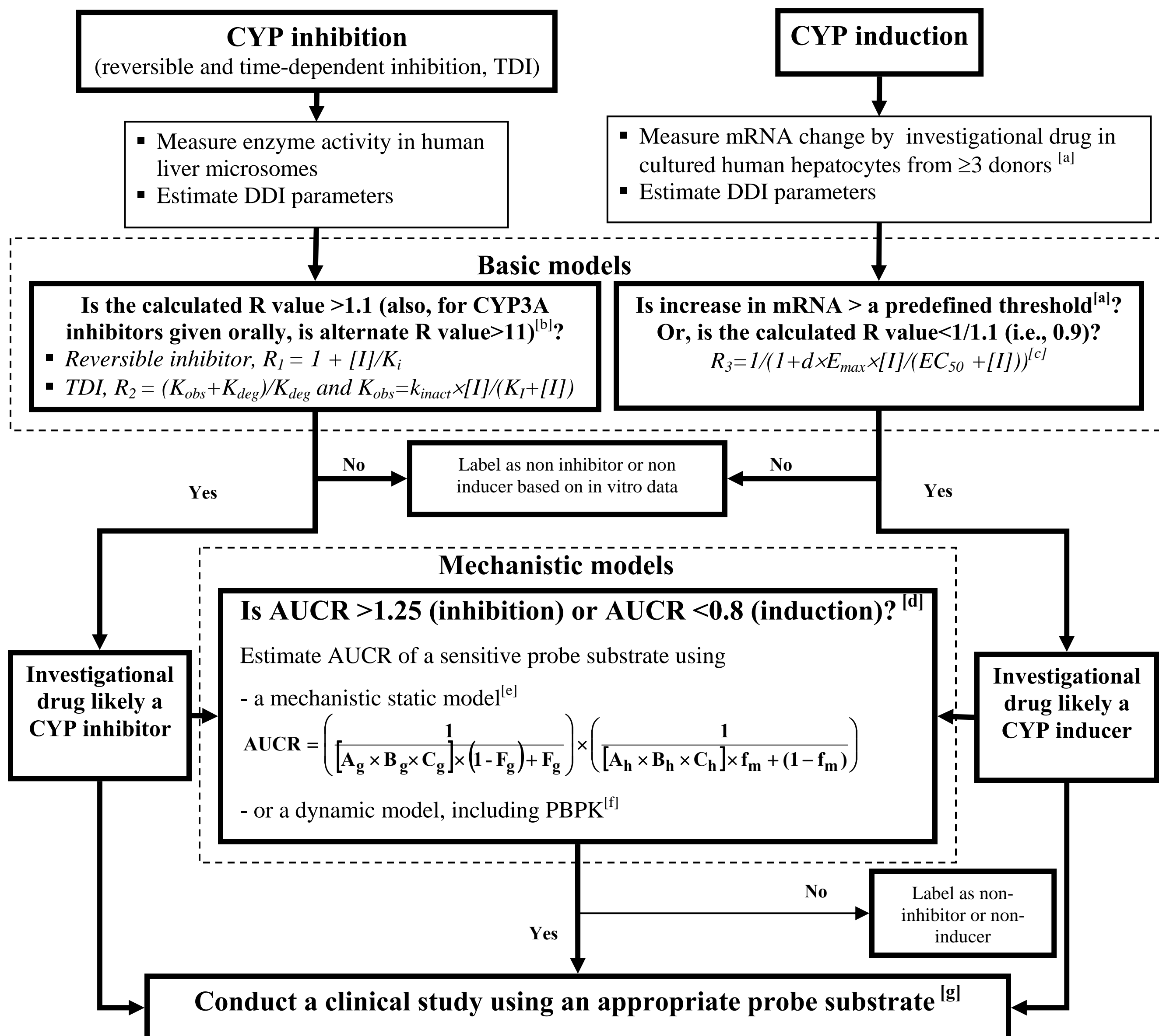
Figure 3. General Scheme of Model-Based Prediction: The Investigational Drug (and Metabolite Present at ≥25% of Parent Drug AUC) as an Interacting Drug of CYP Enzymes



[a] An in vitro induction system may be established in cultured human hepatocytes from ≥3 donors. Use sufficient numbers of clinical inducers and non-inducers to determine a cutoff value (e.g., as described in Fahmi, Kish et al, *Drug Metab Dispos.* 38(9):1605-1611, 2010). Note that these cutoff values may vary among different laboratories because of the variability among hepatocyte lots.

[b] Equations are as described in Bjornsson et al. *J Clin Pharmacol.* 43: 443-469, 2003. [I] can be estimated by the maximal total (free and bound) systemic inhibitor concentration in plasma and the cutoff for R is 1.1. In addition, for CYP3A inhibitors that are dosed orally, [I] should also be estimated by $[I]=I_{gut}$=Molar Dose/250 mL and the cutoff for this alternate R is 11 (Zhang et al. *Xenobiotica*. 38:709-724, 2008). K_{deg} is the apparent first order degradation rate constant of the affected enzyme; K_i is the unbound reversible inhibition constant determined in vitro; k_{inact} and K_I are maximal inactivation rate constant and apparent inactivation constant, respectively; K_{obs} is the apparent inactivation rate constant and $K_{obs}= k_{inact}\times[I]/(K_I+[I])$; and R is the ratio of intrinsic clearance by metabolizing enzyme in the absence and in the presence of inhibitor.

[c] Equation is described in Fahmi et al. 2009. EC_{50} is the concentration causing half maximal effect; E_{max} is the maximum induction effect; and [I] is maximal total (free and bound) systemic inducer concentration in plasma; d is a scaling factor that is assumed as 1 for the basic model.

[d] These are suggested values according to the lower and upper limit of equivalence range. However, we are open to discussion based on sponsors' interpretation. If the calculated AUCR using a mechanistic static model is outside the equivalence range, the sponsor has the option to use a dynamic model (e.g., a PBPK model) supported by available clinical pharmacokinetic data to calculate AUCR and determine whether or not there is a need to conduct clinical drug-drug interaction studies.

[e] A mechanistic static model (or a "net effect model") is modified from that reported by Fahmi et al. *Drug Metab Dispos.* 37(8):1658-1666, 2009.

	Gut	Liver
Reversible inhibition	$A_g = \dfrac{1}{1+\dfrac{[I]_g}{K_i}}$	$A_h = \dfrac{1}{1+\dfrac{[I]_h}{K_i}}$
Time-dependent inhibition	$B_g = \dfrac{k_{deg,g}}{k_{deg,g} + \dfrac{[I]_g \times k_{inact}}{[I]_g + K_I}}$	$B_h = \dfrac{k_{deg,h}}{k_{deg,h} + \dfrac{[I]_h \times k_{inact}}{[I]_h + K_I}}$
Induction	$C_g = 1 + \dfrac{d \bullet E_{max} \bullet [I]_g}{[I]_g + EC_{50}}$	$C_h = 1 + \dfrac{d \bullet E_{max} \bullet [I]_h}{[I]_h + EC_{50}}$

Where F_g is the fraction available after intestinal metabolism; f_m is the fraction of systemic clearance of the substrate mediated by the CYP enzyme that is subject to inhibition/induction; subscripts "h" and "g" denote liver and gut, respectively; $[I]_h=f_{u,b}\times([I]_{max,b}+F_a\times K_a\times Dose/Q_h)$ (Ito et al. *AAPS PharmSci.* 4(4): 53-60, 2002); $[I]_g = F_a\times K_a\times Dose/Q_{en}$ (Rostami-Hodjegan and Tucker, *Drug Discov. Today Technol.* 1, 441–448, 2004). In these equations, $f_{u,b}$ is the unbound fraction in blood, when it is difficult to measure due to high protein binding in plasma, a value of 0.01 should be used for fu,b; $[I]_{max,b}$ is the maximal total (free and bound) inhibitor concentration in the blood at steady state; Fa is the fraction absorbed after oral administration, a value of 1 should be used when the data is not available; K_a, is the first order absorption rate constant in vivo and a value of 0.1 min^{-1} (Ito et al. *Pharmacol Rev.* 50 (3): 387-412, 1998) can be used when the data is not available; and Q_{en} and $Q_{h,}$ are blood flow through enterocytes (e.g., 18 L/hr/70 kg, Yang et al. *Drug Metab Dispos.* 35(3):501-502, 2007) and hepatic blood flow (e.g., 97 L/hr/70 kg, Yang et al. *Curr Drug Metab.* 8(7):676-684, 2007), respectively.

[f] Dynamic models, including physiologically-based pharmacokinetic (PBPK) models, can be developed using both in vitro drug disposition data (e.g., protein/tissue binding, metabolism, transport, and drug-drug interaction) and physicochemical properties. The model should be refined when human pharmacokinetic data become available. The model can then be used to evaluate the drug-drug interaction potential with a sensitive substrate of the CYP enzymes of interest (Rostami-Hodjegan and Tucker, *Nat Rev Drug Discov.* 6(2):140-148, 2007). The model of the substrate needs to be developed and drug interaction mechanisms should be appropriately defined by linking the models of the substrate and the interacting drug (see Figure 4 for more details). If a metabolite is involved in a drug-drug interaction, a model for the metabolite can be established and linked to the parent drug to evaluate its inhibition/induction potential.

[g] See Table 7 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classSub) and Zhang et al. *Toxicol Appl Pharmacol.* 243(2):134-145, 2010.